Joint Hypermobility – Effect of a Resistance Training Program on Disability and Function

Gerhard "Gere" Luder

THESIS SUBMITTED IN FULFILLEMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR IN REHABILITATION SCIENCES AND PHYSIOTHERAPY

Brussel 2023

Examination board

Prof. Dr Bruno Tassignon, Vrije Universiteit Brussel, Belgium (Chair)

Prof. Dr Nele Adriaenssens, Vrije Universiteit Brussel, Belgium

Prof. Dr. Aldo Scafoglieri, Vrije Universiteit Brussel, Belgium

Dr. Erich Hohenauer, University of Applied Sciences and Arts of Southern Switzerland, Landquart, Switzerland

Prof. Dr Ulrike Van Daele, University of Antwerp, Belgium

Promotors

Prof. Dr. em. Jean-Pierre Baeyens, Vrije Universiteit Brussel, Belgium

Prof. Dr. Erik Cattrysse, Vrije Universiteit Brussel, Belgium

PD Dr. med. Daniel Aeberli, Bern University Hospital and Bern University, Switzerland

PD Dr. Martin L. Verra, Bern University Hospital, Switzerland

Advisory Commission

Prof. Dr. Shea Palmer, Coventry University and University Hospitals, Coventry, United Kingdom

For Isabelle, Petra, Justine, Bea, Mira, Eliane, Katharina,

Astrid, Neva, Tanja, Katrin, Fabienne, …

… and all the other hypermobile women,

who inspired me to listen and look exactly …

… to ask the right questions …

and to mistrust the easy answers.

“We may get a glimpse of the vastness of our ignorance
when we contemplate the vastness of the heavens:
though the mere size of the universe is not the deepest cause of our ignorance,
it is one of its causes.”

Karl R. Popper

Conjectures and Refutations: The Growth of Scientific Knowledge, 1963

„Wir ahnen die Unermesslichkeit unserer Unwissenheit,
wenn wir die Unermesslichkeit des Sternenhimmels betrachten.
Die Grösse des Weltalls ist zwar nicht der tiefste Grund unserer Unwissenheit;
aber sie ist doch einer der Gründe.“

Karl R. Popper

Vermutungen und Widerlegungen: das Wachstum der wissenschaftlichen Erkenntnis, 1963

Table of Content

Preface and acknowledgements

Movement is the key to human life; without movement no life is possible. Movement is already essential for breathing and circulation, and neither eating nor digestion would be possible without the ability to move. And it goes without saying that the movements of our body form the basis of our daily life, from getting up and getting dressed, to cooking and housekeeping, to work and sports.

The ability to move and thus the function in daily life can be challenged over time and also by disease or injury. Changes in the body due to pathological processes or aging can reduce mobility and the ability to move. In physiotherapy we see such patients very often: a shoulder joint has become stiff after inflammation, osteoarthritis limits the mobility in the knee, after a stroke daily activities can no longer be performed. In these cases, the goal of therapy is to improve mobility and regain normal function.

Little known, not only by physiotherapists, is the fact that there can also be too much mobility and movement. A joint that is hypermobile and thus becomes unstable, joints that subluxate without much force being applied, movements that cannot be controlled and overshoot their target. There are many unanswered questions about how movements can be controlled, how mobility in a joint might be reduced, or how daily life can be managed with hypermobile joints. This PhD-thesis aims to address some of these questions.

Why research on hypermobility?

My interest in science and research was initiated during my training as a physical therapist (1993-1997). However, at that time, no independent research existed in the field of physical therapy and the education was not yet at an academic level. Then I had the opportunity to work in the Movement Analysis Group of the Laboratory of Biomechanics at ETH in Zurich (Switzerland), gaining insights into gait analysis and the measurement of movement (1999-2003). Finally, in 2006, a couple of physiotherapists from the Rheumatology Department of the Inselspital, University Hospital of Bern (Switzerland) got together to develop some research ideas, actively and strongly supported by the sports scientist Lorenz Radlinger.

We had some measuring equipment in a biomechanical laboratory, we were all interested in movement and movement control, in the properties of muscles and bones, in muscle strength and how this strength contributes to the execution of everyday activities. During the discussions, the idea emerged to study certain basic properties of movement using hypermobile individuals. Thus, the pilot project "Generalized benign hypermotility - influence of active and passive tone" was born. By means of various measurements, the characteristics of muscles and other tissues were investigated and compared between 13 women with and 18 women without generalized joint hypermobility.

Encouraging evidence of possible differences in strength and balance between the two groups subsequently led to the planning of a larger cross-sectional study. Between 2010 and 2012, a total of 195 women were examined, 128 of whom had generalized hypermobility. In addition to strength, standing balance, anterior translation of the tibia, and an analysis of walking and stair climbing, the subjects' complaints were also questioned and further documented over six months. This resulted in, among four other papers, the publication on aspects of stair climbing, which is reproduced in Chapter 3 of this thesis.

Already during these projects, I had the opportunity to complete a Master of Science in Physiotherapy at the Academy Thim van der Laan in Landquart (2008-2011), where I also got in contact with Jean-Pierre Baeyens, who was lecturing there. For the MSc thesis, which was supervised by Jean-Pierre Baeyens, I have done an analysis of the measured data during stair climbing, which later resulted in the publication mentioned above. After that, I was encouraged by several people to pursue a PhD as a next step, and with great support I started planning a randomized controlled trial in this area. Between 2013 and 2016, this clinical trial was conducted at the Inselspital, University Hospital Bern (Switzerland) and since 2013 I am enrolled as a PhD student at the Vrije Universiteit Brussels (VUB, Belgium), again with Jean-Pierre Baeyens as my supervisor and promoter. Out of this project, after some detours and hurdles, came the three other publications of this thesis (Chapters 4, 5, and 6). And now I stand here at the end of this long road, and I am very grateful for all the support I have received over the past years and all the people who have accompanied, motivated and encouraged me, but also cheered and celebrated with me.

My personal acknowledgements

My first “Thank you” goes to Prof. Dr. Lorenz Radlinger, who inspired me to do research already in my basic training and later on was project leader for the above-mentioned cross-sectional projects. He always encouraged me to keep at it, he knew how to ask the right questions and always actively supported me and many others in the daily groundwork on measurement systems and Excel spreadsheets. I would also like to thank Ursula Kissing, former senior physiotherapist at the Inselspital, who jumped over her shadow in 2003 and employed me in a small part-time position to do research project. Until her retirement in 2008, she always supported research in physiotherapy and looked for ways to improve the framework conditions. I cannot thank PD Dr. Martin Verra enough. He has been the director of the Institute of Physical Therapy since 2009 and during this time he has constantly developed the research and supported me in every possible way. He gave and still gives me the freedom to carry out various projects, he supported and encouraged me throughout these years and always has an open ear for my concerns. I am convinced that our common path will continue, and I am looking forward to everything that is yet to come.

A big thank you goes to my main promoter Prof. Dr. em. Jean-Pierre Baeyens from the VUB. After supervising my Master's thesis, he was immediately willing to support my PhD and supervise me on this way. He was always patient and understanding when things did not progress properly for various reasons and always responded quickly to my questions and problems and suggested possible solutions. In addition, I would also like to thank Prof. Dr. Erik Cattrysse, who joined me as deputy promoter after the retirement of Jean-Pierre Baeyens and supported me around the formal aspects of the thesis preparation.

Further, my thanks go to all collaborators and co-authors in the projects. First, this is PD Dr. med. Daniel Aeberli, who acted as Primary Investigator of my main study and provided valuable support especially with the ethics application. Thanks for all comments and corrections on the various manuscripts and for the willingness to be present as co-promoter in the defence of this thesis. A special thanks goes to Christine Müller Mebes, who has been involved in all projects and was responsible for recruiting subjects for the clinical trial. Bettina Haupt-Bertschy provided valuable support in planning and conducting the resistance training intervention. Furthermore, Patrick Probst, Karin Struppler and Ursula Stutz provided valuable assistance during the conduct of the study. PD Dr. Stefan Schmid, Matthias Stettler, PD Dr. med. Hans-Ruedi Ziswiler, Prof. Dr. med. Peter M. Villiger and Astrid Amstutz provided valuable input in the planning and implementation of the projects.

A big thank you goes to the four students of the MSc Physiotherapy at the Bern University of Applied Sciences, who performed various evaluations of the measurement data in their internships: Michaela Hähni, Sarah Mahnig, Martina Aebi and Franziska Iff. Likewise, thanks go to Dr. Patrick Eichelberger for assistance in analysing the measurement data during walking and Dr. Prisca Eser and Inna Galli-Lysak for assistance with the measurements with the pQCT and the respective analysis.

Over the years, various students in the BSc Physiotherapy at Bern University of Applied Sciences have worked on topics related to hypermobility for their bachelor's theses, generating new ideas and shedding more light on exciting aspects of the phenomenon. Thanks for the great commitment and the always good collaboration to Meret Anneler & Fabio Kölliker, Roger Ernst & Marion Meier, Sarina Bucher & Lisa Dohnke, Marita Hotz & Nadja Soltermann and Michelle Morand & Nathalie Rüttimann.

Research always takes place in collaboration and exchange. Very concretely in the projects with all the people mentioned above, but also much more abstractly with authors of publications and researchers around the globe. I am therefore equally grateful for all the discussions at congresses and symposia, for talks and posters that inspired me, for articles that I read with enthusiasm and interest. I particularly remember a situation at the end of a long day at a very large congress, in the poster hall with about 1200 posters. Many had yet left the congress venue and finally three of us were discussing the topic of hypermobility in front of one of the posters: Prof. Dr. Shea Palmer, Dr. Mark C. Scheper and myself. Just one of many inspiring moments and meetings. Shea Palmer deserves additional thanks as a member of my Advisory Commission for his suggestions and comments on my annual progress reports to the faculty. My clinical visit on hypermobility in Bristol and London is also a special memory. Thanks to Shea Palmer, Sarah Bennett, Jane Simmonds, Rosmarie Kerr, and Alan Hakim for providing insight into their work.

A very special thanks goes to Max Spring, the cartoonist, who did the drawings included in this thesis and also used for presentations and posters. At a coffee we discussed various aspects of hypermobility and I tried to explain him, which problems and difficulties these persons experience in their daily life. Afterwards he created these wonderful drawings illustrating the problems, but also the possible advantages of being hypermobile.

A last, special thanks belong to my environment besides research. It is not always easy when there is not enough time to meet friends, to celebrate birthdays or to go on excursions together because of research. Thanks to all my colleagues and friends for their understanding. Thanks also to my parents, who made this path of learning possible for me and have always supported me. A heartfelt thank you to our three sons for their understanding when their father was away again and for their interest in my work and in the subject of hypermobility. And a very heartfelt thank you to my wife Claudia, who has always supported and accompanied me throughout the years, not only in research but in everything I have done. It has been over 25 very good years together with her and I hope that many more will come.

Gere Luder, Bern, June 2023

Abbreviations

5PQ	Five-point questionnaire (by Hakim & Grahame)
BGJH	Benign Generalized Joint Hypermobility (Syndrome)
BIoH	Bristol Impact on Hypermobility Questionnaire
BS	Beighton Score
CFS	Chronic Fatigue Syndrome
EDS	Ehlers-Danlos Syndrome
GJH	Generalized Joint Hypermobility
HSD	Hypermobility Spectrum Disorder
ICC	Intra-Class Correlation Coefficient
JHS	Joint Hypermobility Syndrome
LLAS	Lower Limb Assessment Scale
MCAS	Mast Cell Activation Syndrome
POTS	Postural Orthostatic Tachycardia Syndrome
pQCT	peripheral Quantitative Computer Tomography
PT	Physiotherapy, physical therapy
QoL	Quality of lif
RCT	Randomised controlled trial
ROM	Range of motion
RT	Resistance training
SCED	Single Case Experimental Design
ULHAT	Upper Limb Hypermobility Assessment Tool

Summary

The subject of this PhD-thesis is joint hypermobility, which means that the mobility of one or several joints exceeds the usual range of motion. A person with multiple large joints of the body being hypermobile is labelled as having Generalized Joint Hypermobility (GJH), which is assessed by means of the Beighton Score. Having GJH is not a pathology, but when associated with pain and other symptoms, it might affect health and daily function. Furthermore, GJH can be associated with various systemic syndromes and disorders and in some cases be one sign of a genetic disorder of the connective tissue.

In many cases persons with GJH experience musculoskeletal symptoms and more or less severe limitations in their daily life, during sports or work-related activities. In these cases, physiotherapy might be a possible treatment option to reduce pain and disability and improve movement quality and loading capacity. However, hard evidence for physiotherapy management is sparse and current therapeutic approaches are mainly based on expert opinions and few small trials. Thus, clinical research in this area is important and aims to support the foundation for better treatment and management of persons with GJH.

In a first step our research group conducted a large cross-sectional study with 195 women, whereof 128 had GJH and 67 were controls. The goal was to compare these two groups in terms of active and passive properties of muscles and connective tissue by the following measurements: knee flexor and extensor strength, standing balance on one leg, passive translation of the tibia and ground reaction forces and electromyography of the thigh muscles and the gastrocnemius during walking and stair climbing. Additionally the experienced individual symptoms were requested in a structured interview and afterwards all participants recorded their symptoms during six months using monthly questionnaires. Based on this the 128 women with GJH were divided into 56 symptomatic and 47 asymptomatic individuals. The article **"Stair climbing - An insight and comparison between women with and without joint hypermobility: A descriptive study"** is one of the five publications resulting from this project. Concerning the muscles, the quadriceps showed lower activity during stair ascent and the quadriceps and the hamstrings during descent in hypermobile women. For women with symptomatic hypermobility these differences were even more accentuated. Hypermobile women seemed to alter their movement pattern slightly during stair climbing, probably in order to avoid high muscle activation. Having symptoms during daily life activities seemed to accentuate these adaptations. The global ground reaction forces and the velocity of stair climbing were comparable to women with normal mobility.

Based on this study, on clinical experience and a comprehensive literature search an interventional study as next step was planned. Resistance training in a mainly self-guided manner seemed a

valuable option and improvements in muscle strength might lead to better dynamic stabilisation of the joints and improve passive stabilisation by an increase of muscle and tendon stiffness. Thus, a single-blind randomised controlled trial (RCT) was designed to evaluate the effects of a 12-week resistance training on muscle properties and function in women with GJH, which is described in **"Effect of Resistance Training on Muscle Properties and Function in Women with Generalized Joint Hypermobility: A Single-Blind Pragmatic Randomized Controlled Trial"**. Unfortunately, no statistically significant improvement in strength or muscle mass was seen in this study. Low resistance levels, as well as the choice of outcome measures were possible reasons, as well as the very high heterogeneity of the study group.

For the baseline data of the RCT a more detailed analysis of the data measured with the pQCT was performed, mainly because for this measurement no data of the previous project was available. In **"Correlation of Muscle and Bone Parameters, Daily Function and Participation in Women with Generalized Joint Hypermobility: a Descriptive Evaluation"** only low correlations were seen between strength and muscle cross-section and no differences of women with GJH compared to published controls. However, this study provides insight into the muscle and bone properties of women with GJH. The rather low correlations between various dimensions indicate the complex relationship between strength, muscle properties and function.

Embedded in the RCT were also some measurements regarding the feasibility of the resistance training and possible burden or adverse events related to the resistance training. The women in the control group of the RCT were after the control period offered to perform the same resistance training as the experimental group. Then the data of the totally 46 women performing this training was analysed and finally published as **"Krafttraining bei Frauen mit generalisierter Hypermobilität: Belastungssteigerung, Beschwerden und Effekte"**. This article was written for a physiotherapy journal in German language for two reasons: On one hand the issues regarding feasibility and possible adverse events mainly address the performance and structure of the resistance training, which is largely done by physiotherapists. On the other hand, the German publication aims to increase visibility and the translational impact of the whole project, since many physiotherapists in Switzerland (and also in Germany) do not regularly read scientific journals in English. So, when publishing one part of the project in German this might gain more attention for the study and the issue of GJH and related disorders in these countries. Since the project was performed in Switzerland and physiotherapy research is still not very popular here it is also important to increase the visibility of such research projects by spreading the results and publications as wide as possible. For this PhD-thesis the English translation of this article is included as **"Resistance Training in Women with Generalized Joint Hypermobility: Load increase, Disorders and Effects"**.

This additional analysis revealed that resistance training was feasible and well tolerated by most women with GJH. Only six women had to finish the training prematurely, whereof one because of back pain and a subsequent lumbar disc hernia without clear relation to the exercise. However, regarding the effect of the training the results of this secondary analysis involving additional women did not differ from the results of the RCT. The mostly self-directed resistance training was not intensive enough to achieve clear and significant effects on strength or muscle mass, even if some participants have clearly benefited.

As a general conclusion it can be stated that the standardized and self-guided resistance training seems not appropriate for this heterogenous group of women with GJH. More individualised and closely supervised programmes should be investigated in future studies. For these studies it seems important to define clear study groups. One possibility is to study mainly persons with few symptoms to grasp the preventive possibilities of resistance training more clearly. On the other hand, clearly defined persons with GJH and additional symptoms might be examined in clinical studies, whereby sufficiently large groups and a good recording of complaints and symptoms are essential. In terms of interventions, beside individualised resistance training also proprioceptive exercise or functional training with a focus on motor control could be integrated. Last but not least, it is important to define meaningful assessments in order to record not only strength and muscle mass, but also pain, other complaints and limitations in everyday life.

1. Background and Introduction of the Thesis

The Definition of Joint Hypermobility

When the mobility of a single joint exceeds the usual range of motion (ROM), this joint is considered hypermobile. A person with multiple large joints of the body moving beyond usual ROM is labelled as having Generalized Joint Hypermobility (GJH). This is often assessed by means of the Beighton Score (BS), including the following movement tests [1,2]:

1.) Dorsal extension of the little finger above 90°
2.) Apposition of the thumb, so that it touches the ulnar side of the forearm
3.) Hyperextension of the elbow over 10°
4.) Hyperextension of the knee over 10°
5.) Ability to touch the floor with the palm of the hands, while both knees are extended

For each possible movement (1-4) one point per side is assigned and with one point for the global movement of the back (5) this results in a possible total of 9 points. In the original publication by Beighton (1973), a person scoring four or more points was diagnosed as having generalized hypermobility. More recent publications postulated higher cut-off values, especially for children, adolescents and young adults [3,4]. In 2017 (see below for details), the cut-off scores for GJH were adjusted and defined according to age. For adults, a score of 5 and above has since been considered positive; for individuals aged 50 and older, four points or the fact that 5 points were achieved in earlier years is sufficient; for children and adolescents the cut-off is at 6 points [5,6]. In our own studies, a cut-off at 6 or more points was always used since the widely used four points could be achieved with hypermobile fingers alone, whereby our research interest was mainly in the lower extremities and in general hypermobility [7–12].

Our adaptations of the cut-offs for the label GJH take into account the fact that joint mobility is age dependent. Children usually have quite good joint mobility, whereas mobility tends to decrease during puberty [13]. In this phase a difference between gender may emerge, i.e. a clear decrease has been described in boys, whereas in girls a decrease and an increase of joint mobility is possible [14]. Later, with increasing age a steady decrease of joint flexibility has been demonstrated [13], furthermore, a reduction in the Beighton score was found for a cohort of 1000 people from 3 to 101 years [3]. Hitherto, the impact of different factors has remained unclear, such as a decrease in daily activities, physiological and pathological wear and tear of ligaments and joints or changes in muscle and tissue elasticity [15].

Overall, women more often have hypermobile joints than men. An Australian study with 1000 participants [3] presented the following prevalence for GJH based on a cut-off of BS ≥ 4/9: 14-19 year-old girls 16.7% and for boys 6.3%; 20-39 year-old women 10.0% and in men 4.0%; and in 40-59 year-old women 1.5% and in men 0%. In the age groups above 60, no person scored 4 points or more. Studies with young adults, mainly students, in different countries sometimes found even higher prevalence: for women of between 15.9% and 36.7% and for men between 9.7% and 23.6% (Scheper 2015 [16] in the Netherlands: 31.9% and 9.7%, Russek 2016 [17] in the USA: 36.7% and 13.7%, Antonio 2018 [18] in Brazil: 27.8% and 23.6%, Noormohammadpour 2019 [19] in Iran: 15.9% (women only). One of the factors stated for the higher prevalence in women is hormonal influence. Quatman and colleagues [14] demonstrated that hypermobility increased in female athletes due to puberty, whereas this was hardly the case in male athletes (before puberty: 10.7%, after 28.5% for females, before 3.2%, after 6.5% for males, with BS≥5), however, anatomical, biomechanical, and neuromuscular variations might also play a role. The lower average muscle mass in women and alterations in the structure and composition of the connective tissue might also play a role [20].

The previously mentioned discussion on cut-offs indicates that the BS might have some shortcomings. The use of cut-off dichotomously represents the GJH condition. The ROMs of joints in the human population range widely across the normally distributed spectrum. Consequently, defining a cut-off for the normal ROM in an individual joint and a normal range is a challenge and the global BS score as a cut-off is questionable [3,21]. This has led to high variation in studies using the BS: some use cut-offs and present percentage values of positive persons [15,22], while others use the BS as a continuous variable reporting central measures as medians or even means for specific groups [23–25]. A few studies even use both ways of dealing with the BS or incorporate additional joints with specific criteria [26,27]. However, a recent review on 24 studies attested to a high value of the BS as a clinical tool with substantial to excellent interrater reliability (ICC's between 0.72 and 0.91)-as well as intrarater reliability (ICC between 0.89 and 0.92), even when used by raters of various professions [28]. In an earlier review, the reliability was found to be moderate or high with similar values, whereas the evidence for the validity of BS was limited and often conflicting [5]. A recent narrative review [29] questioned the use of the BS as a diagnostic tool for GJH, at least not without additional measures. The BS was originally developed as an epidemiologic tool to classify people in groups, but it gradually entered more widespread use in the clinical setting to diagnose individuals. Only one validation study in children has ever been undertaken, whereby no data regarding validity exists for adults. As the authors stated there is no gold standard to assess GJH and the BS is not suitable for clinical diagnostics. One main problem is that GJH based on BS cut-offs rarely correlated with hypermobility in joints not included in the BS, like shoulder, ankle, or temporomandibular joint. It has been suggested that BS must be supplemented by additional tests and that a score below the cut-off should not be taken as an indicator for the absence of GJH [30,31]. Nevertheless, in the 2017 GJH diagnostic criteria the BS is still part of the criteria, alongside other signs and symptoms that define GJH as one aspect of a Hypermobility Spectrum Disorder and/or hypermobile Ehlers-Danlos Syndrome diagnosis.

As a general concern, it is not clear how the hypermobility of a single or several joints influences the other joints of the body. As early as 1986, Silman and colleagues [32] looked for relevant associations.

They measured the ROM for index finger extension, for lower limb rotation, and for forearm rotation in healthy persons but did not find any correlations between these movements. More recently, studies exploring possible associations between GJH and hypermobility in an individual joint yielded the following results: no significant association between GJH and shoulder laxity scores [33]; significantly higher ankle dorsiflexion in persons with GJH [34]; significantly increased hip flexion and internal and external rotation in those with GJH [35]. In a large Australian cohort cervical flexion and extension correlated low to moderately with BS, with age, gender and BS explaining only 19% of the variability in flexion and 51% in extension [23]. Regarding the knee, another large Australian study found no association between GJH and knee joint hypermobility [36]. Finally, looking at temporomandibular hypertranslation no correlation with GJH has been reported [37]. Consequently, the relation between GJH and hypermobility in individual joints remains unclear. Despite the open questions regarding validity and the use of the BS, it remains a widely used clinical tool to obtain a first idea of the hypermobility of a patient. It is quick to perform and, depending on the resulting score, additional clinical tests and assessments can be carried out.

Besides the widely used BS some other assessment tools exist for GJH. The Hospital del Mar criteria are based on the BS, but include additional movements like hip abduction, hyperextension of the first metatarsophalangeal joint, patellar hypermobility, passive ankle dorsiflexion and eversion and knee hyperflexion [38–40]. Additionally, two self-assessment questionnaires for hypermobility exist. The so-called "5-point-questionnaire" (5PQ) consists of five questions, including actual and historical information about joint hypermobility and is claimed to have good reproducibility in addition to satisfactory sensitivity (84%) and specificity (80%) [41]. Finally, the self-reported BS was introduced as a screening tool where the patients themselves check movements using pictures on an information sheet [35].

Joint Hypermobility - Advantage, Problem, or Disease?

Having a high BS and thus being hypermobile is not a clinical diagnosis. It is a sign that the person is near the upper end of the spectrum of joint mobility. The debate remains as to whether GJH might be an advantage for some sports, for dance or for other activities [42,43]. Several studies have found, that GJH is more frequent in various groups of ballet dancers [26,44,45]. This might be due to a specific choice of persons with GJH to do these activities because of the advantage of their hypermobile joints. On the other hand, regular exercise in ballet may lead to an increased ROM in various joints, leading to a higher prevalence of GJH. In a remarkable study with 660 musicians the authors stated that hypermobility of joints with repetitive motion (fingers and wrist in violinists) might be an asset, while hypermobility in joints with supportive function (knee or spine in flutists) might be a liability [46]. This is illustrated by the historical example of Pier Paganini, an excellent violinist in the 19th century, who was suspected to have hypermobile finger and wrist joints, which helped him to play his instrument in an excellent manner [47]. A Swedish study revealed similar results for industrial workers: in jobs requiring change of body posture a hypermobile spine was an asset, whereas in a standing or sitting position a hypermobile spine was a liability leading to more low back pain episodes [48].

Similarly, GJH might be an advantage in certain situations or activities, but in other circumstances might be a disadvantage, leading to negative consequences. Primarily, any hypermobile joint can become an unstable joint. Note, that it is important to differentiate between joint hypermobility, sometimes also referred to as joint laxity, and instability of a joint [49]. Hypermobility is the presence of an increased angular and/or translational movement of a joint, which can be asymptomatic. The stabilisation of a joint is, on the one hand, based on passive components like bones, joint capsules, and ligaments, which may be in an altered state in persons with GJH. In dynamic situations stability cannot usually be maintained by passive structures only, both an active muscle system and neuromuscular control is necessary. Having adequate muscle strength and proper motor control can provide joint stability, even in the presence of joint laxity. But reduced muscle strength, impaired proprioception or decreased motor control might lead to joint instability in persons with GJH as well as in those with stable passive structures. Thus, functional instability of a joint is a pathological condition that occurs when the neuromuscular system is not able to stabilise a joint during specific movements, which is more often seen in persons with local joint laxity or with GJH [49]. Depending on the affected joint and respective activity this might lead to shoulder subluxation, patellar dislocation, or ankle sprains [50–52]. Such symptoms may sometimes herald the beginning of longer complaints associated with GJH, especially when seen for the first time during puberty or in young women. A misstep when walking downhill, overstretched fingers when playing volleyball, or a subluxation of the shoulder when cleaning the windows are typical situations. In some cases, the problems decrease after adolescence and disappear; in other cases the problems persist and can even spread to other joints [53].

Within GJH the concept of "generalization" is of importance. Problems in one joint can trigger complaints in neighbouring joints by both mechanical and neuromuscular mechanisms. But different joints can also cause local problems independently from each other leading to systemic reactions such as altered pain perception or increased fear of movement and strain. Moreover, chronic problems can develop over time due to recurrent pain and discomfort. As an example, the proportion of people with GJH is significantly higher in patients with fibromyalgia [54,55], indicating that hypermobile joints might contribute to the development of this chronic and disabling condition. Additionally, deconditioning can also occur over time through avoidance of activities, which then affects other systems such as the metabolism, heart or lungs.

Finally, at the systemic level, GJH may be associated with other systemic complaints. This is especially the case if the hypermobility is partly or completely determined by changes in the connective tissue. Connective tissue is a very complex and variable structural element incorporating multiple tasks in structure and function of almost all body tissues. Thus, variations in the connective tissue can lead to many different complaints: an increased overstretching of the skin and problems with wound healing; disturbances in vascular regulation and aneurysms of the large arteries; problems with the heart valves; digestive disorders or even neuropathies [49,56]. Some of these problems have been well known for a long time and can be directly traced back to the connective tissue; for others it is unclear whether hypermobility is directly or indirectly linked to it [57]. To conclude, there are indicators in the literature that GJH can affect a person's health, function, and daily life activities in various ways.

Diagnostic Labels in Joint Hypermobility

Having GJH is in many cases a sign of a systemic disorder affecting the connective tissue, in many cases genetic like the Ehlers-Danlos Syndrome (EDS), Marfan Syndrome or Osteogenesis Imperfecta. These and other heritable disorders of the connective tissue show more or less pronounced hypermobility in all or some joints. The most frequent of these connective tissue disorders is the EDS, currently presenting in 14 types [6,56]. All except the hypermobile EDS (hEDS) are clearly associated with mutations in specific genes, mainly encoding for proteins of the connective tissue. It is noteworthy that 80% to 90% of patients with EDS present with the hypermobility type [49,58]. Nevertheless, to date no genetic marker for this type has been discovered. Vascular EDS and classic EDS account for about 2% and 0.5% respectively of cases, while the other types present very rarely with dozens or hundreds of cases reported worldwide [56]. In terms of severity the hEDS is often at the lower end of the spectrum, while the other types frequently involve life-threatening issues or severe deformations of the musculoskeletal system [56].

As connective tissue disorders, these genetic diseases affect various organs and body systems. For instance, in vascular EDS vessels are strongly involved, and the individual presents with varicose veins, arterial rupture, bruising without trauma or translucent skin. In classical EDS the skin is strongly affected, showing soft and velvety skin, easy bruising, and atrophic scarring. Other features in some of the various types are organ prolapses, cardiac valvular insufficiency, scoliosis and joint deformities or thin cornea and early periodontitis. A comprehensive overview of the various EDS types, the associated symptoms and possible biochemical mechanisms was presented by Malfait and colleagues in 2020 [56]. Some of the specific symptoms of the more severe types can also be seen in hEDS and sometimes even in persons showing GJH without formal diagnosis of EDS.

In terms of diagnosis and classification of persons with GJH and additional symptoms various systems have been used in the past decades, whereby the nomenclature changed several times. For a relatively long time two classifications existed in parallel. The revised Villefranche nosology from 1997 for EDS was based on six subtypes, amongst which the second type was referred to as "hypermobility type" [59]. The other classification evolved from a group of British rheumatologists who, in 1998, presented the Brighton criteria for the so called Benign Joint Hypermobility Syndrome (BJHS) [60]. The debate on similarities between BJHS and the EDS hypermobility type has continued ever since. A lack of clinical distinctions between the two syndromes was postulated and the call for a new and consistent classification became more and more urgent [61–63]. In parallel several authors suggested discarding the term "benign" in BJHS since the syndrome was often associated with disability and limitations in daily life [61,64]. In 2014 Jacobs & da Silva published an overview of the various diagnostic criteria and illustrated the considerable overlap between them [55].

Finally, an expert panel met in 2016 in New York and developed a new classification for EDS and hypermobility associated disorders, which was published in 2017 after some refinements [6,30,65]. The diagnostic criteria for hypermobile EDS were more strictly defined. A person with a clear inherited disorder was diagnosed as having hypermobile EDS, despite the lack of any genetic foundation for this EDS type. A person with GJH and additional symptoms, who did not fulfil the criteria for hEDS, was diagnosed using the new diagnostic term of "Hypermobility Spectrum Disorder" (HSD). The term GJH was reserved as a descriptor for a person with increased mobility in several joints not associated with other symptoms or syndromes. The spectrum of hypermobility and the broad range of possible associated symptoms was comprehensively described in two papers [30,53]. However, clear criteria for the allocation of the diagnosis HSD are to date still missing. A diagnosis of HSD is often given after excluding all EDS types and other syndromes associated with hypermobility.

These changes as well as the lack of clarity in classification and diagnostic labels over time hinder the comparison of studies in the field of joint hypermobility. An exact description of the population involved is often missing and even the applied cut-off of the BS is very variable. Additionally, the implementation of the new classifications in research and clinical practice is often slow, leading to various descriptions and labels presented in parallel. The research project of this PhD-thesis was also influenced by this problem. Our first research projects in the field started around 2006 and mainly involved women with GJH. Later on, symptomatic women with GJH were also incorporated, but often without a formal diagnosis of BJHS or JHS. The study protocol for the main study, the randomised controlled trial, was developed in 2012 and included checking the Brighton criteria during participant inclusion, whereby fulfilling these criteria for JHS was not mandatory. Recruitment for the trial was done between August 2013 and November 2015 and the last follow-up measurements were in December 2016. Consequently, for the publication of the results the new nosology was available. However, the classification of the participants could not be performed according to the new criteria due to the lack of retrospective information. Therefore, for the publications incorporated in this thesis, the terminology before 2017 has been used to maintain consistency.

Disorders and Syndromes Associated with Joint Hypermobility

Having GJH is often associated with various syndromes and disorders and in many clinical cases it remains unclear if and to what extent the various symptoms are related. In the context of a genetic variant some of the associations are obvious, but even then, the relationship between various symptoms often remains unclear.

As described in the various EDS types several tissues can be involved. Also, in hEDS and even in patients with HSD other body systems may be more or less affected. Very typical for an associated disorder is skin involvement. This can be thin, velvety or stretchy skin as well as reduced wound healing capacity and atrophic scaring [57,66]. Weakness in the connective tissue may lead to hernias and organ prolapses [67,68]. Regarding the cardiovascular system, many symptoms have been described in the literature, ranging from varicose veins and low blood pressure to cardiac valve prolapse in about 6% of cases [69,70]. Postural orthostatic tachycardia syndrome (POTS) was described in 15% to 22% of patients with hEDS and recently a prevalence for GJH of 55% was found in a group of 91 patients with POTS [57,71,72]. In terms of neurology small fibre neuropathy and neuropathic pain was seen in all of 20 patients with hEDS [73] and prevalence of headache, especially migraine was 3 times higher in women with JHS with earlier onset of symptoms (12.7 vs. 17 years), more symptomatic days (15 vs. 9.7 days(month) and higher symptom levels and impact on quality of life [74,75]. Frequently described gastrointestinal problems include abdominal pain, reflux symptoms, constipation and diarrhoea, as well as eating disorders [69,76,77]. In two large questionnaire studies about 50% of persons, mainly female, with JHS or hEDS have reported functional gastrointestinal syndrome with reduced quality of life and increased use of medication. [58,78]. Sleep disorders like obstructive sleep apnoea were found in 36% of EDS patients [79] and chronic fatigue syndrome (CFS) seems to be associated very often with hypermobility. In a group of 68 CFS patients 20% had GJH and 40% fulfilled criteria for JHS [80], while in reverse studies between 75% and 82% of participants with hypermobile EDS or JHS were diagnosed with CFS [81–83]. Furthermore, the immunological system may be involved with histamine intolerance and mast cell activation syndrome (MCAS) [84–86]. With the occurrence of Long-COVID (also termed Post-COVID Syndrome) possible associations of these symptoms with GJH and EDS were discussed [86] and even a new clinical phenotype of Post-COVID syndrome with fibromyalgia and GJH was proposed [87]. Finally, even psychological disorders can be associated with GJH: higher rates of anxiety, depression and fears have been reported [88–90] and one study even found a higher amount of chocolate consumption for adults with GJH, which was explained as a possible self-treatment attempt of sub-syndromic anxiety [91].

Recently a lot of research has been carried out on the symptoms and problems associated with GJH. An up-to-date and extensive overview has been provided by Gensemer et al.[57] and some interesting thoughts on possible associations and mechanisms have been presented by Eccles et al.[86].

Consequences of Joint Hypermobility

Besides the symptoms and problems possibly associated with GJH, what are the direct consequences of hypermobile joints? The distinction between association and consequence is not easy and, in many cases, both mechanisms may overlap. However, in the relevant literature several differences in terms of physiology, movement control, biomechanical factors, or injury risk between persons with and without GJH were described.

Yet, as mentioned above, the association of GJH with the mobility of one single joint is not always clear. In terms of muscle strength, the picture is also inconsistent with several studies describing a tendency for lower strength levels [16,92,93], while others found no clear difference [94] or even higher values for rate of force development, but not for maximum strength [7]. In functional activities like gait, alterations in movement patters and kinematic and kinetic variables have been observed [8,95,96]. Similarly for stair climbing altered movement patterns that aim to avoid high muscle activation have been described [9]. These alterations in movement match research that describes impaired proprioception [97–99] and reduced standing balance ability in persons with GJH [7,100].

In the longer term GJH seems to be a risk factor for knee [101] and spine osteoarthritis [15] and is related to worse outcomes after treatment of lumbar disc herniations [102]. In general, the risk of developing pain is about two times higher for knee symptoms [103] and for lower back pain [19]. A large cohort study in the UK described an increased risk for knee, shoulder and ankle pain in young adults with GJH [104]. With GJH industrial workers and musicians have a higher risk for pain, especially with standing or sitting postures for longer time periods [46,48]. Finally, even in pregnant women the risk of developing pelvic girdle pain is higher in those with GJH [105,106].

Regarding leisure activities such as sports, dance or music performance several studies looked at injury risk as well as the question of whether being hypermobile might be an advantage in some disciplines. The evidence in general remains inconclusive. Some studies have demonstrated a higher risks for athletic people or dancers [107–109]. However, other studies have not seen associations between GJH and an increased risk for injury, whether for general populations or for athletes [17,110,111]. One review found a higher risk for ACL ruptures, but no clear association with the outcomes of the rehabilitation [112]. Another review described a higher injury risk for the lower limb, but inconclusive evidence for the upper limb or the severity of the injuries [113]. To evaluate the individual's injury risk the high inter-individual variability in the degree of GJH and the respective consequences appears to be crucial and must be taken in account.

Finally, a few rather complex studies have tried to incorporate the various factors influencing GJH and its possible consequences. A tendency for persons with GJH to avoid certain activities has been demonstrated [114], together with a decreased functional status [115]. Moreover, it has been suggested that persons with GJH might have some disabilities, but are generally less affected than those with JHS [116]. Even structural changes in the brain have been observed in persons with GJH [99], but in terms of psychological issues the picture still remains unclear. Nevertheless, a recent publication suggested that having GJH combined with a higher level of anxiety may lead to a more disabling condition and more symptoms in daily life [117]. Furthermore, a coincidence of GJH with chronic pain and fear-avoidance tendencies has been proposed [118]. But for the moment it remains unclear if these are causative associations or just correlations.

Management of Joint Hypermobility

Concerning the management of GJH, there is still debate as to whether having GJH is a problem that requires therapeutic or medical interventions. For sure, not every person with a high BS needs therapy and support. Nevertheless, there are many situations where persons with GJH struggle in their sport or leisure activity, their work-situation or even daily-life activities and could benefit from support. In each situation, it is important that the patient and the professional(s) decide jointly what kind of intervention might be helpful for a better quality of life (QoL).

Once the need for support emerges, it is essential to differentiate between two different conditions and subsequent management goals. In a situation with acute pain in one or several joints, with subluxations or myofascial trigger points the management of these symptoms is the primary goal. Additionally, in these acute conditions the general health condition of a patient with GJH and symptoms in other regions of the body should not be ignored. The other condition is when a patient is in a more stable phase and has little or no acute problems. Albeit prevention remains very important. Specific aims are to avoid overload of joints and muscles as well as subluxations or dislocations, and to provide the patient with the best conditions for the individually required activities. Finally, the long-term management of persons with GJH and related symptoms is of concern. Since to date no cure is available, it is crucial to support patients for the self-management of their condition, whereby patient education is crucial. Persons with GJH need to anticipate possible flare-ups and learn to cope with changing exercise tolerance or pain situations. In addition, patient support groups with peers involved and counselled by professional experts provide help to better sustain daily life activities as well as leisure-time and occupational demands [119,120].

Evidence for the management of GJH is very sparse. The current therapy options and management propositions are mainly based on expert opinions and personal experience. In general, an accurate diagnosis is important to recognize the individual needs and specific problems of each patient. While the distinction between HSD and hEDS does not seem very important in terms of management, identification of all affected body parts and organ systems is the foundation for the various treatment modalities. In many cases management remains mainly symptom-based and must be adapted continuously over time [121,122]. To support patients facing the challenge of long-term management numerous countries have elaborate networks of self-support groups, which publish personal experiences and keep patients informed via their website offerings and printed material. In several qualitative studies these groups and other social support networks as well as better informed and understanding health professionals were mentioned as important by patients with HSD and EDS

[119,123,124]. An important resource for these support groups and for all interested persons is the Ehlers-Danlos-Society [125], which not only covers questions about the more severe EDS types, but also on hEDS, HSD and hypermobility in general.

In terms of evidence, three systematic reviews on interventions are available. In 2021 Palmer and colleagues included 8 studies with adults in a review looking at the effectiveness of conservative interventions in syndromic JH [126]. Very heterogeneous interventions of variable durations and weakness of study quality hindered firm conclusions. Based on three RCTS's weak evidence for various interventions were found, including inspiratory muscle strength exercise [127], lumbar spinal stabilization [128] and proprioceptive knee exercise [129]. Furthermore, Ferrell and colleagues in 2004 [128] and Sahin and colleagues in 2008 [129] found that symptoms were improved by programs focusing on exercise and proprioceptive training. At least three additional feasibility pilot studies have been done to date, two of which looked at complex [130] or multidisciplinary [131] interventions and one researched heavy shoulder strength training [132]. All three studies proved feasibility, but so far no reports of full trials have been published for two of the pilot studies. Only the last trial looking at shoulder strengthening was conducted as a fully powered trial, showing improved shoulder function by high-load strengthening in comparison to low-load exercises [133]. In a pre-post study looking at temporomandibular disorders in association with GJH a PT program lasting 3 weeks was attended by a group of 76 patients, of which 26 had GJH. The program focused on reduction of myofascial pain and restoring coordination of the mandible. The outcomes were similar in both groups with decreased pain and improved movement coordination [134].

Additionally, three clinical trials were performed with children and adolescents having JHS. Kemp and colleagues compared a generalized versus a targeted physiotherapy program in 2010 [135], Pacey and colleagues looked at knee exercise in 2013 [136] and Bale and colleagues compared a multidisciplinary program with a single advice session by a physiotherapist in 2019 [136,137] . In all three studies, improvements in the various groups were seen, but no difference between the comparators was found. Thus, the best and most effective exercise and therapy program is still not available for these patients, whether they have a formal diagnosis of JHS or just cope with pain and disability in association with their GJH.

Finally, an interesting paper by To & Alexander (2019) deserves mention. This study looked at patients with anterior knee pain and incorporated three groups: patients with GJH having BS ≤4, patients with JHS according to the Brighton criteria, and patients without GJH as controls. All 102 participants performed a progressive strength training program for 16 weeks and muscle torque of the leg was measured every two weeks. Interestingly, all three groups showed comparable improvements in strength over time, but the starting level in the JHS group was significantly lower than for the controls, while those with GJH showed significantly higher strength than the controls. The authors concluded that patients with JHS (and also with GJH) can gain strength in a similar way to other patients, but that they need up to three months to reach the same strength level as patients without JHS had before training [92].

Resistance Training in Physiotherapy

A wide range of various movements and exercise regimens are used in physiotherapy (PT). One important goal of exercise is to increase muscle strength and muscle mass and for that purpose strength training is a possible option. Probably one of the most effective and quite popular forms of muscle strength training is resistance training (RT), mainly by means of weights or elastic bands. The goal is to increase muscle strength, muscle mass or performance in daily movements, leisure activities or sports [138]. The three main principles in applying RT are: (1) performance of a small number of repetitions until fatigue, (2) sufficient rest between exercises for recovery, and (3) increase of the resistance following the increasing ability to generate force [139]. Detailed exercises have been presented in various publications, i.e. the guidelines of the American College of Sports Medicine [140,141].

Impairments in motor control, reduced proprioception and even pain are often associated with muscle weakness with impact on daily activities [16]. Consequently, in musculoskeletal PT the use of RT has been initiated in various patient groups. An overview in 2005 [139] found five systematic reviews presenting the positive effects of RT in the context of musculoskeletal PT on strength, pain and QoL with no or very few adverse events. More recently, three Cochrane reviews found consistently positive effects for RT, one for elderly persons with improvements not only in strength, but also in pain and functional ability [142], one in patients with fibromyalgia [143] and the last in various muscle diseases [144]. All these reviews included only a few studies and showed partially small effects, and all stated that more trials with higher quality are needed in this field. Recent reviews presented with positive effects on pain and QoL for RT in women with chronic lower back pain [145], patients with knee osteoarthritis [146], and also in women with fibromyalgia [147]. In terms of possible effects a broad overview of RT in children and adolescents with various diseases published in stated that although randomized controlled trials are rare, the research indicates that RT might be a potent tool to improve mental and physical health by improving muscle strength, body composition, self-concept or functionality, reducing pain or injury risk [148].

Beside these specific applications, RT and exercise is also recommended for healthy persons [149,150]. These exercise recommendations build part of the general recommendations for a healthy lifestyle, including also nutrition, sleeping habits, stress management, tobacco cessation and reducing screen time. Combined with regular physical activity these habits not only help to prevent musculoskeletal disorders but can also be part of the non-pharmacological interventions to manage chronic conditions [151]. Recommendations for regular physical activity and also specific RT were also published for children and adolescents [152] and for women throughout pregnancy [153]. Furthermore, in a comprehensive review, exercise as medicine was proposed for a total of 26 chronic conditions [154], illustrating the huge potential of exercise in general and thus also for RT.

Resistance Training and Joint Hypermobility

As shown in the previous chapters, reduced muscle mass and strength, impaired proprioception and decreased motor control are often seen in persons with GJH [94–96,98]. Thus, resistance training might be a possible and important part of the management of persons with GJH, whether with or without acute symptoms and disability. The generation of an exercise program for GJH requires finding the balance between two focal points. From one point of view, physical activity, incorporating aerobic exercise and RT appear to be valid management options, promising improvements in muscle strength, joint stability, better proprioception, and motor control to the point of better performance in daily life activities. On the other hand, high loads and impact forces as well as maintained positions or poorly controlled movement patterns might lead to pain, overuse of structures, like ligaments, tendons, or bursae and possibly to injuries and chronic disability.

Consequently, tailored and specific exercise programs are needed for persons with GJH as well as for those with JHS, HSD and hypermobile EDS. However, as described above, the recommendations for management are mainly based on expert opinions and little high-level evidence is available for the implementation of exercise and especially RT. Current recommendations for JHS have mainly been based on the RCT by Kemp and colleagues in 2010 [135] including 57 children and adolescents. They compared a general strength exercise program versus targeted PT with a focus on motion control. In both groups pain was significantly less and a tendency for improved function was found, but without differences between the two groups. In a small feasibility trial by Møller and colleagues with three EDS patients an RT program lasting four months with three times weekly sessions was performed and not only improved muscle strength, but also improved balance and reduced stiffness, and subjective fatigue [155]. For persons with GJH the study by To and colleagues [92] is the only trial available, indicating that persons with GJH can improve their strength by RT.

Considering this body of evidence and the theoretical aspects, exercise and specifically RT might be helpful for persons with GJH for several reasons:

- Muscle weakness can be an issue in persons with GJH and thus improvements in muscle strength can be an important part of the management [92,121].
- Altered motor control and reduced proprioception are widely seen in persons with GJH, and muscle strengthening has the potential to improve proprioception and to provide better stability for joints throughout movements [128,129].

- Specific RT might also improve muscle mass and in the longer-term help to increase muscle and tendon stiffness. Such an increase can provide better support for the joints and thus improve motor control [156,157].
- An increase in muscle strength has the potential to increase body awareness and self-efficacy and might benefit daily life activities as well as work or leisure related activities by enabling better performance [143,149].

To conclude, it is generally accepted that physical activity, general exercise and also resistance training are important parts in the management of persons with hypermobility, whether they have GJH, JHS, HSD or even a specific form of EDS. But many questions remain and have not been answered by high level, quality studies: What kind of exercise is the most appropriate? How often and how intensely should exercise be performed? How much support and individual guidance or coaching is needed? Would it be good to offer some group training? Is a more individual and tailored approach the better way? For all these questions very, little hard evidence is currently available and thus the aim of this thesis project was to add a small piece of knowledge at the crossroads of general hypermobility and exercise prescription.

2. Aims of the thesis project

The research group at the Rheumatology Department of the Bern University Hospital started the first project to address hypermobility in 2006. The starting point was a cross-sectional pilot study looking at mechanical and tissue properties in women with GJH. Men were not included in the first or any subsequent projects because most people with GJH are women. Based on this decision, more homogeneous participant groups were achieved; but with the disadvantage that no information about men with GJH has been derived from these projects

The pilot study included 31 women and measured various muscle properties of the lower leg as well as functional activities and disability in daily life. The main findings were slight differences in strength, primarily the rate of force development and balance properties [7]. Based on this pilot study a large comprehensive cross-sectional study was planned and performed. A total of 195 women between 18 and 40 years of age were included, of which 128 had GJH and 67 served as controls with a Beighton score of 0 or 1 allowed. Measurements in this study included isometric knee strength, single leg balance, gait and stair climbing and questionnaires for disability in daily life. After the measurements the participants kept a diary for six months to record pain and symptoms. Based on these data the 128 women with GJH were divided in two subgroups, 56 with symptoms and 47 asymptomatic. The results of this large study were published in several papers [8–12], of which the one with the analysis of muscle activity and ground reaction forces during stair climbing is included as the first paper in this thesis (Chapter 3).

Based on the results of this cross-sectional study, the personal experience of the authors and the available literature, a clinical trial with an intervention for women with GJH showing symptoms was developed. Based on theoretical considerations and literature it was assumed that not only more muscle strength might be helpful for these women, but also that higher muscle mass might help provide better support and joint stabilisation. Thus, a standardized resistance training program was developed with the aim of muscle hypertrophy. The measurements in the trial not only aassessed for muscle strength but also for muscle cross-sectional area, using peripheral quantitative computer tomography (pQCT). Note, that many of the studies mentioned in the introduction, especially most of the clinical trials, had not yet been published at the time when this trial was designed, thus important considerations and propositions from those papers could not be incorporated. To investigate the possible effects of this program a randomised controlled trial (RCT) was conducted, with the following main questions:

- Is resistance training feasible and safe for women with GJH?
- Can women with GJH increase their strength and muscle mass by participating in a 12-week resistance training program?
- Does the 12-week resistance training have any influence on daily activities such as stair climbing and/or on disability in daily life?

The RCT was prospectively registered in the ISRCTN registry on July 16, 2013, as ISRCTN90224545 and recruitment took place between August 2013 and November 2015.

The results of the RCT were published in BMC Sports Science, Medicine and Rehabilitation, and that paper is included as chapter 4 in this thesis. Additionally, a detailed descriptive analysis of the baseline data was performed, which is presented as chapter 5. Finally, a detailed analysis of the training performance and possible adverse events were published together with the main results in a German journal to increase dissemination and visibility of the research project. This paper is included in the original version as chapter 6.a and in a translated English version as chapter 6.b.

3. Stair climbing - An insight and comparison between women with and without joint hypermobility: A descriptive study

J Electromyogr Kinesiol. 2015; 25(1):161-167

Gere Luder, Stefan Schmid, Matthias Stettler, Christine Mueller Mebes,
Ursula Stutz, Hans-Rudolf Ziswiler, Lorenz Radlinger

Journal of Electromyography and Kinesiology 25 (2015) 161–167

Contents lists available at ScienceDirect

Journal of Electromyography and Kinesiology

journal homepage: www.elsevier.com/locate/jelekin

Stair climbing – An insight and comparison between women with and without joint hypermobility: A descriptive study

Gere Luder [a,b,*], Stefan Schmid [b], Matthias Stettler [b], Christine Mueller Mebes [a], Ursula Stutz [a], Hans-Rudolf Ziswiler [c], Lorenz Radlinger [b]

[a] Department of Physiotherapy, Bern University Hospital, Bern, Switzerland
[b] Bern University of Applied Sciences, Health Division, Discipline of Physiotherapy, Bern, Switzerland
[c] Osteo Rheuma Bern, Zentrum für muskuloskelettale Medizin, Bern, Switzerland

ARTICLE INFO

Article history:
Received 17 December 2013
Received in revised form 30 June 2014
Accepted 1 July 2014

Keywords:
Ground reaction forces
Surface EMG
Joint stabilization
Movement control

ABSTRACT

Generalized joint hypermobility (GJH) is a frequent entity in rheumatology with higher prevalence among women. It is associated with chronic widespread pain, joint dislocations, arthralgia, fibromyalgia and early osteoarthritis. Stair climbing is an important functional task and can induce symptoms in hypermobile persons. The aim of this study was to compare ground reaction forces (GRF) and muscle activity during stair climbing in women with and without GJH. A cross-sectional study of 67 women with normal mobility and 128 hypermobile women was performed. The hypermobile women were further divided into 56 symptomatic and 47 asymptomatic. GRFs were measured by force plates embedded in a six step staircase, as well as surface electromyography (EMG) of six leg muscles. Parameters derived from GRF and EMG were compared between groups using *t*-test and ANOVA. For GRF no significant differences were found. EMG showed lower activity for the quadriceps during ascent and lower activity for hamstrings and quadriceps during descent in hypermobile women. For symptomatic hypermobile women these differences were even more accentuated. The differences in EMG may point towards an altered movement pattern during stair climbing, aimed at avoiding high muscle activation. However, differences were small, since stair climbing seems to be not demanding.

1. Introduction

Joint hypermobility is a frequent and important entity in rheumatology, which has not received adequate attention. Hypermobility can occur in a single joint or can be generalized and affect several joints. This generalized joint hypermobility (GJH) depends on age, sex and ethnic group, whereby women are usually more often affected than men and joint mobility commonly diminishes with greater age (Grahame and Hakim, 2008). In a recent survey (Mulvey et al., 2013) the prevalence of GJH in a general population was 18%. A strong association between GJH and musculoskeletal complaints was found in this study, with 40% increased risk of reporting severe chronic widespread pain. Furthermore, recurrent joint and soft tissue injuries, arthralgia and back pain were associated with joint hypermobility (Grahame, 2009), as well as fibromyalgia (Sendur et al., 2007) and early osteoarthritis (Dolan et al., 2003).

The diagnosis of GJH is generally established by the Beighton score (Remvig et al., 2007), which assesses the angular range of motion of selected joints. Although the reliability of this score is quite good, validity studies are lacking (Juul-Kristensen et al., 2007; Remvig et al., 2007). An important limitation of the Beighton score is that movements are performed passively and it is mainly based on passive properties. Thus, it does not take into account active stability and movement control, which are important in functional movements. During every movement the active and passive properties determine the quality and the quantity and provide together joint stability. The active part mainly depends on muscle activation, whereas on the passive side, the viscous-elastic properties of the structures, such as capsules, ligaments and fasciae are important (Gajdosik, 2001).

The major problems in people affected by GJH were found to be perceived joint instability, a higher risk of joint distortions and, consequently, chronic pain (Grahame, 2009; Mulvey et al., 2013). Thus, an important issue in people with hypermobile joints seems to be the stabilization of the joints during functional activities, but few studies looked at movement control in hypermobile persons.

* Corresponding author at: Department of Physiotherapy, Bern University Hospital, PKT2 U1 551, CH-3010 Bern, Switzerland. Tel.: +41 31 632 06 79.
E-mail address: gere.luder@insel.ch (G. Luder).

http://dx.doi.org/10.1016/j.jelekin.2014.07.005
1050-6411/

Described were differences in reflex function (Ferrell et al., 2004) and an enhanced proprioception (measured as joint position sense) by a home exercise program (Ferrell et al., 2007). Higher knee joint moments were reported during gait (Simonsen et al., 2012) as well as an impaired knee function in persons with GJH (Juul-Kristensen et al., 2012).

Stair climbing is an important daily life activity and although it seems to be slow and undemanding, the analysis of vertical ground reaction forces (GRF) revealed high force peaks, mainly in stair descent. It has been shown that in healthy individuals on a standard stair the maximal vertical force reaches 1.6 times body weight and the time to peak force in loading response is about 140–170 ms during stair descent (Luder et al., 2007; Stacoff et al., 2005). The major issue in stair descent is the control of the relatively high forces occurring in short times, demanding quick stabilization of the lower limb joints by fast muscle activation or passive structures. Additionally, adequate strength is needed to push the body up onto the next step in ascent or to slow down body weight in descent (McFadyen and Winter, 1988).

Despite the importance of stair climbing only few studies reported GRF or EMG data during stair climbing (Larsen et al., 2008; Leitner et al., 2011; Riener et al., 2002). Stacoff et al. (2005) described GRF-patterns different from those in level gait during stair descent: a considerably higher first peak, disappearance of the second peak or a rather flat second part of the curve. Concerning EMG mainly healthy individuals were researched (McFadyen and Winter, 1988; Riener et al., 2002), with comparisons between young and elderly (Hsu et al., 2007; Larsen et al., 2008). Some studies focused on specific pathologies like patellofemoral pain syndrome (Sheehy et al., 1998), beginning osteoarthritis (Lessi et al., 2012) or diabetic neuropathy (Onodera et al., 2011), but large studies are lacking.

To our knowledge there are no studies that have looked at GRF and EMG during stair climbing in adults with GJH. Therefore, a descriptive cross-sectional study was designed with the primary aim of exploring whether there are differences in GRF and EMG between women with and without GJH during stair climbing. The secondary aim was to investigate possible differences between hypermobile women with and without symptoms in daily life.

2. Methods

2.1. Participants

In this descriptive cross-sectional study 195 women participated. Recruitment of volunteers was conducted among students of the University of Applied Science, the university hospital's employees and the local physiotherapy association. Inclusion criteria for the study were:

(1) Women, between 18 and 40 years old.
(2) Body mass index between 18 and 30 kg/m^2.
(3) No acute pain or clinically relevant problems in the legs or the back, which could affect measurements.

Exclusion criteria from the study were the following

(1) Pregnancy.
(2) Surgery or trauma of lower limb or lumbar spine within the last two years.
(3) Performing competitive sports or more than 4 h intense training per week.
(4) Known diagnosis of Marfan–Syndrome, Ehlers–Danlos–Syndrome (except hypermobility-type), and Osteogenesis imperfecta.

Hypermobility was identified using the Beighton score (Juul-Kristensen et al., 2007; Remvig et al., 2007). Women with at least 6 of 9 points were classified as hypermobile (Hypermobile group), as suggested by (Tobias et al., 2013). Because this study was focused on lower leg function and measurements took place mainly around the right knee, the points for the right knee (over 10° hyperextension) and the ability to touch the floor with flat hands were mandatory. For the control group with normal mobility women were allowed to have a maximum of 1 point (Normomobile group).

The hypermobile women were further categorized either into symptomatic or asymptomatic, based on a follow-up questionnaire, asking about pain and disability in daily life. At the time of the measurements all women were interviewed about their main complaints during daily activities and to rate their level of disability. The two most important activities, together with "lifting weights", "descending stairs" and "holding positions" were then defined as the five items on the individual follow-up questionnaire. For each item the person had to score how often during the last month the problem occurred, what the symptoms were and how strong they impaired the person. The questionnaire had to be filled in by all participants monthly for a six-month period after the measurements. All women mentioning at least once in the six months symptoms while descending stairs, were for this project classified as Hypermobile-symptomatic ($n = 56$) and all others as Hypermobile-asymptomatic ($n = 47$). Twenty-five women with hypermobility did not return the questionnaire and could therefore not be categorized. All participants gave written informed consent and the study was approved by the local ethics committee.

2.2. Instrumentation

To measure GRF and EMG during stair climbing a custom-built wooden six-step staircase was used (riser height 17.9 cm, tread 29 cm, inclination 30.4° (Stacoff et al., 2005)). The stair had a handrail on both sides and ended with a platform, which allowed comfortable turning. All steps were covered with a non-slippery mat. GRFs were measured using two force plates (Type 9286BA, Kistler Winterthur, Switzerland), that were embedded in the 3rd and 4th step of the staircase and integrated into a free standing heavyweight frame made of steel. The signals of the force plates were transmitted via a custom-built amplifier (uk-labs, Kempen, Germany) to the recording device.

The activity of the following six muscles of the right leg was measured by surface EMG: vastus medialis (VM), vastus lateralis (VL), semitendinosus (ST), biceps femoris (BF), gastrocnemius medialis (GM) and tibialis anterior (TA). Electrode placement and measurement procedure were defined according to the recommendations of ISEK (Merletti, 1999) and SENIAM (Hermens et al., 1999). In brief, the skin was prepared by shaving and cleaning and two oval pre-gelled AgCl-electrodes (Ambu Blue Sensor N, Ambu A/S, Ballerup, Denmark) of 5 mm diameter were placed 2 cm apart for each muscle. Skin impedance for each pair of electrodes had to be below 5 kΩ, otherwise electrodes were replaced. A single reference electrode was placed on the anterior tibia. Electrodes were connected via pre-amplifiers (baseline noise < 1uV RMS, input impedance > 100 MΩ, common mode rejection ratio > 100 dB, input range of +/− 10 mV, base gain of 500, additionally a 10–500 Hz bandpass filter) to a telemetry system (TeleMyo 2400T/R G2, Noraxon, Scottsdale, Arizona, USA). To determine the second foot contact of the stride, which was not measured on a force plate, a tri-axial accelerometer (Model 317A, Noraxon, Scottsdale, Arizona, USA) was attached to the right lateral malleolus and also connected to the telemetry system. All signals were recorded in sync at a sampling rate of 1 kHz using a 12-bit analog–digital converter (Meilhaus ME-2600i, SisNova Engineering, Zug, Switzerland) and the software package "ads" (version 1.12, uk-labs, Kempen, Germany).

For the normalization of the EMG signals maximum voluntary isometric contraction (MVC) was chosen as a basis (Burden and Bartlett, 1999). MVC was tested against manual resistance for five seconds, three times for each muscle, after a short instruction and test familiarization. Knee extensors and flexors were measured while sitting on a therapy table with the hip and knee joints in 90° flexion, applying resistance just above the ankle joint. TA was also measured while sitting, with the ankle joint in neutral position and applying resistance at the top of the forefoot and toes. Since it is difficult to apply maximal manual resistance to the GM muscle manually, the maximum activation during toe standing on the right leg for five seconds was chosen as a base for normalization and defined as the functional maximum (FCM).

2.3. Procedure

Prior to the measurements, all participants were clinically examined and assessed for hypermobility using the Beighton-score (Juul-Kristensen et al., 2007; Remvig et al., 2007) by an experienced and trained physical therapist. Testing was done in a separate room to ensure blinding of the laboratory investigators. After having the right leg equipped with electrodes and accelerometer, the participants walked up and down the stair 10 times at a normal, self-selected speed, preceded by two rehearsals. The stair climbing task was performed barefoot and use of the handrail was not allowed, otherwise the trial was repeated. A trial was considered valid when the participant hit the force plate on the third step with the right foot. Finally, the participants were given the follow-up questionnaires and instructed to fill them in monthly, and to return them afterwards by regular mail.

2.4. Data reduction

All data processing was conducted using a custom-made LabVIEW program (National Instruments, Austin, Texas, USA). The measurements were visually inspected and the trials 3–8 were extracted for the analysis, and treated separately for stair ascent and descent according to existing recommendations (Shiavi, 1990). The first two trials were discarded as test trials. The vertical force–time curves were lowpass filtered (second-order Butterworth, cutoff 30 Hz), normalized to each participant's body weight in Newton and parameterized using an automated software algorithm based on existing protocols (Leitner et al., 2011; Stacoff et al., 2005). Foot contact and foot off were defined as the time points when the vertical force exceeded and fell below 3% of the person's body weight. The foot contact at the end of the stride was determined by visual analysis of the raw accelerometer signal. The maximum force-peak during weight acceptance was calculated in %body weight (Fmax1), as was the respective time after the starting point (t1). Total contact time (stance) was defined as the time between foot contact and foot off. As additional time variable the cadence in steps/minute was calculated as a measure for the velocity of stair climbing.

For the EMG of the MVC tests maximum activation was determined by RMS calculation over 500 ms. The dynamic EMG raw data was baseline corrected, full-wave rectified and normalized to the corresponding 100%MVC value. Smoothing by lowpass-filtering (second-order Butterworth, cutoff 20 Hz (Hug, 2011)) was applied to build linear envelopes, whereof peak (*MUSCLE*peak) and mean (*MUSCLE*mean) activation during stance were calculated, as well as the activation level at t1. Finally, for all parameters of GRF, time and EMG the mean value from six trials for each participant and condition was calculated.

2.5. Statistical analysis

All statistical calculations were done using the software package SPSS (Version 21, IBM Corp., Armonk, NY, USA). Descriptive statistics of the selected parameters were presented as means and standard deviations. All variables were tested for normal distribution using the Kolmogorov–Smirnov test. Subsequently, variables were compared between the groups Normomobile and Hypermobile using independent samples *t*-test and between the groups Normomobile, Hypermobile-symptomatic and Hypermobile-asymptomatic using one-way analyses of variance (ANOVA) with Tukey post hoc test. For all significant differences the effect size as well as the respective power were calculated post hoc. For the comparisons between Hypermobile and Normomobile all 195 participants were considered, whereas the 25 hypermobile women who could not further classified were excluded from the comparisons between Normomobile, Hypermobile-symptomatic and Hypermobile-asymptomatic. Differences in the participant demographics were explored using the same statistical methods. The demographics of the excluded were compared to the hypermobile women included with independent *t*-test. The accepted significance level was for all tests set at $p \leqslant 0.05$.

3. Results

The demographics of the groups are presented in Table 1. No significant differences in age, weight, height or BMI were found between groups. Furthermore the hypermobile women without classification did not differ significantly from the others. Regarding the range of motion right knee flexion was significantly higher in Hypermobile ($p = 0.005$, es = 0.44, $P = 0.90$) and Hypermobile-symptomatic ($p = 0.001$, es = 0.67, $P = 0.67$) compared to Normomobile, and right knee extension was significantly higher in Hypermobile ($p < 0.001$, es = 3.0, $P = 1.0$), Hypermobile-symptomatic ($p < 0.001$, es = 2.8, $P = 1.0$) and Hypermobile-asymptomatic ($p < 0.001$, es = 3.4, $P = 1.0$), each compared to Normomobile.

3.1. GRF derived variables

The GRF derived parameters for each group are depicted in Table 2. No significant differences between the groups were seen for GRF, whether during stair ascent or descent.

3.2. EMG in stair ascent

The EMG parameters for stair ascent are shown in Table 3. The comparison between Hypermobile and Normomobile revealed significantly lower EMG values in the Hypermobile group for VMpeak ($p = 0.009$, es = 0.39, $P = 0.83$), VMmean ($p = 0.021$, es = 0.34, $P = 0.74$) and VM at t1 ($p = 0.039$, es = 0.33, $P = 0.70$), as well as VLpeak ($p = 0.031$, es = 0.35, $P = 0.76$). For the subgroups according to symptoms, significantly lower EMG values were only found in Hypermobile-symptomatic for VMpeak ($p = 0.013$, es = 0.83, $P = 0.89$) and VMmean ($p = 0.021$, es = 0.52, $P = 0.89$), while this was not seen in Hypermobile-asymptomatic.

3.3. EMG in stair descent

The EMG parameters for stair descent are shown in Table 4. The comparison between Hypermobile and Normomobile revealed significantly lower EMG values in the Hypermobile for STpeak ($p = 0.008$, es = 0.39, $P = 0.83$) and STmean ($p = 0.017$, es = 0.37, $P = 0.79$) as well as VMpeak ($p = 0.035$, es = 0.31, $P = 0.67$) and VLpeak ($p = 0.042$, es = 0.31, $P = 0.66$). For the subgroups according to symptoms, significantly lower EMG values were only found in

Table 1
Group characteristics as means (standard deviation).

Variable	Unit	Normo-mobile *n* = 67	Hypermobile *n* = 128	Hypermobile symptomatic *n* = 56	Hypermobile asymptomatic *n* = 47	Hypermobile without subclassification *n* = 25
Age	years	24.8(5.4)	25.8(5.4)	25.3(5.4)	25.7(5.3)	27.1(5.8)
Height	m	1.66(0.06)	1.67(0.06)	1.67(0.06)	1.67(0.05)	1.66(0.06)
Weight	kg	60.1(6.9)	61.2(8.2)	60.2(7.6)	61.6(7.6)	62.8(10.4)
BMI	kg/m^2	21.9(2.4)	22.0(2.7)	21.6(2.5)	22.1(2.5)	22.9(3.4)
Right knee flexion	degree	152.1(5.6)	154.5(5.3)	155.6(4.8)	153.3(5.5)	154.5(5.8)
Right knee extension	degree	4.1(2.2)	11.6(2.8)	12.2(3.5)	11.0(1.8)	11.6(1.8)

Table 2
Parameters of the vertical ground reaction forces for both groups as means (standard deviation).

Variable	Unit	Normo-mobile *n* = 67	Hypermobile *n* = 128	*p*-Value (*t*-test)	Hypermobile symptomatic *n* = 56	Hypermobile asymptomatic *n* = 47	*p*-Value (ANOVA)
Fmax1 up	%BW	109.5(6.5)	109.6(7.5)	0.945	110.9(8.4)	108.6(6.8)	0.263
t1 up	ms	196.2(30.0)	195.4(32.6)	0.872	192.1(31.9)	200.7(34.0)	0.396
Stance up	ms	717.8(97.2)	725.2(106.8)	0.636	726.4(102.6)	725.7(109.8)	0.877
Cadence up	1/min	103.0(12.6)	102.9(12.6)	0.947	102.3(12.5)	103.1(12.1)	0.929
Fmax1 down	%BW	149.0(28.5)	147.5(24.4)	0.692	146.8(15.6)	146.4(32.3)	0.835
t1 down	ms	152.0(20.5)	152.3(24.0)	0.923	152.7(25.7)	153.3(18.3)	0.953
Stance down	ms	675.9(103.1)	690.7(111.4)	0.365	689.5(103.7)	693.8(121.0)	0.644
Cadence down	1/min	111.9(15.8)	111.3(16.3)	0.796	110.6(16.3)	111.5(15.4)	0.903

Fmax1 = maximal ground reaction force during weight acceptance, t1 = time of Fmax1 after foot contact, BW = body weight.

Table 3
Maximum and mean muscle activity in %MVC, respectively %FCM for GM during stance and at selected time points in stair ascent as means (standard deviation).

Variable	Normo-mobile *n* = 67	Hypermobile *n* = 128	*p*-Value (*t*-test)	Hypermobile symptomatic *n* = 56	Hypermobile asymptomatic *n* = 47	*p*-Value (ANOVA)
Tibialis anterior peak	18.0(9.4)	16.5(7.1)	0.268	16.1(6.6)	16.7(6.2)	0.418
Tibialis anterior mean	4.3(2.0)	3.9(1.6)	0.131	3.8(1.5)	4.1(1.4)	0.263
Tibialis anterior at t1	4.0(3.8)	3.4(2.3)	0.236	3.3(2.3)	3.3(1.6)	0.354
Gastrocnemius medialis peak	67.3(15.7)	64.5(14.7)	0.225	65.3(13.7)	63.8(15.1)	0.461
Gastrocnemius medialis mean	18.4(4.8)	18.4(5.1)	0.945	18.4(5.2)	18.4(5.2)	0.998
Gastrocnemius medialis at t1	9.8(7.2)	9.9(7.2)	0.950	10.2(7.4)	10.0(7.4)	0.959
Semitendinosus peak	22.8(9.1)	20.0(9.9)	0.061	19.1(8.0)	20.4(10.0)	0.078
Semitendinosus mean	4.8(2.0)	4.5(2.1)	0.315	4.3(1.9)	4.6(2.3)	0.372
Semitendinosus at t1	4.2(2.5)	3.9(2.6)	0.455	3.7(2.1)	4.0(3.3)	0.613
Biceps femoris peak	26.7(17.9)	25.7(21.0)	0.757	29.4(27.9)	23.1(14.5)	0.331
Biceps femoris mean	7.2(4.4)	7.3(4.6)	0.920	7.9(5.4)	6.9(4.2)	0.556
Biceps femoris at t1	8.8(7.6)	8.9(7.2)	0.953	9.8(8.3)	8.2(6.5)	0.568
Vastus medialis peak	110.2(43.9)	93.9(39.2)	0.009	88.4(32.6)[a]	98.2(47.1)	0.018
Vastus medialis mean	22.6(9.6)	19.6(7.7)	0.021	18.4(6.0)[b]	21.0(9.6)	0.028
Vastus medialis at t1	26.6(13.5)	22.7(10.0)	0.039	21.9(9.7)	23.5(11.0)	0.079
Vastus lateralis peak	91.4(44.3)	78.1(29.4)	0.031	78.3(27.9)	79.8(33.2)	0.105
Vastus lateralis mean	18.6(8.9)	16.5(6.3)	0.089	16.4(6.7)	17.0(6.5)	0.266
Vastus lateralis at t1	22.2(11.7)	19.6(8.0)	0.104	19.3(8.2)	19.8(7.9)	0.218

MVC = maximum voluntary contraction, FCM = maximal activation during single-legged toe standing, t1 = time of the maximal vertical ground reaction force during weight acceptance.
[a] $p = 0.013$ between hypermobile symptomatic and normal mobility (post hoc Tukey-test).
[b] $p = 0.021$ between hypermobile symptomatic and normal mobility (post hoc Tukey-test).

Hypermobile-symptomatic for STpeak ($p = 0.044$, es = 0.42, $P = 0.75$) and STmean ($p = 0.027$, es = 0.47, $P = 0.83$), while this was not seen in Hypermobile-asymptomatic. No further statistically significant differences were found for the EMG variables.

4. Discussion

The GRF parameters showed no significant differences between the groups and were comparable to values reported in the literature for healthy persons (Hamel et al., 2005; Stacoff et al., 2005). This may indicate that the global movement pattern of women with and without GJH is comparable. The step frequency was also comparable to values from the literature (Larsen et al., 2008) and did not differ between groups, indicating that other differences found may not depend on velocity.

Muscle activity during stair ascent was found to be lower in the quadriceps for Hypermobile compared to Normomobile, with a decrease of 16.3% MVC for the peak activation of VM and 13.3% MVC for the VL. Mean activation level of VM during stance phase was at 22% MVC comparable to the results of Larsen et al. (2008) for young people, however, hypermobile women yielded a significantly lower mean activation level. The lower activation levels were even more accentuated when the hypermobile group was divided according to symptoms: Hypermobile-symptomatic still had significantly lower values for the peak and mean activation

Table 4
Maximum and mean muscle activity in %MVC, respectively %FCM for GM during stance and at selected time points in stair descent as means (standard deviation).

Variable	Normo-mobile $n = 67$	Hypermobile $n = 128$	p-Value (t-test)	Hypermobile symptomatic $n = 56$	Hypermobile asymptomatic $n = 47$	p-Value (ANOVA)
Tibialis anterior peak	22.0(9.1)	22.4(8.3)	0.739	23.0(7.8)	21.4(8.2)	0.637
Tibialis anterior mean	4.6(2.5)	4.3(2.0)	0.465	4.1(1.5)	4.2(1.7)	0.454
Tibialis anterior at t1	5.0(4.1)	4.5(3.4)	0.395	3.9(2.4)	4.4(2.8)	0.179
Gastrocnemius medialis peak	41.7(10.1)	40.6(10.2)	0.477	42.0(11.6)	39.7(9.5)	0.505
Gastrocnemius medialis mean	7.9(2.8)	7.9(2.5)	0.912	8.0(2.7)	7.7(2.6)	0.871
Gastrocnemius medialis at t1	6.0(4.5)	6.5(3.4)	0.409	6.7(3.7)	6.0(2.7)	0.507
Semitendinosus peak	37.6(23.0)	29.6(17.4)	0.008	28.8(18.5)[a]	30.3(15.9)	0.036
Semitendinosus mean	7.7(3.7)	6.4(3.3)	0.017	6.1(3.0)[b]	6.2(2.6)	0.016
Semitendinosus at t1	4.6(3.0)	4.3(2.7)	0.505	4.1(2.3)	4.4(2.7)	0.615
Biceps femoris peak	42.6(27.1)	39.6(25.6)	0.464	40.1(27.2)	37.1(24.6)	0.570
Biceps femoris mean	11.5(7.5)	12.0(8.6)	0.677	11.8(8.0)	11.8(9.3)	0.967
Biceps femoris at t1	9.1(7.1)	10.1(8.0)	0.374	9.8(7.20)	10.1(8.2)	0.749
Vastus medialis peak	42.8(23.9)	35.9(19.9)	0.035	36.5(19.7)	34.2(20.2)	0.092
Vastus medialis mean	11.3(5.5)	10.3(5.7)	0.218	10.2(5.9)	10.0(5.4)	0.371
Vastus medialis at t1	11.0(6.6)	11.0(6.9)	0.991	10.4(6.7)	11.2(6.8)	0.804
Vastus lateralis peak	77.7(28.7)	68.8(28.3)	0.042	70.6(29.4)	68.0(24.6)	0.162
Vastus lateralis mean	20.0(6.4)	19.2(7.7)	0.505	19.1(7.9)	19.5(6.8)	0.782
Vastus lateralis at t1	22.7(11.7)	21.6(11.5)	0.526	21.0(11.1)	22.7(12.6)	0.687

MVC = maximum voluntary contraction, FCM = maximal activation during single-legged toe standing, t1 = time of the maximal vertical ground reaction force during weight acceptance
[a] $p = 0.044$ between hypermobile symptomatic and normal mobility (post hoc Tukey-test).
[b] $p = 0.027$ between hypermobile symptomatic and normal mobility (post hoc Tukey-test).

of VM, while hypermobile-asymptomatic women were not different from women with normal mobility.

The lower activation of the quadriceps in stair ascent may point towards a more cautious movement pattern of hypermobile women, especially in those who reported symptoms during stair climbing. There could be different explanations for this: First, it is known that pain can lead to inhibition of related muscle activity and changes in movement patterns (Hart et al., 2010; Thomee et al., 1995) and therefore a recurrent sensation of pain in hypermobile women may reduce the activation level of the quadriceps during daily life activities like stair climbing. Another reason for reduced activity could be the avoidance of high activation of the weight-bearing muscles, and thus higher internal joint moments and subsequent higher joint contact forces (Nordin and Victor, 2001). This then may lead to pain, joint irritation or inflammation in these women and thus will be avoided. Finally, even small, clinically undetectable effusion may cause important inhibition (Palmieri-Smith et al., 2013) and thus reduce muscle activity, in this case mainly of the quadriceps, because it is the predominantly active muscle in stair ascent.

Although quadriceps activation was found to be lower, hypermobile individuals still need to produce the required power to lift their body onto the next step. One possible compensatory mechanism might be higher activation of the gluteus medius and maximus muscles (Dwyer et al., 2013; Lyons et al., 1983), mastering the step more by hip extension than knee extension. Another way to compensate might be an increased trunk forward lean to produce higher external knee extensor moment, as described for persons with knee osteoarthritis (Asay et al., 2009). Furthermore a slightly slower movement in this particular phase of the stride might also occur, even though the total timing was comparable (Bjerke et al., 2014). However, all these explanation remain speculative since the respective data was not measured in the current study and thus further research needs to focus on compensatory strategies in hypermobile women during stair ascent.

During stair descent the main difference was seen in STpeak activation with 8% MVC lower level and also in STmean. Again the difference was more accentuated in Hypermobile-symptomatic, but was not seen in Hypermobile-asymptomatic. Quadriceps peak activation was also lower, for VM 6.9% MVC and for VL 8.9% MVC. This may support the suggestion of a more cautious movement pattern, trying to reduce muscle activation and thus internal moments and joint contact forces. During stair descent the hamstrings are the important muscles for the eccentric control of weight lowering, and quadriceps contributes to controlling knee flexion during weight acceptance and while lowering the contralateral leg (McFadyen and Winter, 1988). Again, this lower activation might need compensatory strategies to maintain the stability of the knee joint during the stance phase. A possible strategy to improve knee control could be the adaptation of a hip movement strategy (Picon et al., 2012).

In general lower muscle activation levels were found in women with GJH during stair climbing. This is in contrast to the recently reported higher activation levels of the VM, VL and GM muscles in hypermobile women during gait (Schmid et al., 2013). The authors explained this higher activation with higher demands for muscular stabilization of the knee in women with GJH. A possible explanation for this discrepancy could be that the activation levels during gait are rather low and thus slightly higher activations might not yet be causing symptoms. During stair climbing, the activation levels are in general considerably higher and therefore, hypermobile women might prefer a mechanism that reduces muscle activation, rather than increasing it even more.

4.1. Strengths and limitations

Size and homogeneity of the groups were considered strengths of the study, whereas the inclusion of only women was considered a limitation. However, women are considerably more often affected by GJH and thus of greater interest in terms of finding adequate diagnosis and treatment. An additional limitation was the inclusion of relatively healthy women, who were not actually seeking medical treatment. Thus, participants were asymptomatic at the time of inclusion and might therefore be a sample of hypermobile women, that were able to manage their symptoms better than others. However, several of these women had during the six months following the measurement symptoms, meaning that pain and disability may not be constant but rather a sort of on–off phenomenon in this population. Anyway, the follow-up questionnaire to report symptoms, on which the sub grouping was based, must be regarded as another limitation. Hence, it could be that a participant suffering from shoulder or low back pain was assigned to the

Hypermobile-symptomatic group, without having symptoms directly affecting the knee. Future studies should therefore be more specific on the questionnaire.

A further limitation of the study is that no kinematic measurements were included. The GRF represents a summary image of the movement but does not offer insights into the joints. Thus, the explanations of the findings remain speculative. Since in the meantime a 3D-recording-symptomatic system has become available at the lab, a project in the future might include measurements with full gait analysis during stair climbing and additional muscles such as gluteus medius and maximus as well as trunk muscles.

The fact that only slight differences were found between Normomobile and Hypermobile might be because stair climbing for these women was not challenging enough to cause clear differences in GRF or EMG. Further studies should therefore include more demanding activities such as jumping or possibly introduce fatigue before measuring stair climbing.

In general, the current study revealed a wide range of new ideas for future research. On the one hand, a more detailed insight into the biomechanics and movement control of hypermobile women seems necessary. In this sense, additional functional movements, more demanding activities such as running, jumping and highly challenging balancing tasks as well as the effects of local muscle fatigue on movement control should be investigated. On the other hand, the clinical importance of such results should be investigated in greater detail. Individuals with more severe symptoms should be included and the effects of different interventions should be evaluated. For example, a currently ongoing clinical trial (ISRCTN90224545) is looking at the effects of a 12-week strength training program on muscle mass, strength and function in women with GJH.

5. Conclusion

Hypermobile women seemed to alter their movement pattern slightly during stair climbing, probably in order to avoid high muscle activation, especially of quadriceps and hamstring muscles. Having symptoms during daily life activities seems to accentuate these adaptations. The global ground reaction forces and the velocity of stair climbing are comparable to women with normal mobility.

Conflict of interest

There are no conflicts of interest.

Acknowledgements

This work was funded by the Swiss National Foundation (13DPD6_127285). The funding source was not involved in the study design, in the collection, analysis or interpretation of data nor in the writing of the manuscript or the decision to submit the manuscript for publication. The authors would like to thank Mr. Patrick Probst for his assistance in the participant's inclusion process and Dr. Jan Taeymans and Mr. Daniel Schnyder for their statistical advice.

References

Asay JL, Mundermann A, Andriacchi TP. Adaptive patterns of movement during stair climbing in patients with knee osteoarthritis. J Orthop Res 2009;27(3):325–9.
Bjerke J, Ohberg F, Nilsson KG, Stensdotter AK. Compensatory strategies for muscle weakness during stair ascent in subjects with total knee arthroplasty. J Arthroplasty 2014;29(7):1499–502.
Burden A, Bartlett R. Normalisation of EMG amplitude: an evaluation and comparison of old and new methods. Med Eng Phys 1999;21(4):247–57.
Dolan AL, Hart DJ, Doyle DV, Grahame R, Spector TD. The relationship of joint hypermobility, bone mineral density, and osteoarthritis in the general population: the Chingford Study. J Rheumatol 2003;30(4):799–803.
Dwyer MK, Stafford K, Mattacola CG, Uhl TL, Giordani M. Comparison of gluteus medius muscle activity during functional tasks in individuals with and without osteoarthritis of the hip joint. Clin Biomech (Bristol, Avon) 2013;28(7):757–61.
Ferrell WR, Tennant N, Sturrock RD, Ashton L, Creed G, Brydson G, et al. Amelioration of symptoms by enhancement of proprioception in patients with joint hypermobility syndrome. Arthritis Rheum 2004;50(10):3323–8.
Ferrell WR, Tennant N, Baxendale RH, Kusel M, Sturrock RD. Musculoskeletal reflex function in the joint hypermobility syndrome. Arthritis Rheum 2007;57(7):1329–33.
Gajdosik RL. Passive extensibility of skeletal muscle: review of the literature with clinical implications. Clin Biomech (Bristol, Avon) 2001;16(2):87–101.
Grahame R. Joint hypermobility syndrome pain. Curr Pain Headache Rep 2009;13(6):427–33.
Grahame R, Hakim AJ. Hypermobility. Curr Opin Rheumatol 2008;20(1):106–10.
Hamel KA, Okita N, Bus SA, Cavanagh PR. A comparison of foot/ground interaction during stair negotiation and level walking in young and older women. Ergonomics 2005;48(8):1047–56.
Hart JM, Pietrosimone B, Hertel J, Ingersoll CD. Quadriceps activation following knee injuries: a systematic review. J Athl Train 2010;45(1):87–97.
Hermens HJ, Freriks B, Merletti R, Stegeman D, Blok J, Rau G, Disselhorst-Klug C, Hägg G. SENIAM 8: European recommendations for surface ElectroMyoGraphy: Roessingh Research and Development b.v.; 1999.
Hsu MJ, Wei SH, Yu YH, Chang YJ. Leg stiffness and electromyography of knee extensors/flexors: comparison between older and younger adults during stair descent. J Rehabil Res Dev 2007;44(3):429–35.
Hug F. Can muscle coordination be precisely studied by surface electromyography? J Electromyogr Kinesiol 2011;21(1):1–12.
Juul-Kristensen B, Rogind H, Jensen DV, Remvig L. Inter-examiner reproducibility of tests and criteria for generalized joint hypermobility and benign joint hypermobility syndrome. Rheumatology (Oxford) 2007;46(12):1835–41.
Juul-Kristensen B, Hansen H, Simonsen EB, Alkjaer T, Kristensen JH, Jensen BR, et al. Knee function in 10-year-old children and adults with Generalised Joint Hypermobility. Knee 2012;19(6):773–8.
Larsen AH, Puggaard L, Hamalainen U, Aagaard P. Comparison of ground reaction forces and antagonist muscle coactivation during stair walking with ageing. J Electromyogr Kinesiol 2008;18(4):568–80.
Leitner M, Schmid S, Hilfiker R, Radlinger L. Test–retest reliability of vertical ground reaction forces during stair climbing in the elderly population. Gait Posture 2011;34(3):421–5.
Lessi GC, da Silva Serrao PR, Gimenez AC, Gramani-Say K, Oliveira AB, Mattiello SM. Male subjects with early-stage knee osteoarthritis do not present biomechanical alterations in the sagittal plane during stair descent. Knee 2012;19(4):387–91.
Luder G, Baumann T, Jost C, Schmid S, Radlinger L. Variabilität der Bodenreaktionskräte gesunder Personen beim Treppensteigen. Physioscience 2007;3(4):181–7.
Lyons K, Perry J, Gronley JK, Barnes L, Antonelli D. Timing and relative intensity of hip extensor and abductor muscle action during level and stair ambulation. An EMG study. Phys Ther 1983;63(10):1597–605.
McFadyen BJ, Winter DA. An integrated biomechanical analysis of normal stair ascent and descent. J Biomech 1988;21(9):733–44.
Merletti R. Standards for reporting EMG data (ISEK/1999). J Electromyogr Kinesiol 1999;9:III–IV.
Mulvey MR, Macfarlane GJ, Beasley M, Symmons DP, Lovell K, Keeley P, et al. Modest association of joint hypermobility with disabling and limiting musculoskeletal pain: results from a large-scale general population-based survey. Arth Care Res 2013;65(8):1325–33.
Nordin M, Victor HF. Basic biomechanics of the musculoskeletal system. Philadelphia: Lippincott Williams & Wilkins; 2001.
Onodera AN, Gomes AA, Pripas D, Mezzarane RA, Sacco IC. Lower limb electromygraphy and kinematics of neuropathic diabetic patients during real-life activities: stair negotiation. Muscle Nerve 2011;44(2):269–77.
Palmieri-Smith RM, Villwock M, Downie B, Hecht G, Zernicke R. Pain and effusion and quadriceps activation and strength. J Athl Train 2013;48(2):186–91.
Picon AP, Sartor CD, Roveri MI, Passaro AC, Ortega NR, Sacco IC. Diabetic patients with and without peripheral neuropathy reveal different hip and ankle biomechanical strategies during stair descent. Rev Bras Fisioter 2012;16(6):528–34.
Remvig L, Jensen DV, Ward RC. Are diagnostic criteria for general joint hypermobility and benign joint hypermobility syndrome based on reproducible and valid tests? A review of the literature. J Rheumatol 2007;34(4):798–803.
Riener R, Rabuffetti M, Frigo C. Stair ascent and descent at different inclinations. Gait Posture 2002;15(1):32–44.
Schmid S, Luder G, Mueller Mebes C, Stettler M, Stutz U, Ziswiler HR, et al. Neuromechanical gait adaptations in women with joint hypermobility – an exploratory study. Clin Biomech (Bristol, Avon) 2013;28(9–10):1020–5.
Sendur OF, Gurer G, Bozbas GT. The frequency of hypermobility and its relationship with clinical findings of fibromyalgia patients. Clin Rheumatol 2007;26(4):485–7.
Sheehy P, Burdett RG, Irrgang JJ, VanSwearingen J. An electromyographic study of vastus medialis oblique and vastus lateralis activity while ascending and descending steps. J Orthop Sports Phys Ther 1998;27(6):423–9.

Shiavi R. Quantitative representation of electromyographic patterns generated during human locomotion. IEEE Eng Med Biol Mag 1990;9(1):58–60.
Simonsen EB, Tegner H, Alkjaer T, Larsen PK, Kristensen JH, Jensen BR, et al. Gait analysis of adults with generalised joint hypermobility. Clin Biomech (Bristol, Avon) 2012;27(6):573–7.
Stacoff A, Diezi C, Luder G, Stussi E, Kramers-de Quervain IA. Ground reaction forces on stairs: effects of stair inclination and age. Gait Posture 2005;21(1):24–38.
Thomee R, Renstrom P, Karlsson J, Grimby G. Patellofemoral pain syndrome in young women. II. Muscle function in patients and healthy controls. Scand J Med Sci Sports 1995;5(4):245–51.
Tobias JH, Deere K, Palmer S, Clark EM, Clinch J. Joint hypermobility is a risk factor for musculoskeletal pain during adolescence: findings of a prospective cohort study. Arthritis Rheum 2013;65(4):1107–15.

Gere Luder is physical therapist and Master of Physiotherapy Science. His main research areas are in rheumatology and orthopedics, as well as in the development of physiotherapy in general. He teaches EBP in the BSc-programme of the Bern University of Applied Science. Currently he is doing his PhD at Vrije Universiteit Brussels (Belgium), investigating the effects of a strength training in women with hypermobility.

Stefan Schmid is a Research Associate at Bern University of Applied Sciences (Switzerland) and a Doctoral Student at ETH Zurich's Institute for Biomechanics (Switzerland). He holds degrees from the School of Physiotherapy Bern (Switzerland) and from New York University (USA). His primary research interests include spinal kinematics and compensatory mechanisms during gait, neuromuscular aspects of joint dysfunctions and biomechanical analyses of movements in sports and daily living.

Matthias Stettler graduated as a Physiotherapist in 1992 in Bern (Switzerland). Currently, he is working in a private local Physiotherapy practice . Since 1999, he is teaching at the School of Physiotherapy in Bern. His course topics include clinical reasoning and therapeutic exercises. In 2008, he was associated to the Physiotherapy Research Division at the Bern University of Applied Sciences. In addition, he got his Masters Degree in Sports-Physiotherapy at the University of Salzburg (Austria) in 2011.

Christine Mueller Mebes is a physiotherapist since 1999 and received her Master of Science in Physiotherapy in 2014. Currently she is working as physiotherapist and as a research scientist at the Inselspital, Bern University Hospital in the Department of Physiotherapy. Her research area is focused on physiotherapy in rheumatology, especially the problems associated with benign generalized joint hypermobility.

Ursula Stutz received the diploma as Physical Therapist in 1985 at the University Hospital of Zürich, Switzerland. She holds a Bachelor of Science in PT and is a Sports Physical Therapist IAS. Currently she is working as physiotherapist in the field of rheumatology and as a research scientist at the Department of Physiotherapy of the Inselspital, Bern University Hospital, Switzerland. Her clinical interest is focused on chronic pain and physical activity as well as hypermobility and since several years she is involved in research associated with benign generalized joint hypermobility.

Hans-Rudolf Ziswiler is MD and Associate Professor at the Berne University, he obtained his MD at the medical faculty of the university in Bern, Switzerland in 1987. He was trained and specialized in internal medicine and rheumatology from 1987 to 1998. His scientific work on ultrasound in rheumatoid arthritis led him to Berlin, University Clinic in Rheumatology at Charité in 2006. He was head of the ambulatory care-unit of the university clinic for rheumatology in Bern from 2000 to 2012. Since 2012 he runs a private center for musculoskeletal medicine in the heart of the city of Bern. His major scientific and clinical interests are diagnostic musculoskeletal ultrasound, biomechanics of the musculoskeletal system, interventional pain treatment and osteology.

Lorenz Radlinger is professor of physiotherapy at the Bern University of Applied Sciences, Switzerland. After his studies of sports and sports science he obtained his PhD in sports science (major subjects: sports medicine and training and movement science) at the German Sport University Cologne, Germany, in 1988. Since 2007 he is the head of Applied Research and Development Physiotherapy at the Bern University of Applied Sciences, Section Health. His major research interests are biomechanical aspects and activity characteristics of lower extremities including pelvic floor muscles during functional movements or exercises like level walking, stair climbing, running, jumping, sit to stand movements or balance and postural control as well as whole body vibration effects.

4. Effect of Resistance Training on Muscle Properties and Function in Women with Generalized Joint Hypermobility: A Single-Blind Pragmatic Randomized Controlled Trial

BMC Sports Science, Medicine and Rehabilitation, 2021; 13:10

Gere Luder, Daniel Aeberli, Christine Müller Mebes, Bettina Haupt-Bertschy,
Jean-Pierre Baeyens, Martin L. Verra

Luder et al. BMC Sports Science, Medicine and Rehabilitation (2021) 13:10
https://doi.org/10.1186/s13102-021-00238-8

BMC Sports Science, Medicine and Rehabilitation

RESEARCH ARTICLE Open Access

Effect of resistance training on muscle properties and function in women with generalized joint hypermobility: a single-blind pragmatic randomized controlled trial

Gere Luder[1,2*], Daniel Aeberli[3], Christine Mueller Mebes[1], Bettina Haupt-Bertschy[1], Jean-Pierre Baeyens[2] and Martin L. Verra[1]

Abstract

Background: Generalized joint hypermobility is defined as an excessive range of motion in several joints. Having joint hypermobility is not a pathology, but when associated with pain and other symptoms, it might affect health and function. Evidence for physiotherapy management is sparse and resistance training might be a possible intervention. Thus, the effects of 12-week resistance-training on muscle properties and function in women with generalized joint hypermobility were evaluated.

Methods: In this single-blind randomized controlled trial women between 20 and 40 years with generalized joint hypermobility (Beighton score at least 6/9) were included. Participants were randomly allocated to 12-week resistance training twice weekly (experimental) or no lifestyle change (control). Resistance training focused on leg and trunk muscles. Primary outcome was muscle strength; additional outcomes included muscle properties, like muscle mass and density, functional activities, pain and disability. Training adherence and adverse events were recorded.

Results: Of 51 participating women 27 were randomised to training and 24 into the control group. In each group 11 women had joint hypermobility syndrome, fulfilling the Brighton criteria, while 24 (89%) in the training group and 21 (88%) in the control group mentioned any pain. The mean strength of knee extensors varied in the training group from 0.63 (sd 0.16) N/bm before training to 0.64 (sd 0.17) N/bm after training and in the control group from 0.53 (sd 0.14) N/bm to 0.54 (sd 0.15) N/bm. For this and all other outcome measures, no significant differences between the groups due to the intervention were found, with many variables showing high standard deviations. Adherence to the training was good with 63% of participants performing more than 80% of sessions. One adverse event occurred during training, which was not clearly associated to the training. Four participants had to stop the training early.

(Continued on next page)

* Correspondence: gere.luder@insel.ch
[1]Department of Physiotherapy, Bern University Hospital, Insel Group, CH-3010 Bern, Switzerland
[2]Faculty of Physical Education and Physical Therapy, Vrije Universiteit Brussel, Pleinlaan 2, 1050 Brussels, Belgium
Full list of author information is available at the end of the article

(Continued from previous page)

Conclusions: No improvement in strength or muscle mass by self-guided resistance training was found. Low resistance levels, as well as the choice of outcome measures were possible reasons. A more individualized and better guided training might be important. However, program adherence was good with few side effects or problems triggered by the resistance training.

Trial registration: This trial was prospectively registered in the ISRCTN registry (www.isrctn.com, BMC, Springer Nature) on July 16, 2013 as ISRCTN90224545. The first participant was enrolled at October 25, 2013.

Keywords: Muscle strength, Exercise therapy, Joint instability, Quality of life

Background

Generalized joint hypermobility (GJH) is defined by a range of motion exceeding the normal limits in several joints. It is usually assessed by the 9 point Beighton score, testing for excessive mobility in the fingers, elbow, knee and lower back [1]. GJH has been found in about 10–30% of all persons, depending on the exact definition [2–4], e.g. Scheper et al. [3] described 22.8% at the cut-off at 4/9 points and 8.8% at 6/9 points in young students. In general, women are more often hypermobile than men, as described by Scheper et al. in 2015 who found 31.9% of women vs. 9.7% of to be generally hypermobile, based on a cut-off at 4/9 points and 13.9% for women vs. 1.5% for men at a cut-off at 6/9 points. Generally there is a decrease of joint mobility with ageing, as illustrated by lower cut-offs used in older persons [4].

By definition, GJH is not necessarily a clinical diagnosis. Numerous persons with GJH do not manifest symptoms and for some sports or in dance it might even be an asset to have extensive mobility [5, 6]. In contrast, having increased joint mobility might result in a wide variety of clinical symptoms [7]. For a long time hypermobile persons with symptoms were diagnosed as having joint hypermobility syndrome (JHS), using the Brighton criteria [8]. They mainly encompassed musculoskeletal complications, but also signs of skin, eye or organ involvement. After years of discussion whether JHS and the hypermobile type of Ehlers-Danlos syndrome (EDS) were the same entity, a new nosology for the EDS was developed in 2017 [9, 10]. As part of this process the definitions and classifications for the spectrum of disorders associated with GJH were revised [7]. The term JHS was discarded and as a new diagnosis, the hypermobility spectrum disorder (HSD) was introduced. Thus, persons with GJH and various symptoms that do not fulfil the new formal criteria for hypermobile Ehlers-Danlos syndrome (hEDS) can now be diagnosed as having HSD.

Nevertheless, having GJH can lead to problems in activities of daily life and is sometimes associated with various impairments and musculoskeletal disorders. Scheper et al. [11] stated that persons with GJH experience more pain, fatigue and disability than controls. In two other reviews was shown that people with GJH have a higher prevalence and incidence of lower limb injuries [12, 13]. A large population study in Denmark found that persons with GJH were more likely to experience knee or shoulder pain and it was up to four times more likely that they avoided some activities due to symptoms [14, 15]. Thus, in the context of prevention it might be important for persons having GJH to stay active to maintain their ability to perform daily life and work-related activities. Additionally, there is a need to find ways to prevent joint pain, disability and possible long-term consequences of the condition.

In terms of interventions, a limited number of studies have been published so far. The review by Scheper et al. [11] found no studies assessing treatments in GJH and only five looking at treatments in persons with JHS, resulting in small effects on pain and inconsistent effects on disability. Comparing persons with GJH to those with normal joint mobility raised several issues, e.g. in a study with 328 adults those with GJH had less strength in the knee, hip, shoulder and forearm and they performed less physical activity [3]. Our previous study with 195 participants presented changes in neuromuscular control during gait and stair climbing [16, 17] as well as in strength, balance and passive tibial translation [18, 19]. People with GJH thus have neuromusculoskeletal impairments, particularly strength deficits, which may make them more susceptible to developing symptoms. It is important to investigate whether such deficits can be improved through preventive rehabilitation.

In physiotherapy, resistance training is well established as an intervention to improve strength and muscle mass, as well as to gain function and decrease impairments [20]. Also, for apparently healthy persons regular exercise is generally recommended and resistance training is an important part in the prevention of diseases and injuries [21]. There is a lack of high quality trials looking at the effects of resistance training in persons with various specific health problems. However, resistance training is regularly prescribed in musculoskeletal physiotherapy and performed by patients with conditions such as low back pain or with osteoarthritis of the hip or knee [20, 22].

Based on the described neuromuscular deficits in persons with GJH the performance of resistance training to gain more strength and muscle mass might help to improve their performance in daily life and to prevent pain, disability and injuries, mainly joint distortions. Not only will the additional muscle strength support the dynamic stabilisation of the joints, but by the strength training also an increase in muscle and tendon stiffness is described, which might also provide more passive support for the joints [23, 24]. Finally, an increase in strength and muscle mass might also improve the impaired proprioception of persons with GJH around the joint and thus provide better joint stabilisation during activities [25, 26].

In this context, the present study was designed to evaluate a guided resistance-training program for women with GJH with or without symptoms. The progressive resistance-training program focussed on increasing muscle mass and strength of leg muscles and the trunk. The primary objective was to measure the immediate effects of this 12 week graded resistance-training program on muscle strength and muscle properties, compared to a control group without training. Secondary aims were to evaluate the impact of the training program on function, pain and disability in women with GJH and to evaluate the feasibility of the training program in terms of adherence and side effects.

Methods

Study design

This study was designed as an assessor-blinded pragmatic randomised controlled trial (RCT). The participants were randomly allocated to either a 12-week mainly self-guided resistance-training program or a control group that did not change their usual lifestyle habits (Fig. 1). The trial was prospectively registered as ISRC

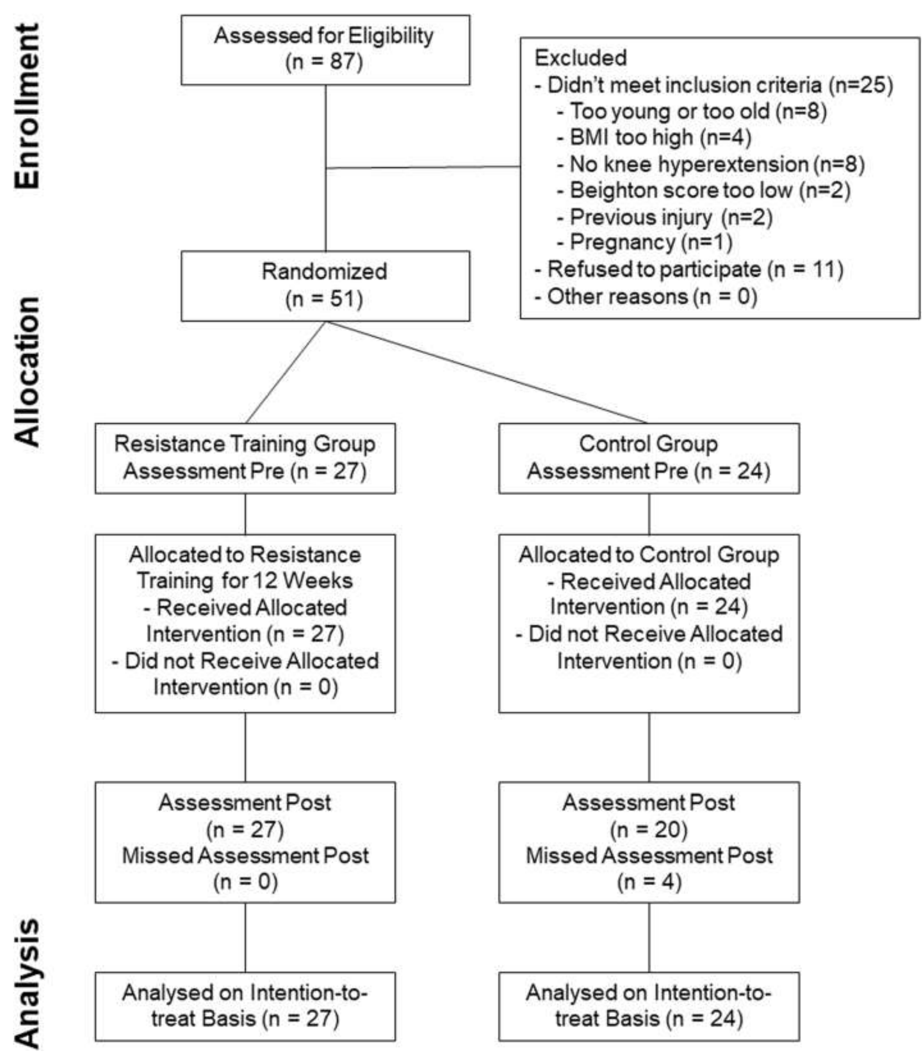

Fig. 1 Study Flowchart (according to CONSORT)

TN90224545 (www.isrctn.com, BMC, Springer Nature) and ethical approval was obtained by the Ethics Committee of Canton Berne, Switzerland (No. 222/12). All participants gave written informed consent and the study was conducted according to the Declaration of Helsinki. This paper follows the CONSORT statement [27] and the intervention is described according to the TIDieR checklist [28].

Participants

Women aged between 20 and 40 years with GJH were eligible for the study if they scored at least 6/9 points on the Beighton score, and right knee hyperextension was mandatory. The higher cut-off was chosen based on more recent publications [29, 30] and knee hyperextension was required because training focused on the lower limb and assessments were performed mainly on the right side. As further inclusion criteria, participants needed to have a body mass index between 18 and 30 kg/m^2 and be able to understand German questionnaires.

Excluded were women who had had surgery of the lower extremities or lumbar spine in the last two years, because this might affect their current condition and the ability to perform strength training. In addition, women with acute pain in the back or lower extremities were excluded. Women who regularly undertook more than four hours per week of sport activities were excluded to ensure better homogeneity of the groups in terms of muscle strength and training experience. Pregnant women and those less than one year after delivery were excluded, since changes in the hormonal state may affect the outcome of strength training [31]. Finally, women with known inherited diseases of the connective tissue, mainly Marfan syndrome and Ehlers-Danlos syndromes except hypermobility type and Osteogenesis imperfecta, were excluded. A formal diagnosis of Ehler-Danlos syndrome, hypermobility type, was not a reason for exclusion. Note that the criteria for this study were defined in 2012 and thus not based on the new 2017 nosology for EDS and HSD [7, 10].

Recruitment, inclusion and allocation

Participants were mainly recruited from an existing database of previous studies [17, 32] and via the staff of Bern University Hospital and students of the Bern University of Applied Sciences, Department of Health, Switzerland. Furthermore, announcements in the local newspapers were published to recruit participants. The recruitment period was between August 2013 and November 2015 and the recruitment, as well as all the measurements and training sessions took place at Bern University Hospital, in Bern, Switzerland.

Interested participants were informed by phone before their first appointment and received information sheets by mail. After signing the informed consent, inclusion and exclusion criteria were confirmed face-to-face by one physiotherapist (CM), with more than 12 years of clinical experience. The participants performed a standard pregnancy test themselves using a urine sample. For the Beighton score the test movements were a.) Hyperextension of elbow more than 10°, b.) Hyperextension of knee more than 10°, c.) Ability to touch the floor with the palms of the hands, keeping the knees fully extended, d.) At least 90° dorsiflexion of 5th metacarpophalangeal joint, and e.) Ability to touch the inner side of the forearm with the thumb [1]. All items, except c.), were tested bilaterally, resulting in a possible total score of 9 points.

The range of motion of the right knee in flexion and extension was measured with a standard inclinometer while lying supine. Additional measures included body weight, body height, arm span, and arm and leg length on both sides. Finally, anamnestic checking of the Brighton criteria [8] was done by semi-structured interview by the same experienced physiotherapist (CM). The Brighton criteria were recorded for a clearer description of the study group and to allow for potential analysis of the effects or the feasibility of the training for women with and without JHS.

After inclusion, the participants were randomised based on an independently computer-generated randomisation list either to the resistance training or to the control group. After recording of the personal and anamnestic data in the database and confirming inclusion, the physiotherapist responsible for the inclusion accessed the allocation electronically to ensure concealment. The randomisation list was kept secret from the assessor and statistician until all analyses had been performed.

Intervention

The intervention for the training group was a mainly self-guided 12-week resistance training program to address hypertrophy, focusing on the muscles of the lower extremities and the trunk. Two training sessions of about 50 min were performed each week in the medical training centre of the Berne University Hospital, resulting in 24 training sessions.

The strength training program was developed based on recommendations of the American College of Sports Medicine [21, 33]. The details of the training program are provided in a supporting information file (Luder-G_S1-file_training-program-intervention.pdf). Resistance was mainly set at 80% of the one repetition maximum and three series with 12 repetitions for each side were performed. Four experienced physiotherapists gave the instructions on a 1:1 basis for the training program. All of them regularly instructed patients and healthy persons in the medical fitness and were specifically instructed for this project. In the first week, a one-hour session was dedicated to basic instructions and determining the one repetition maximum. In week three a half-hour session aimed to reassess exercise performance and adapt the resistance. Finally, in week six an additional half-hour session was spent monitoring the proper practice. All other training sessions were performed individually and not directly supervised; however, a responsible physiotherapist was always available in the training room for questions and support. Participants were encouraged to increase the resistance gradually whenever more than 12 repetitions were possible. If pain or discomfort occurred because of the exercise, the women could always refer to the physiotherapist in charge. During the instruction sessions possible adaptations to pain or muscular problems were discussed and suggested, e.g. reduction of resistance, increased rest time between series or a reduction to one or two training series instead of three.

The participants in the control group were advised not to change their lifestyle habits for the next 12 weeks. After the post-measurement, all participants of the control group were offered to participate in the same structured training program as the intervention group.

Adherence and problems triggered by training

A secondary aim of the project was to assess the feasibility of the resistance training for women with GJH. Thus, the participants recorded the number of training sessions and the exercises performed with all details in a diary. Additionally, personal notes and experiences were documented, e.g. pain, discomfort, or reasons for reduced performance. Performance of more than 80% of the training sessions was deemed as acceptable adherence.

Furthermore, during the training pain and disability in the daily life of the participants were monitored with a face-validated questionnaire using 5-point Likert-scales. The first two questions asked for details of disability or pain during and after the training. Three additional questions asked for other pain or impairments during the week. For every question, the location of the problems and additional information could be provided. The questionnaire was developed based on a previous study [34].

Outcome assessments

GJH may affect an individual in several dimensions of life, as defined in the International Classification of Functioning, Disability and Health (ICF) [35]. The outcome assessments in this study aimed to evaluate the effects of resistance training in various dimensions of the ICF: muscle strength and properties as body structures, muscle activity during stair climbing in terms of function; and a set of patient reported questionnaires regarding activities and participation to detect impairments and restrictions in daily life. A detailed description of all assessments and the respective analyses is provided in a supporting information file (Luder-G_S2-file_outcome-measures.pdf).

In brief, muscle strength was measured as maximum isometric contraction and rate of force development of the knee extensors and knee flexors on a custom-built strength table using a strain gauge. For each muscle group three measurements were performed. Maximum strength and rate of force development as the slope of the force curve between 20 and 80% of maximum were calculated, the values normalised to body mass and the best attempt taken for calculations [18]. The muscle properties of the thigh were measured using peripheral quantitative computer tomography (pQCT) and muscle cross sectional area, and muscle mass and density were calculated as previously described [36]. The cross-sectional area parameters were all calculated in relation to body mass.

During stair climbing on a standard six-step stair-case [16, 37] the ground reaction forces were measured by a force plate embedded in the 3rd step. Simultaneously the muscle activity of the vastus medialis, vastus lateralis, semitendinosus and biceps femoris was measured using electromyography (EMG). Electrode placement and measurement procedure were defined according to the recommendations of SENIAM [38]. The participants had to climb up and down the stair ten times at a comfortable, self-selected speed barefoot and without using the handrail. All ground reaction forces, and electromyography data were processed with custom-made software and six trials were selected for the analyses of stair ascent and descent. Dynamic EMG data were normalised to the corresponding 100% maximum voluntary contraction value and peak and mean muscle activation during stance were calculated. The vertical ground reaction force curves were normalised to body mass and standard parameters for force and time were calculated as means of six trials for each condition [37].

To measure general health the widely used Medical Outcomes Study Short Form 36-Item (SF-36) health survey was completed and the scores calculated according to the standard method [39]. As a measure of disability in daily life the Arthritis Impact Measurement Scales 2 (AIMS-2), originally developed for patients with rheumatoid arthritis [40], was used, since there was no specific questionnaire for persons with GJH at the time of the study preparation. All scores were calculated according to the described methods [41]. Additionally, and based on previous studies a face-validated questionnaire for hypermobility (HM-Q) was used, asking for pain at specific sites and disability in selected daily life activities. All items were rated on a five-point Likert scale and the sum score for the whole questionnaire calculated.

All assessments were performed by a single investigator (GL), blinded to group allocation. The first assessment took place before the training or control period and the second within two weeks after the end of training or the 12-week control period of the control group.

Primary and secondary outcomes

The primary outcome for the effect of resistance training was defined as the increase in muscle strength in relation to body mass, measured as maximum voluntary isometric contraction of the knee flexors and extensors. Secondary outcomes included rate of force development of these knee muscles, the cross-sectional area parameters of the thigh, as well as muscle mass and density. All further variables were analysed in an exploratory manner.

Regarding the feasibility of the training intervention, the percentage of completed training sessions was the main parameter. Additionally, pain and disability in daily life as detected by the weekly questionnaire served as further descriptive outcomes.

Power estimation

As this was the first trial to investigate a resistance training program in individuals with GJH there were only approximate data available for the power calculation. In a previous study [32] a 16.2% higher normalised rate of force development was found for hypermobile women compared to women with normal mobility. With a similar change induced by the training, a hypothetical medium effect size of about 0.6 could be expected.

Derived from this data, a power estimation was performed using G*Power 3.1.5 [42]. For an estimated effect size of 0.6 with the significance level (α) set at $p \leq 0.05$, a sample size of 21 in each group (total of 42 subjects) was necessary to achieve a power of 0.8. Since some dropouts were expected, the aim was to enrol 50 women in the study.

Statistical analysis

All analyses were performed on an intention-to-treat basis and included all randomised participants. Missing data was processed by means of imputation based on linear regression per group, except by "last carry forward" for the HM-Q. Missing data for EMG measurements due to technical reasons was not imputed. All statistics were performed on a blinded basis, whereby the randomisation code was only broken after completion of the statistical evaluation.

Descriptive statistics for all clinically relevant parameters are presented. Normal distribution of the data was checked by the Shapiro-Wilk test and Q-Q-plotting to decide whether parametric or non-parametric tests were used for significance testing. At baseline, the comparability between the groups in terms of demographic and prognostic factors was assessed using the independent t-test.

For parametric testing the primary outcomes of the two groups were compared by a mixed analysis of variance (ANOVA) with time as the within subjects factor and group as a between subject factor. To account for possible baseline differences all prognostic variables with significant t-test at baseline between the two groups were additionally introduced as co-variates in the model (ANCOVA). The significance level was Bonferroni-corrected to account for multiple testing (two primary variables) and set at $p < 0.025$ as the accepted significance level.

For the main parameters, mean differences of change for each group as well as 95% confidence intervals (CI) are presented and the respective effect sizes calculated as partial eta square and converted to Cohens d. The additional outcomes of the secondary analyses were not tested for significance but are reported as descriptive data, with mean difference between pre and post and the respective 95% confidence interval (95% CI). A tendency for a change was noted when the 95% CI for the mean difference did not cross the zero line.

Results

Participants

Of 87 women assessed for eligibility 51 participated in the study, as depicted in the flow chart (Fig. 1). 25 women were excluded for various reasons, mainly age, high body mass index, not fulfilling the right knee hypermobility criterion, pregnancy or Beighton score too low. Additionally, 11 women declined participation, mainly due to lack of time for the training. The main characteristics of the participants at baseline are shown in Table 1. No differences between groups were seen in terms of age, height, weight, and body mass index. Despite randomisation, the subjects in the training group showed on average significantly higher values for maximum voluntary contraction of the knee extensors (mean (sd) = 0.53 (0.14) vs 0.63 (0.16) N/bm, $p = 0.015$) and flexors (mean (sd) = 0.34 (0.12) vs 0.26 (0.11) N/bm, $p = 0.016$). Consequently, these two variables were introduced as co-variates in the statistical analysis of the outcomes.

About one third of the participants had a Beighton score of 9/9, another third had 8/9 and the rest 6 or 7/9. Regarding the Brighton criteria, about 43% fulfilled them and might be diagnosed as having JHS. In addition, 45 of the 51 participants (88.2%) mentioned some pain in the

Table 1 Group Characteristics at Baseline as Mean (Standard Deviation)

	All Participants (*n* = 51)	Control Group (*n* = 24)	Training Group (*n* = 27)	t-test *p*-value
Age [years]	26.5 (4.5)	27.0 (4.9)	26.1 (4.2)	0.520
Height [m]	1.68 (0.06)	1.69 (0.07)	1.67 (0.05)	0.329
Weight [kg]	62.6 (10.1)	62.9 (10.5)	62.3 (9.9)	0.822
BMI [kg/m^2]	22.1 (2.8)	22.0 (2.9)	22.2 (2.8)	0.786
MVC knee extensors [N/bm]	0.58 (0.16)	0.53 (0.14)	0.63 (0.16)	0.015
RFD knee extensors [N/s/bm]	2.38 (1.26)	2.03 (1.31)	2.70 (1.16)	0.058
MVC knee flexors [N/bm]	0.30 (0.13)	0.26 (0.11)	0.34 (0.12)	0.016
RFD knee flexors [N/s/bm]	1.07 (0.87)	0.87 (0.81)	1.25 (1.90)	0.122
mCSA thigh [mm^2/bm]	13.1 (1.9)	13.1 (2.1)	13.0 (1.7)	0.919
Muscle mass [mg]	659 (96)	645 (94)	645 (92)	0.994
Beighton score				
6/9 [n (%)]	6 (11.8)	2 (8.3)	4 (14.8)	
7/9 [n (%)]	10 (19.6)	6 (25.0)	4 (14.8)	
8/9 [n (%)]	17 (33.3)	8 (33.3)	9 (33.3)	
9/9 [n (%)]	18 (35.3)	8 (33.3)	10 (37.0)	
Brighton criteria yes [n (%)]	22 (43.1)	11 (45.8)	11 (40.7)	
GJH + pain [n (%)]	47 (92.2)	21 (87.5)	24 (88.8)	

BMI body mass index, *MVC* maximum voluntary contraction strength, *RFD* rate of force development, *mCSA* muscle cross-sectional area, *bm* body mass, *GJH* Generalized Joint Hypermobility

HM-Q at baseline and thus might be diagnosed as having some kind of hypermobility spectrum disorder. The distribution of these participants in both groups was equal (Table 1).

Primary and secondary outcomes

For both primary outcomes, namely the maximum voluntary strength of knee extensors and flexors, no significant difference was found between the groups when controlling for the baseline difference (ANCOVA $p = 0.256$ for MVC of knee extensors and $p = 0.365$ for MVC of knee flexors) and the effect sizes indicated small effects in favour of the control group (Cohens d = − 0.33 for MVC of knee extensors and - 0.26 for MVC of knee flexors). The secondary outcomes also showed no significant differences between groups with small and heterogeneous effect sizes (Tables 2 and 3).

Additional measurements

For additional measurements, the descriptive data are presented in supplementary tables provided in a supporting information file (Luder-G_S3-file_SupportingTables-T4-T7.pdf). For the ground reaction forces all parameters showed no difference in change, indicated by the 95% CI's which all crossed the zero line (Supporting table T4). In the EMG parameters, the vastus medialis

Table 2 Descriptive Data Before and After Training and for the Control Group as Mean Values (Standard Deviation)

	Control Group (n = 24)		Training Group (*n* = 27)	
	Pre	Post	Pre	Post
MVC knee extensors [N/bm]	0.53 (0.14)	0.54 (0.15)	0.63 (0.16)	0.64 (0.17)
RFD knee extensors [N/s/bm]	2.03 (1.31)	1.75 (0.83)	2.70 (1.16)	2.52 (1.23)
MVC knee flexors [N/bm]	0.26 (0.11)	0.29 (0.10)	0.34 (0.12)	0.35 (0.11)
RFD knee flexors [N/s/bm]	0.87 (0.81)	0.74 (0.43)	1.25 (0.90)	0.98 (0.51)
CSA thigh [mm^2/bm]	24.6 (2.0)	24.4 (1.9)	24.0 (1.6)	24.2 (1.5)
mCSA thigh [mm^2/bm]	13.1 (2.1)	13.2 (2.1)	13.1 (1.7)	13.3 (1.8)
Muscle mass [mg]	645 (94)	653 (93)	645 (92)	664 (101)
Muscle density [mg/mm^2]	80.5 (1.8)	80.4 (1.3)	80.8 (1.6)	81.2 (1.2)

MVC maximum voluntary contraction strength, *RFD* rate of force development, *CSA* cross sectional area, *mCSA* muscle cross sectional area, *bm* body mass

Table 3 Change in Primary and Secondary Variables as Mean Difference and 95% Confidence Interval (CI), Statistical Tests of Group Differences (Including Co-Variates) and Effect Sizes as Cohens d

	Control Group (n = 24)			Training Group (n = 27)			p-value [a]	Effect Size[b]
	Mean Diff	Lower 95% CI	Upper 95% CI	Mean Diff	Lower 95% CI	Upper 95% CI		
MVC knee extensors [N/bm]	0.011	−0.017	0.038	0.006	−0.034	0.046	0.256	−0.33
RFD knee extensors [N/s/bm]	−0.280	−0.657	0.098	−0.178	−0.563	0.208	0.243	+0.34
MVC knee flexors [N/bm]	0.033	0.002	0.065	0.007	−0.033	0.047	0.365	−0.26
RFD knee flexors [N/s/bm]	−0.125	0.357	0.107	−0.264	−0.522	−0.007	0.689	−0.16
CSA thigh [mm^2/bm]	−0.18	−0.34	−0.02	0.21	0.02	0.41	0.419	+0.23
mCSA thigh [mm^2/bm]	0.13	−0.01	0.27	0.22	0.04	0.40	0.169	+0.40
Muscle mass [mg]	7.6	1.8	13.4	19.1	8.3	29.9	0.936	+0.02
Muscle density [mg/mm^2]	−0.02	−0.42	0.38	0.40	−0.27	1.06	0.131	+0.44

diff difference, *MVC* maximum voluntary contraction strength, *RFD* rate of force development, *pSA* cross sectional area, *mCSA* muscle cross sectional area, *bm* body mass
[a]p value for change between groups, using ANCOVA
[b]Effect size between groups as Cohens d: positive values favours resistance training, negative values favours control

muscle showed a tendency for increased activity during stair descent in the training group, in the control group during descent the vastus lateralis muscle showed a tendency for increased activity, while the biceps femoris muscle tended to decrease during descent. All other comparisons showed no difference, again indicated by the 95% CI's crossing the zero line (Supporting table T5).

In the various dimensions of the SF-36 no changes related to training or the control period in the control group were seen, only the "social role functioning" for the control group showed a tendency to increase and for "physical functioning" in the training group a tendency to decrease was seen (Supporting table T6). Finally, only the "pain" dimension of the AIMS-2 showed for the training group a tendency to decrease, while no difference was seen in the HM-Q (Supporting table T7).

Adherence to training and adverse events

The 27 participants in the training group performed a mean of 19.4 (sd 5.3) out of 24 training sessions. 17 women (63.0%) fulfilled more than 20 sessions and thus more than 80% of the program. The mean resistance with one leg on the leg press was 26 kg at the beginning, meaning 42.5% of body mass (sd 24.1). In the last session, the mean resistance was 51 kg and thus 83.5% of body mass (sd 31.5).

In the training group, four participants stopped their training early: Two women due to lack of time, after 5 and 6 sessions respectively. One person stopped after a knee injury not associated with the training and one due to an exacerbation of low back pain, which was classified as an adverse event. Afterwards a lumbar disc hernia was diagnosed and the patient finally underwent surgery. According to the surgeon and an independent physician, it remained unclear if the exacerbation of the pre-existing back problems was activated by the resistance training.

In the control group, 20 of the 24 women took the opportunity to do the resistance training program. However, this was not part of the randomised control trial.

Discussion

This study evaluated the effects of a 12-week self-guided resistance-training program in women with GJH with and without symptoms. Contrary to our hypothesis, no significant changes in muscle strength or muscle mass compared to the control group were found. Furthermore, the additional functional measurements and questionnaires showed no training-induced changes in daily life function, disability, or pain. This contrasts with several other training studies, i.e. with patients having knee osteoarthritis and performing resistance exercise for the knee muscles. In these studies strength improvements of 15–34% were shown [43], as well as increased muscle cross sectional area of 3–8% [44] and relevant improvements in quality of life and pain [22]. Regarding resistance training in young healthy women strength gains of 20–32% following a 12 week program were demonstrated [45, 46] and improvements in muscle size of 12–17% [47, 48].

When looking at persons with GJH, in three recent studies improvements of muscle strengths were shown, which could not been reproduced in our trial. In 2018 To & Alexander [49] described the same ability to gain strength for persons with JHS, GJH and control subjects by an individualized exercise program, with improvements of about 100% of knee extensor muscle torque in all three groups. Notably, this gain was reached by an exercise program, which was mainly performed home-based with the own body weight, but adaptation and instruction was done every second week by a physiotherapist. Additionally, they found that persons with JHS (according to the Brighton criteria) had about 30% lower muscle torque than controls, while those with GJH (based on the Beighton score) showed about 30% higher torques than controls. These differences in muscle strength might explain the high heterogeneity in our group, since we included both, women with GJH and some with JHS. Liaghat et al. found in 2020 [50] in a feasibility study for heavy shoulder strengthening that participants with HSD (based on Beighton score and a history of shoulder pain) were able to perform a 16-week strength training program and gained about 30% in shoulder strength. In this study the training was performed twice weekly supervised by a physiotherapist and once weekly self-guided. Celenay and Kaya [51] investigated the effect of a 8 week spinal stabilization program performed three time a week in groups and every session guided by a physiotherapist. They found improvements of trunk muscle endurance of about 50%, however their study has some methodological limitations, like a high drop-out rate and missing of blinding. Note, that all these studies were published after the end of our trial and thus the results could not be incorporated in the planning or conduct of our project.

Despite concealed randomisation in our study there was a difference in the baseline parameters between the two groups for maximum strength in knee flexors and extensors. We think, this resulted mainly by chance, since the variability of strength throughout the participants was high. This is indicated by the standard deviations, which are in both cases clearly higher than the mean difference. Furthermore, both parameters were introduced as co-variates in the analysis of covariance. Additional testing without the co-variates did not reveal a difference in the significance testing.

Based on the above-mentioned studies and our own experience during the training sessions, there might be several reasons for the lack of strength and muscle mass improvements in our study. A first problem was the measurement of strength, which was done isometrically, although the training was dynamic. Thus, even when some dynamic strength gain occurred in these participants, this might not have been transferred to the measurement situation and thus could not be detected by our methods. However, if really large changes had occurred, these might be also visible in the isometric contractions, thus we conclude that the dynamic strengths gain, if existing, might be small. Second, many participants exercised at rather low resistance levels. This is illustrated by the fact that the mean resistance during training in the single leg press exercise at the ed. of the 12 weeks was only 83.5% of body mass, with only 8 (of 27) participants using more than their own body weight as training resistance. Third, the training volume with two sessions per week might be not enough, however for persons with little or no experience in resistance training three sessions per week might be quite hard. Additionally, the individual changes due to training showed great variation, which is indicated by the large confidence intervals in both groups. This might be due to the high heterogeneity of the study group, including women fulfilling the Brighton criteria and others who had no symptoms.

In this study the training was mainly performed unsupervised and participants had only three (of 24) sessions with instruction and training adaptation. The last training control and adaptation session was in week six of twelve. Based on the training protocols we recognized that many participants did no longer increase their resistance after week six. Possibly, more guidance during the training and closer supervision of the individual sessions would help these participants to reach the necessary training intensity for a gain in strength and muscle mass. Additionally, a barrier to exercise with higher resistance might have been the fear of an increase in pain or some prior experience of pain reactions after resistance.

The most important limitation of this study might be the heterogeneity of the study group, with some recruits being pre-clinical. Thus, we had participants with few problems and rare pain episodes and others who experienced daily pain and impairments of several daily-life activities. The rather high scores and the large variability in the SF-36 and the AIMS-2, as well as the high standard deviations for the strength and muscle parameters were indications of this. Another indicator for this heterogeneity is the fact that about 43% of the participants fulfilled the Brighton criteria, meaning that we included women with GJH and JHS as well. Recently it was shown that the strength level of these two groups might be quite different [49].

Additional limitations were the outcome measurements. The isometric strength test was difficult to perform for inexperienced participants and possibly did not reflect dynamic changes in muscle strength. In the peripheral quantitative computer tomography, a tendency towards improved muscle density and muscle cross sectional area was seen, but the intensity during the 12 weeks training may not have been high enough to really build up muscle mass. Additionally, nutrition and especially protein intake was not recorded or altered in this study, which might influence the building of new muscle mass [52]. Stair climbing, on the other hand, was an activity that placed minimal demands on the women, so that no changes in their movement patterns were seen. Similarly, the questionnaires showed some ceiling effects, with several participants not having pain or disability in their daily-life. A barrier in this sense was that, at the time of the study, no specific validated questionnaire for hypermobile persons was available. This has now changed, because in 2017 Palmer and colleagues published the Bristol Impact of Hypermobility questionnaire [53]. Then, regarding the intervention, the resistance training program was thoroughly standardised and thus specific adaptations to the individual needs of some of these patients were not possible. In addition, no other interventions were provided, e.g. pain relief techniques or advice on function in daily-life activities. Finally, this study did not incorporate a comparison with women with normal mobility doing the same training program. However, the goal of the project was to compare the strength gain by training in comparison to a control without training in women with GJH, not to compare the strength gains between women with and without GJH. Thus, it was not possible to include two additional groups with women with normal mobility.

One strength of this study was that the program was well suited to the women and the adherence to the training program was good. Several participants mentioned at the end of the program that they intend to continue the resistance training on their own. Only four participants had to stop the training early, three of these for reasons besides the training. In one person with increased low back pain and subsequent lumbar disc hernia, it remained unclear whether the resistance training contributed to this problem.

For future research, it would be of great importance to better define the study group and to include, if possible, mainly asymptomatic persons with GJH. The question of whether these patients can gain muscle mass and strength similar to that of healthy persons has not been finally answered, and more investigation is required as to the best way to guide and monitor such a resistance-training program. Additionally, the training program might be more individualised and could include not just strength exercises but also some functional training or proprioceptive exercises.

Conclusions

The present study could not identify any effect of a mainly self-guided 12-week resistance training program in women with GJH, compared to a control group. The response to the low intensity resistance training was highly variable and the groups in the study might have been too heterogeneous in terms of symptoms and baseline strength. Possibly, a better guided resistance training program including specific adaptations to the individual needs might be better suitable for these patients. To confine this, more studies with better structure and better suitable training programs are needed.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13102-021-00238-8.

Additional file 1: S1. Detailed description of training program.

Additional file 2: S2. Detailed description of the outcome measurements.

Additional file 3: S3. Result tables of additional parameters.

Additional file 4: S4. Basic dataset supporting the conclusions of this article.

Abbreviations

AIMS-2: Arthritis Impact Measurement Scales 2; bm: Body mass; BMI: Body mass index; CSA: Cross sectional area; EDS: Ehlers-Danlos syndrome; EMG: Electromyography; GJH: Generalized joint hypermobility; HM-Q: Questionnaire for hypermobility; HSD: Hypermobility spectrum disorder; JHS: Joint hypermobility syndrome; mCSA: Muscle cross-sectional area; MVC: Maximum voluntary contraction strength; pQCT: Peripheral quantitative computer tomography; RFD: Rate of force development; sd: Standard deviation; SF-36: Medical Outcomes Study Short Form

Acknowledgements

The authors wish to thank Prisca Eser, PhD, and Inna Galli-Lyssak for instructions concerning the use and evaluation of the pQCT; Prof. Lorenz Radlinger and Prof. Peter Villiger for support during the development of the study idea and protocol; Ursula Stutz, Patrick Probst and Karin Seifritz for critical discussion on clinical issues and their support during the realization of the study; Michaela Hähni and Matthias Stettler for the images to illustrate the project; and Michaela Hähni and Sarah Mahnig for their support by the data analysis.

Authors' contributions

All authors were involved in the design of the study protocol. DA was the principal investigator in this project and the contact person responsible for ethical approval. CM and GL developed the inclusion criteria and the assessments, BB reviewed the training program and JPB, DA and MV provided supervision and support throughout the development process. CM was responsible for the recruitment and inclusion and GL conducted all outcome measures. BB and CM were responsible for the training instructions. Responsibility for the data analysis was by GL. The writing of the manuscript was guided by GL. All authors contributed to parts of the manuscript and have read and approved the final manuscript.

Authors' information

JPB is a full professor at Vrije Universiteit Brussels, Belgium. DA is a senior lecturer at Bern University, Bern, Switzerland and clinical rheumatologist in the Bern University Hospital, Bern, Switzerland. MLV is director of the Department of Physiotherapy at Bern University Hospital, Bern, Switzerland, and was responsible for financial and material support for this project. BB and CM are physical therapists at Bern University Hospital, Bern, Switzerland, in the rheumatology and orthopaedic departments, respectively. GL is a physical therapist and research assistant at Bern University Hospital, Berne, Switzerland.

Funding

No external funding was obtained for this study.

Availability of data and materials

The basic dataset supporting the conclusions of this article is included within the article as an additional file (Additional file "Luder-G_S4_HM-Training_basic-data-file.xlsx").

Ethics approval and consent to participate

Ethical approval was obtained by the Ethics Committee of Canton Berne, Switzerland (No. 222/12). All participants gave written informed consent prior to inclusion and the study was conducted according to the Declaration of Helsinki.

Consent for publication
The model depicted in the description of the training program (Additional file "Luder-G_S1-file_training-program-intervention.pdf") gave consent to publish the pictures in scientific journals.

Competing interests
All authors declare that they have no competing interests.

Author details
[1]Department of Physiotherapy, Bern University Hospital, Insel Group, CH-3010 Bern, Switzerland. [2]Faculty of Physical Education and Physical Therapy, Vrije Universiteit Brussel, Pleinlaan 2, 1050 Brussels, Belgium. [3]Department of Rheumatology, Clinical Immunology and Allergology, Bern University Hospital and University of Bern, CH-3010 Bern, Switzerland.

Received: 17 August 2020 Accepted: 27 January 2021
Published online: 08 February 2021

References
1. Remvig L, Jensen DV, Ward RC. Are diagnostic criteria for general joint hypermobility and benign joint hypermobility syndrome based on reproducible and valid tests? A review of the literature. J Rheumatol. 2007; 34:798–803.
2. Russek LN, Errico DM. Prevalence, injury rate and, symptom frequency in generalized joint laxity and joint hypermobility syndrome in a "healthy" college population. Clin Rheumatol. 2015;35:1029–39.
3. Scheper MC, de Vries J, Beelen A, De Vos R, Nollet F, Engelbert R. Generalized Joint Hypermobility , Muscle Strength and Physical Function in Healthy Adolescents and Young Adults. Curr Rheumatol Rev. 2015;10:117–25.
4. Singh H, McKay M, Baldwin J, Nicholson L, Chan C, Burns J, et al. Beighton scores and cut-offs across the lifespan: cross-sectional study of an Australian population. Rheumatology. 2017;56:1857–64.
5. Foley EC, Bird HA. Hypermobility in dance: asset, not liability. Clin Rheumatol. 2013;32:455–61.
6. Baeza-Velasco C, Gély-Nargeot MC, Pailhez G, Vilarrasa AB. Joint hypermobility and sport: a review of advantages and disadvantages. Curr Sports Med Rep. 2013;12:291–5.
7. Castori M, Tinkle B, Levy H, Grahame R, Malfait F, Hakim A. A framework for the classification of joint hypermobility and related conditions. Am J Med Genet Part C Semin Med Genet. 2017;175:148–57. https://doi.org/10.1002/ajmg.c.31539.
8. Grahame R. The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). J Rheumatol. 2000;27:1777–9.
9. Bloom L, Byers P, Francomano C, Tinkle B, Malfait F. The international consortium on the Ehlers–Danlos syndromes. Am J Med Genet Part C Semin Med Genet. 2017;175:5–7.
10. Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet Part C Semin Med Genet. 2017;175:8–26. https://doi.org/10.1002/ajmg.c.31552.
11. Scheper MC, Juul-Kristensen B, Rombaut L, Rameckers EA, Verbunt J, Engelbert RH. Disability in adolescents and adults diagnosed with hypermobility related disorders: a meta-analysis. Arch Phys Med Rehabil. 2016;97:2174–87.
12. Pacey V, Nicholson LL, Adams RD, Munn J, Munns CF. Generalized joint hypermobility and risk of lower limb joint injury during sport: a systematic review with meta-analysis. Am J Sports Med. 2010;38:1487–97.
13. Tingle A, Bennett O, Wallis A, Palmer S. The links between generalized joint laxity and the incidence, prevalence and severity of limb injuries related to physical exercise: a systematic literature review. Phys Ther Rev. 2018;23:259–72. https://doi.org/10.1080/10833196.2018.1481626.
14. Junge T, Henriksen P, Hansen S, Østengaard L, Golightly YM, Juul-Kristensen B. Generalised joint hypermobility and knee joint hypermobility: prevalence, knee joint symptoms and health-related quality of life in a Danish adult population. Int J Rheum Dis. 2017;27:9. https://doi.org/10.1111/1756-185X.13205.
15. Juul-Kristensen B, Østengaard L, Hansen S, Boyle E, Junge T, Hestbaek L. Generalised joint hypermobility and shoulder joint hypermobility, – risk of upper body musculoskeletal symptoms and reduced quality of life in the general population. BMC Musculoskelet Disord. 2017;18:1–9.
16. Luder G, Schmid S, Stettler M, Mueller Mebes C, Stutz U, Ziswiler HR, et al. Stair climbing - an insight and comparison between women with and without joint hypermobility: a descriptive study. J Electromyogr Kinesiol. 2015;25:161–7. https://doi.org/10.1016/j.jelekin.2014.07.005.
17. Schmid S, Luder G, Mueller Mebes C, Stettler M, Stutz U, Ziswiler HR, et al. Neuromechanical gait adaptations in women with joint hypermobility - an exploratory study. Clin Biomech. 2013;28:1020–5.
18. Mueller Mebes C, Luder G, Schmid S, Stettler M, Stutz U, Ziswiler H-R, et al. Aspects of isometric contractions and static balance in women with symptomatic and asymptomatic joint hypermobility. Int J Phys Med Rehabil. 2016;4:347.
19. Stettler M, Luder G, Schmid S, Mebes CM, Stutz U, Ziswiler H, et al. Passive anterior tibial translation in women with and without joint hypermobility: an exploratory study. Int J Rheum Dis. 2018;21:1756–62.
20. Bremander A, Bergman S. Non-pharmacological management of musculoskeletal disease in primary care. Best Pract Res Clin Rheumatol. 2008;22:563–77.
21. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc. 2011;43:1334–59.
22. Fransen M, McConnell S, Harmer AR, Van Der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee: a Cochrane systematic review. Br J Sports Med. 2015;49:1554–7.
23. Magnusson SP, Julsgaard C, Aagaard P, Zacharie C, Ullman S, Kobayasi T, et al. Viscoelastic properties and flexibility of the human muscle-tendon unit in benign joint hypermobility syndrome. J Rheumatol. 2001;28:2720–5.
24. Gruber M, Bruhn S, Gollhofer A. Specific adaptations of neuromuscular control and knee joint stiffness following sensorimotor training. Int J Sports Med. 2006;27:636–41.
25. Ferrell WR, Tennant N, Sturrock RD, Ashton L, Creed G, Brydson G, et al. Amelioration of symptoms by enhancement of proprioception in patients with joint hypermobility syndrome. Arthritis Rheum. 2004;50:3323–8.
26. Sahin N, Baskent A, Cakmak A, Salli A, Ugurlu H, Berker E. Evaluation of knee proprioception and effects of proprioception exercise in patients with benign joint hypermobility syndrome. Rheumatol Int. 2008;28:995–1000.
27. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010:340. https://doi.org/10.1136/bmj.c332.
28. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014;348:g1687.
29. Tobias JH, Deere K, Palmer S, Clark EM, Clinch J. Joint hypermobility is a risk factor for musculoskeletal pain during adolescence: findings of a prospective cohort study. Arthritis Rheum. 2013;65:1107–15.
30. Clinch J, Deere K, Sayers A, Palmer S, Riddoch C, Tobias JH, et al. Epidemiology of generalized joint laxity (hypermobility) in fourteen-year-old children from the UK: a population-based evaluation. Arthritis Rheum. 2011; 63:2819–27.
31. Constantini NW, Dubnov G, Lebrun CM. The menstrual cycle and sport performance. Clin Sports Med. 2005;24:e51–82.
32. Mebes C, Amstutz A, Luder G, Ziswiler HR, Stettler M, Villiger PM, et al. Isometric rate of force development, maximum voluntary contraction, and balance in women with and without joint hypermobility. Arthritis Care Res. 2008;59:1665–9.
33. Ratamess NA, Alvar BA, Evetoch TK, Housh TJ, Kibler BW, Kraemer WJ, et al. Progression models in resistance training for healthy adults. Med Sci Sport Exerc. 2009;41:687–708.
34. Mueller Mebes C, Luder G, Schmid S, Stettler M, Stutz U, Radlinger L. Symptoms in daily life and activity level of women with and without hypermobility. Rheumatol Curr Res. 2018;8:1–7.
35. World Health Organisation. International classification of functioning, disability, and health: ICF. 2001.
36. Aeberli D, Eser P, Bonel H, Widmer J, Caliezi G, Varisco PA, et al. Reduced trabecular bone mineral density and cortical thickness accompanied by increased outer bone circumference in metacarpal bone of rheumatoid arthritis patients: a cross-sectional study. Arthritis Res Ther. 2010;12:R119. https://doi.org/10.1186/ar3056.
37. Stacoff A, Diezi C, Luder G, Stüssi E, Kramers-De Quervain IA. Ground reaction forces on stairs: effects of stair inclination and age. Gait Posture. 2005;21:24–38.

38. Hermens HJ. Development of recommendations for SEMG sensors and sensor placement procedures. J Electromyogr Kinesiol. 2000;10:361–74.
39. Busija L, Pausenberger E, Haines TP, Haymes S, Buchbinder R, Osborne RH. Adult measures of general health and health-related quality of life. Arthritis Care Res (Hoboken). 2011;63:S383–412. https://doi.org/10.1002/acr.20541.
40. Rosemann T, Szecsenyi J. Cultural adaptation and validation of a German version of the arthritis impact measurement scales (AIMS2). Osteoarthr Cartil. 2007;15:1128–33.
41. Gignac MA, Cao X, McAlpine J, Badley EM. Measures of disability. Arthritis Care Res. 2011;63:S308–24.
42. Faul F, Erdfelder E, Lang A-G, Buchner A. G*power: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39:175–91. https://doi.org/10.3758/BF03193146.
43. Jan M, Lin J, Liau J, Lin Y, Lin D. Investigation of clinical effects of high- and low-resistance training for patients with knee osteoarthritis: a randomized controlled trial. Phys Ther. 2008;88:427–36.
44. Gür H, Çakin N, Akova B, Okay E, Küçükoğlu S. Concentric versus combined concentric-eccentric isokinetic training: effects on functional capacity and symptoms in patients with osteoarthrosis of the knee. Arch Phys Med Rehabil. 2002;83:308–16.
45. Botton CE, Radaelli R, Wilhelm EN, Rech A, Brown LE, Pinto RS. Neuromuscular adaptations to unilateral vs. bilateral strength training in women. J Strength Cond Res. 2016;30:1924–32.
46. Dorgo S, Edupuganti P, Smith DR, Ortiz M. Comparison of lower body specific resistance training on the hamstring to quadriceps strength ratios in men and women. Res Q Exerc Sport. 2012;83:143–51.
47. Hubal MJ, Gordish-Dressmann H, Thompson PD, Price TE, Hoffman EP, Angelopoulos TJ, et al. Variability in muscle size and strength gain after unilateral resistance training. Med Sci Sport Exerc. 2005;37:964–72. https://doi.org/10.1016/S0162-0908(08)70354-4.
48. Peterson MD, Pistilli E, Haff GG, Hoffman EP, Gordon PM. Progression of volume load and muscular adaptation during resistance exercise. Eur J Appl Physiol. 2011;111:1063–71.
49. To M, Alexander CM. Are people with joint hypermobility syndrome slow to strengthen? Arch Phys Med Rehabil. 2019;100:1243–50. https://doi.org/10.1016/j.apmr.2018.11.021.
50. Liaghat B, Skou ST, Jørgensen U, Sondergaard J, Søgaard K, Juul-Kristensen B. Heavy shoulder strengthening exercise in people with hypermobility spectrum disorder (HSD) and long-lasting shoulder symptoms: a feasibility study. Pilot Feasibility Stud. 2020;6:1–13.
51. Celenay ST, Ozer KD. Effects of spinal stabilization exercises in women with benign joint hypermobility syndrome: a randomized controlled trial. Rheumatol Int. 2017;37:1461–8. https://doi.org/10.1007/s00296-017-3713-6.
52. Morton RW, Murphy KT, Mckellar SR, Schoenfeld BJ, Henselmans M, Helms E, et al. A systematic review, meta-analysis and meta- regression of the effect of protein supplementation on resistance training-induced gains in muscle mass and strength in healthy adults. Br J Sports Med. 2018;52:376–84.
53. Palmer S, Cramp F, Lewis R, Gould DB, Clark EM. Development and initial validation of the Bristol Impact of Hypermobility questionnaire. Physiother (United Kingdom). 2017;103:186–92. https://doi.org/10.1016/j.physio.2016.04.002.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

5. Correlation of Muscle and Bone Parameters, Daily Function and Participation in Women with Generalized Joint Hypermobility: a Descriptive Evaluation

Journal of Musculoskeletal and Neuronal Interaction 2022; 22(1):15-26

Gere Luder, Christine Mueller Mebes, Bettina Haupt-Bertschy, Daniel Aeberli, Jean-Pierre Baeyens, Martin L. Verra

J Musculoskelet Neuronal Interact 2022; 22(1):15-26

Journal of Musculoskeletal and Neuronal Interactions JMNI

Original Article

Correlation of muscle and bone parameters, daily function and participation in women with generalized joint hypermobility: a descriptive evaluation

Gere Luder[1,2], Daniel Aeberli[3], Christine Mueller Mebes[1,4], Bettina Haupt-Bertschy[1], Martin L. Verra[1], Jean-Pierre Baeyens[2,5]

[1]Department of Physiotherapy, Bern University Hospital, Bern, Switzerland;
[2]Faculty of Physical Education and Physical Therapy, Vrije Universiteit Brussel, Belgium;
[3]Department of Rheumatology and Immunology, Bern University Hospital, Bern, Switzerland;
[4]Physiotherapie Postmarkt AG, Kirchstrasse 1, Grenchen, Switzerland;
[5]Thim Van Der Laan AG, International University of Applied Sciences THIM, Landquart, Switzerland

Abstract

Objectives: Generalized joint hypermobility (GJH) has a prevalence in women of 15% to 35%. GJH may lead to impaired movement control, frequent sprains or subluxations and pain, and can be associated with early osteoarthritis or chronic fatigue. Aim of this project was to analyse muscle strength, muscle cross-sectional area (mCSA) and daily function in women with GJH and to analyse correlations between these measurements. **Methods**: Descriptive cross-sectional study of women with GJH, defined by Beighton score ≥6/9. Assessments included muscle strength, mCSA by peripheral Quantitative Computed Tomography (pQCT), stair climbing, as well as two questionnaires. Spearman's correlations between parameters were calculated. **Results**: 51 women with a mean age of 26.5 years participated, whereof 18 (35%) had a Beighton score of 9/9 and 17 (33%) attained 8/9. Internal correlations between strength measurements were high, whereas pQCT parameters were less correlated. Strength was moderately correlated with mCSA, while correlations with stair climbing and SF-36 were not significant. **Conclusions**: This study provides insight into the muscle and bone properties of women with GJH. Only slight differences were seen compared to normative values. Correlations between various dimensions were middle or low, indicating the complex relationship between strength, muscle properties and function.

Keywords: Beighton Score, Disability, Muscle Cross-Sectional-Area, Muscle Strength, Stair Climbing

Introduction

Joint hypermobility is a condition with increased range of motion in a joint compared to the general population, taking into account gender, age and ethnicity[1]. When several joints are affected it is called Generalised Joint Hypermobility (GJH), which is diagnosed by the Beighton score, measuring fingers, thumbs, elbows, knees and spine[2]. This GJH is mainly a characteristic of a person and not a clinical diagnosis. Notably women are significantly more likely to have GJH, with reported prevalence between 15% and 35%[3-6].

GJH is associated with different clinical presentations with variations in terms of severity, duration, and localisation of symptoms. Possible short-term effects of a hypermobile joint include difficulties with movement control, frequent sprains or subluxations or painful inflammation of tendons or ligaments. In the long term or when occurring recurrently, such symptoms may lead to joint damage, early osteoarthritis, chronic pain or fibromyalgia[7-9]. Experiencing symptoms due to GJH may also result in avoidance of physical activity and thus lead to deconditioning and fear of movement, with consequent loss of work ability, social withdrawal and restrictions in leisure time activities[10,11]. Several other issues

The authors have no conflict of interest.

Corresponding author: Gere Luder, Department of Physiotherapy, Inselspital, Bern University Hospital, CH-3010 Bern, Switzerland
E-mail: gere.luder@insel.ch

Edited by: G. Lyritis
Accepted 23 August 2021

may arise in association with GJH, namely skin problems, delayed wound healing, problems with blood vessels or the heart, neurological disorders, chronic fatigue or dizziness[12,13].

Up until 2017, these general symptoms were documented by means of the Brighton criteria and, if fulfilled, a Joint Hypermobility Syndrome (JHS) was diagnosed[14]. In parallel, the Ehlers-Danlos Syndromes (EDS), a group of hereditary connective tissue disorders, included the hypermobility type (or type III), which was often discussed as if it was the same as JHS[15,16]. At an expert conference new diagnostic criteria were developed and published in 2017[8,17]. Persons with GJH and fulfilling several criteria are now diagnosed with hypermobile EDS and all those who do not meet the criteria can be diagnosed with Hypermobility Spectrum Disorder (HSD). The term GJH is still used and refers to the characteristic of being generally hypermobile. Which and how many symptoms a person must have in order to be diagnosed with HSD has not been definitively clarified[8,18].

As described, joint hypermobility primarily affects the structural level of the body. Ligaments may be more flexible, tendons more elastic, muscles may be weaker or joint proprioception may be impaired[6,19,20]. According to the International Classification of Functioning (ICF) model on disease and disability, structural changes affect several levels, such as function, activities and participation[21]. For example, a problem with the stabilisation of the knee joint may cause pain when going down stairs and thus reduce stair capacity. Over time, this might lead to an avoidance of stair climbing, which then has a negative effect on physical condition or causes a person not to visit certain places.

Several studies were published about the physiological and biomechanical characteristics of people with GJH, but little is known about its impact on various tissues and possible interactions with different body systems. One study reported reduced muscle strength in persons with GJH[6], while others found values comparable to those in healthy controls[22,23]. Changes in movement control during walking were described[24,25] as well as higher moments and loads on the joints[26]. In a comprehensive review of 2016[12], the limitations and symptoms of various forms of hypermobility were investigated. For pain, fatigue, activity limitations and depression and anxiety, it was shown that persons with GJH were less affected than those with JHS or EDS, but still showed clear and significant differences compared to healthy persons. Finally, it was recently reported that people with JHS have lower values for various bone parameters and a reduced cross-sectional area of the lower leg muscles[27].

So far, to the knowledge of the authors, no research has been published looking at correlations between muscle and bone parameters in persons with GJH. There are some other studies in this area, in which the majority have studied athletes or healthy individuals. In general, fairly low correlations were found between muscle strength and cross-sectional area. As early as 1983 Maughan et al.[28] published a correlation of 0.51 for women for isometric maximum strength and muscle area measured by computer tomography for the knee extensors. In 2003 Gür et al.[29] found correlations of between 0.68 and 0.78 for the quadriceps and the cross-sectional area in women with knee osteoarthritis. In a brief review, Jones et al. in 2008[30] also pointed out that the correlation between force and muscle cross section is complex and that, in most studies, not very high correlations were found. Thus, a mean correlation in the range of 0.5 was also expected for persons with GJH for the relationship between thigh strength and muscle cross-sectional area.

The primary aim of this descriptive cross-sectional study was therefore twofold: To analyse and describe muscle strength, muscle cross-sectional area and stair climbing as a functional activity in a group of individuals with GJH and to analyse the correlations between the different parameters. In addition, in the sense of a subgroup analysis, we investigated whether there were differences in the above parameters between persons who fulfil the criteria for JHS and those who did not.

Materials and Methods

Study design

A descriptive cross-sectional analysis of various measurements in women with GJH was performed using the baseline data of a randomised controlled trial, of which the results have been presented elsewhere[31]. No external funding was received, and ethical approval was obtained by the Ethics Committee of Canton Bern, Switzerland. All participants gave written informed consent before testing.

Participants

Included in the study were women between 20 and 40 years with GJH, meaning a Beighton score of at least 6/9 points[3,32]. The BMI had to be in a range between 18-30 kg/m^2 and they had to be able to understand the German questionnaires used in the project. A formal diagnosis of GJH or JHS was not necessary.

Excluded were women who had had surgery of the lower extremities or lumbar spine in the last two years and women doing more than four hours per week of regular intense sports. Additionally, women who were pregnant or less than one year after delivery were excluded. Finally, women with a known diagnosis of a genetic disease of the connective tissue, mainly Marfan syndrome, EDS other than the hypermobility type and Osteogenesis imperfecta, were also excluded.

Inclusion and subgrouping

Participants were recruited from those in previous studies as well as from the staff of Bern University Hospital and the student body of the Bern University of Applied Science, Health Department, Switzerland. Interested participants were informed by phone and in print before the first appointment. After signing the informed consent, inclusion and exclusion criteria were checked face-to-face by one physiotherapist (CM) with more than 12 years clinical experience. For the Beighton score the test movements were: a) hyperextension of elbow more than 10°, b) hyperextension of knee more than 10°, c) ability to touch the floor with the palms of the hands, keeping the knees fully extended, d) at least 90° dorsiflexion of 5^{th} metacarpophalangeal joint, and e) ability to touch the inner side of the forearm with the thumb[2]. All items, except c), were tested bilaterally, resulting in a possible total score of 9 points.

Additional measurements at inclusion incorporated body weight, body height, arm span, and arm and leg length, as well as knee flexion and extension and hip internal and external rotation. Anamnestic checking of the Brighton criteria[14] was done by semi-structured interview by the same experienced physiotherapist (CM). The major Brighton criteria were: a) Beighton score of 4/9 or more (as checked and already fulfilled when included in the study) and b) arthralgia for longer than 3 months in 4 or more joints. The minor criteria included: a) arthralgia in one to three joints or back pain (>3 months), spondylosis, spondylolysis/spondylolisthesis, b) dislocation/subluxation in more than one joint, or in one joint on more than one occasion, c) soft tissue rheumatism with >3 lesions, d) Marfanoid habitus, e) abnormal skin: striae, hyperextensibility, thin skin, f) eye signs, and g) varicose veins or hernia or uterine/rectal prolapse. Participants were rated as having JHS when both major criteria or one major and two minor criteria were fulfilled. The Brighton criteria of all participants were recorded for subgrouping and to analyse differences between women with or without JHS. Note, that this study was conducted between October 2013 and November 2015 and thus the 2017 diagnostic criteria where not yet in place. Hence, throughout this article the term JHS is used for women fulfilling the Brighton criteria.

Assessments

GJH may affect an individual in several dimensions of life, like body functions, body structures, activities and participation, as defined in the International Classification of Functioning, Disability and Health (ICF)[21]. The assessments used in this study aimed to analyse the women with GJH in several dimensions of the ICF: muscle strength and muscle and bone properties as body structures; muscle activity and forces during stair climbing in terms of function and the SF-36 as general measure of activity and participation. All assessments were performed on one day, first the strength testing and stair climbing analysis, followed by the pQCT measurement and the questionnaires.

Peripheral quantitative computed tomography (pQCT)

Using a Stratec XCT 3000 scanner (Stratec Medizintechnik), the muscle and bone properties of the thigh at 33% above the knee joint and the lower leg at 33% below the knee joint were measured using standard protocols. At each site the total cross-sectional area (CSA) was calculated, as well as the respective values for muscle cross-sectional area (mCSA), bone cross-sectional area (bCSA) and fat cross-sectional area (fCSA). Additionally, muscle and bone mass (mMass and bMass) and density (mDens and bDens) were determined; all parameters as previously described[33,34]. All calculations were done with the integrated software of the device.

Muscle strength

The maximum isometric strength (MVC) and the rate of force development (RFD) were measured for the right knee extensors and flexors while sitting on a custom-built strength measurement table with a one-dimensional strain gauge (KM 1500S; Megatron) calibrated in Newton (N). The participant sat on the table with the knee and hip in 90° flexion with a sling attached above the ankle was connected to the force transducer. Study participants were then asked to pull forward respectively backwards as fast and as strong as possible and to hold the highest possible force for five seconds. After familiarization and two test trials, three measuring trials were performed at intervals of 30 s.

The MVC was calculated as the maximal force in Newton and the RFD as the slope of the force curve between 20% and 80% of MVC in Newton/second and the highest value of three trials was used. Beside the values for knee extensors and knee flexors the sum of both MVC's was calculated, as well as the ratio of MVC/mCSA for extensors and flexors and the sum MVC.

Electromyography (EMG)

The muscle activity of vastus medialis (VM) and vastus lateralis (VL) and semitendinosus (ST) and biceps femoris (BF) of the right leg was measured using surface EMG. Electrode placement and measurement procedure were defined according to the recommendations of SENIAM[35]. After marking the electrode positions and skin preparation two pre-gelled AgCl-electrodes (Ambu Blue Sensor N, Ambu A/S) of 5 mm diameter were placed in parallel 2 cm apart. Additionally, a reference electrode was placed laterally over the femoral condyle. Skin impedance for each pair of electrodes had to be below 5 kΩ. All electrodes were connected by cable via pre-amplifiers (baseline noise <1uV RMS, input impedance >100MΩ, common mode rejection ratio >100dB, input range of +/- 10mV, base gain of 500, 10-500Hz bandpass filter) to a small telemetry box (TeleMyo 2400T G2, Noraxon) on the participant's back. From there the signals were transmitted to the receiver (TeleMyo 2400R G2, Noraxon) and recorded at a sampling rate of 1000 Hz using a 12-bit analog-digital converter (Meilhaus ME-2600i, SisNova Engineering) and the software package "ads" (version 1.12, uk-labs).

Stair climbing

To measure ground reaction forces (GRF) and EMG during stair climbing a custom-built wooden six-step stair was used (riser height 17.9 cm, tread 29 cm, inclination 30.4°, according to Stacoff et al.[36]), with a handrail on both sides and a platform of 1m length to allow comfortable turning. GRF were measured using two force plates (Type 9286BA, Kistler) that were embedded in the 3^{rd} and 4^{th} step of the stair and supported by an independent steel frame. The force signals were transmitted via a custom-built amplifier (uk-labs) to the recording computer. To determine the second foot contact of the stride, which was not measured with a force plate, a tri-axial accelerometer (Model 317A, Noraxon) was attached to the right malleolus and connected to the EMG telemetry system described above. All signals were then recorded in sync and registered in the software package "ads" (version 1.12, uk-labs). The participants had to climb up and down the stair barefoot ten times at a comfortable self-selected speed without using the handrail.

Data Processing of EMG and GRF

All data was processed using a custom-made MATLAB toolbox (The MathWorks) in accordance with previously described algorithms[37]. All measurements were visually inspected and six trials selected for analysis of stair ascent and descent in accordance with existing recommendations[38]. The EMG of the MVC measurements was used for normalization, calculated by RMS over 500 ms and using the highest value out of three trials. Dynamic EMG data was baseline corrected, full rectified and normalized to the corresponding 100% MVC value and linear envelopes built by lowpass-filtering (second-order Butterworth, cutoff 20 Hz)[39]. Peak muscle activation during stance was calculated from the linear envelope.

The vertical force-time curves were lowpass filtered (second-order Butterworth, cutoff 30 Hz), normalized to body mass and parameterized according to the previously described method[36]. Foot contact and foot off were defined as the time points when the vertical force exceeded or fell below 3% of the subject's body mass, respectively. Foot contact at the end of the stride was determined by visual analysis of the raw accelerometer signal. The maximum force-peak during weight acceptance (Fmax) was calculated as well as the respective time after foot contact (t to Fmax), the slope of the force curve during the loading phase (loading rate, LR), and the contact time. For all parameters, the mean value from six trials for each subject and condition was calculated.

Medical Outcomes Study Short Form 36-Item (SF-36)

The SF-36 is a widely used multi-item generic health survey intended to measure "general health", which is available in German. The psychometric properties are good and well documented, and there exist normative values for many patient groups, including some in the field of rheumatology[40]. The questionnaire is self-administered and takes about 10 minutes to complete. The SF-36 scores were calculated according to the standard method described[40], resulting in scores between 0-100 for eight dimensions, with higher values indicating better health-related quality of life. Additionally, the physical and psychological sum scores were calculated.

Hypermobility Questionnaire (HM-Q)

Since at the time of the measurements no specific assessment for joint hyper mobility and related disabilities was available, a own face-validated questionnaire was used to record the pain and restrictions in daily life experienced by the participants. The questionnaire consisted of 28 items, of which 16 targeted pain in different body regions, and 12 asked about disability in daily activities like bending, stair climbing, sitting for more than one hour or carrying loads. A sum score was calculated and scaled between 20 and 100 with lower values indicating better health. The activities in the questionnaire were chosen based on the most frequently mentioned problem situations identified in a previous cross-sectional study[41].

Statistical analysis

For all parameters descriptive statistics are presented with mean and standard deviation or median and interquartile range, for the whole group and for the subgroups, respectively. For group comparison the mean differences are reported as absolute values and in percent and the 95% confidence interval (CI) is given. Differences between groups were tested for significance with Mann-Whitney U test since normal distribution, as checked with the Levene-test, was not given for most parameters. Significance level was set at $p \leq 0.05$, despite multiple testing, because of the exploratory nature of this analysis. Additionally, based on the resulting effect sizes between the subgroups, sample size considerations for future studies were done with calculations using G*Power Version 3.1.9.6[42].

In a first step the self-correlations of the parameters of each measurement were calculated using the Spearman rank test and the correlation matrix plotted. Parameters with high internal correlation, indicated by Spearman's $\rho \geq 0.8$, were discarded and then the correlations between measurements were calculated for selected parameters. Correlations were flagged as highly significant at $p \leq 0.005$ and as significant when $p \leq 0.05$. All statistics were calculated using the software JAMOVI (The JAMOVI project, Version 1.1.9.0).

Results

Participants

A total of 51 women with a mean age of 26.5 (sd 4.5) years participated in this study (Table 1). According to the Brighton criteria 22 of them were classified as having JHS, whereas 29 did not fulfill the Brighton criteria and were labelled as GJH. No differences between these groups were found in terms of age, weight and height, nor for mobility of the knee and hip or the Beighton score. Note that 18 women (35%) had a Beighton score of 9/9, 17 (33%); attained 8/9 points and the rest had 6 or 7 points on the 9-point scale.

Descriptive comparison between JHS and GJH

Regarding strength measurements (Table 2) the values for persons with JHS were often lower than those for persons with GJH, however only the MVC of the knee flexors showed a significant difference between these two

Table 1. Descriptive characteristics of participants as mean±standard deviation (sd).

		All (n=51) mean±sd	GJH (n=29) mean±sd	JHS (n=22) mean sd	Mann-Whitney-U p
Age (years)		26.5±4.5	26.4±4.1	26.7±5.0	0.962
Height (m)		1.68±0.06	1.68±0.06	1.68±.05	0.917
Weight (kg)		62.6±10.1	62.3±10.4	62.9±10.0	0.864
BMI (kg/m²)		22.1±2.8	22.1±2.8	22.1±2.9	1.000
Right knee flexion (°)		152±6	153±6	152±6	0.613
Right knee extension (°)		12±2	13±2	12±2	0.379
Left knee flexion (°)		152±7	151±7	152±7	0.350
Left knee extension (°)		12±3	12±3	12±2	0.690
Right hip internal rotation (°)		49±10	49±12	50±9	0.924
Right hip external rotation (°)		44±9	46±9	42±8	0.210
Left hip internal rotation (°)		47±10	47±12	47±8	0.893
Left hip external rotation (°)		44±9	43±9	44±9	0.572
Beighton score	6	6 (12)	4 (13)	2 (9)	χ^2
n (%)	7	10 (20)	5 (17)	5 (23)	p = 0.848
	8	17 (33)	10 (35)	7 (32)	
	9	18 (35)	10(35)	8 (36)	

GJH = Generalized Joint Hypermobility, JHS = Joint Hypermobility Syndrome.

Table 2. Descriptive comparison of muscle strength measurements as mean±standard deviation (sd).

		All (n=51) mean±sd	GJH (n=29) mean±sd	JHS (n=22) mean±sd	Mann-Whitney-U p	Mean diff.	Mean diff. %	95% CI	
								Lower	Upper
MVC knee extensors	N	358±100	365±99	347±103	0.340	-18	-5.0	-76	39
RFD knee extensors	N/s	1564±858	1637±890	1469±823	0.515	-168	-10.3	-568	322
MVC knee flexors	N	185±75	205±68	159±79	**0.029**	-46	-22.3	-87	-4
RFD Knee flexors	N/s	702±723	817±888	551±389	0.411	-266	-32.6	-674	142
MVC knee sum	N	543±163	570±158	506±165	0.447	-64	-11.2	-135	27
RFD knee sum	N/s	2266±1374	2454±1541	2020±1102	0.175	-434	-17.7	-1213	344
MVC/bm knee extensors	N/bm	0.58±0.16	0.59±0.14	0.57±.018	0.291	-0.02	-4.0	-0.11	0.07
RFD/bm knee extensors	N/s/bm	2.38±1.26	2.43±1.22	2.32±1.34	0.704	-0.12	-4.8	-0.84	0.61
MVC/bm knee flexors	N/bm	0.30±0.13	0.33±0.10	0.27±0.15	0.060	-0.06	-18.6	-0.13	0.01
RFD/bm Knee flexors	N/s/bm	1.07±0.87	1.16±0.95	0.95±0.75	0.390	-0.21	-18.0	-0.70	0.29
MVC ext/ mCSA thigh	N/cm²	4.46±1.08	4.55±1.03	4.34±1.15	0.411	-0.21	-4.6	-0.83	0.40
MVC flex/ mCSA thigh	N/cm²	2.32±0.91	2.55±0.74	2.02±1.03	**0.024**	-0.53	-21.0	-1.03	-0.04
MVC sum/ mCSA thigh	N/cm²	6.79±1.81	7.11±1.64	6.36±1.96	0.128	-0.74	-10.5	-1.76	0.27

GJH = Generalized Joint Hypermobility, JHS = Joint Hypermobility Syndrome, diff = difference, CI = Confidence Interval, MVC = Maximum Voluntary Contraction, RFD = Rate of Force Development, bm = body mass, mCSA = muscle Cross-Sectional Area. Significant differences between groups (p>0.05) are in bold.

groups. For all parameters high standard deviations were observed, ranging between a third and half of the mean values, which also resulted in wide confidence intervals for group differences, mainly crossing the zero line. An additional significant decrease for persons with JHS was seen in the ratio of knee flexor strength to the muscle CSA of the thigh.

For the tissue properties of thigh and shank, as measured by pQCT (Table 3), no significant differences were found, as indicated additionally by the 95% confidence intervals of the

Table 3. Descriptive comparison of tissue properties as measured by pQCT as mean±standard deviation (sd).

		All (n=51) mean±sd	GJH (n=29) mean±sd	JHS (n=22) mean±sd	Mann-Whitney-U	Mean diff.	Mean diff. %	95% CI	
								Lower	Upper
Parameters for thigh									
Total CSA	cm^2	150.9±28.4	151.8±29.7	149.8±27.2	0.903	-1.9	-1.3	-18.2	14.4
mCSA	cm^2	79.9±10.9	80.0±11.3	80.0±10.7	0.903	0.04	0.1	-6.2	6.3
Bone CSA	cm^2	6.0±0.8	6.0±0.8	6.1±0.8	0.419	0.1	1.7	-0.4	0.6
Fat CSA	cm^2	63.4±23.1	64.2±24.2	62.2±22.0	0.932	-2.1	-3.2	-15.3	11.2
mCSA/bm	mm^2/bm	13.1±1.8	13.1±1.9	13.1±1.8	0.827	-0.0	-0.2	-1.1	1.0
Muscle mass	mg	645±92	647±95	644±91	0.977	-3	-0.5	-56	50
Bone mass	mg	400±44	401±43	400±47	0.676	-1	-0.3	-26	24
mDensity	mg/cm^3	80.6±1.7	80.8±1.8	80.4±1.6	0.962	-0.5	-0.6	-1.4	0.5
Bone density	mg/cm^3	673±70	679±68	665±75	0.515	-14	-2.1	-54	26
Parameters for shank									
Total CSA	cm^2	102.3±16.7	102.6±16.4	101.7±17.4	0.658	-0.9	-0.9	-10.5	8.7
Muscle CSA	cm^2	69.7±10.6	69.0±9.5	70.5±12.1	0.770	1.4	2.1	-4.7	7.5
Bone CSA	cm^2	5.7±0.7	5.7±0.7	5.7±0.7	0.655	-3	-0.5	-0.4	0.4
Fat CSA	cm^2	25.6±10.1	26.6±11.6	24.3±7.9	0.917	-2.3	-8.6	-8.1	3.5
MCSA/bm	mm^2/bm	11.4±1.6	11.3±1.7	11.4±1.6	0.962	0.1	1.2	-0.8	1.1
Muscle mass	mg	564±86	560±77	568±98	0.917	8	1.4	-41	57
Bone mass	mg	458±53	459±55	456±51	0.962	-3	-0.7	-33	27
mDensity	mg/cm^3	81.0±1.6	81.2±1.7	80.7±1.4	0.517	-0.5	-0.6	-1.4	0.4
Bone density	mg/cm^3	808±54	808±46	808±64	0.970	-0	0.1	-30	31

pQCT = Peripheral Quantitative Computer Tomgraphy, GJH = Generalized Joint Hypermobility, JHS = Joint Hypermobility Syndrome, diff = difference, CI = Confidence Interval, CSA = Cross-sectional area, mCSA = muscle cross-sectional area, mDensity = Muscle density, bm = body mass.

Table 4. Descriptive comparison of stair climbing as a functional activity. Parameters of ground reaction force and electromyography as mean±standard deviation (sd).

		All (n=51) mean±sd	GJH (n=29) mean±sd	JHS (n=22) mean±sd	Mann-Whitney-U p	Mean diff.	Mean diff. %	95% CI	
								Lower	Upper
t to Fmax up	ms	0.203±0.030	0.209±0.031	0.196±0.029	0.117	-0.013	-6.2	-0.030	0.004
Fmax/bm up	%bm	109.0±6.3	108.0±5.6	110.0±7.1	0.332	2.1	1.9	-1.5	5.6
Loading rate up	%bm/s	118.0±42.2	114.0±46.8	123.0±35.7	0.189	8.9	7.8	-15.2	33.0
Contact time up	ms	0.750±0.088	0.774±0.084	0.719±0.084	**0.015**	-0.056	-7.2	-0.103	-0.008
t to Fmax down	ms	0.164±0.022	0.163±0.023	0.166±0.020	0.304	0.003	2.1	-0.009	0.016
Fmax/bm down	%bm	141.0±13.2	143.0±12.8	138.0±13.4	0.140	-5.0	-3.5	-12.4	2.5
Loading rate down	%bm/s	162.0±46.6	162.0±44.4	161.0±50.4	0.947	-0.9	-0.6	-27.7	25.8
Contact time down	ms	0.717±0.094	0.741±0.088	0.685±0.095	**0.032**	-0.056	-7.6	-0.108	-0.004
Biceps femoris max up	%MVC	13.6±14.8	9.1±5.4	18.9±20.0	**0.026**	9.7	106.5	1.5	17.9
Semitendinosus max up	%MVC	15.8±13.8	13.1±9.2	19.0±17.6	0.355	5.9	45.4	-1.9	13.8
Vastus lateralis max up	%MVC	40.2±21.7	35.0±17.0	47.2±25.5	0.074	12.3	35.0	-0.1	24.5
Vastus medialis max up	%MVC	40.5±26.1	37.3±28.3	45.0±22.6	0.099	7.7	20.6	-7.3	22.7
Biceps femoris max down	%MVC	7.4±8.8	5.9±4.2	9.3±12.1	0.576	3.4	58.1	-1.7	8.5
Semitendinosus max down	%MVC	9.5±10.7	8.3±9.1	11.1±12.4	0.912	2.8	34.2	-3.4	9.0
Vastus lateralis max down	%MVC	22.6±14.0	21.3±15.8	24.5±11.3	0.095	3.2	15.2	-4.9	11.3
Vastus medialis max down	%MVC	22.9±14.0	21.1±15.3	25.2±11.8	0.087	4.1	19.3	-4.0	12.1

GJH = Generalized Joint Hypermobility, JHS = Joint Hypermobility Syndrome, diff = difference, CI = Confidence Interval, Fmax = maximum force peak during weight acceptance. Significant differences between groups (p>0.05) are in bold.

Table 5. Descriptive comparison of general health as measured by SF-36 and HM-Q, presented as median (interquartile range 25th - 75th).

	All (n=51) median (25th-75th)	GJH (n=29) median (25th-75th)	JHS (n=22) median (25th-75th)	Mann-Whitney U p
SF36 physical functioning	100 (95-100)	100 (95-100)	95 (90-100)	**0.029**
SF36 role functioning	100 (100-100)	100 (100-100)	100 (100-100)	0.555
SF36 bodily pain	84 (62-100)	100 (72-100)	73 (54.5-84)	0.053
SF36 health perception	82 (72-89.5)	85 (77-92)	77 (68.3-87)	0.240
SF36 vitality	60 (45-70)	60 (50-70)	55 (45-69.2)	0.486
SF36 social role	100 (87.5-100)	100 (87.5-100)	93.8 (75-100)	0.097
SF36 emotional role	100 (100-100)	100 (100-100)	100 (100-100)	0.830
SF36 mental health	80 (64-84)	80 (68-84)	75.5 (60-84)	0.213
SF36 physical health (sum score)	55.1 (50.9-58.2)	56.9 (52.0-58.9)	53.8 (50.4-56.6)	0.110
SF36 mental health (sums core)	52 (45.8-55.6)	52.6 (47.1-55.9)	50.1 (44.8-54.2)	0.458
HM-Q sum score	27.1 (24.3-35)	25.7 (22.1-32.9)	31.1 (26.4-37.3)	**0.032**

GJH = Generalized Joint Hypermobility, JHS = Joint Hypermobility Syndrome, SF-36 = Medical Outcomes Study Short Form 36-Item Questionnaire (scale 0-100, with higher values indicating better health, sums core with reference to US-population with 50 indicating the population mean), HM-Q = Hypermobility Questionnaire (scale 20-100, with higher values indicating more pain and disability). Significant differences between groups (p>0.05) are in bold.

mean difference, the latter being symmetrical on both sides of the zero line. Muscle mass at thigh and shank was on a comparable as was muscle density, while bone density was clearly higher for the shank.

In the parameters measured during stair climbing (Table 4) some differences between persons with JHS and GJH were seen. A significantly shorter contact time on the step indicates faster stair ascent and descent velocity for persons with JHS, while the parameters for the first force peak were comparable between groups. EMG values showed a tendency for higher muscle activation in persons with JHS, whereby only the EMG of the biceps femoris was significantly higher in persons with JHS.

Finally, no significant differences between groups were recorded on the SF-36, although notably high values were found in several domains, like role functioning, emotional role and physical functioning. The hypermobility questionnaire revealed significantly higher pain and impairments in daily life for persons with JHS compared to those with GJH, with rather low values in both groups.

Sample size considerations

Based on the two significant differences between the subgroups in maximum knee flexor strength and flexor strength to mCSA ratio for the effect size according to Cohen were calculated as d=0.52 and d=0.51, respectively, which corresponded with an achieved statistical power of 35% and 31% respectively. When calculating the necessary sample size for 80% power for a future study a minimum of 124 and 130 persons respectively, will be necessary.

Internal correlations

For strength measurements all 13 parameters were highly correlated with p-values below 0.005 and Spearman's ρ between 0.40 and 0.98.

The 18 pQCT parameters were less highly correlated with 53 (35%) comparisons being highly correlated and 16 (11%) correlated at p<0.05. Generally, the density parameters were not correlated to the CSA measurements, while the same parameters of thigh and shank were all highly correlated with Spearman's ρ between .44 and .87.

In terms of stair measurements there were no significant correlations between GRF and EMG. Of the 8 GRF parameters 17 (61%) correlations were highly significant and 3 (11%) were significant, with very variable coefficients (Spearman's ρ between 0.04 and 0.88). For the 8 parameters of the EMG all correlations were significant with only 3 (11%) being not highly significant and with rather high correlation coefficients (Spearman's ρ between 0.32 and 0.79).

In the questionnaires the face-validated hypermobility questionnaire correlated well with some dimensions of the SF-36, i.e. highly significant with a Spearman's ρ=0.68 on the pain subscale. In total 24 (44%) correlations were highly significant and 9 (16%) were significant, including the self-correlations of the various dimensions of the SF-36.

Correlations between the dimensions

Regarding the correlations between the dimensions of selected parameters the significant values are depicted in Table 6.

The MVC parameters were moderately correlated with the muscle CSA of the thigh, whereby persons with JHS showed

Table 6. Significant Spearman's correlations between selected parameters of the various domains for all participants and both subgroups.

		MVC extensors/bm	RFD extensors/bm	MVC flexors/bm	RFD flexors/bm	mCSA thigh/bm	Fmax up	contact time up	Fmax down	contact time down	%EMG Bic fem up	%EMG Vast lat up	%EMG Bic fem down
RFD extensors/bm	All	**0.57**											
	GJH	**0.50**											
	JHS	**0.56**											
MVC flexors/bm	All	**0.79**	**0.51**										
	GJH	**0.76**	**0.54**										
	JHS	**0.82**	**0.46**										
RFD flexors/bm	All	**0.55**	**0.70**	**0.67**									
	GJH	0.37	**0.61**	**0.53**									
	JHS	**0.70**	**0.71**	**0.79**									
mCSA thigh/bm	All	0.44		0.38									
	GJH	0.37											
	JHS	0.54		0.54									
Fmax up	All	0.29				**0.55**							
	GJH					0.52							
	JHS					0.59							
Contact time up	All					0.36	**-0.59**						
	GJH						**-0.58**						
	JHS						-0.57						
Fmax down	All			0.31									
	GJH												
	JHS			0.55									
Contact time down	All					-0.37	**0.48**	**0.88**					
	GJH							**0.85**					
	JHS					-0.43	-0.55	**0.87**					
%EMG bic fem up	All	-0.36	-0.31	**-0.51**	**-0.49**								
	GJH												
	JHS	-0.63		**-0.64**	-0.60								
%EMG vast lat up	All	-0.33	-0.39	**-0.46**	**-0.48**						**0.46**		
	GJH												
	JHS	-0.53	-0.63	**-0.66**	-0.64						0.58		
%EMG bic fem down	All	-0.29		**-0.49**	-0.44						**0.78**	0.42	
	GJH										**0.80**		
	JHS	-0.53		**-0.64**	**-0.67**						**0.79**	**0.69**	
%EMG vast lat down	All	**-0.46**	**-0.49**	**-0.58**	**-0.47**						**0.57**	**0.78**	**0.57**
	GJH		-0.40								0.41	**0.68**	0.42
	JHS	-0.57	-0.58	**-0.63**	-0.64						0.62	**0.83**	**0.70**

Bold numbers = correlation significant with p < 0.005, all others = correlation significant with p < 0.05. RFD = rate of force development, MVC = maximum voluntary contraction, bm = body mass, mCSA = muscle cross-sectional area, Fmax = peak ground reaction force. Note: Shaded areas are self-correlations in one measurement.

slightly higher values than those with GJH. Correlations of strength parameters with ground reaction forces were mainly not significant, while the EMG parameters correlated moderately negatively with the strength parameters, illustrating lower activation levels in persons with more strength. This was again more accentuated in the JHS group. The muscle CSA of the thigh correlated moderately positively with the peak force during stair up and with contact time up and moderately negatively with contact time down, but not with the EMG parameters. Finally, between the GRF parameters and the EMG no significant correlation was found. No significant correlations were seen between the self-reported questionnaires and the various other dimensions, indicating that no direct association could be found between body structures and function, on the one hand and disability and participation on the other.

Discussion

The first aim of this descriptive analysis was to compare women with GJH and those with JHS in terms of strength, muscle and bone properties and functional activities. The parameters mainly showed no differences between groups, however, there was a tendency towards lower strength in women with JHS compared to women with GJH. This is in line with the results of To et al.[43], whereas our previous study[22] did not find significant differences between symptomatic and asymptomatic women with GJH. The evidence regarding muscle strength in persons with various forms of joint hypermobility is still conflicting[44] and a possible reason might be the variability of symptoms and disability even in persons with the same diagnosis. In our study this is illustrated by the high standard deviations of strength parameters in both groups with average amounts of 30% to 50% of the respective mean value, resulting in large 95% CI for the mean differences. In the bone and muscle parameters no differences between the subgroups were seen and all values were in the normal range[27,45]. However, comparison with other studies is difficult since only a few studies were done with young women and, furthermore, measurement methods and sites were very variable. In stair climbing women with JHS had significantly shorter (minus 7%) contact times than those with GJH, pointing to faster speeds on the stair. Within this task only the biceps femoris during stair up demonstrated higher maximal activation, indicating that the faster speeds did not generally influence the muscle activation patterns. Finally, on the SF-36, no differences were seen for high values, indicating possible ceiling effects in this study group with fairly few disabilities and mild pain. Only for bodily pain was a tendency towards greater pain (indicated by lower values) identified in the JHS group. On the Hypermobility questionnaire significantly higher values were seen in participants with JHS versus GJH, pointing towards more pain and greater disability. However, the differences were small and all values still in the lower third of the scale. Thus, from the questionnaire and the functional measurements, we conclude that our participants were mostly not severely affected and were mainly able to manage their daily life.

A second endpoint of this study was analysis of the correlations of the various parameters in the different dimensions of the ICF. First, internal consistency was checked by analysing each dimension individually. A high number of high or moderate significant correlations were seen in all the measurements, indicating good internal consistency of the assessments. MVC and RFD of the same muscle were highly correlated. In the pQCT the muscle density was independent of CSA whereas during stair climbing GRF and EMG were not clearly correlated, indicating that additional factors like body position and movement control have high influence on these two parameters. The self-developed hypermobility questionnaire correlated well with the SF-36, suggesting its ability to evaluate the disabilities of persons with joint hypermobility correctly. However, since now the Bristol Impact on Hypermobility questionnaire as a validated alternative has now been as published[46], this self-developed questionnaire will no longer be used.

Finally, correlations between selected parameters of the various measurements were analysed. The correlations between MVC and muscle CSA were only moderate, which confirms that it is not only muscle area or muscle mass that determines the ability to generate strength, but also neurological and metabolic factors, as has already been described by similar correlation values for healthy persons and athletes[28,47]. Moderate and significant negative correlations between strength and muscle activation on stairs were found for those with JHS and, subsequently, for the whole group, but were lower and not significant for those with GJH. Since the women with JHS had a tendency towards lower strength and higher muscle activation, a possible explanation might be that these women were performing closer to their limit and thus using a consistently greater amount of their maximum strength. Similar mechanisms have already been described for elderly women[48] and for persons with knee osteoarthritis[29], but not for young women. Finally, the lack of significant correlations between the measurements and the questionnaires might indicate that the young participants in this study were not really impaired in their daily life. They showed some concerns regarding pain and disability but were still able to perform their daily activities and had enough capacity in terms of strength and muscle area to live a normal life.

Limitations

This descriptive study has several limitations in terms of the participants and the measurements performed. A main issue is that it was not possible to incorporate a control group without joint hypermobility. Thus, we have to rely for comparisons on the literature and partially on our previous cross-sectional study, where women with normal mobility were compared to those with joint hypermobility[22,37,41]. While the subgrouping, based on the Brighton criteria for JHS, was done after the inclusion of the participants, the two groups were not similar in size. Additionally, most of the participants in this study were not severely affected by their GJH and thus did not experience a lot of pain and disability. Consequently, the differences between those with JHS and those with GJH were not very clear. This illustrates the fact that these two entities are more part of a spectrum than two clearly distinguishable clinical pictures. In the current 2017 nosology nearly all the participants would be described as having Hypermobility Spectrum Disorder (HSD), with maybe a few fulfilling the criteria for hypermobile EDS[8,17]. Since no systematic data on the familial history and presence of joint hypermobility in relatives was gathered, it is impossible to clearly classify the participants retrospectively.

Regarding the sample size the present study was clearly underpowered. Since this is an additional and descriptive analysis of the baseline data of a randomised controlled trial the power calculation in the present project was based on the respective intervention and the expected changes. Thus, for this comparison of subgroups at baseline the study reached a power of about 35% and for future comparisons larger groups with about 130 to 150 participants might be necessary.

Additional limitations are related to the assessments used in the study. The strength measurement was performed isometrically, which was not easy for all participants to perform since not all were used to performing maximum contractions against resistance. This might have increased the variability between participants since experienced users had more strength and were able to perform better, while inexperienced women may not have reached their absolute maximum. On the stair it was not possible to measure kinematics, which might have shown differences in movement control and could help to explain the variance in terms of GRF and EMG. In hindsight, stair climbing as an activity was perhaps insufficiently demanding to illicit differences between the groups and bring the participants to their limits. Possibly, it would have been better to use jumping or running as activities to provoke higher muscle activation and thus establish the limits in the various groups. On the other hand, it might be difficult to find enough participants with JHS who are willing to perform such demanding activities, which might trigger pain or even injury.

Further research

To our knowledge only a few studies exist that look at differences between persons with joint hypermobility in various grades. Our study adds a small piece to this knowledge, but further research is needed. On the one hand, it is important to find better parameters for the description of the impairments and disabilities that persons with various grades of joint hypermobility experience. It is important to know which measurements might distinguish between persons who are more or less affected and which parameters may also serve as prognostic factors for future developments of pain and disabilities. On the other hand, a better description of the disabilities and deficits in persons with joint hypermobility would help to improve management and to design appropriate and targeted interventions for these patients. Since no curative therapy is available for joint hypermobility the long-term management and the individual support of affected persons is crucial. Future research should provide the foundation for this and thus better equip health professionals to manage the condition and patients.

Conclusion

The aim of this project was to provide an insight into various parameters of body structures, body function, daily activities and participation of young women with joint hypermobility. Only small and non-relevant differences to healthy young women were found in terms of muscle strength, muscle and bone properties, forces and muscle activation during stair climbing and in self-reported health. The participants in our study were not severely affected, thus the assessments used may not have been sufficiently sensitive to provide a deeper insight into the phenomenon of hypermobile joints.

Authors' contributions

All authors contributed to the design and planning of this study; GL and DA were responsible for all the assessments, CM for recruitment and inclusion of participants. GL was responsible for data analysis and statistics. The writing of this manuscript was guided by GL, all authors contributed to the manuscript and have read and approved the final version. GL has the full responsibility for the conduct of the study and the integrity of the data analysis.

Acknowledgements

The authors like to thank several people for their support during the conduct of this study: Prisca Eser, PhD, and Inna Galli-Lyssak for instructions concerning the use and evaluation of the pQCT. Michaela Hähni and Sarah Mahnig for support in data analysis.

References

1. Simmonds JV, Keer RJ. Hypermobility and the hypermobility syndrome. Man Ther 2007;12(4):298-309.
2. Remvig L, Jensen DV, Ward RC. Are Diagnostic Criteria for General Joint Hypermobility and Benign Joint Hypermobility Syndrome Based on Reproducible and Valid Tests? A Review of the Literature. J Rheumatol 2007;34(4):798-803.
3. Singh H, McKay M, Baldwin J, et al. Beighton scores and cut-offs across the lifespan: cross-sectional study of an Australian population. Rheumatology 2017;56(11):1857-64.
4. Russek LN, Errico DM. Prevalence, injury rate and, symptom frequency in generalized joint laxity and joint hypermobility syndrome in a "healthy" college population. Clin Rheumatol 2016;35(4):1029-39.
5. Noormohammadpour P, Borghei A, Mirzaei S, et al. The Risk Factors of Low Back Pain in Female High-School Students. Spine (Phila Pa 1976) 2019;44(6):1.
6. Scheper MC, de Vries J, Beelen A, Vos R De, Nollet F, Engelbert R. Generalized Joint Hypermobility, Muscle Strength and Physical Function in Healthy Adolescents and Young Adults. Curr Rheumatol Rev 2015;10(2):117-25.
7. Flowers PPE, Cleveland RJ, Schwartz TA, et al. Association between general joint hypermobility and knee, hip, and lumbar spine osteoarthritis by race: A cross-sectional study. Arthritis Res Ther

2018;20(1):1-7.
8. Castori M, Tinkle B, Levy H, Grahame R, Malfait F, Hakim A. A framework for the classification of joint hypermobility and related conditions. Am. J. Med. Genet. Part C Semin. Med. Genet. 2017;175(1):148-57.
9. Ofluoglu D, Gunduz OH, Kul-Panza E, Guven Z. Hypermobility in women with fibromyalgia syndrome. Clin. Rheumatol. 2006;25(3):291-3.
10. Bennett SE, Walsh N, Moss T, Palmer S. Understanding the psychosocial impact of joint hypermobility syndrome and Ehlers-Danlos syndrome hypermobility type: a qualitative interview study. Disabil Rehabil 2019;0(0):1-10.
11. Sætre E, Eik H. Flexible bodies - Restricted lives: A qualitative exploratory study of embodiment in living with joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type. Musculoskeletal Care 2019;(April):1-8.
12. Scheper MC, Juul-Kristensen B, Rombaut L, Rameckers EA, Verbunt J, Engelbert RH. Disability in adolescents and adults diagnosed with hypermobility related disorders: a meta-analysis. Arch Phys Med Rehabil 2016;97(12):2174-87.
13. Guarnieri V, Castori M. Clinical Relevance of Joint Hypermobility and Its Impact on Musculoskeletal Pain and Bone Mass. Curr Osteoporos Rep 2018;16(4):333-43.
14. Grahame R. The Revised (Brighton 1998) Criteria for the Diagnosis of Benign Joint Hypermobility Syndrome (BJHS). J Rheumatol 2000;27(7):1777-9.
15. Tinkle BT, Bird HA, Grahame R, Lavallee M, Levy HP, Sillence D. The lack of clinical distinction between the hypermobility type of Ehlers-Danlos syndrome and the joint hypermobility syndrome (a.k.a. hypermobility syndrome). Am J Med Genet Part A 2009;149(11):2368-70.
16. Castori M, Colombi M. Generalized joint hypermobility, joint hypermobility syndrome and Ehlers-Danlos syndrome, hypermobility type. Am J Med Genet Part C Semin Med Genet 2015;169(1):1-5.
17. Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet Part C Semin Med Genet 2017;175(1):8-26.
18. Tinkle BT, Levy HP. Symptomatic Joint Hypermobility: The Hypermobile Type of Ehlers-Danlos Syndrome and the Hypermobility Spectrum Disorders. Med Clin North Am 2019;103(6):1021-33.
19. Smith TO, Easton V, Bacon H, et al. The relationship between benign joint hypermobility syndrome and psychological distress: A systematic review and meta-analysis. Rheumatol (United Kingdom) 2013;53(1):114-22.
20. Alsiri N, Al-Obaidi S, Asbeutah A, Almandeel M, Palmer S. The impact of hypermobility spectrum disorders on musculoskeletal tissue stiffness: an exploration using strain elastography. Clin Rheumatol 2018;1-11.
21. World Health Organisation. International classification of functioning, disability, and health: ICF. 2001;
22. Mueller Mebes C, Luder G, Schmid S, et al. Aspects of Isometric Contractions and Static Balance in Women with Symptomatic and Asymptomatic Joint Hypermobility. Int J Phys Med Rehabil 2016;4:347.
23. Jensen BR, Olesen AT, Pedersen MT, et al. Effect of generalized joint hypermobility on knee function and muscle activation in children and adults. Muscle and Nerve 2013;48(5):762-9.
24. Schmid S, Luder G, Mueller Mebes C, et al. Neuromechanical gait adaptations in women with joint hypermobility - An exploratory study. Clin Biomech 2013;28(9-10):1020-5.
25. Alsiri N, Cramp M, Barnett S, Palmer S. Gait biomechanics in joint hypermobility syndrome: a spatiotemporal, kinematic and kinetic analysis. Musculoskeletal Care 2020;(January):msc.1461.
26. Simonsen EB, Tegner H, Alkjaer T, et al. Gait analysis of adults with generalised joint hypermobility. Clin Biomech 2012;27(6):573-7.
27. Banica T, Coussens M, Verroken C, et al. Higher fracture prevalence and smaller bone size in patients with hEDS/HSD - a prospective cohort study. Osteoporos Int 2020;31(5):849-56.
28. Maughan R, Watson JS, Weir J. Strength and cross-sectional area of human skeletal muscle. J Physiol. 1983;338:37-49.
29. Gür H, Çakin N. Muscle mass, isokinetic torque, and functional capacity in women with osteoarthritis of the knee. Arch Phys Med Rehabil 2003;84(10):1534-41.
30. Jones EJ, Bishop PA, Woods AK, Green JM. Cross-Sectional Area and Muscular Strength. A Brief Review. Sport Med 2008;36(12):987-94.
31. Luder G, Aeberli D, Mueller Mebes C, Haupt-Bertschy B, Baeyens J-P, Verra ML. Effect of resistance training on muscle properties and function in women with generalized joint hypermobility: a single-blind pragmatic randomized controlled trial. BMC Sports Sci Med Rehabil 2021;13(1).
32. Tobias JH, Deere K, Palmer S, Clark EM, Clinch J. Joint hypermobility is a risk factor for musculoskeletal pain during adolescence: Findings of a prospective cohort study. Arthritis Rheum 2013;65(4):1107-15.
33. Aeberli D, Eser P, Bonel H, et al. Reduced trabecular bone mineral density and cortical thickness accompanied by increased outer bone circumference in metacarpal bone of rheumatoid arthritis patients: A cross-sectional study. Arthritis Res Ther 2010;12(3):R119.
34. Eser P, Bonel H, Seitz M, Villiger PM, Aeberli D. Concise report Patients with diffuse idiopathic skeletal hyperostosis do not have increased peripheral bone mineral density and geometry. Rheumatology 2010;(February):977-81.
35. Hermens HJ. Development of recommendations for SEMG sensors and sensor placement procedures. J. Electromyogr. Kinesiol. 2000;10:361-74.
36. Stacoff A, Diezi C, Luder G, Stüssi E, Kramers-De

Quervain IA. Ground reaction forces on stairs: Effects of stair inclination and age. Gait Posture 2005; 21(1):24-38.
37. Luder G, Schmid S, Stettler M, et al. Stair climbing - An insight and comparison between women with and without joint hypermobility: A descriptive study. J Electromyogr Kinesiol 2015;25(1):161-7.
38. Jason Chen JJ, Shiavi R. Temporal Feature Extraction and Clustering Analysis of Electromyographic Linear Envelopes in Gait Studies. IEEE Trans. Biomed Eng 1990;37(3):295-302.
39. Hug F. Can muscle coordination be precisely studied by surface electromyography? J Electromyogr Kinesiol 2011;21(1):1-12.
40. Busija L, Pausenberger E, Haines TP, Haymes S, Buchbinder R, Osborne RH. Adult measures of general health and health-related quality of life. Arthritis Care Res (Hoboken) 2011;63(S11):S383-S412.
41. Mueller Mebes C, Luder G, Schmid S, Stettler M, Stutz U, Radlinger L. Symptoms in Daily Life and Activity Level of Women with and without Hypermobility. Rheumatol Curr Res 2018;8(3):1-7.
42. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39(2):175-91.
43. To M, Alexander CM. Are People With Joint Hypermobility Syndrome Slow to Strengthen? Arch Phys Med Rehabil 2019;100(7):1243-50.
44. van Meulenbroek T, Huijnen I, Stappers N, Engelbert R, Verbunt J. Generalized joint hypermobility and perceived harmfulness in healthy adolescents; impact on muscle strength, motor performance and physical activity level. Physiother Theory Pract 2020; 00(00):1-10.
45. Wilks DC, Winwood K, Gilliver SF, et al. Bone mass and geometry of the tibia and the radius of master sprinters, middle and long distance runners, race-walkers and sedentary control participants: A pQCT study. Bone 2009;45(1):91-7.
46. Palmer S, Cramp F, Lewis R, Gould DB, Clark EM. Development and initial validation of the Bristol Impact of Hypermobility questionnaire. Physiother (United Kingdom) 2017;103(2):186-92.
47. Anliker E, Toigo M. Functional assessment of the muscle-bone unit in the lower leg. J Musculoskelet Neuronal 2012;12(2):46-55.
48. Takai Y, Sawai S, Kanehisa H, Kawakami Y, Fukunaga T. Age and Sex Differences in the Levels of Muscular Activities during Daily Physical Actions. Int J Sport Heal Sci 2008;6(1997):169-81.

6.a Krafttraining bei Frauen mit generalisierter Hypermobilität: Machbarkeit, Beschwerden und Effekte – Eine Pre-post Studie

[Resistance training in women with generalized joint hypermobility:

feasibility, symptoms, and effects – a pre-post study]

Physioscience 2023;19:86-94 [Publication in German with English abstract]

Gere Luder, Christine Mueller Mebes, Bettina Haupt-Bertschy, Martin L. Verra,
Daniel Aeberli, Jean-Pierre Baeyens

Krafttraining bei Frauen mit generalisierter Hypermobilität: Machbarkeit, Beschwerden und Effekte – Eine Pre-post Studie

ABSTRACT

Hintergrund: Eine generalisierte Hypermobilität liegt vor, wenn die Beweglichkeit in mehreren Gelenken das übliche Maß übersteigt. Bis zu 30% der Frauen und 10% der Männer sind betroffen. Die Hypermobilität ist keine Pathologie, aber wenn sie mit Schmerzen und weiteren Symptomen einhergeht, kann sie Gesundheit und Alltagsfunktion beeinträchtigen. Zur physiotherapeutischen Behandlung gibt es wenige Studien, wobei Krafttraining eine mögliche Intervention sein könnte.

Ziel: Erfassung der Machbarkeit und des Effekts eines Krafttrainings für Frauen mit generalisierter Hypermobilität.

Methode: In dieser pre-post Studie absolvierten hypermobile Frauen (Beighton-Score>5) zwischen 20 und 40 Jahren während 12 Wochen ein Krafttraining an Geräten, fokussiert auf Beine und Rücken. Mithilfe eines Protokolls und wöchentlicher Fragebogen wurden das Training und dadurch ausgelöste Beschwerden analysiert. Vor und nach dem Training wurde die Kraft der Knieflexoren und -extensoren und der Muskelquerschnitt am Oberschenkel gemessen. Die Analyse erfolgte primär deskriptiv, zusätzlich erfolgte ein Vergleich zweier Subgruppen mittels Mann-Whitney-U und Chi^2-Test.

Ergebnisse: 46 Frauen (26.3±4.3 Jahre) absolvierten das Training. Sechs davon haben vorzeitig abgebrochen, davon eine wegen Rückenschmerzen aufgrund einer Diskushernie. 72.5% der verbleibenden 40 Frauen haben 20 oder mehr Trainings absolviert. Nur in 34% der Trainingswochen wurden geringe Beschwerden angegeben, mehrheitlich an Knie und Rücken. Die verwendeten Gewichte waren oft tief, so wurde auf der Legpress mit durchschnittlich 44.8% des Körpergewichts begonnen und nach 12 Wochen lag das Trainingsgewicht im Mittel bei 52.2 kg, was 85.7% des Körpergewichtes entspricht. Sowohl bei der Kraft wie beim Muskelquerschnitt wurde keine signifikante Verbesserung erreicht, wobei bis zu 17 Frauen (42.5%) eine Verbesserung von mehr als 10% erreichten.

Schlussfolgerung: Das Krafttraining war für die meisten Frauen machbar und gut verträglich. Das mehrheitlich selbstgesteuerte Training war zu wenig intensiv, um eindeutige Auswirkungen auf Kraft oder Muskelmasse zu erreichen, auch wenn einzelne Trainierende durchaus davon profitiert haben. In weiteren Studien sollten individuellere und enger begleitete Programme untersucht werden.

Schlüsselwörter: Hypermobilitätssyndrom, Maximalkraft, Schnellkraft, Muskelquerschnitt, Physiotherapie.

EINLEITUNG

Eine generalisierte Gelenkshypermobilität (engl. Generalized Joint Hypermobility, GJH) liegt vor, wenn der Bewegungsumfang in mehreren Gelenken das übliche Maß übersteigt. Sie wird in der Regel mit dem Beighton-Score festgestellt, der eine übermäßige Beweglichkeit in Daumen und kleinem Finger, Ellenbogen, Knien und bei der Rumpf-Vorneigung überprüft [1]. Je nach Definition und Bevölkerungsgruppe liegt die Prävalenz der GJH zwischen 10% und 35%, wobei Frauen deutlich häufiger betroffen sind als Männer [2,3]. So befanden Scheper und Kollegen [4] bei einem Cut-off von 4/9 Punkten 31.9% der Frauen und 9.7% der Männer in einer großen Gruppe von Studierenden als hypermobil. Bei einem Cut-off von 6/9 Punkten waren noch 13,9 % der Frauen und 1,5 % der Männer hypermobil. Generell nimmt die Beweglichkeit mit zunehmendem Alter ab, was durch niedrigere Cut-offs bei älteren Personen verdeutlicht wird [3].

Eine generalisierte Hypermobilität ist noch keine klinische Diagnose. Zahlreiche Personen mit GJH zeigen kaum Symptome und für manche Sportarten oder im Tanz kann es sogar von Vorteil sein, eine ausgeprägte Beweglichkeit zu haben [5,6]. Allerdings kann eine generell erhöhte Gelenksbeweglichkeit zu klinischen Symptomen führen und mit weiteren Syndromen verknüpft sein. Dazu gehören einerseits muskuloskelettale Beschwerden, wie Distorsionen, Subluxationen oder Muskelschmerzen, andererseits auch Zeichen einer systemischen Beteiligung der Haut, der Gefäße oder verschiedener Organe [7]. Lange Zeit wurden hypermobile Personen mit solchen Symptomen anhand der Brighton-Kriterien [8] mit einem Hypermobilitätssyndrom (engl. Joint Hypermobility Syndrome, JHS) diagnostiziert. Nach langer Diskussion, ob es sich bei JHS und dem hypermobilen Typ des Ehlers-Danlos-Syndroms (EDS) um die gleiche Entität handelt, wurde 2017 eine neue Nosologie für das EDS entwickelt [9]. Im Rahmen dieses Prozesses wurden die Definitionen und Klassifikationen für das Spektrum der mit GJH assoziierten Störungen ebenfalls überarbeitet. Der Begriff JHS wurde verworfen und als neue Diagnose wurde die «Hypermobility Spectrum Disorder» (HSD) eingeführt. Damit werden Personen diagnostiziert die eine GJH und verschiedene Symptome aufweisen, jedoch nicht die formalen Kriterien für das hypermobile Ehlers-Danlos-Syndrom (hEDS) erfüllen [7].

Unabhängig von der exakten Diagnose kann eine GJH zu Problemen bei Aktivitäten des täglichen Lebens führen und ist manchmal mit verschiedenen Beeinträchtigungen verbunden. Scheper et al. [10] stellten 2016 mittels Metaanalyse fest, dass Personen mit GJH öfter Schmerzen, Müdigkeit und Behinderungen aufweisen als Kontrollpersonen. In zwei weiteren Übersichtsarbeiten wurde gezeigt, dass Menschen mit GJH eine höhere Prävalenz und Inzidenz von Verletzungen der unteren Extremitäten aufweisen [11,12]. Eine dänische Studie ergab, dass Personen mit GJH mit höherer Wahrscheinlichkeit Knie- oder Schulterschmerzen hatten und es bis zu viermal wahrscheinlicher war, dass sie einige Aktivitäten aufgrund der Symptome vermieden [13,14]. Im Sinne einer Prävention könnte es für Personen mit GJH entscheidend sein, aktiv zu trainieren, um langfristig alltägliche und arbeitsbezogene Aktivitäten ohne Einschränkungen durchführen zu können. Weiter ist es wichtig Gelenk- und Muskelschmerzen, Funktionsverlust und Behinderungen, wie auch mögliche Langzeitfolgen bedingt durch die GJH zu verhindern.

Im Hinblick auf mögliche Interventionen wurden bisher nur wenige Studien durchgeführt. Für Personen mit GJH hat eine Studie ohne Kontrollgruppe positive Effekte für Physiotherapie des Kiefergelenkes nachgewiesen [15] und eine britische Studie konnte zeigen, dass Personen mit GJH und vorderem Knieschmerz in ähnlicher Weise Kraft aufbauen können wie Kontrollpersonen [16]. Einige weitere Studien fanden bei Personen mit JHS positive Effekte durch komplexe Interventionen mit Übungen, Beratung und manueller Therapie oder durch angeleitete Heimprogramme. Zusammenfassend stellte ein aktueller Review über acht Studien fest, dass keine bis geringe Evidenz besteht für die Wirksamkeit verschiedener konservativer Interventionen [17]. Darum basiert das therapeutische Management von Personen mit GJH und JHS weiterhin primär auf Erfahrung und Expertenmeinungen [18].

Der Vergleich von Personen mit GJH und solchen mit normaler Gelenksbeweglichkeit zeigt verschiedene Unterschiede auf. So wiesen in einer Studie mit 328 Erwachsenen diejenigen mit GJH weniger Kraft in Knie, Hüfte, Schulter und Unterarm auf und sie führten weniger körperliche Aktivität durch [4]. Eine frühere Studie unserer Gruppe mit 195 Teilnehmenden zeigte Unterschiede in der neuromuskulären Kontrolle beim Gehen [19] und Treppensteigen [20] sowie in der Kraft, dem Gleichgewicht und der passiven anterioren Translation der Tibia [21,22]. Menschen mit GJH weisen somit neuromuskuläre und muskuloskelettale Abweichungen auf, insbesondere Kraftdefizite, die sie möglicherweise anfälliger für die Entwicklung von Symptomen machen. Es ist daher wichtig, zu untersuchen, ob solche Defizite durch Training verbessert werden können.

In der Physiotherapie ist Krafttraining als Intervention zur Verbesserung von Kraft und Muskelmasse sowie zum Funktionsgewinn und Abbau von Beeinträchtigungen seit langem durch Studien belegt [23]. Auch für gesunde Personen wird regelmäßige Bewegung allgemein empfohlen und Krafttraining gilt als wichtiges Element in der Prävention von Krankheiten und Verletzungen [24]. Dabei können abhängig von Trainingsform, Intensität und Dauer des Trainings Verbesserungen der Kraft zwischen 15% und 30% erreicht werden, wobei Frauen mehrheitlich höhere relative Veränderungen erreichen als Männer [23,25]. Für verschiedene Gruppen wurde gezeigt dass Krafttraining positive Effekte hat, so für ältere Personen [26], bei Rückenschmerzen [27], Kniearthrose [28] wie auch bei Fibromyalgie [29]. Kaum Studien gibt es dagegen mit jüngeren Personen, insbesondere mit jüngeren Frauen und konkret mit Personen mit GJH oder JHS.

Aus diesen Gründen wurde in einem zweiteiligen Projekt ein Krafttrainingsprogramm für Frauen mit GJH durchgeführt und evaluiert. Das progressive Trainingsprogramm an Geräten konzentrierte sich dabei die Verbesserung der Kraft und Muskelmasse der Beine und des Rumpfes. Der erste Teil in Form einer randomisierten Studie fokussierte auf die Effektivität des Trainings[30]. Im hier dargestellten zweiten Teil war das primäre Ziel die Machbarkeit des Trainings und mögliche negative Auswirkungen zu untersuchen. Ergänzend wurde der unmittelbare Effekt des 12-wöchigen Trainingsprogramms auf die Kraft und den Muskelquerschnitt auch hier analysiert.

METHODIK

Diese Studie ist ein Vergleich von Frauen mit GJH vor und nach einem 12-wöchigen Krafttraining für Beine und Rücken an Geräten (pre-post). Es handelt sich um eine zusätzliche Analyse im Nachgang einer bereits publizierten randomisierten Studie mit Interventions- und Kontrollgruppe [30]. Den Frauen in der damaligen Kontrollgruppe ohne Intervention wurde nach der Studie das Krafttrainingsprogramm der Interventionsgruppe ebenfalls angeboten. Im Anschluss wurden die Daten all dieser Probandinnen vor und nach dem Training ausgewertet und verglichen. Die Primärstudie wurde prospektiv als ISRCTN90224545 registriert (www.isrctn.com, BMC, Springer Nature) und die Bewilligung zur Durchführung von der Ethikkommission des Kantons Bern, Schweiz, erteilt (Nr. 222/12). Alle Teilnehmerinnen gaben ihr schriftliches Einverständnis und die Studie wurde gemäß der Deklaration von Helsinki durchgeführt. Das Reporting in diesem Artikel lehnt sich an das „Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group“ an [31]. Das Krafttraining als Intervention wird gemäß den Vorgaben der TIDieR-Checkliste für Interventionen [32] beschrieben.

Teilnehmerinnen

Für die Studie wurden Frauen im Alter zwischen 20 und 40 Jahren rekrutiert, die mindestens einen Beighton-Score von 6/9 Punkten aufwiesen, wobei die Hyperextension des rechten Knies zwingend war. Diese war erforderlich, weil sich das Training auf die untere Extremität bezog und die Messungen in der Studie am rechten Bein durchgeführt wurden. Weiter mussten die Teilnehmerinnen einen Body-Mass-Index (BMI) zwischen 18-30 kg/m^2 aufweisen und die deutschen Fragebogen beantworten können.

Ausgeschlossen wurden Frauen, die in den letzten zwei Jahren an der unteren Extremität oder der Lendenwirbelsäule operiert worden waren, da dies den aktuellen Zustand und die Fähigkeit zur Durchführung des Krafttrainings beeinflussen könnte. Weiter wurden Frauen mit akuten Schmerzen im Rücken oder in den unteren Extremitäten ausgeschlossen. Frauen, die regelmäßig mehr als vier Stunden Sport pro Woche ausübten, durften nicht teilnehmen, um eine gewisse Homogenität der Gruppen in Bezug auf Muskelkraft und Trainingserfahrung zu gewährleisten. Schwangere Frauen und solche, die weniger als ein Jahr nach der Entbindung waren, wurden ausgeschlossen, weil mögliche Veränderungen im Hormonstatus die Wirkung des Krafttrainings beeinflussen können. Schließlich wurden Frauen mit bekannten erblichen

Erkrankungen des Bindegewebes, hauptsächlich Marfan-Syndrom und Ehlers-Danlos-Syndrom, mit Ausnahme des hypermobilen Typs, und Osteogenesis imperfecta, ausgeschlossen. Zu beachten ist, dass die Kriterien für diese Studie im Jahr 2012 definiert wurden und somit nicht auf der Nosologie 2017 für EDS und HSD basieren [7,9].

Rekrutierung und Einschluss

Für die Studie wurden freiwillige Probandinnen via eine bestehende Datenbank und über das Personal des Universitätsspitals Bern sowie Studierende der Berner Fachhochschule rekrutiert. Der Rekrutierungszeitraum lag zwischen August 2013 und November 2015, und die Rekrutierung sowie das Training und die Untersuchungen fanden am Universitätsspital Bern, Schweiz, statt. Nach dem Einverständnis wurden die Ein- und Ausschlusskriterien von einer Physiotherapeutin (CM) mit mehr als 12 Jahren klinischer Erfahrung geprüft. Der Beighton-Score wurde standardisiert erfasst, dazu die Beweglichkeit des rechten Knies, das Körpergewicht, die Körpergröße, die Armspanne sowie die Arm- und Beinlänge auf beiden Seiten gemessen. Schließlich erfolgte die anamnestische Überprüfung der Brighton-Criteria [8] durch ein halbstrukturiertes Interview durch dieselbe Physiotherapeutin. Basierend darauf wurden die Probandinnen in zwei Subgruppen eingeteilt, diejenigen mit erfüllten Brighton-Criteria und folglich JHS und diejenigen, welche nur die Kriterien für GJH erfüllten.

Intervention

Das durchgeführte Krafttraining an Geräten war mehrheitlich selbstgesteuert und dauerte 12 Wochen. Ziel des Trainings war eine Muskelhypertrophie und der Schwerpunkt lag auf der unteren Extremität und dem unteren Rumpf. Pro Woche wurden zwei Trainings von ca. 50 Minuten durchgeführt, was ein Total von 24 geplanten Trainings ergibt. Für das Training wurden Geräte von Technogym (Technogym SpA, Cesena, Italien) verwendet und das Programm umfasste folgende Übungen: Beinpresse, Knieextension und Knieflexion in offener Kette, Hüftabduktion, Fersenheben auf der Beinpresse, Rückenstreckung und Rumpfflexion. Vor dem Training fand ein 10-minütiges Aufwärmen auf dem Velo oder Crosstrainer statt.

Das Trainingsprogramm wurde auf Basis der Empfehlungen des American College of Sports Medicine [33] entwickelt. Alle Details zum Trainingsprogramm finden sich im elektronischen Anhang zu diesem Artikel. Generell wurde das Trainingsgewicht auf 80% des Maximums bei einer Wiederholung (1RM) festgelegt und es wurden drei Serien mit 12 Wiederholungen pro Seite durchgeführt. Vier erfahrene Physiotherapeutinnen mit Weiterbildung in Sport- und Trainingstherapie instruierten den Patientinnen das Trainingsprogramm. Zunächst wurden in einer einstündigen Sitzung die Übungen eingeführt und die Prinzipien zur Belastung und Anpassung erläutert. In der dritten und sechsten Woche fand je eine halbstündige Sitzung zur Kontrolle der Übungen und Anpassung des Trainingsgewichtes statt. Alle übrigen Trainingseinheiten wurden individuell durchgeführt und waren nicht betreut. Jedoch war stets eine Physiotherapeutin im Trainingszentrum anwesend für Fragen und zur Unterstützung. Die Teilnehmerinnen wurden ermutigt, die Gewichte schrittweise selber zu erhöhen, wenn mehr als 12 Wiederholungen möglich waren. Beim Auftreten von Schmerzen oder Beschwerden konnten sich die Frauen jederzeit an die anwesende Physiotherapeutin wenden. Während der Instruktionssitzungen wurden mögliche Anpassungen bei Schmerzen oder muskulären Problemen besprochen und vorgeschlagen, beispielsweise eine vorübergehende Reduktion des Widerstands, eine Erhöhung der Pause zwischen den Serien oder eine Reduktion der Serien.

Erfassung von Adhärenz, Belastung und Beschwerden

Ein Ziel dieser Studie war die Durchführbarkeit eines Krafttrainings für Frauen mit GJH zu prüfen. Bezüglich Adhärenz wurde erfasst wie viele Trainings von jeder Person absolviert wurden.

Zur Erfassung der Belastung durch das Training dienten primär das verwendete Gewicht und die Anzahl Wiederholungen pro Übung. Die Teilnehmerinnen hielten diese Angaben für alle Trainingseinheiten fest. Für die Analyse wurden die verwendeten Gewichte auf das jeweilige Körpergewicht bezogen. Zusätzlich wurde die Zunahme des Trainingsgewichts von der 1. zur 6. Woche und von der 1. zur 12. Woche in Prozent berechnet.

Schließlich wurde während der Trainingsperiode jeweils Ende Woche ein eigens entwickelter, kurzer Fragebogen zu auftretenden Schmerzen und Beeinträchtigungen ausgefüllt. Basierend auf früheren Studien [34,35] und klinischer Erfahrung wurden Schmerzen während oder nach dem Training erfragt mit der Möglichkeit die Schmerzlokalisation anzugeben. Weiter wurde erfragt ob im Alltag Schmerzen aufgetreten waren und falls ja, wo und warum. Schließlich konnten auch Einschränkungen bei Aktivitäten im Alltag und der allgemeine Gesundheitszustand angegeben werden. Bei allen Fragen erfolgte die quantitative Einschätzung durch die Probandinnen auf einer 5-Punkte-Likert Skala und zusätzlich konnten als Freitext Anmerkungen zur Art, Lokalisation und vermuteten Ursache der Beschwerden angefügt werden. Die Fragebogen wurden auf Papier ausgefüllt und in einer Box im Trainingsraum deponiert. Zur Analyse wurde die Anzahl Trainingswochen aufsummiert und jeweils die Anzahl Wochen ohne Beschwerden (= 1 auf der Skala), mit geringen Beschwerden (= 2 auf der Skala) und mit mäßigen bis starken Beschwerden (= 3 bis 5 auf der Skala) erfasst.

Erfassung der Effekte des Trainings

Zur Bestimmung der Effekte des Krafttrainings wurden Messungen der Muskelkraft und des Muskelquerschnittes am rechten Oberschenkel durchgeführt. Für die Flexoren und Extensoren des Knies wurde die isometrische Maximalkraft und die Schnellkraft in sitzender Position auf einem Messtisch mittels Kraftsensor gemessen. Nach einem kurzen Aufwärmen und bis zu drei Testmessungen wurden für jede Muskelgruppe drei Messungen durchgeführt und der jeweils höchste Wert ausgewählt. Die Maximalkraft und die Schnellkraft als Anstieg der Kraftkurve zwischen 20 % und 80 % des Maximums wurden berechnet und die Werte auf das

Körpergewicht normiert [21]. Mittels peripherer quantitativer Computertomographie (pQCT) wurden am Oberschenkel 20 cm oberhalb der Patellaspitze Querschnittsmessungen durchgeführt. Aus den Bildern wurde mittels der integrierten Analysesoftware nach Standardverfahren [36] der Gesamtquerschnitt des Oberschenkels und die Muskelquerschnittsfläche berechnet und auf das Körpergewicht normalisiert.

Alle Messungen wurden von einem Untersucher (GL) durchgeführt. Die erste Testung fand vor der Trainingsperiode statt und die zweite innerhalb von drei Wochen nach dem Training.

Statistische Auswertung

Es werden primär deskriptive Statistiken für die klinisch relevanten Parameter dargestellt. Für die primäre Analyse wurden alle eingeschlossenen Probandinnen als eine Gruppe betrachtet. Ergänzend wurden für die beiden Subgruppen GJH (Patientinnen ohne erfüllte Brighton-Criteria) und JHS (Patientinnen mit erfüllten Brighton-Criteria) die Daten separat analysiert und verglichen. Aufgrund der geringen Anzahl Probandinnen wurde für die Signifikanztestung der Unterschiede zwischen diesen Subgruppen der nicht-parametrische Mann-Whitney-U Test verwendet, mit einem Signifikanzniveau von $p \leq 0.05$. Die Anzahl Wochen mit oder ohne Beschwerden wurde zwischen den Subgruppen mittels Chi^2-Test auf Unterschiede getestet. Die Effekte des Trainings wurden als prozentuale Veränderung berechnet und inklusive 95% Konfidenzintervall dargestellt. Schließlich wurde die Anzahl Probandinnen mit einer prozentualen Zunahme der Kraft von mehr als 10% berechnet, was im unteren Bereich der erwartbaren Veränderung durch 12 Wochen Krafttraining liegt.

RESULTATE

Für die Originalstudie wurden 51 Frauen (26.5±4.5 Jahre) randomisiert. Alle 27 Frauen der Trainingsgruppe haben das Training durchgeführt und von den 24 der Kontrollgruppe haben fünf anschließend nicht trainiert. Gründe waren dreimal Zeitmangel, einmal psychische Probleme und einmal eine generelle Skepsis gegenüber dem Training an Geräten. Folglich haben 46 Frauen das Krafttraining absolviert. Davon haben 20 Frauen die Brighton-Criteria erfüllt und wurden als JHS klassifiziert. Die Basisdaten dieser Probandinnen sind in Tabelle 1 zusammengestellt und die Testung mittels Mann-Whitney-U ergab keine signifikanten Unterschiede zwischen denjenigen mit GJH und JHS.

Tabelle 1: Probandinnendaten als Mittelwert (Standardabweichung)

		Alle (n = 46)	**GJH** (n = 26)	**JHS** (n = 20)
Alter	Jahre	26.3 (4.3)	26.2 (4.1)	26.3 (4.8)
Größe	m	1.68 (0.06)	1.67 (0.06)	1.68 (0.05)
Gewicht	kg	61.9 (9.6)	61.6 (10.4)	62.3 (8.7)
Body Mass Index	kg/m^2	22.0 (2.8)	22.0 (2.9)	22.1 (2.7)
Beighton Score n/9 (%)	9/9 8/9 7/9 6/9	16 (34.8%) 16 (34.8%) 9 (19.6%) 5 (10.9%)	9 (34.6%) 10 (38.5%) 4 (15.4%) 3 (11.5%)	7 (35%) 6 (30%) 5 (25%) 2 (10%)
GJH = Generelle Hypermobilität, JHS = Hypermobilitätssyndrom				

Adhärenz

Sechs Frauen haben das Training zwar begonnen, jedoch vorzeitig abgebrochen. Die Gründe dafür waren zweimal Zeitmangel, einmal Unzufriedenheit mit der Organisation des Trainings und zweimal wurde kein Grund angegeben. Eine Teilnehmerin schließlich musste das Training nach 11 Sitzungen abbrechen wegen der Zunahme von vorbestehenden Rückenschmerzen. Bei dieser Probandin wurde danach eine lumbale Diskushernie mit Ausstrahlungen diagnostiziert und operativ behandelt. Weder die behandelnden Ärzte noch ein unabhängiger Arzt konnten einen direkten Zusammenhang des Trainings mit der Diskushernie bestätigen. Von den sechs Abbrecherinnen hatten fünf JHS und nur eine war in der Gruppe GJH.

Somit haben 40 Frauen das Training während 12 Wochen durchgeführt, davon hatten 25 GJH und 15 JHS. Von den 40 Frauen haben 10 alle 24 Trainings absolviert (25%), weitere 21 haben 20-23 Trainings absolviert (52.5%) und 9 Frauen haben weniger als 20 Trainings durchgeführt (22.5%). Gründe für die fehlenden Trainings waren primär Ferien und Zeitmangel. Für die weitere Analyse wurden nur die Daten dieser 40 Probandinnen verwendet.

Intensität

Das beim Training verwendete Gewicht der 40 Frauen mit mehreren Trainings auf der Beinpresse beidbeinig ist in Tabelle 2 ersichtlich, einerseits absolut in kg und andererseits prozentual zum Körpergewicht. Generell wurde mit tiefen Gewichten im Bereich von 15-30 kg gestartet, was einem Trainingsgewicht von durchschnittlich weniger als 50% des Körpergewichtes entspricht. Nach 6 Wochen lagen die verwendeten Gewichte im Bereich von 40-50 kg und damit zwischen 67% und 76% des Körpergewichtes. Am Ende des Trainings lag das mittlere Gewicht bei 52.5 kg und damit im Mittel immer noch deutlich unter 100%, also dem eigenen Körpergewicht. Die Steigerung bis zur 12. Woche belief sich auf etwas über 100%, mit leicht höheren Werten für diejenigen mit GJH und leicht tieferen für diejenigen mit JHS. Trotz der überall tendenziell leicht tieferen Werte der Probandinnen mit JHS gegenüber denjenigen mit

GJH zeigte die Testung mittels Mann-Whitney-U keine signifikanten Unterschiede. Die Werte für die weiteren Übungen sind nicht im Detail dargestellt, lagen jedoch im ähnlichen Rahmen.

Tabelle 2: Trainingsgewicht auf der Beinpresse im Laufe des Trainings absolut [kg] und prozentual [%] zum Körpergewicht, sowie prozentuale Steigerung des Trainingsgewichtes [jeweils Mittelwert (95% Konfidenzintervall)]

	Alle (n = 40)	**GJH** (n = 25)	**JHS** (n = 15)
Woche 1 [kg]	27.3 (23.9 bis 30.6)	28.0 (23.4 bis 32.6)	26.0 (21.2 bis 30.8)
Woche 6 [kg]	44.6 (40.5 bis 48.8)	46.0 (40.4 bis 51.6)	42.3 (36.3 bis 48.4)
Woche 12 [kg]	52.2 (47.5 bis 57.5)	54.8 (48.0 bis 61.6)	48.7 (41.9 bis 55.5)
Woche 1 [%]	44.3 (38.3 bis 50.3)	45.9 (38.1 bis 53.7)	41.7 (32.3 bis 51.5)
Woche 6 [%]	73.1 (65.0 bis 81.1)	76.2 (65.8 bis 86.7)	67.9 (55.3 bis 80.5)
Woche 12 [%]	85.7 (76.4 bis 94.9)	90.5 (78.5 bis 102.5)	77.7 (63.8 bis 91.7)
Steigerung W1-W6 [%]	73.7 (58.1 bis 89.4)	76.1 (53.1 bis 99.2)	69.7 (52.8 bis 86.5)
Steigerung W1-W12 [%]	106.9 (83.1 bis 130.6)	113.8 (77.5 bis 150.0)	95.3 (76.0 bis 114.7)
GJH = Generelle Hypermobilität, JHS = Hypermobilitätssyndrom			

Beschwerden

Von den 40 Trainierenden mit vollständigem Training haben fünf die wöchentlichen Fragebogen zu ihren Beschwerden nicht oder nur einmal ausgefüllt. Somit verblieben 35 auswertbare Reihen von Fragebogen, deren Auswertung in Tabelle 3 dargestellt ist. Generell wurden nur in rund 34% der Trainingswochen Beschwerden während dem Training angegeben und in 29% der Wochen nach dem Training, wobei meistens geringe Beschwerden angegeben wurden. Die Probandinnen mit JHS hatten signifikant häufiger Beschwerden während ($p>0.001$) und nach ($p=0.003$) dem Training, allerdings gaben 47% keine Beschwerden und knapp 45% nur geringe Beschwerden an, während nur 7.7% mäßige oder erhebliche Beschwerden angegeben haben. Insgesamt neun Trainierende haben mehr als fünf Mal Beschwerden während des Trainings angegeben, hauptsächlich an den Knien und am Rücken. Acht davon haben auch nach dem Training Beschwerden angegeben und zwei weitere haben nur nach dem Training Beschwerden verspürt, ebenfalls primär an den Knien und am Rücken.

Tabelle 3: Anzahl Trainingswochen mit keinen, geringen oder mäßig bis erheblichen Beschwerden oder Schmerzen während und nach dem Training (Prozent der Trainingswochen total)

	Alle (n = 403)	**GJH** (n = 249)	**JHS** (n = 154)
Keine während Training	265 (65.8)	192 (77.1)	73 (47.4)
Geringe während Training	111 (27.5)	42 (16.9)	69 (44.8)
Mäßige oder erhebliche während Training	27 (6.7)	15 (6.0)	12 (7.8)
Keine nach dem Training	285 (70.7)	190 (76.3)	95 (61.7)
Geringe nach dem Training	93 (23.1)	44 (17.7)	49 (31.8)
Mäßige oder erhebliche nach dem Training	25 (6.2)	15 (6.0)	10 (6.5)
GJH = Generelle Hypermobilität, JHS = Hypermobilitätssyndrom. Anzahl auswertbarer Probandinnen = 35, GJH = 22, JHS = 13			

Effekte

Die Effekte des Trainings auf die Muskelkraft und die Querschnitte am Oberschenkel sind in Tabelle 4 dargestellt. Die Effekte waren generell klein und mehrheitlich gehen die 95%-Konfidenzintervalle für den mittleren Effekt über die Nulllinie, so dass keine signifikanten und klinisch relevanten Veränderungen festgestellt werden konnten. Die Querschnittsflächen am Oberschenkel in der Gesamtgruppe wie bei den Frauen mit GJH zeigten eine positive Veränderung, jedoch nur im Bereich von 2% bis 2.5%.

Tabelle 4: Prozentuale Veränderung der Kraft der Knieflexoren und -extensoren und der Querschnitte am Oberschenkel durch das Krafttraining [jeweils Mittelwert (95% Konfidenzintervall)]

	Alle (n = 40)	**GJH (n = 25)**	**JHS (n = 15)**
Maximalkraft Extensoren	4.2 (-1.4 bis 9.7)	1.9 (-3.8 bis 7.7)	7.9 (-3.3 bis 19.1)
Schnellkraft Extensoren	5.7 (-4.9 bis 16.3)	1.9 (-10.6 bis 14.3)	13.2 (-6.7 bis 33.0)
Maximalkraft Flexoren	6.2 (-3.2 bis 15.6)	3.9 (-8.3 bis 16.1)	10.7 (-4.0 bis 25.3)
Schnellkraft Flexoren	-2.8 (-15.7 bis 10.1)	-12.3 (-28.7 bis 4.2)	14.1 (-4.0 bis 32.2)
Querschnitt Gesamt	0.8 (0.1 bis 1.6)	1.0 (-0.3 bis 2.0)	0.6 (-0.6 bis 1.7)
Querschnitt Muskel	2.0 (1.0 bis 3.0)	2.5 (1.4 bis 3.5)	1.2 (-0.9 bis 3.2)
GJH = Generelle Hypermobilität, JHS = Hypermobilitätssyndrom			

Wegen der breiten Konfidenzintervalle wurde zusätzliche geprüft wie viele Trainierende eine Veränderung von mehr als 10% erreichten. Für die Kraft der Extensoren war dies bei 10 Frauen (25%) der Fall, für die Flexoren bei 17 Frauen (42.5%) und bei der Muskelquerschnittsfläche am Oberschenkel bei 8 Frauen (20%).

DISKUSSION

Diese Studie untersuchte die Machbarkeit und den Effekt eines 12-wöchigen Krafttrainingsprogramms bei Frauen mit GJH und analysierte zusätzlich eine Subgruppe mit JHS. Generell war das Training gut machbar, es gab wenige Abbrecherinnen und geringe Beschwerden durch das Training. Die Effekte des Trainings in der Gesamtgruppe waren analog den Ergebnissen der randomisierten Studie[30] klein und entsprachen nicht den Erwartungen vor der Studie.

Die Machbarkeit eines Krafttrainingsprogramms über 12 Wochen erwies sich hingegen als sehr gut. Nur sechs von 46 Frauen beendeten das Training vorzeitig und mehr als 75% absolvierten über 20 der 24 vorgesehenen Trainingseinheiten. Fünf der sechs Abbrüche wurden mit organisatorischen Mängeln oder fehlender Zeit begründet. Nur eine Person musste das Programm aus medizinischen Gründen abbrechen, da bei ihr verstärkte Rückenschmerzen auftraten. Es konnte nicht geklärt werden, ob die Schmerzen einen Zusammenhang mit dem Trainingsprogramm hatten.

Ausgelöst durch das Training traten bei wenigen Frauen geringe Schmerzen auf, mehrheitlich betraf dies Knie und Rücken. Die Schmerzen klangen jeweils nach kurzer Zeit wieder ab und keine der Frauen gab dadurch Einschränkungen im Alltag an. Einzelne Probandinnen gaben mäßige oder gar erhebliche Schmerzen an, welche jedoch durch Anpassungen des Trainings bezüglich Intensität und Übungen reduziert werden konnten. Somit bewegen sich die Nebenwirkungen des Krafttrainings im Bereich der Erfahrungen gesunder Menschen im Sport oder in Fitnesscentern, wo ebenfalls gelegentlich und für kurze Zeit Beschwerden ausgelöst werden können [37]. Insgesamt erwies sich das Trainingsprogramm als gut durchführbar und gut verträglich für diese Patientinnen.

In einem gewissen Gegensatz zur guten Durchführbarkeit des Trainings steht die Art und Weise wie das Training umgesetzt wurde. Der hohen Adhärenz stehen tiefe Belastungswerte gegenüber. Nur wenige Trainierende haben das Gewicht auf der beidbeinigen Beinpresse über das eigene Körpergewicht gesteigert. Hier zeigte sich ein Schwachpunkt des selbstgesteuerten Trainings. Trotz dreimaliger Instruktion und dem Hinweis, das Trainingsgewicht zu erhöhen, wenn die 12 Wiederholungen problemlos durchgeführt werden können, wurde dies von den Probandinnen kaum umgesetzt. So haben 18 Frauen das Trainingsgewicht auf der Beinpresse zwischen Woche 6 und Woche 12 nicht mehr erhöht. Auf Nachfrage wurde als Begründung mehrfach die Angst vor zunehmenden Schmerzen bei höheren Gewichten angegeben. Insofern hängen die tiefen Werte der ausgelösten Beschwerden auch mit den niedrigen Gewichten während des Trainings zusammen. Eine engere Begleitung der Probandinnen mit dem Ziel sie zu höherer Ausbelastung zu motivieren wäre hier sinnvoll. Durch ein vollständig überwachtes und individuell begleitetes Training wäre eine gezieltere Steuerung des Trainings möglich.

Ein weiterer Schwachpunkt des Trainingsprogramms war die fehlende Individualisierung. Das Programm war standardisiert und beinhaltetet neben dem Gerätetraining keine weiteren Elemente wie Gleichgewichtstraining oder Übungen für die motorische Kontrolle. Das standardisierte Training hat den Vorteil, dass mögliche Effekte klar zugeordnet werden können; der Nachteil ist, dass es kaum dem physiotherapeutischen Alltag entspricht, wo Patientinnen selten direkt in ein selbstgesteuertes Krafttraining eingegliedert werden. In den meisten Fällen würde davor eine individuelle Vorbereitung stattfinden, was leider im Rahmen dieser Studie nicht möglich war.

Entgegen den Erwartungen zeigten sich durch das Krafttraining keine eindeutigen Veränderungen der Muskelkraft und der Querschnittsfläche, weder im randomisierten Vergleich der Trainings- und Kontrollgruppe [30] noch im hier präsentierten pre-post- Vergleich mit einer größeren Anzahl Probandinnen. Dies steht im Gegensatz zu verschiedenen anderen Trainingsstudien. Beispielsweise erzielten Patienten mit Kniearthrose, die ein Widerstandstraining für die Kniemuskulatur durchführten Kraftverbesserungen von 15-34% [38]. Für ein Krafttraining junger gesunder Frauen wurden nach einem 12-wöchigen Programm Kraftsteigerungen von 20-32% [39] nachgewiesen. Solche Werte wurden in unserer Studie nicht annähernd erreicht, im Mittel zeigte sich kein signifikanter Effekt und bei der Analyse der einzelnen Personen erreichten nur etwa ein Viertel der Teilnehmerinnen Verbesserungen von mehr als 10%.

Neben den bereits angeführten niedrigen Trainingsgewichten haben möglicherweise auch andere Faktoren zum fehlenden Nachweis eines Effekts beigetragen. Ein mögliches Problem betrifft die Messung der Kraft, welche isometrisch durchgeführt wurde, obwohl das Training dynamisch war. Somit könnte ein allfälliger dynamischer Kraftzuwachs nicht auf die statische Messsituation übertragen worden sein. Weiter könnte das Trainingsvolumen mit zwei Trainings pro Woche zu gering sein, um eine Verbesserung der Kraft zu erreichen. Schließlich zeigten die individuellen Veränderungen durch das Training eine große Variation, was auf die hohe Heterogenität der Studiengruppe zurückzuführen sein könnte. Die Gruppe umfasste sowohl Frauen mit wenig Beschwerden im Alltag wie auch solche mit deutlichen Einschränkungen.

Auch im Vergleich mit Trainingsstudien bei Personen mit Hypermobilität ist der geringe Effekt in dieser Studie auffällig. Mindestens drei neuere Studien zeigten, dass ein Training auch bei diesen Personen einen Effekt haben kann. In einer englischen Studie [16] wurde die Kraftentwicklung beim Quadriceps über 16 Wochen bei Personen mit GJH, mit JHS und mit einer Kontrollgruppe verglichen. In allen drei Gruppen war ein ähnlicher Kraftzuwachs im Bereich einer ungefähren Verdoppelung feststellbar, wobei diejenigen mit JHS ein deutlich tieferes Ausgangsniveau zeigten als die Kontrollgruppe und diejenigen mit GJH höhere Ausgangswerte aufwiesen. Bemerkenswert ist, dass dieser Zuwachs durch ein Übungsprogramm erreicht wurde, das hauptsächlich zu Hause mit dem eigenen Körpergewicht durchgeführt wurde, wobei die Anpassung und Anleitung alle zwei Wochen durch eine Physiotherapeutin erfolgte. In einer dänischen Machbarkeitsstudie [40] zur Schulterkräftigung zeigte sich, dass Teilnehmerinnen mit HSD (basierend auf dem Beighton-Score und einer Vorgeschichte von Schulterschmerzen) ein 16-wöchiges Krafttrainingsprogramm durchführen konnten und etwa 30% an Schulterkraft gewannen. In dieser Studie wurde das Training zweimal wöchentlich unter Aufsicht eines Physiotherapeuten und einmal wöchentlich selbstgesteuert durchgeführt. Schließlich untersuchte eine türkische Studie [41] den Effekt eines 8-wöchigen Programms zur Stabilisierung der Wirbelsäule, das dreimal wöchentlich in Gruppen unter Anleitung eines Physiotherapeuten durchgeführt wurde. Sie fanden Verbesserungen der Rumpfmuskelausdauer von ca. 50%, allerdings weist diese Studie einige methodische Einschränkungen auf, wie eine hohe Drop-out-Rate und eine fehlende Verblindung der Untersucher. Zu beachten ist, dass alle diese Studien nach der vorliegenden Studie veröffentlicht wurden und somit die Ergebnisse nicht in die Planung des Projektes einfließen konnten.

Zusammenfassend scheint der fehlende Effekt des Trainings in dieser Studie nicht an der Hypermobilität der Teilnehmenden zu liegen. Es scheint dafür mehrere wesentlichen Faktoren zu geben: a) die zu geringe Belastung während des Trainings, b) die Unzulänglichkeiten der verwendeten Assessments, c) die fehlende intensive Begleitung während des Trainings, und d) die Heterogenität der eingeschlossenen Versuchspersonen.

Die vorliegende Studie weist mehrere Schwachpunkte auf, welche möglicherweise zu den unklaren Ergebnissen beigetragen haben. Zunächst handelt es sich um eine pre-post Studie ohne Kontrollgruppe, so dass kein Vergleich möglich ist. Allerdings zeigte der entsprechende Vergleich im RCT ebenfalls keine klaren Ergebnisse. Weiter wurde die Studie von Anfang an als Machbarkeits- und Effektivitätsstudie geplant, was im Nachhinein wohl besser als zwei separate Projekte gemacht worden wäre. Schließlich wies der selbst entwickelte Fragebogen zu den Beschwerden Schwachpunkte bezüglich der Auswertbarkeit auf und es wäre sinnvoll gewesen zusätzlich Befragungen der Probandinnen zur Machbarkeit und Verträglichkeit ins Projekt zu integrieren.

Für die weitere Forschung scheint eine möglichst klare Definition der Studiengruppen zwingend. Zum einen könnten mehrheitlich asymptomatische Personen mit GJH untersucht werden, um die präventiven Möglichkeiten von Krafttraining klarer zu erfassen. Zum anderen sollten für klinische Studien klar definierte Personen mit HSD und/oder hypermobilem EDS untersucht werden, wobei genügend große Gruppen und eine gute Erfassung der Beschwerden und Symptome wesentlich sind. Bezüglich Interventionen scheinen enger begleitete und individuelle Programme mehr Erfolg zu versprechen. Dabei könnten auch propriozeptive Übungen oder funktionelles Training mit Fokus auf der motorischen Kontrolle integriert werden. Nicht zuletzt gilt es sinnvolle Assessments zu definieren, um nicht nur Kraft und Muskelmasse zu erfassen, sondern auch Schmerzen, weitere Beschwerden und Einschränkungen im Alltag.

[Literatur siehe am Ende der englischen Version ab Seite 88 / For references see at the end of the English version, page 88]

Zustimmung zur Veröffentlichung: Nicht zutreffend.

Verfügbarkeit von Daten und Materialien: Die in dieser Studie generierten und/oder analysierten Daten sind auf begründete Anfrage beim korrespondierenden Autor erhältlich.

Finanzielle Unterstützung: Diese Studie wurde finanziell nicht unterstützt.

Beiträge von Autor*innen: Konzeption der Arbeit: GL, CM, BHB, MV, DA. Erhebung, Analyse und Interpretation der Daten: GL, BHB, CM, DA. Entwurf des Manuskripts: GL, MV. Kritische Überarbeitung des Manuskripts hinsichtlich wichtiger geistiger Inhalte: GL, CM, MV, DA, JPB. Alle Autor*innen erklären, dass sie für alle Aspekte der Arbeit verantwortlich sind und gewährleisten, dass Fragen im Zusammenhang mit der Richtigkeit oder Integrität eines jeden Teils der Arbeit angemessen untersucht und gelöst wurden.

Interessenkonflikt: Die Autorinnen/Autoren geben an, dass kein Interessenkonflikt besteht.

6.b Resistance Training in Women with Generalized Joint Hypermobility: Feasibility, Symptoms and Effects – A Pre-post Study [English translation of the German publication]

Physioscience 2023;19:86-94 [Publication in German with English abstract]

Gere Luder, Christine Mueller Mebes, Bettina Haupt-Bertschy, Martin L. Verra, Daniel Aeberli, Jean-Pierre Baeyens,

Resistance Training in Women with Generalised Hypermobility: Feasibility, Symptoms, and Effects – A Pre-post Study

ABSTRACT

Background: Generalised hypermobility is when the mobility in several joints exceeds the usual level. Up to 30% of women and 10% of men are affected. Hypermobility is not a pathology, but when it is accompanied by pain and other symptoms, it can affect health and daily function. There are few studies on physiotherapy treatment, although strength training could be a possible intervention.

Aim: To assess the feasibility and effect of strength training for women with generalised hypermobility.

Methods: In a pre-post study, hypermobile women (Beighton-Score>5) aged 20-40 years underwent 12 weeks of strength training on machines focused on legs and back. A training protocol and weekly questionnaires were used to analyse the training and the resulting symptoms. The strength of the knee flexors and extensors and the muscle cross-section of the thigh were measured before and after the training.

Results: 46 women (26.3±4.3 years) completed the training. Six of them dropped out prematurely, one of them because of back pain due to lumbar disc hernia. 72.5% of the remaining 40 women completed 20 or more training sessions. Only in 34% of the training weeks mostly minor complaints were reported, mainly in the knees and back. The weights used were often low, i.e., on the leg press they started with an average of 44.8% of body weight and after 12 weeks the average weight was 52.2 kg, which corresponds to 85.7% of body weight. Neither strength nor cross-sectional area showed significant improvements, however up to 17 women (42.5%) achieved improvements of more than 10%.

Conclusion: Strength training was feasible and well tolerated by most women. The mostly self-directed training was not intensive enough to achieve clear effects on strength or muscle mass, even if some participants have clearly benefited. More individualised and closely supervised programmes should be investigated in future studies.

Keywords: hypermobility syndrome, maximum strength, rate of force development, muscle cross-section, physiotherapy

INTRODUCTION

Generalised Joint Hypermobility (GJH) is when the range of motion in several joints exceeds the normal range. It is usually diagnosed with the Beighton score, which checks for excessive mobility in the thumb and little finger, elbows, knees and trunk forward bend [1]. Depending on the definition and population, the prevalence of GJH ranges from 10% to 35%, with women being affected significantly more often than men [2,3]. Thus by Scheper and colleagues [4] at a cut-off of 4/9 points, 31.9% of women and 9.7% of men in a large group of students were found to be hypermobile. At a cut-off of 6/9 points, 13.9% of women and 1.5% of men still were hypermobile. In general, mobility decreases with age, which is illustrated by lower cut-offs in older persons [3].

Generalised hypermobility is not yet a clinical diagnosis. Numerous people with GJH show hardly any symptoms and for some sports or in dance it can even be an advantage to have marked mobility [5,6]. However, generally increased joint mobility can lead to clinical symptoms and be linked to other syndromes. These include, on the one hand, musculoskeletal complaints such as sprains, subluxations or muscle pain, and, on the other hand, signs of systemic involvement of the skin, vessels or various organs [7]. For a long time, hypermobile persons with such symptoms were diagnosed according to the Brighton criteria [8] with Joint Hypermobility Syndrome (JHS). After much debate as to whether JHS and the hypermobile type of Ehlers-Danlos syndrome (EDS) are the same entity, a new nosology for EDS was developed in 2017 [9]. As part of this process, the definition and classification for the spectrum of disorders associated with GJH was also revised. The term JHS was discarded, and Hypermobility Spectrum Disorder (HSD) was introduced as a new diagnosis; which is assigned to individuals who have GJH and various symptoms but do not meet the formal criteria for hypermobile Ehlers-Danlos syndrome (hEDS) [7].

Regardless of the exact diagnosis, GJH can lead to problems with activities of daily living and is sometimes associated with various impairments. Scheper et al. [10] found 2016 in a meta-analysis that people with GJH experience pain, fatigue and disability more often than controls. Two other reviews have shown that people with GJH have a higher prevalence and incidence of lower limb injuries [11,12]. A Danish study observed that people with GJH were more likely to have knee or shoulder pain and were up to four times more likely to avoid some activities due to symptoms [13,14]. In terms of prevention, it may be crucial for people with GJH to actively exercise in order to be able to perform daily and work-related activities without limitations in the long term. It is also important to prevent joint and muscle pain, loss of function and disability, as well as possible long-term consequences due to GJH.

Regarding possible interventions, only a few studies have been conducted so far. For people with GJH, a study without a control group has demonstrated positive effects for physiotherapy of the TMJ [15] and a British study has shown that people with GJH and anterior knee pain can build up strength in a similar way to control subjects [16]. Some other studies found positive effects in people with JHS through complex interventions involving exercises, counselling, and manual therapy or through guided home programmes. In summary, a recent review of eight studies found that there was little to no evidence for the effectiveness of various conservative interventions [17]. Therefore, therapeutic management of people with GJH and JHS continues to be based primarily on experience and expert opinion [18].

Comparing people with GJH and those with normal joint mobility reveals several differences. For example, in a study of 328 adults, those with GJH had less strength in the knee, hip, shoulder and forearm and they performed less physical activity [4]. An earlier study of our group with 195 participants showed differences in neuromuscular control during walking [19] and stair climbing [20] as well as in strength, balance and passive anterior translation of the tibia [21,22]. People with GJH thus have neuromuscular and musculoskeletal abnormalities, particularly strength deficits, which may make them more susceptible to developing symptoms. It is therefore important to investigate whether such deficits can be improved through training.

In physiotherapy, resistance training has long been supported by studies as an intervention to improve strength and muscle mass, as well as to gain function and reduce impairment [23]. Regular exercise is also widely recommended for healthy individuals and resistance training is considered an important element in the prevention of disease and injury [24]. Depending on the type of training, intensity and duration, improvements in strength of between 15% and 30% can be achieved, with the majority of women achieving higher relative changes than men [23,25]. Resistance training has been shown to have positive effects for various groups, such as older people [26], for back pain [27], knee osteoarthritis [28] as well as fibromyalgia [29]. In contrast, there are hardly any studies with younger people, especially with younger women and specifically with people with GJH or JHS.

For these reasons, a resistance training programme for women with GJH was implemented and evaluated in a two-part project. The progressive training programme on equipment focused on improving strength and muscle mass of the legs and trunk. The first part, in the form of a randomised trial, focused on the effectiveness of the training [30]. In the second part presented here, the primary aim was to investigate the feasibility of the training and possible negative effects. In addition, the immediate effect of the 12-week training programme on strength and muscle cross-section was also analysed here.

METHODOLOGY

This study is a comparison of women with GJH before and after 12 weeks of resistance training for legs and back on weight machines (pre-post). It is an additional analysis following a published randomised trial with intervention and control group [30]. The women in the former control group without intervention were also offered the resistance training programme of the intervention group after the study. Subsequently, the data of all these test persons were evaluated and compared before and after the training. The primary study was prospectively registered as ISRCTN90224545 (www.isrctn.com, BMC, Springer Nature) and permission to conduct it was granted by the Ethics Committee of the Canton of Bern, Switzerland (No. 222/12).

All participants gave written informed consent, and the study was conducted in accordance with the Declaration of Helsinki. The reporting in this article is based on the "Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group" [31]. Resistance training as an intervention is reported according to the guidelines of the TIDieR checklist for interventions [32].

Participants

The study recruited women in the age between 20 and 40 years who had at least a Beighton score of 6/9 points, and hyperextension of the right knee was mandatory. This was necessary because the training was related to the lower limb and the measurements in the study were taken on the right leg. Furthermore, the participants had to have a body mass index (BMI) between 18-30 kg/m^2 and be able to answer the German questionnaires.

Women who had undergone lower limb or lumbar spine surgery in the last two years were excluded as this could affect the current condition and ability to perform resistance training. Further, women with acute pain in the back or lower extremities were excluded. Women who regularly exercised more than four hours per week were not allowed to participate to ensure some homogeneity of the groups in terms of muscle strength and training experience. Pregnant women and those who were less than one year postpartum were excluded because possible changes in hormone status may influence the effect of resistance training. Finally, women with known hereditary connective tissue disorders, mainly Marfan syndrome and Ehlers-Danlos syndrome, except for the hypermobile type, and osteogenesis imperfecta, were excluded. It should be noted that the criteria for this study were defined in 2012 and thus were not based on the 2017 nosology for EDS and HSD [7,9].

Recruitment and inclusion

For the study, female volunteers were recruited via an existing database and via the staff of the University Hospital of Bern as well as students at the Bern University of Applied Sciences. The recruitment period was between August 2013 and November 2015, and the recruitment, training and examinations took place at the University Hospital of Bern, Switzerland. After informed consent, inclusion and exclusion criteria were reviewed by a physiotherapist (CM) with more than 12 years of clinical experience. The Beighton score was recorded in a standardised manner, and the mobility of the right knee, body weight, body height, arm span, and arm and leg length were measured on both sides. Finally, the Brighton criteria [8] were checked through a semi-structured interview by the same physiotherapist. Based on this, the subjects were divided into two subgroups, those with fulfilled Brighton criteria and consequently JHS and those who only fulfilled the criteria for GJH.

Intervention

The resistance training performed on weight machines was mostly self-directed and lasted 12 weeks. The goal of the training was muscle hypertrophy, and the focus was on the lower extremities and the lower trunk. The workouts of approximately 50 minutes were performed twice per week, resulting in a total of 24 planned workouts. Technogym equipment (Technogym SpA, Cesena, Italy) was used for the training and the programme included the following exercises: Leg press, knee extension and knee flexion in open chain, hip abduction, heel lift on leg press, back extension and trunk flexion. The training was preceded by a 10-minute warm-up on the ergobike or cross trainer.

The training programme was developed based on the recommendations of the American College of Sports Medicine [33]. Full details of the training programme can be found in the electronic appendix to this article. In general, the training weight was set at 80% of the maximum for one repetition (1RM) and three series of 12 repetitions per side were performed. Four experienced physiotherapists with advanced training in sports and exercise therapy instructed the patients in the training programme. First, the exercises were introduced in a one-hour session and the principles of loading and adaptation were explained. In the third and sixth week, there was a half-hour session each to check the exercises and adjust the training weight. All other training sessions were conducted individually and were not supervised. However, a physiotherapist was always present at the training centre for questions and support. The participants were encouraged to gradually increase the weights themselves when more than 12 repetitions were possible. If any pain or discomfort occurred, the women could contact the physiotherapist present at any time. During the instruction sessions, possible adjustments in case of pain or muscular problems were discussed and suggested, for example, a temporary reduction of the resistance, an increase of the pause between the series or a reduction of the series.

Recording of adherence, strain, and complaints

One aim of this study was to assess the feasibility of resistance training for women with GJH. In terms of adherence, the number of workouts completed by each person was recorded.

The weight used and the number of repetitions per exercise were the primary means of recording the load of the training. The participants recorded this information for all training sessions. For the analysis, the weights used were related to the respective body weight. In addition, the increase in training weight from week 1 to week 6 and from week 1 to week 12 was calculated as a percentage.

Finally, a specially developed, short questionnaire on pain and impairment was completed at the end of each week during the training period. Based on previous studies [34,35] and clinical experience, the questionnaire asked about pain during or after training, with the option to indicate the location of the pain. The questionnaire also asked whether pain had occurred in everyday life and, if so, where, and why. Finally, limitations in activities of daily living and the general state of health could be indicated. For all questions, the respondents were asked to give a quantitative assessment on a 5-point Likert scale and could also add free text comments on the type, location, and suspected cause of the complaints. The questionnaires were filled out on paper and deposited in a box in the training room. For analysis, the number of training weeks was added up and the number of weeks without complaints (= 1 on the scale), with minor complaints (= 2 on the scale) and with moderate to severe complaints (= 3 to 5 on the scale) was recorded.

Recording the effects of the training

To determine the effects of the resistance training, measurements of muscle strength and muscle cross-section were taken on the right thigh. For the flexors and extensors of the knee, the isometric maximum force and rate of force development were measured in a seated position on a measuring table using a force sensor. After a short warm-up and up to three test contractions, three measurements were taken for each muscle group and the highest value was selected. The maximum force as well as the rate of force development as the increase in the force curve between 20% and 80% of the maximum were calculated and the values were normalised to the body weight [21]. Peripheral quantitative computed tomography (pQCT) was used to perform cross-sectional measurements on the thigh 20 cm above the tip of the patella. The images were analysed using the integrated analysis software according to standard procedures [36]; the total cross-section of the thigh and the muscle cross-sectional area were calculated and normalised to the body weight.

All measurements were taken by one investigator (GL). The first test took place before the training period and the second within three weeks after training.

Statistical evaluation

Primarily descriptive statistics for the clinically relevant parameters are presented. For the primary analysis, all included subjects were considered as one group. In addition, the data for the two subgroups GJH (patients without fulfilled Brighton criteria) and JHS (patients with fulfilled Brighton criteria) were analysed and compared separately. Due to the small number of subjects, the non-parametric Mann-Whitney-U test was used for significance testing of the differences between these subgroups, with a significance level of $p \leq 0.05$. The number of weeks with or without complaints was tested for differences between the subgroups using the Chi^2 test. The effects of training were calculated as percentage change and presented including 95% confidence interval. Finally, the number of subjects with a percentage increase in strength of more than 10% was calculated, which is in the lower range of the expected change through 12 weeks of resistance training.

RESULTS

For the original study, 51 women (26.5±4.5 years) were randomised. All 27 women in the training group did the training and of the 24 in the control group, five did not train afterwards. The reasons were three times lack of time, once psychological problems and once a general scepticism towards training on weight machines. Consequently, 46 women completed the resistance training. Of these, 20 women met the Brighton Criteria and were classified as JHS. The baseline data for all subjects are summarised in Table 1 and testing using Mann-Whitney-U revealed no significant differences between those with GJH and JHS.

Table 1: Participant data as mean (standard deviation)

		All (n = 46)	**GJH** (n = 26)	**JHS** (n = 20)
Age	Years	26.3 (4.3)	26.2 (4.1)	26.3 (4.8)
Height	m	1.68 (0.06)	1.67 (0.06)	1.68 (0.05)
Weight	kg	61.9 (9.6)	61.6 (10.4)	62.3 (8.7)
Body Mass Index	kg/m^2	22.0 (2.8)	22.0 (2.9)	22.1 (2.7)
Beighton Score n/9 (%)	9/9	16 (34.8%)	9 (34.6%)	7 (35%)
	8/9	16 (34.8%)	10 (38.5%)	6 (30%)
	7/9	9 (19.6%)	4 (15.4%)	5 (25%)
	6/9	5 (10.9%)	3 (11.5%)	2 (10%)
GJH = Generalized Joint Hypermobility, JHS = Joint Hypermobility Syndrome				

Adherence

Six women started the training but dropped out prematurely. The reasons were twice lack of time, once dissatisfaction with the organisation of the training and twice no reason was given. Finally, one participant had to stop the training after 11 sessions because of an increase in pre-existing back pain. This participant was subsequently diagnosed with a lumbar disc hernia with radiation and was treated surgically. Neither the treating physicians nor an independent physician could confirm a direct connection between the training and the disc hernia. Of the six dropouts, five had JHS and only one was in the GJH group.

Thus, 40 women completed the training for 12 weeks, of which 25 had GJH and 15 JHS. Of the 40 women, 10 completed all 24 trainings (25%), another 21 completed 20-23 trainings (52.5%) and 9 women completed less than 20 trainings (22.5%). Reasons for missing trainings were primarily holidays and lack of time. For the further analysis, only the data of these 40 test persons were used.

Intensity

The weight used in the training of the 40 women with several training sessions on the double-legged leg press is shown in Table 2, on the one hand in absolute kg and on the other hand as a percentage of body weight. In general, the training started with low weights in the range of 15-30 kg, which corresponds to an average training weight of less than 50% of the body weight. After 6 weeks, the weights used were in the range of 40-50 kg and thus between 67% and 76% of body weight. At the end of the training, the average weight was 52.5 kg and thus still well below 100%, i.e., one's own body weight. The increase up to week 12 was slightly over 100%, with slightly higher values for those with GJH and slightly lower values for those with JHS. Despite the slightly lower values of the subjects with JHS compared to those with GJH, the Mann-Whitney-U test showed no significant differences. The values for the other exercises are not shown in detail but were within a similar range.

Table 2: Training weight on the leg press in the course of training in absolute terms [kg] and as a percentage [%] of body weight, as well as percentage increase in training weight [mean value (95% confidence interval)].

	All (n = 40)	**GJH** (n = 25)	**JHS** (n = 15)
Week 1 [kg]	27.3 (23.9 to 30.6)	28.0 (23.4 to 32.6)	26.0 (21.2 to 30.8)
Week 6 [kg]	44.6 (40.5 to 48.8)	46.0 (40.4 to 51.6)	42.3 (36.3 to 48.4)
Week 12 [kg]	52.2 (47.5 to 57.5)	54.8 (48.0 to 61.6)	48.7 (41.9 to 55.5)
Week 1 [%]	44.3 (38.3 to 50.3)	45.9 (38.1 to 53.7)	41.7 (32.3 to 51.5)
Week 6 [%]	73.1 (65.0 to 81.1)	76.2 (65.8 to 86.7)	67.9 (55.3 to 80.5)
Week 12 [%]	85.7 (76.4 to 94.9)	90.5 (78.5 to 102.5)	77.7 (63.8 to 91.7)
Increase W1-W6 [%]	73.7 (58.1 to 89.4)	76.1 (53.1 to 99.2)	69.7 (52.8 to 86.5)
Increase W1-W12 [%]	106.9 (83.1 to 130.6)	113.8 (77.5 to 150.0)	95.3 (76.0 to 114.7)
GJH = Generalized Joint Hypermobility, JHS = Joint Hypermobility Syndrome			

Complaints

Of the 40 trainees with complete training, five did not fill in the weekly questionnaires on their complaints or only once. This left 35 evaluable series of questionnaires, the evaluation of which is shown in table 3. In general, complaints during training were only reported in about 34% of the weeks and in 29% of the weeks after training, with mostly minor complaints being reported. The subjects with JHS were significantly more likely to have complaints during ($p>0.001$) and after ($p=0.003$) training, but 47% reported no complaints and almost 45% only minor complaints, while no more than 7.7% reported moderate or significant complaints. A total of nine participants reported discomfort more than five times during exercise, mainly in the knees and back. Eight of them also reported discomfort after training and two others only experienced discomfort after training, also primarily in the knees and back.

Table 3: Number of training weeks with no, little or moderate to considerable discomfort or pain during and after training (percentage of total training weeks)

	All (n = 403)	**GJH** (n = 249)	**JHS** (n = 154)
None during training	265 (65.8)	192 (77.1)	73 (47.4)
Low during training	111 (27.5)	42 (16.9)	69 (44.8)
Moderate or significant during training	27 (6.7)	15 (6.0)	12 (7.8)
None after training	285 (70.7)	190 (76.3)	95 (61.7)
Low after training	93 (23.1)	44 (17.7)	49 (31.8)
Moderate or significant after exercise	25 (6.2)	15 (6.0)	10 (6.5)

GJH = Generalized Joint Hypermobility, JHS = Joint Hypermobility Syndrome.
Number of evaluable women = 35, GJH = 22, JHS = 13

Effects

The effects of training on muscle strength and thigh cross-sectional area are shown in table 4. The effects were generally small and the majority of the 95% confidence intervals for the mean effect cross the zero line, so that no significant and clinically relevant changes could be detected. The cross-sectional areas of the thigh in the total group as well as in the women with GJH showed a positive change, but only in the range of 2% to 2.5%.

Table 4: Percentage change in the strength of the knee flexors and extensors and the cross-sectional area of the thigh because of resistance training [mean (95% confidence interval)].

	All (n = 40)	**GJH (n = 25)**	**JHS (n = 15)**
Maximum strength extensors	4.2 (-1.4 to 9.7)	1.9 (-3.8 to 7.7)	7.9 (-3.3 to 19.1)
Rate of force development extensors	5.7 (-4.9 to 16.3)	1.9 (-10.6 to 14.3)	13.2 (-6.7 to 33.0)
Maximum strength flexors	6.2 (-3.2 to 15.6)	3.9 (-8.3 to 16.1)	10.7 (-4.0 to 25.3)
Rate of force development flexors	-2.8 (-15.7 to 10.1)	-12.3 (-28.7 to 4.2)	14.1 (-4.0 to 32.2)
Total cross section	0.8 (0.1 to 1.6)	1.0 (-0.3 to 2.0)	0.6 (-0.6 to 1.7)
Cross section muscle	2.0 (1.0 to 3.0)	2.5 (1.4 to 3.5)	1.2 (-0.9 to 3.2)

GJH = Generalized Joint Hypermobility, JHS = Joint Hypermobility Syndrome

Because of the wide confidence intervals, an additional check was made to see how many participants achieved a change of more than 10%. For extensor strength this was the case for 10 women (25%), for flexors for 17 women (42.5%) and for thigh muscle cross-sectional area for 8 women (20%).

DISCUSSION

This study investigated the feasibility and effect of a 12-week resistance training programme in women with GJH and analysed a subgroup with JHS. In general, the training was feasible, there were few dropouts and little discomfort from the training. The effects of the training in the whole group were analogous to the results of the randomised trial [30] and did not correspond to the expectations before the study.

The feasibility of a resistance training programme over 12 weeks, on the other hand, proved to be very good. Only six out of 46 women terminated the training prematurely and more than 75% completed more than 20 of the 24 scheduled training sessions. Five of the six discontinuations were due to organisational deficiencies or lack of time. Only one person had to discontinue the programme for medical reasons due to increased back pain. It could not be clarified whether the pain was related to the training programme.

A few women experienced minor pain because of the training, mostly in the knees and back. The pain lessened after a short time and none of the women reported restrictions in their daily lives. A few women reported moderate or even severe pain, but this could be reduced by adjusting the training intensity and exercises. Thus, the side effects of resistance training are within the range of experiences of healthy people in sports or in fitness centres, where complaints can also be triggered occasionally and for a short time [37]. Overall, the training programme proved to be easy to carry out and well tolerated by these patients.

In some contrast to the good feasibility of the training is the way the training was implemented. The high adherence contrasts with low load values. Only a few trainees increased the weight on the double-legged leg press above their own body weight. This was a weak point of the self-directed training. Despite three instructions and the advice to increase the training weight if the 12 repetitions can be performed without problems, this was hardly implemented by the test persons. Thus, 18 women did not increase the training weight on the leg press between week 6 and week 12. When asked, the reason given several times was the fear of increasing pain with higher weights. In this respect, the low values of the triggered complaints are also related to the low weights during the training. Closer monitoring of the test persons with the aim of motivating them to work harder would make sense here. A more targeted control of the training would be possible through a fully monitored and individually accompanied training.

Another weak point of the training programme was the lack of individualisation. The programme was standardised and did not include other elements such as balance training or exercises for motor control. Standardised training has the advantage that possible effects can be clearly assigned; the disadvantage is that it hardly corresponds to usual physiotherapy, where patients are rarely directly integrated into self-directed resistance training. In most cases, individual preparation would take place beforehand, which unfortunately was not possible in the context of this study.

Contrary to expectations, resistance training did not show any clear changes in muscle strength and cross-sectional area, neither in the randomised comparison of the training and control group [30] nor in the pre-post comparison with a larger number of female subjects presented here. This contrasts with several other training studies. For example, patients with knee osteoarthritis who performed resistance training for the knee muscles achieved strength improvements of 15-34% [38]. For resistance training of young healthy women strength increases of 20-32% were reported after a 12-week programme [39]. Such values were not nearly achieved in our study, on average there was no significant effect and when analysing the individuals only about a quarter of the participants achieved improvements of more than 10%.

Besides the low training weights already mentioned, other factors may have contributed to the lack of evidence of an effect. One possible problem concerns the measurement of strength, which was carried out isometrically although the training was dynamic. Thus, any dynamic increase in strength might not have been transferred to the static measurement situation. Furthermore, the training volume of two training sessions per week could be too low to achieve an improvement in strength. Finally, the individual changes through training showed a large variation, which could be due to the high heterogeneity of the study group. The group included women with few complaints in everyday life as well as those with significant limitations.

The small effect in this study is also striking when compared with training studies in people with hypermobility. At least three recent studies showed that training can also have an effect in these individuals. An English study [16] compared quadriceps strength development over 16 weeks in people with GJH, with JHS and with a control group. All three groups showed a similar increase in strength in the range of approximately doubling, with those with JHS showing a significantly lower baseline level than the control group and those with GJH showing higher baseline values. It is noteworthy that this gain was achieved through an exercise programme performed mainly at home with the patient's own body weight, with adaptation and instruction every fortnight by a physiotherapist. In a Danish feasibility study [40] on shoulder strengthening, it was shown that participants with HSD (based on the Beighton score and a history of shoulder pain) could undertake a 16-week strength training programme and gain approximately 30% in shoulder strength. In this study, training was supervised by a physiotherapist twice a week and self-directed once a week. Finally, a Turkish study [41] investigated the effect of an 8-week spinal stabilisation programme done three times a week in groups under the supervision of a physiotherapist. They found improvements in trunk muscle endurance of about 50%, but this study has some methodological limitations, such as a high dropout rate and a lack of blinding of the investigators. It should be noted that all these studies were published after the present study and thus the results could not be included in the planning of the project.

In summary, the lack of effect of the training in this study does not seem to be due to the hypermobility of the participants. There seem to be several major factors for this: a) the too low load during the training, b) the inadequacies of the assessments used, c) the lack of intensive monitoring during the training, and d) the heterogeneity of the subjects included.

The present study has several limitations, which may have contributed to the unclear results. First, it is a pre-post study without a control group, so that no comparison is possible. However, the corresponding comparison in the RCT also showed no clear results. Further, the study was planned from the beginning as a feasibility and effectiveness study, which in retrospect would probably have been better done as two separate projects. Finally, the self-developed questionnaire on the complaints had limitations with regard to the evaluability and it would have made sense to additionally integrate surveys of the test persons on feasibility and tolerability into the project.

For further research, it seems important to define the study groups as clearly as possible. On the one hand, a majority of asymptomatic persons with GJH could be studied in order to more clearly grasp the preventive possibilities of resistance training. On the other hand, clearly defined persons with HSD and/or hypermobile EDS should be examined in clinical studies, whereby sufficiently large groups and a good recording of complaints and symptoms are essential. In terms of interventions, more closely monitored and individualised programmes seem to promise more success. Proprioceptive exercises or functional training with a focus on motor control could also be integrated. Last but not least, it is important to define meaningful assessments in order to record not only strength and muscle mass, but also pain, other complaints and limitations in everyday life.

Consent for publication: Not applicable.

Availability of data and materials: The data generated and/or analysed in this study are available on reasonable request from the corresponding author.

Financial support: There was no financial support for this study.

Author contributions: Conception of the work: GL, CM, BHB, MV, DA. Data collection, analysis and interpretation: GL, BHB, CM, DA. Drafting of the manuscript: GL, MV. Critical revision of the manuscript for important intellectual content: GL, CM, MV, DA, JPB. All authors declare that they are responsible for all aspects of the work and ensure that issues relating to the accuracy or integrity of any part of the work have been adequately investigated and resolved.

Conflict of interest: The authors declare that there is no conflict of interest.

REFERENCES

[1] Juul-Kristensen B, Schmedling K, Rombaut L, et al. Measurement properties of clinical assessment methods for classifying generalized joint hypermobility-A systematic review. Am J Med Genet Part C Semin Med Genet 2017; 175: 116-147. doi:10.1002/ajmg.c.31540.

[2] [Russek LN, Errico DM. Prevalence, injury rate and symptom frequency in generalized joint laxity and joint hypermobility syndrome in a "healthy" college population. Clin Rheumatol 2016; 35: 1029-1039. doi:10.1007/s10067-015-2951-9.

[3] Singh H, McKay M, Baldwin J, et al. Beighton scores and cut-offs across the lifespan: cross-sectional study of an Australian population. Rheumatology 2017; 56: 1857-1864. doi:10.1093/rheumatology/kex043

[4] Scheper MC, de Vries J, Beelen A, et al. Generalized Joint Hypermobility, Muscle Strength and Physical Function in Healthy Adolescents and Young Adults. Curr Rheumatol Rev 2015; 10: 117-125. doi:10.2174/1573397111666150120112925

[5] Foley EC, Bird HA. Hypermobility in dance: asset, not liability. Clin Rheumatol 2013; 32: 455-461. doi:10.1007/s10067-013-2191-9

[6] Baeza-Velasco C, Gély-Nargeot MC, Pailhez G, et al. Joint hypermobility and sport: A review of advantages and disadvantages. Curr Sports Med Rep 2013; 12: 291-295. doi:10.1249/JSR.0b013e3182a4b933

[7] Castori M, Tinkle B, Levy H, et al. A Framework for the Classification of Joint Hypermobility and Related Conditions. Am J Med Genet Part C Semin Med Genet 2017; 175: 148-157. doi:10.1002/ajmg.c.31539

[8] Grahame R. The Revised (Brighton 1998) Criteria for the Diagnosis of Benign Joint Hypermobility Syndrome (BJHS). J Rheumatol 2000; 27: 1777-1779

[9] Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet Part C Semin Med Genet 2017; 175: 8-26. doi:10.1002/ajmg.c.31552

[10] Scheper MC, Juul-Kristensen B, Rombaut L, et al. Disability in adolescents and adults diagnosed with hypermobility-related disorders: a meta-analysis. Arch Phys Med Rehabil 2016; 97: 2174-2187. doi:10.1016/j.apmr.2016.02.015

[11] Pacey V, Nicholson LL, Adams RD, et al. Generalized joint hypermobility and risk of lower limb joint injury during sport: a systematic review with meta-analysis. Am J Sports Med 2010; 38: 1487-1497. doi:10.1177/0363546510364838

[12] Tingle A, Bennett O, Wallis A, et al. The links between Generalized Joint Laxity and

the incidence, prevalence and severity of limb injuries related to physical exercise: a systematic literature review. Phys Ther Rev 2018; 23: 259-272. doi:10.1080/10833196.2018.1481626.

[13] Junge T, Henriksen P, Hansen S, et al. Generalised joint hypermobility and knee joint hypermobility: prevalence, knee joint symptoms and health-related quality of life in a Danish adult population. Int J Rheum Dis 2019; 22: 288-296. doi:10.1111/1756-185X.13205

[14] Juul-Kristensen B, Østengaard L, Hansen S, et al. Generalised joint hypermobility and shoulder joint hypermobility, - Risk of upper body musculoskeletal symptoms and re-duced quality of life in the general population. BMC Musculoskelet Disord 2017; 18: 1-9. doi:10.1186/s12891-017-1595-0

[15] Kulesa-Mrowiecka M, Piech J, Gazdik TS. The Effectiveness of Physical Therapy in Patients with Generalized Joint Hypermobility and Concurrent Temporomandibular Disorders - A Cross-Sectional Study. J Clin Med 2021; 10: 1-10

[16] To M, Alexander CM. Are People With Joint Hypermobility Syndrome Slow to Strengthen? Arch Phys Med Rehabil 2019; 100: 1243-1250. doi:10.1016/j.apmr.2018.11.021

[17] [Palmer S, Davey I, Oliver L, et al. The effectiveness of conservative interventions for the management of syndromic hypermobility: a systematic literature review. Clin Rheumatol 2021; 40: 1119-1129. doi:10.1007/s10067-020-05284-0.

[18] Simmonds J V. Masterclass: Hypermobility and hypermobility related disorders. Mus-culoskelet Sci Pract 2022; 57: 102465. doi:10.1016/j.msksp.2021.102465

[19] Schmid S, Luder G, Mueller Mebes C, et al. Neuromechanical gait adaptations in women with joint hypermobility - An exploratory study. Clin Biomech 2013; 28: 1020-1025. doi:10.1016/j.clinbiomech.2013.09.010

[20] Luder G, Schmid S, Stettler M, et al. Stair climbing - An insight and comparison be-tween women with and without joint hypermobility: A descriptive study. J Electromyogr Kinesiol 2015; 25: 161-167. doi:10.1016/j.jelekin.2014.07.005

[21] Mueller Mebes C, Luder G, Schmid S, et al. Aspects of Isometric Contractions and Static Balance in Women with Symptomatic and Asymptomatic Joint Hypermobility. Int J Phys Med Rehabil 2016; 4: 347. doi:10.4172/2329-9096.1000347.

[22] Stettler M, Luder G, Schmid S, et al. Passive anterior tibial translation in women with and without joint hypermobility: an exploratory study. Int J Rheum Dis 2018; 21: 1756-1762. doi:10.1111/1756-185X.12917

[23] [Taylor NF, Dodd KJ, Damiano DL. Progressive resistance exercise in physical

therapy: a summary of systematic reviews. Phys Ther 2005; 85: 1208-1223. doi:10.1093/ptj/85.11.1208.

[24] Garber CE, Blissmer B, Deschenes MR, et al. Quantity and Quality of Exercise for Developing and Maintaining Cardiorespiratory, Musculoskeletal, and Neuromotor Fitness in Apparently Healthy Adults: Guidance for Prescribing Exercise [ACSM Position Stand]. Med Sci Sports Exerc 2011; 43: 1334-1359. doi:10.1249/MSS.0b013e318213fefb

[25] Dias RMR, Cyrino ES, Salvador EP, et al. Impact of an eight-week weight training program on the muscular strength of men and women. Rev Bras Med do Esporte 2005; 11: 224-228. doi:10.1590/s1517-86922005000400004

[26] Liu C, Latham N. Progressive resistance resistance traiing for improving physical function in older adults. Cochrane Database Syst Rev 2009; 244-246. doi:10.1002/14651858.CD002759.pub2

[27] Wewege MA, Booth J, Parmenter BJ. Aerobic vs. resistance exercise for chronic nonspecific low back pain: A systematic review and meta-analysis. J Back Musculoskelet Rehabil 2018; 31: 889-899. doi:10.3233/BMR-170920.

[28] Jansen MJ, Viechtbauer W, Lenssen AF, et al. Resistance traiing alone, exercise therapy alone, and exercise therapy with passive manual mobilisation each reduce pain and disability in people with knee osteoarthritis: A systematic review. J Physiother 2011; 57: 11-20. doi:10.1016/S1836-9553(11)70002-9

[29] Busch AJ, Webber SC, Richards RS, et al. Resistance exercise training for fibromyalgia. Cochrane Database Syst Rev 2014; doi:10.1002/14651858.CD010884.www.cochranelibrary.com

[30] Luder G, Aeberli D, Mueller Mebes C, et al. Effect of resistance training on muscle properties and function in women with generalized joint hypermobility: a single-blind pragmatic randomized controlled trial. BMC Sports Sci Med Rehabil 2021; 13. doi:10.1186/s13102-021-00238-8

[31] National Institute of Health. Study Quality Assessment Tools. 2021; On the Internet: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools; Status: 19.05.2022

[32] [Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: Template for intervention description and replication (TIDieR) checklist and guide. BMJ 2014; 348: g1687. doi:10.1136/bmj.g1687

[33] Ratamess NA, Alvar BA, Evetoch TK, et al. Progression Models in Resistance Training for Healthy Adults [ACSM Position Stand]. Med Sci Sport Exerc 2009; 41: 687-708.

doi:10.1249/MSS.0b013e3181915670.

[34] Mueller Mebes C, Luder G, Schmid S, et al. Symptoms in Daily Life and Activity Level of Women with and without Hypermobility. Rheumatol Curr Res 2018; 8: 1-7. doi:10.4172/2161-1149.1000241

[35] Mebes C, Amstutz A, Luder G, et al. Isometric rate of force development, maximum voluntary contraction, and balance in women with and without joint hypermobility. Arthritis Care Res 2008; 59: 1665-1669. doi:10.1002/art.24196

[36] Aeberli D, Eser P, Bonel H, et al. Reduced trabecular bone mineral density and cortical thickness accompanied by increased outer bone circumference in metacarpal bone of rheumatoid arthritis patients: A cross-sectional study. Arthritis Res Ther 2010; 12: R119. doi:10.1186/ar3056

]37] [Dannecker EA, Koltyn KF. Pain during and within hours after exercise in healthy adults. Sport Med 2014; 44: 921-942. doi:10.1007/s40279-014-0172-z

[38] Jan M, Lin J, Liau J, et al. Investigation of Clinical Effects of High- and Low-Resistance Training for Patients With Knee Osteoarthritis: A Randomized Controlled Trial. Phys Ther 2008; 88: 427-436. doi:10.2522/ptj.20060300

[39] Botton CE, Radaelli R, Wilhelm EN, et al. Neuromuscular Adaptations to Unilateral vs. Bilateral Resistance traiing in Women. J Strength Cond Res 2016; 30: 1924-1932

[40] Liaghat B, Skou ST, Jørgensen U, et al. Heavy shoulder strengthening exercise in people with hypermobility spectrum disorder (HSD) and long-lasting shoulder symptoms: A feasibility study. Pilot Feasibility Stud 2020; 6: 1-13. doi:10.1186/s40814-020-00632-y

[41] Toprak Celenay S, Ozer Kaya D. Effects of spinal stabilization exercises in women with benign joint hypermobility syndrome: a randomized controlled trial. Rheumatol Int 2017; 37: 1461-1468. doi:10.1007/s00296-017-3713-6.

General Discussion

Strength and Limitations

Future Research

7. General discussion

The main topic of this PhD project was to investigate the effects of resistance training in women with GJH. This chapter discusses the results and the strengths and limitations of the research and includes suggestions for future research.

In short, the following answers can be given to the main questions raised in chapter 2:

- *Is resistance training feasible and safe for women with GJH?*
  → Yes, resistance training is a possible treatment option and the risks for pain and injuries does not seem to be increased in comparison to the general population.
- *Can women with GJH increase their strength and muscle mass by participating in a 12-week resistance training program?*
  → Not necessarily, at least not with the self-guided 12-week training program used in our study. The women did not significantly increase strength and muscle mass.
- *Does the 12-week resistance training have any influence on daily activities such as stair climbing or the level of disability in daily life?*
  → It seems not. In the present study no changes were seen for activities with low intensities like stair climbing and daily function.

However, in parallel to the present study several other groups performed similar studies looking at exercise and strength training in persons with various forms of hypermobility. To & Alexander in 2019 showed a similar increase of strength over 16 weeks for persons with knee pain and JHS or GJH as for those without hypermobility [92]. Also in 2019 Daman and colleagues reported reduced pain and increased quality of life in women with JHS after a 4-week exercise program[158]. In 2022 Liaghat and colleagues described better shoulder function in patients with hypermobile shoulders after 16 weeks of high-load shoulder strengthening compared to low-load exercise[133]. These and other studies suggest that people with GJH, as well as those with HSD or hEDS, can possibly increase their strength by exercise and resistance training despite the negative results of the present trial.

The possible reasons for the lack of strength gain and muscle mass increase in our study are described in detail in the publications in chapter 4 and 6. In brief, low resistance levels in general, slow, or even no progression and a high individual variability of strength levels were observed. Additionally, the predominantly self-guided nature of the program hampered progression, indicating that closer support and better guidance might be important for these patients.

When drawing conclusions from this clinical trial it is important to keep in mind the specific characteristics of the participants: Only women were included and they were mainly young adults, with those over 40 years excluded. Thus, the results are not directly applicable to elderly women during or after menopause and therefore with a different hormonal situation. Furthermore, the participants were obliged to have normal BMI and thus the implications might not be applicable for overweight or even obese women. Also, there can be drawn no direct conclusions regarding the management of men, because no male participants were included.

Resistance Training for Joint Hypermobility

Based on our own experience during the study and current literature, discussion of the importance of resistance training and exercise in general might be expanded. Comments on the experience from the participating women and the clinical experience of the physiotherapists involved led to additional impressions supplemental to the measured parameters. Several women described their fear of pain and negative reactions, especially for the knee and back, when increasing the weights more than normal for them. Some reported previous experience with resistance training in fitness centres or even with active physiotherapy, which increased their pain and led to more disability. Patients with GJH and JHS often reported that previous physiotherapy incorporating exercise had not helped them, but in contrast had increased their problems.

Another issue was an aversion to training machines and fitness centres by some of the participants. They agreed to try this training for the study, but normally they would not do this type of exercise. Many participants mentioned that they would be more likely do some more gentle sports, like Pilates or yoga. This is in line with a study that asked about 1000 persons with JHS and hEDS about their exercise preferences, where the three most appreciated modalities were swimming, walking and Pilates. Only 18% of respondents mentioned gentle strengthening as an activity helpful to their hypermobility [159]. Thus, the question remains open as to whether strength training really is the best option for the treatment of these patients. At least for some persons other exercise modalities might be easier to implement in their daily life. So, the question of the personal goals and individual preferences might be quite important in the clinical setting, but it was not possible to incorporate these individual factors in the design of the present clinical trial, which is, in general, often a problem of controlled studies in physiotherapy.

Beside the three recent trials mentioned above [92,133,158] and our own trial several other studies with a focus on resistance training were published. In 2022 a narrative review by Zabriskie [160] summarised the evidence, based on six case studies, three trials with children and ten investigations of adults, including the present clinical trial. The author found very high variability between the studies, with various goals incorporated for the training, a high variety of exercise and progression models and diversity on inclusion criteria and thus study population. In terms of resistance, most of the trials used the own body weight or resistance bands and only two incorporated free weights or machines into exercise. In conclusion, resistance training was reported as possible and, at least in some cases, effective but many questions remain regarding the best modality for these patients and a standard rehabilitation protocol is still lacking. Unfortunately, the review itself is of questionable quality since it was not a systematic review, and it was performed by a single author. No comprehensive search strategy is reported, and the quality assessment of the evaluated studies remains unclear. However, this paper does give an overview of the current evidence and also provides suggestions for further research.

Developments in the Field of “Hypermobility”

When starting the initial research projects in 2005 the main interest of the group was the difference between normal and excessive movements. The idea was to find parameters which could discriminate persons with excessive mobility, the hypermobile, and those with normal ROM. Soon we realised that persons with hypermobility were quite heterogeneous with some having no problems and doing leisure or even performance sports and others having frequent pain and being disabled by their hypermobility in their daily life. In a large cross-sectional study, we tried to separate the persons with and without symptoms and found some parameters discriminating these two groups. This is described in detail in the paper in chapter 3 and the additional papers derived from this project [8,10–12]. When planning the present trial one aim was to incorporate stringent inclusion and exclusion criteria to get a clearly defined study group. However, in retrospect, this was not successful. The study group was still too heterogeneous and the impact of the GJH on the various participants was very diverse.

Besides this problem with the definition of the study group, the definitions of disorders and syndromes associated with GJH evolved during the planning, performing, analysing and the publication of the clinical trial. In 2012 there was still discussion as to whether JHS and hEDS are the same entity and what might be a way to incorporate new and more concise diagnostic criteria [61,62]. In 2014 Remvig and colleagues reported a lack of consensus about the diagnostic criteria among clinicians [161] and, in an invited comment, Castori and colleagues supported the need for re-thinking the clinical presentations and diagnostic criteria [63]. Based on these suggestions the 2016 International Symposium of the Ehlers-Danlos Society in New York was organised and subsequently new diagnostic criteria were published in 2017, including the new term HSD and discarding the diagnosis of JHS [6,30,65,162].

Besides these changes in classification, research and publication activity in the field has increased in the last 20 years significantly. With the search term “joint hypermobility” the database of the National Library of medicine (PubMed) reveals about 500 to 600 results in the years around 2000. Around 2010 a total of 1200 results appear and in 2019, 2020 and 2021 more than 2000 publications are listed. The increase is even more impressive when using the search term "Ehlers-Danlos Syndrome": less than 100 hits by 2010 and almost 300 publications in 2021. This increase reflects on the one hand, growing interest in the problems surrounding hypermobility and its associated symptoms and syndromes and, on the other hand, the progress in genetic and molecular biological research in the quest for the exact causes of hypermobility. In addition, as mentioned above, more studies have been conducted and recommendations published in the field of treatment, including physiotherapy options.

Many questions remain unanswered, and the last International Symposium of the Ehlers-Danlos Society in Rome (September 2022) showed that new research possibilities and growing interest are more likely to generate new questions than to answer old ones. Improved diagnostic criteria for hEDS are being worked on and, in particular, clearer criteria for the diagnosis of HSD are in preparation. The problem of substantial heterogeneity is widely accepted and therefore, especially for research projects, clear and concise criteria are important.

A further issue is the validity of the measurements and assessments used to define hypermobility. In a narrative review by Malek and colleagues (2021) the validity, specificity and reliability of the BS was criticized and the association of the score with GJH was questioned [29]. On the other hand, new tools were developed to test the hypermobility of the upper limb (Upper Limb Hypermobility Assessment Tool [163]) and the lower limb (Lower Limb Assessment Scale [164]), which could be used for more specific assessments involving more joints than the BS. Both assessments test a total of 12 movements of the upper and lower limb respectively, and a person with more than 7 points is scored as having hypermobility in this extremity. No specific studies have been done up to now to establish an association with the BS and/or with specific symptoms.

The possible associations of GJH with other symptoms and systemic syndromes remain a large field of research with many open questions. These are not only important from a scientific point of view, but also for the clinical care of these patients. Many times, associated symptoms are overlooked or not seen as associated, and in other cases specific additional symptoms may remain untreated since they are not seen as specific targets for therapy. Thus, not only the complexity of the hypermobility itself, but also the associated disorders remain a challenge in research and clinical management.

Finally, the hEDS remains the only type of EDS without a clear genetic marker. Thus, many projects are currently running to detect possible genes associated with hEDS and possibly even with HSD and to find molecular markers to refine or confirm the diagnosis. However, in terms of management these attempts will not change things in the foreseeable future. Even when genetic variants are found and molecular targets can be identified, it will be years from now before specific treatments will be ready for the market and for these to be applied in daily routine. Until then, the management remains basically symptom-oriented and needs to be individualized according to the various problems and disabilities of a patient.

Clinical Implications

Based on the present study and the available literature some suggestions can me made regarding the management of persons with joint hypermobility and associated problems in general and specifically when implementing resistance exercise.

The management should be always multimodal and, depending on the involved organ systems and occurring problems, also multidisciplinary. For the musculoskeletal part a comprehensive evaluation of the symptoms and movements leading to pain or feelings of instability is fundamental. Furthermore, the individual experience with movement and training are important, as well as expectations regarding daily activities and movements of an individual patient. The preferences of a patient regarding exercise and sports should be respected in the planning of the therapy and according to this suitable training regimens, home exercise and sports recommendations can be implemented.

When it comes specifically to resistance training as a treatment modality the following aspects might be considered in the performance of an exercise regimen.

- Resistance training aiming at hypertrophy might be a basic approach since increase of muscle strength and muscle mass are important basic factors to perform activities.
- A preparatory phase before the resistance training could be helpful to improve performance during the training. Improvement of motor control and the comprehensive learning of the relevant exercise might support the training. Lower weight and higher numbers of repetitions might be applied in this phase.
- After the resistance training or yet in a later phase it might be accompanied by functional exercises and proprioceptive training. For the lower extremity this can be standing on an unstable surface, balance tasks or various jump exercises. Also, a shift to higher weights and less repetitions is possible, when tolerated and desired by the patient.
- Regarding speed it is important that the movement always can be controlled. Thus, to begin slow movements might be the better choice to avoid overuse of passive structures. Later, when patients are experienced with resistance training and the specific movements, the speed can be varied and also faster contractions are crucial, again when tolerated.
- For range of motion the end-positions of a joint should be avoided, at least in the beginning. For example, on the leg press the knee should not be exercised in a hyperextended range, since control is very difficult and overuse of some structured might occur. Also, in daily life these patients should be taught to avoid using the joints in locked end-positions, like hyperextension of the knee or elbow.

In the present trial a general resistance training for legs and trunk was performed for persons without specific complaints. In the physiotherapy setting patients will usually present with specific problems in one or several joints and limitations of the movement and possibly daily life activities. These complaints should always be considered and therefore the prescribed exercise adapted. This is supported by two studies incorporating heavy shoulder strengthening for patients with shoulder pain [133] and specific knee exercises for patients with anterior knee pain [92], respectively. It can be assumed that in these cases also the motivation of the patients to exercise might be higher, since there is a clear association between the experienced problems and the exercise the therapy. During individual physiotherapy it is then easier to adapt the exercise and add specific tasks related to the goals of the patient and individual expectations.

The overall aim in the management should always be to stabilise the joints during daily life activities and to find the balance between the movements performed during work, sports or leisure time and the ability on the body to perform these movements with optimal control and without pain or overuse of some structures.

8. General Strengths and Limitations

In terms of strength and management detailed discussions are provided in the published paper, especially in the report of the RCT (Chapter 4) and in the baseline evaluation (Chapter 5). As described this project was one of the first controlled studies in the field of management and, especially, exercise for persons with GJH, HSD or hEDS. This can be considered a general strength, but it is also the reason for some of the limitations since not much experience or published evidence was available during the planning phase of the project.

The main strength of the study was the adequate group size and the good to very good adherence of the participants to the resistance training schedule. The clear and comprehensive description of the training program facilitated its implementation in clinical practice and the structured and standardized program provides a good foundation for the further development of possible interventions, especially in terms of adaptation and individualization. A further strength is the broad spectrum of outcome measurements, including all three aspects of the ICF and ranging from muscle strength and mass to quality of life and disability in daily life.

The main limitation in the project was the heterogeneous study group and especially the partially subclinical population in terms of pain level and impairments. The changes in diagnostic criteria over time and the various diagnostic labels used for persons with hypermobility complicated the clear definition of the inclusion and exclusion criteria for the study and later on hindered the comparison of the results with other studies. Regarding the outcome measurements the functional assessments like stair climbing were not sufficiently demanding for the young and mainly active population, resulting in small changes and a lack of statistical significance. Similarly, some ceiling effects were seen in the questionnaires, where several participants reached the full score at inclusion and therefore had no potential for improvement. Also, the questionnaires were not specifically designed for the specific impairments and disabilities associated with joint hypermobility since no such questionnaires existed when preparing the study. It was only in 2017 that the Bristol Impact of Hypermobility (BIoH) questionnaire was developed and published. This questionnaire will potentially be better suited for future projects in the field [165,166].

Finally, the measurement with the pQCT in terms of tissue properties and muscle mass were an interesting addition but did not provide much additional information. The analysis was interesting and provided specific insights, however, the individual variation in terms of cross-sectional area was very high and the relation between muscle mass and performance in daily life activities remains questionable.

9. General Conclusion and Suggestions for Further Research

This thesis project and especially the RCT evaluating resistance training in women with joint hypermobility provides an additional piece of knowledge and information for the management of persons with hypermobility and associated conditions. Even without a clear result regarding effects, the experience builds the foundation for further research and has raised important new questions. In general, the management of musculoskeletal symptoms associated with hypermobility remains challenging and should include exercise and active physiotherapy as important components. It is still not possible to give general recommendations or to provide a comprehensive exercise program for all patients.

An individually tailored therapy program might be of importance for these patients, taking into account both the affected joints and other regions of the body, on the one hand, and the current health status of the person in terms of actual strength, pain experience, and the specific problems they face in daily life, leisure or work activities at the time of presentation. Additionally, gender, age, body weight or hormonal factors might influence the choice of therapy options, as well as the personal preferences of the individual patient. A possible instrument to research such individualized treatments in one or very few patients is by studies with a single case experimental design (SCED), where each participant sets up his own control and is mainly analysed longitudinally [167]. Currently, a project of this nature has been prepared and is being carried out by Christine Müller, one of the co-workers on this project.

An important issue for future studies is the implementation of better tools for the description of the population involved and for the measurement of the outcomes. In terms of assessing GJH two new tools were developed involving additional joints and movement directions: The Lower Limb Assessment Scale (LLAS) [164,168] and the Upper Limb Hypermobility Assessment Tool (ULHAT) [163]. Both assessments involve 12 movement tests on each side and provide specific information on the extent of hypermobility in the specific limb. The assessments are currently being translated into German within the framework of two bachelor theses at the Berne University of Applied Science. Further tests on the practicability and reliability of these assessments will provide the foundation for their implementation in future research projects as well as in clinical routine.

The above mentioned BIoH questionnaire is currently available in English and was just recently translated into Arabic, but not yet into German. Thus, for the future use of this questionnaire in the clinical setting here in Switzerland and for research projects, a translation and adaptation into German is needed. A possible future project should provide such a translation and establish the psychometric properties for the German version of the BIoH. With such a reliable and specific questionnaire evaluation of the management of patients with hypermobility would be easier and the outcome assessments of research projects might be more comparable.

As described above the number of publications in the field is currently increasing, indicating higher interest in the topic and showing various research groups in several countries contributing to the body of evidence. Additionally, the Ehlers-Danlos Society [125] provides financial support for research projects in the area and also runs several working groups and committees to coordinate and promote the research as well as the proper management of these patients. In the Allied Health Professionals Working Group, in which I am also involved, the focus currently is on the development of a core data set for outcome measures, both in adults and children. More information on the work and the directions of this working group were published in a recent publication by some of the members [49].

Finally, a comprehensive description of future directions for research was suggested by Zabriskie [160] in their recent narrative review on the rationale and feasibility of resistance training in hEDS and HSD, where the following recommendations are stated (derived from table 4):

- Identify and validate specific outcome measures that can be used in the hEDS/HSD population to enhance comparison between studies.
- Conduct more research on children and adolescents utilizing control groups.
- Identify proper progression of exercises and modes in adults and report ample detail on the exercises and modes being employed to allow for replication and implementation.
- Investigate a proactive exercise prescription that can be recommended upon diagnosis.
- Explore the relationship between baseline physical fitness and response to training programs in the hEDS/HSD population.

In this context the present thesis builds a part of the foundation for future research and the suggestions presented above for future research and planned projects fit well with these existing proposals.

10. References

[1] Beighton PH, Solomon L, Soskolne CL. Articular mobility in an African population. Ann Rheum Dis 1973; 32: 413–418. doi:10.1136/ard.32.5.413

[2] Remvig L, Jensen D V, Ward RC. Are Diagnostic Criteria for General Joint Hypermobility and Benign Joint Hypermobility Syndrome Based on Reproducible and Valid Tests? A Review of the Literature. J Rheumatol 2007; 34: 798–803

[3] Singh H, McKay M, Baldwin J, et al. Beighton scores and cut-offs across the lifespan: cross-sectional study of an Australian population. Rheumatology 2017; 56: 1857–1864. doi:10.1093/rheumatology/kex043

[4] Clinch J, Deere K, Sayers A, et al. Epidemiology of generalized joint laxity (hypermobility) in fourteen-year-old children from the UK: A population-based evaluation. Arthritis Rheum 2011; 63: 2819–2827. doi:10.1002/art.30435

[5] Juul-Kristensen B, Schmedling K, Rombaut L, et al. Measurement properties of clinical assessment methods for classifying generalized joint hypermobility-A systematic review. Am J Med Genet Part C Semin Med Genet 2017; 175: 116–147. doi:10.1002/ajmg.c.31540

[6] Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet Part C Semin Med Genet 2017; 175: 8–26. doi:10.1002/ajmg.c.31552

[7] Mebes C, Amstutz A, Luder G, et al. Isometric rate of force development, maximum voluntary contraction, and balance in women with and without joint hypermobility. Arthritis Care Res 2008; 59: 1665–1669. doi:10.1002/art.24196

[8] Schmid S, Luder G, Mueller Mebes C, et al. Neuromechanical gait adaptations in women with joint hypermobility - An exploratory study. Clin Biomech 2013; 28: 1020–1025. doi:10.1016/j.clinbiomech.2013.09.010

[9] Luder G, Schmid S, Stettler M, et al. Stair climbing - An insight and comparison between women with and without joint hypermobility: A descriptive study. J Electromyogr Kinesiol 2015; 25: 161–167. doi:10.1016/j.jelekin.2014.07.005

[10] Stettler M, Luder G, Schmid S, et al. Passive anterior tibial translation in women with and without joint hypermobility: an exploratory study. Int J Rheum Dis 2018; 21: 1756–1762. doi:10.1111/1756-185X.12917

[11] Mueller Mebes C, Luder G, Schmid S, et al. Symptoms in Daily Life and Activity Level of Women with and without Hypermobility. Rheumatol Curr Res 2018; 8: 1–7. doi:10.4172/2161-1149.1000241

[12] Mueller Mebes C, Luder G, Schmid S, et al. Aspects of Isometric Contractions and Static Balance in Women with Symptomatic and Asymptomatic Joint Hypermobility. Int J Phys Med Rehabil 2016; 4: 347. doi:10.4172/2329-9096.1000347

[13] McKay MJ, Baldwin JN, Ferreira P, et al. Normative reference values for strength and flexibility of 1,000 children and adults. Neurology 2017; 88: 36–43. doi:10.1212/WNL.0000000000003466

[14] Quatman CE, Ford KR, Myer GD, et al. The effects of gender and pubertal status on generalized joint laxity in young athletes. J Sci Med Sport 2008; 11: 257–263. doi:10.1016/j.jsams.2007.05.005

[15] Flowers PPE, Cleveland RJ, Schwartz TA, et al. Association between general joint hypermobility and knee, hip, and lumbar spine osteoarthritis by race: A cross-sectional study. Arthritis Res Ther 2018; 20: 1–7. doi:10.1186/s13075-018-1570-7

[16] Scheper MC, de Vries J, Beelen A, et al. Generalized Joint Hypermobility, Muscle Strength and Physical Function in Healthy Adolescents and Young Adults. Curr Rheumatol Rev 2015; 10: 117–125. doi:10.2174/1573397111666150120112925

[17] Russek LN, Errico DM. Prevalence, injury rate and, symptom frequency in generalized joint laxity and joint hypermobility syndrome in a “healthy” college population. Clin Rheumatol 2016; 35: 1029–1039. doi:10.1007/s10067-015-2951-9

[18] Antonio DH, Magalhaes CS. Survey on joint hypermobility in university students aged 18-25 years old. Adv Rheumatol 2018; 58: 1–7. doi:10.1186/s42358-018-0008-x

[19] Noormohammadpour P, Borghei A, Mirzaei S, et al. The Risk Factors of Low Back Pain in Female High-School Students. Spine (Phila Pa 1976) 2019; 44: 1. doi:10.1097/brs.0000000000002837

[20] Voermans NC, Knoop H. Both pain and fatigue are important possible determinants of disability in patients with the Ehlers-Danlos syndrome hypermobility type. Disabil Rehabil 2011; 33: 706–707. doi:10.3109/09638288.2010.531373

[21] Mikkelsson M, Salminen JJ, Kautiainen H. Joint Hypermobility is not a Contributing Factor to Musculoskeletal Pain in Pre-Adolescents. J Rheumatol 1996; 23: 1963–1967

[22] Hanzlíková I, Richards J, Athens J, et al. The Influence of Asymptomatic Hypermobility on Unanticipated Cutting Biomechanics. Sports Health 2021; XX: 1–6. doi:10.1177/1941738121999063

[23] Nicholson LL, McKay MJ, Baldwin JN, et al. Is there a relationship between sagittal cervical spine mobility and generalised joint hypermobility? A cross-sectional study of 1000 healthy Australians. Physiother (United Kingdom) 2021; 112: 150–157. doi:10.1016/j.physio.2020.12.003

[24] Alahmari KA, Kakaraparthi VN, Reddy RS, et al. Foot Posture Index Reference Values among Young Adults in Saudi Arabia and Their Association with Anthropometric Determinants, Balance, Functional Mobility, and Hypermobility. Biomed Res Int 2021; 2021: 1–10. doi:10.1155/2021/8844356

[25] Krahe AM, Adams RD, Nicholson LL. Features that exacerbate fatigue severity in joint hypermobility syndrome/Ehlers–Danlos syndrome – hypermobility type. Disabil Rehabil 2018; 40: 1989–1996. doi:10.1080/09638288.2017.1323022

[26] McCormack M, Briggs J, Hakim A, et al. Joint laxity and the benign joint hypermobility syndrome in student and professional ballet dancers. J Rheumatol 2004; 31: 173–178

[27] Liaghat B, Skou ST, Søndergaard J, et al. A randomised controlled trial of heavy shoulder strengthening exercise in patients with hypermobility spectrum disorder or hypermobile Ehlers-Danlos syndrome and long-lasting shoulder complaints: study protocol for the Shoulder-MOBILEX study. Trials 2020; 21: 1–18. doi:10.1186/s13063-020-04892-0

[28] Bockhorn LN, Vera AM, Dong D, et al. Interrater and Intrarater Reliability of the Beighton Score: A Systematic Review. Orthop J Sport Med 2021; 9: 1–11. doi:10.1177/2325967120968099

[29] Malek S, Reinhold EJ, Pearce GS. The Beighton Score as a measure of generalised joint hypermobility. Rheumatol Int 2021; doi:10.1007/s00296-021-04832-4

[30] Castori M, Tinkle B, Levy H, et al. A Framework for the Classification of Joint Hypermobility and Related Conditions. Am J Med Genet Part C Semin Med Genet 2017; 175: 148–157. doi:10.1002/ajmg.c.31539

[31] Castori M. Deconstructing and reconstructing joint hypermobility on an evo-devo perspective. Rheumatol 2021; 60: 2537–2544

[32] Silman AJ, Haskard D, Day S. Distribution of joint mobility in a normal population: Results of the use of fixed torque measuring devices. Ann Rheum Dis 1986; 45: 27–30. doi:10.1136/ard.45.1.27

[33] Whitehead NA, Mohammed KD, Fulcher ML. Does the Beighton Score Correlate With Specific Measures of Shoulder Joint Laxity? Orthop J Sport Med 2018; 6: 1–7. doi:10.1177/2325967118770633

[34] Benhamu-Benhamu S, Garcia-De-la-peña R, Gijon-Nogueron G, et al. Range of ankle dorsiflexion in a group of adults with ligamentous laxity. J Am Podiatr Med Assoc 2018; 108: 245–252. doi:10.7547/16-060

[35] Naal FD, Hatzung G, Müller A, et al. Validation of a self-reported Beighton score to assess hypermobility in patients with femoroacetabular impingement. Int Orthop 2014; 38: 2245–2250. doi:10.1007/s00264-014-2424-9

[36] Chan C, Qi HH, Baldwin JN, et al. Joint hypermobility and its association with self-reported knee health: A cross-sectional study of healthy Australian adults. Int J Rheum Dis 2021; 1–7. doi:10.1111/1756-185X.14096

[37] Conti PCR, Miranda JES, Araujo CRP. Relationship between Systemic Joint Laxity, TMJ Hypertranslation, and Intra-articular Disorders. Cranio 2000; 18: 192–197. doi:10.1080/08869634.2000.11746132

[38] Chahal J, Leiter J, McKee MD, et al. Generalized ligamentous laxity as a predisposing factor for primary traumatic anterior shoulder dislocation. J Shoulder Elb Surg 2010; 19: 1238–1242. doi:10.1016/j.jse.2010.02.005

[39] Bulbena A, Duro JC, Porta M, et al. Clinical Assessment of Hypermobility of Joints: Assembling Criteria. J Rheumatol 1992; 19: 115–122

[40] Rotes Querol J, Granados Duran J, Ribas Subiros R, et al. La Laxité articulaire comme facteur d'alterations de l'appareil locomoteur (Nouvelle étude 1971) [French]. Rhumatologie 1972; 24: 51–65

[41] Hakim AJ, Grahame R. A simple questionnaire to detect hypermobility: an adjunct to the assessment of patients with diffuse musculoskeletal pain. Int J Clin Pr 2003; 57: 163–166

[42] Baeza-Velasco C, Gély-Nargeot MC, Pailhez G, et al. Joint hypermobility and sport: A review of advantages and disadvantages. Curr Sports Med Rep 2013; 12: 291–295. doi:10.1249/JSR.0b013e3182a4b933

[43] Foley EC, Bird HA. Hypermobility in dance: Asset, not liability. Clin Rheumatol 2013; 32: 455–461. doi:10.1007/s10067-013-2191-9

[44] Bird HA. The performing artist as an elite athlete. Rheumatology 2009; 48: 1469–1470. doi:10.1088/978-0-7503-1164-9ch6

[45] Grahame R, Jenkins JM. Joint hypermobility - asset or liability? A study of joint mobility in ballet dancers. Ann Rheum Dis 1972; 31: 109–112. doi:10.1136/ard.31.2.109

[46] Larsson L-G, Baum J, Mudholkar GS, et al. Benefits and Disadvantages of Joint Hypermobility among Musicians. N Engl J Med 1993; 329: 1079–1082

[47] Smith RD, Worthington JW. Paganini. The Riddle and Connective Tissue. JAMA 1967; 199: 156–160

[48] Larsson L-G, Mudholkar GS, Baum J, et al. Benefits and liabilities of hypermobility in the back pain disorders of industrial workers. J Intern Med 1995; 238: 461–467. doi:10.1111/j.1365-2796.1995.tb01224.x

[49] Nicholson LL, Simmonds J, Pacey V, et al. International Perspectives on Joint Hypermobility. J Clin Rheumatol 2022; Publish Ah: 1–7. doi:10.1097/rhu.0000000000001864

[50] Saccomanno MF, Fodale M, Capasso L, et al. Generalized joint laxity and multidirectional instability of the shoulder. Joints 2013; 1: 171–179. doi:10.11138/jts/2013.1.4.171

[51] Smith TO, Donell ST, Chester R, et al. What activities do patients with patellar instability

perceive makes their patella unstable? Knee 2011; 18: 333–339. doi:10.1016/j.knee.2010.07.003

[52] Azma K, Mottaghi P, Hosseini A, et al. Benign joint hypermobility syndrome in soldiers; what is the effect of military training courses on associated joint instabilities? J Res Med Sci 2014; 19: 639–643

[53] Baban A, Castori M. Pharmacological resources, diagnostic approach and coordination of care in joint hypermobility-related disorders. Expert Rev Clin Pharmacol 2018; 11: 689–703. doi:10.1080/17512433.2018.1497973

[54] Eccles JA, Thompson B, Themelis K, et al. Beyond bones: The relevance of variants of connective tissue (hypermobility) to fibromyalgia, ME/CFS and controversies surrounding diagnostic classification: An observational study. Clin Med J R Coll Physicians London 2021; 21: 53–58. doi:10.7861/CLINMED.2020-0743

[55] Jacobs JWG, da Silva JAP. Hypermobility syndromes from the clinician's perspective: An overview. Acta Reumatol Port 2014; 39: 124–136

[56] Malfait F, Castori M, Francomano CA, et al. The Ehlers-Danlos syndromes. Nat Rev Dis Prim 2020; 30: 64

[57] Gensemer C, Burks R, Kautz S, et al. Hypermobile Ehlers-Danlos syndromes: Complex phenotypes, challenging diagnoses, and poorly understood causes. Dev Dyn 2021; 250: 318–340. doi:10.1002/dvdy.220

[58] Zeitoun JD, Lefèvre JH, De Parades V, et al. Functional digestive symptoms and quality of life in patients with Ehlers-Danlos syndromes: Results of a national cohort study on 134 patients. PLoS One 2013; 8: 1–8. doi:10.1371/journal.pone.0080321

[59] Beighton PH, De Paepe A, Steinmann B, et al. Ehlers-danlos syndromes: Revised nosology, Villefranche, 1997. Am J Med Genet 1998; 77: 31–37. doi:10.1002/(SICI)1096-8628(19980428)77:1<31::AID-AJMG8>3.0.CO;2-O

[60] Grahame R. The Revised (Brighton 1998) Criteria for the Diagnosis of Benign Joint Hypermobility Syndrome (BJHS). J Rheumatol 2000; 27: 1777–1779

[61] Tinkle BT, Bird HA, Grahame R, et al. The lack of clinical distinction between the hypermobility type of Ehlers-Danlos syndrome and the joint hypermobility syndrome (a.k.a. hypermobility syndrome). Am J Med Genet Part A 2009; 149: 2368–2370. doi:10.1002/ajmg.a.33070

[62] Remvig L, Engelbert RH, Berglund B, et al. Need for a consensus on the methods by which to measure joint mobility and the definition of norms for hypermobility ...: is revision of criteria for joint hypermobility syndrome and Ehlers-Danlos syndrome hypermobility type indicated? [Letter to the Edit. Rheumatology (Oxford) 2011; 50: 1169–1171. doi:10.1093/rheumatology/ker140

[63] Castori M, Morlino S, Grammatico P. Towards a re-thinking of the clinical significance of generalized joint hypermobility, joint hypermobiity syndrome, and Ehlers-Danlos syndrome, hypermobility type [Invited comment]. Am J Med Genet Part A 2014; 164: 588–590. doi:10.1002/ajmg.a.36437

[64] Adib N, Davies K, Grahame R, et al. Joint hypermobility syndrome in childhood. A not so benign multisystem disorder? Rheumatology 2005; 44: 744–750. doi:10.1093/rheumatology/keh557

[65] Tinkle B, Castori M, Berglund B, et al. Hypermobile Ehlers–Danlos syndrome (a.k.a. Ehlers–Danlos syndrome Type III and Ehlers–Danlos syndrome hypermobility type): Clinical description and natural history. Am J Med Genet Part C Semin Med Genet 2017; 175: 48–69. doi:10.1002/ajmg.c.31538

[66] Castori M. Ehlers-Danlos Syndrome, Hypermobility Type: An Underdiagnosed Hereditary Connective Tissue Disorder with Mucocutaneous, Articular, and Systemic Manifestations. ISRN

Dermatol 2012; 2012: 1–22. doi:10.5402/2012/751768

[67] Mastoroudes H, Giarenis I, Cardozo L, et al. Prolapse and sexual function in women with benign joint hypermobility syndrome. BJOG An Int J Obstet Gynaecol 2013; 120: 187–192. doi:10.1111/1471-0528.12082

[68] Nazem M, Mottaghi P, Hoseini A. Benign joint hypermobility syndrome among children with inguinal hernia. J Res Med Sci 2013; 18: 904–905

[69] Castori M, Camerota F, Celletti C, et al. Natural history and manifestations of the hypermobility type Ehlers-Danlos syndrome: A pilot study on 21 patients. Am J Med Genet Part A 2010; 152: 556–564. doi:10.1002/ajmg.a.33231

[70] Asher SB, Chen R, Kallish S. Mitral valve prolapse and aortic root dilation in adults with hypermobile Ehlers–Danlos syndrome and related disorders. Am J Med Genet Part A 2018; 176: 1838–1844. doi:10.1002/ajmg.a.40364

[71] Roma M, Marden CL, De Wandele I, et al. Postural tachycardia syndrome and other forms of orthostatic intolerance in Ehlers-Danlos syndrome. Auton Neurosci Basic Clin 2018; 215: 89–96. doi:10.1016/j.autneu.2018.02.006

[72] Miller AJ, Stiles LE, Sheehan T, et al. Prevalence of hypermobile Ehlers-Danlos syndrome in postural orthostatic tachycardia syndrome. Auton Neurosci Basic Clin 2020; 224: 102637. doi:10.1016/j.autneu.2020.102637

[73] Cazzato D, Castori M, Lombardi R, et al. Small fiber neuropathy is a common feature of Ehlers-Danlos syndromes. Neurology 2016; 87: 155–159. doi:10.1212/WNL.0000000000002847

[74] Puledda F, Vigano A, Celletti C, et al. A study of migraine characteristics in joint hypermobility syndrome a.k.a. Ehlers-Danlos syndrome, hypermobility type. Neurol Sci 2015; doi:10.1007/s10072-015-2173-6

[75] Bendik EM, Tinkle BT, Al-shuik E, et al. Joint hypermobility syndrome: A common clinical disorder associated with migraine in women. Cephalalgia 2011; 31: 603–613. doi:10.1177/0333102410392606

[76] Zarate N, Farmer AD, Grahame R, et al. Unexplained gastrointestinal symptoms and joint hypermobility: Is connective tissue the missing link? Neurogastroenterol Motil 2010; 22. doi:10.1111/j.1365-2982.2009.01421.x

[77] Baeza-Velasco C, Lorente S, Tasa-Vinyals E, et al. Gastrointestinal and eating problems in women with Ehlers–Danlos syndromes. Eat Weight Disord - Stud Anorexia, Bulim Obes 2021; doi:10.1007/s40519-021-01146-z

[78] Lam CY, Palsson OS, Whitehead WE, et al. Rome IV Functional Gastrointestinal Disorders and Health Impairment in Subjects With Hypermobility Spectrum Disorders or Hypermobile Ehlers-Danlos Syndrome. Clin Gastroenterol Hepatol 2021; 19: 277-287.e3. doi:10.1016/j.cgh.2020.02.034

[79] Gaisl T, Giunta C, Bratton DJ, et al. Obstructive sleep apnoea and quality of life in Ehlers-Danlos syndrome: A parallel cohort study. Thorax 2017; 72: 729–735. doi:10.1136/thoraxjnl-2016-209560

[80] Nijs J, Aerts A, De Meirleir K. Generalized joint hypermobility is more common in chronic fatigue syndrome than in healthy control subjects. J Manipulative Physiol Ther 2006; 29: 32–39. doi:10.1016/j.jmpt.2005.11.004

[81] Hakim AJ, De Wandele I, O'Callaghan C, et al. Chronic fatigue in Ehlers–Danlos syndrome—Hypermobile type. Am J Med Genet Part C Semin Med Genet 2017; 175: 175–180. doi:10.1002/ajmg.c.31542

[82] Voermans NC, Knoop H, van de Kamp N, et al. Fatigue Is a Frequent and Clinically Relevant Problem in Ehlers-Danlos Syndrome. Semin Arthritis Rheum 2010; 40: 267–274.

doi:10.1016/j.semarthrit.2009.08.003

[83] Castori M, Celletti C, Camerota F, et al. Chronic fatigue syndrome is commonly diagnosed in patients with Ehlers-Danlos syndrome hypermobility type/joint hypermobility syndrome [Letter]. Clin Exp Rheumatol 2011; 29: 597–598. doi:10.1016/0196-4399(91)90007-i

[84] Kohn A, Chang C. The Relationship Between Hypermobile Ehlers-Danlos Syndrome (hEDS), Postural Orthostatic Tachycardia Syndrome (POTS), and Mast Cell Activation Syndrome (MCAS). Clin Rev Allergy Immunol 2020; 58: 273–297. doi:10.1007/s12016-019-08755-8

[85] Seneviratne SL, Maitland A, Afrin L. Mast cell disorders in Ehlers-Danlos syndrome. Am J Med Genet Part C Semin Med Genet 2017; 236: 226–236. doi:10.1002/ajmg.c.31555

[86] Eccles JA, Davies KA. The challenges of chronic pain and fatigue. Clin Med 2021; 21: 19–27. doi:10.7861/clinmed.2020-1009

[87] Gavrilova N, Soprun L, Lukashenko M, et al. New Clinical Phenotype of the Post-Covid Syndrome: Fibromyalgia and Joint Hypermobility Condition. Pathophysiology 2022; 29: 24–29. doi:10.3390/pathophysiology29010003

[88] Wasim S, Suddaby JS, Parikh M, et al. Pain and gastrointestinal dysfunction are significant associations with psychiatric disorders in patients with Ehlers–Danlos syndrome and hypermobility spectrum disorders: a retrospective study. Rheumatol Int 2019; 1241–1248. doi:10.1007/s00296-019-04293-w

[89] Singh D, Rocio Martinez W, Anand N, et al. The ALPIM (Anxiety, Laxity, Pain, Immune, and Mood) Syndrome in Adolescents and Young Adults: A Cohort Study. J Neuropsychiatry Clin Neurosci 2019; 1–7. doi:10.1176/appi.neuropsych.18080174

[90] Smith TO, Easton V, Bacon H, et al. The relationship between benign joint hypermobility syndrome and psychological distress: A systematic review and meta-analysis. Rheumatol (United Kingdom) 2013; 53: 114–122. doi:10.1093/rheumatology/ket317

[91] Pailhez G, Rosado S, Bulbena Cabré A, et al. Joint hypermobility, fears, and chocolate consumption. J Nerv Ment Dis 2011; 199: 903–906. doi:10.1097/NMD.0b013e318234a022

[92] To M, Alexander CM. Are People With Joint Hypermobility Syndrome Slow to Strengthen? Arch Phys Med Rehabil 2019; 100: 1243–1250. doi:10.1016/j.apmr.2018.11.021

[93] Liaghat B, Juul-Kristensen B, Frydendal T, et al. Competitive swimmers with hypermobility have strength and fatigue deficits in shoulder medial rotation. J Electromyogr Kinesiol 2018; 39: 1–7. doi:10.1016/j.jelekin.2018.01.003

[94] Ewertowska P, Trzaskoma Z, Sitarski D, et al. Muscle strength, muscle power and body composition in college-aged young women and men with Generalized Joint Hypermobility. PLoS One 2020; 15: e0236266. doi:10.1371/journal.pone.0236266

[95] Zhong G, Zeng X, Xie Y, et al. Prevalence and dynamic characteristics of generalized joint hypermobility in college students. Gait Posture 2021; 84: 254–259. doi:10.1016/j.gaitpost.2020.12.002

[96] Simonsen EB, Tegner H, Alkjaer T, et al. Gait analysis of adults with generalised joint hypermobility. Clin Biomech 2012; 27: 573–577. doi:10.1016/j.clinbiomech.2012.01.008

[97] Mallik AK, Ferrell WR, McDonald GA, et al. Impaired proprioceptive acuity at the proximal interphalangeal joint in patients with the hypermobility syndrome. Rheumatology 1994; 33: 1193. doi:10.1093/rheumatology/33.12.1193

[98] Smith TO, Jerman E, Easton V, et al. Do people with benign joint hypermobility syndrome (BJHS) have reduced joint proprioception? A systematic review and meta-analysis. Rheumatol Int 2013; 33: 2709–2716. doi:10.1007/s00296-013-2790-4

[99] Eccles JA, Beacher FDC, Gray MA, et al. Brain structure and joint hypermobility: Relevance to

the expression of psychiatric symptoms. Br J Psychiatry 2012; 200: 508–509. doi:10.1192/bjp.bp.111.092460

[100] Schmidt H, Pedersen TL, Junge T, et al. Hypermobility in Adolescent Athletes: Pain, Functional Ability, Quality of Life, and Musculoskeletal Injuries. J Orthop Sport Phys Ther 2017; 47: 792–800. doi:10.2519/jospt.2017.7682

[101] Shiue KY, Cleveland RJ, Schwartz TA, et al. Is the association between knee injury and knee osteoarthritis modified by the presence of general joint hypermobility? Osteoarthr Cartil Open 2020; 2: 100045. doi:10.1016/j.ocarto.2020.100045

[102] Lee GW, Lee S-M, Suh B-G. The impact of generalized joint laxity on the occurrence and disease course of primary lumbar disc herniation. Spine J 2015; 15: 65–70. doi:10.1016/j.spinee.2014.06.028

[103] Junge T, Henriksen P, Hansen S, et al. Generalised joint hypermobility and knee joint hypermobility: prevalence, knee joint symptoms and health-related quality of life in a Danish adult population. Int J Rheum Dis 2019; 22: 288–296. doi:10.1111/1756-185X.13205

[104] Tobias JH, Deere K, Palmer S, et al. Joint hypermobility is a risk factor for musculoskeletal pain during adolescence: Findings of a prospective cohort study. Arthritis Rheum 2013; 65: 1107–1115. doi:10.1002/art.37836

[105] Stendal Robinson H, Lindgren A, Bjelland EK. Generalized joint hypermobility and risk of pelvic girdle pain in pregnancy: does body mass index matter? Physiother Theory Pract 2021; 00: 1–8. doi:10.1080/09593985.2021.1913774

[106] Ahlqvist K, Bjelland EK, Pingel R, et al. The Association of Self-Reported Generalized Joint Hypermobility with pelvic girdle pain during pregnancy: A retrospective cohort study. BMC Musculoskelet Disord 2020; 21: 1–10. doi:10.1186/s12891-020-03486-w

[107] Pacey V, Nicholson LL, Adams RD, et al. Generalized joint hypermobility and risk of lower limb joint injury during sport: a systematic review with meta-analysis. Am J Sports Med 2010; 38: 1487–1497. doi:10.1177/0363546510364838

[108] Konopinski MD, Graham I, Johnson MI, et al. The effect of hypermobility on the incidence of injury in professional football: A multi-site cohort study. Phys Ther Sport 2016; 21: 7–13. doi:10.1016/j.ptsp.2015.12.006

[109] Bronner S, Bauer NG. Risk factors for musculoskeletal injury in elite pre-professional modern dancers: A prospective cohort prognostic study. Phys Ther Sport 2018; 31: 42–51. doi:10.1016/j.ptsp.2018.01.008

[110] Reuter PR. Joint hypermobility and musculoskeletal injuries in a university-aged population. Phys Ther Sport 2021; 49: 123–128. doi:10.1016/j.ptsp.2021.02.009

[111] Blokland D, Thijs KM, Backx FJGG, et al. No Effect of Generalized Joint Hypermobility on Injury Risk in Elite Female Soccer Players. Am J Sports Med 2017; 45: 286–293. doi:10.1177/0363546516676051

[112] Sundemo D, Hamrin Senorski E, Karlsson L, et al. Generalised joint hypermobility increases ACL injury risk and is associated with inferior outcome after ACL reconstruction: A systematic review. BMJ Open Sport Exerc Med 2019; 5. doi:10.1136/bmjsem-2019-000620

[113] Tingle A, Bennett O, Wallis A, et al. The links between Generalized Joint Laxity and the incidence, prevalence and severity of limb injuries related to physical exercise: a systematic literature review. Phys Ther Rev 2018; 23: 259–272. doi:10.1080/10833196.2018.1481626

[114] Juul-Kristensen B, Østengaard L, Hansen S, et al. Generalised joint hypermobility and shoulder joint hypermobility, - Risk of upper body musculoskeletal symptoms and reduced quality of life in the general population. BMC Musculoskelet Disord 2017; 18: 1–9. doi:10.1186/s12891-017-1595-0

[115] Scheper MC, de Vries JE, Juul-Kristensen B, et al. The functional consequences of Generalized Joint Hypermobility: a cross-sectional study. BMC Musculoskelet Disord 2014; 15: 243. doi:10.1186/1471-2474-15-243

[116] Scheper MC, Juul-Kristensen B, Rombaut L, et al. Disability in adolescents and adults diagnosed with hypermobility related disorders: a meta-analysis. Arch Phys Med Rehabil 2016; 97: 2174–2187. doi:10.1016/j.apmr.2016.02.015

[117] de Vries J, Verbunt J, Stubbe J, et al. Generalized Joint Hypermobility and Anxiety in Adolescents and Young Adults, the Impact on Physical and Psychosocial Functioning. Healthc (Basel, Switzerland) 2021; 9. doi:10.3390/healthcare9050525

[118] Van Meulenbroek T, Huijnen IPJJ, Simons LE, et al. Exploring the underlying mechanism of pain-related disability in hypermobile adolescents with chronic musculoskeletal pain. Scand J pain 2020; 21: 22–31. doi:10.1515/sjpain-2020-0023

[119] Palomo-Toucedo IC, Leon-Larios F, Reina-Bueno M, et al. Psychosocial Influence of Ehlers–Danlos Syndrome in Daily Life of Patients: A Qualitative Study. Int J Environ Res Public Health 2020; 17: 1–14. doi:10.3390/ijerph17176425

[120] Clark CJ, Knight I. A humanisation approach for the management of Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome-Hypermobility Type (JHS/EDS-HT). Int J Qual Stud Health Well-being 2017; 12: 1371993. doi:10.1080/17482631.2017.1371993

[121] Simmonds J V. Masterclass: Hypermobility and hypermobility related disorders. Musculoskelet Sci Pract 2022; 57: 102465. doi:10.1016/j.msksp.2021.102465

[122] Atwell K, Michael W, Dubey J, et al. Diagnosis and Management of Hypermobility Spectrum Disorders in Primary Care. J Am Board Fam Med 2021; 34: 838–848. doi:10.3122/jabfm.2021.04.200374

[123] Knight I. The role of narrative medicine in the management of joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type. Am J Med Genet Part C Semin Med Genet 2015; 169: 123–129. doi:10.1002/ajmg.c.31428

[124] Bennett SE, Walsh N, Moss T, et al. Understanding the psychosocial impact of joint hypermobility syndrome and Ehlers–Danlos syndrome hypermobility type: a qualitative interview study. Disabil Rehabil 2021; 43: 795–804. doi:10.1080/09638288.2019.1641848

[125] Ehlers-Danlos Society T. The Ehlers-Danlos Society. 2022; Im Internet: https://www.ehlers-danlos.com/

[126] Palmer S, Davey I, Oliver L, et al. The effectiveness of conservative interventions for the management of syndromic hypermobility: a systematic literature review. Clin Rheumatol 2021; 40: 1119–1129. doi:10.1007/s10067-020-05284-0

[127] Reychler G, Liistro G, Piérard GE, et al. Inspiratory muscle strength training improves lung function in patients with the hypermobile Ehlers–Danlos syndrome: A randomized controlled trial. Am J Med Genet Part A 2019; 179: 356–364. doi:10.1002/ajmg.a.61016

[128] Ferrell WR, Tennant N, Sturrock RD, et al. Amelioration of symptoms by enhancement of proprioception in patients with joint hypermobility syndrome. Arthritis Rheum 2004; 50: 3323–3328. doi:10.1002/art.20582

[129] Sahin N, Baskent A, Cakmak A, et al. Evaluation of knee proprioception and effects of proprioception exercise in patients with benign joint hypermobility syndrome. Rheumatol Int 2008; 28: 995–1000. doi:10.1007/s00296-008-0566-z

[130] Palmer S, Cramp F, Clark EM, et al. The feasibility of a randomised controlled trial of physiotherapy for adults with joint hypermobility syndrome. 2016

[131] Bathen T, Hångmann AB, Hoff M, et al. Multidisciplinary treatment of disability in ehlers-danlos syndrome hypermobility type/hypermobility syndrome: A pilot study using a combination of

physical and cognitive-behavioral therapy on 12 women. Am J Med Genet Part A 2013; 161: 3005–3011. doi:10.1002/ajmg.a.36060

[132] Liaghat B, Skou ST, Jørgensen U, et al. Heavy shoulder strengthening exercise in people with hypermobility spectrum disorder (HSD) and long-lasting shoulder symptoms: A feasibility study. Pilot Feasibility Stud 2020; 6: 1–13. doi:10.1186/s40814-020-00632-y

[133] Liaghat B, Skou ST, Søndergaard J, et al. Short-term effectiveness of high-load compared with low-load strengthening exercise on self-reported function in patients with hypermobile shoulders: a randomised controlled trial. Br J Sports Med 2022; 1–10. doi:10.1136/bjsports-2021-105223

[134] Kulesa-Mrowiecka M, Piech J, Gazdik TS. The Effectiveness of Physical Therapy in Patients with Generalized Joint Hypermobility and Concurrent Temporomandibular Disorders — A Cross-Sectional Study. J Clin Med 2021; 10: 1–10

[135] Kemp S, Roberts I, Gamble C, et al. A randomized comparative trial of generalized vs targeted physiotherapy in the management of childhood hypermobility. Rheumatology 2010; 49: 315–325. doi:10.1093/rheumatology/kep362

[136] Pacey V, Tofts L, Adams RD, et al. Exercise in children with joint hypermobility syndrome and knee pain: a randomised controlled trial comparing exercise into hypermobile versus neutral knee extension. Pediatr Rheumatol Online J 2013; 11: 30. doi:10.1186/1546-0096-11-30

[137] Bale P, Easton V, MacGregor A, et al. The effectiveness of a multidisciplinary intervention strategy for the treatment of benign joint hypermobility in childhood: a randomised, single centre parallel group trial (The Bendy Study). BMC Pediatr Rheumatol 2019; 17. doi:10.1136/archdischild-2015-308599.259

[138] Westcott WL. Resistance training is medicine: Effects of strength training on health. Curr Sports Med Rep 2012; 11: 209–216. doi:10.1249/JSR.0b013e31825dabb8

[139] Taylor NF, Dodd KJ, Damiano DL. Progressive resistance exercise in physical therapy: A summary of systematic reviews. Phys Ther 2005; 85: 1208–1223. doi:10.1093/ptj/85.11.1208

[140] Ratamess NA, Alvar BA, Evetoch TK, et al. Progression Models in Resistance Training for Healthy Adults [ACSM Position Stand]. Med Sci Sport Exerc 2009; 41: 687–708. doi:10.1249/MSS.0b013e3181915670

[141] Kraemer WJ, Adams K, Cafarelli E, et al. Progression Models in Resistance Training for Healthy Adults. Med Sci Sports Exerc 2002; 34: 364–380. doi:10.1097/00005768-200202000-00027

[142] Liu C, Latham N. Progressive resistance strength training for improving physical function in older adults. Cochrane Database Syst Rev 2009; 244–246. doi:10.1002/14651858.CD002759.pub2

[143] Busch AJ, Webber SC, Richards RS, et al. Resistance exercise training for fibromyalgia. Cochrane Database Syst Rev 2014; doi:10.1002/14651858.CD010884.www.cochranelibrary.com

[144] Voet NBM, van der Kooi EL, van Engelen BGM, et al. Strength training and aerobic exercise training for muscle disease. Cochrane Database Syst Rev 2019; 2019. doi:10.1002/14651858.CD003907.pub5

[145] Wewege MA, Booth J, Parmenter BJ. Aerobic vs. resistance exercise for chronic non-specific low back pain: A systematic review and meta-analysis. J Back Musculoskelet Rehabil 2018; 31: 889–899. doi:10.3233/BMR-170920

[146] Jansen MJ, Viechtbauer W, Lenssen AF, et al. Strength training alone, exercise therapy alone, and exercise therapy with passive manual mobilisation each reduce pain and disability in people with knee osteoarthritis: A systematic review. J Physiother 2011; 57: 11–20. doi:10.1016/S1836-9553(11)70002-9

[147] Larsson A, Palstam A, Löfgren M, et al. Resistance exercise improves muscle strength, health status and pain intensity in fibromyalgia-a randomized controlled trial. Arthritis Res Ther 2015;

17. doi:10.1186/s13075-015-0679-1

[148] Legerlotz K. The Effects of Resistance Training on Health of Children and Adolescents With Disabilities. Am J Lifestyle Med 2020; 14: 382–396. doi:10.1177/1559827618759640

[149] Garber CE, Blissmer B, Deschenes MR, et al. Quantity and Quality of Exercise for Developing and Maintaining Cardiorespiratory, Musculoskeletal, and Neuromotor Fitness in Apparently Healthy Adults: Guidance for Prescribing Exercise [ACSM Position Stand]. Med Sci Sports Exerc 2011; 43: 1334–1359. doi:10.1249/MSS.0b013e318213fefb

[150] Pollock MM, Gaesser GA, Butcher J, et al. The Recommended Quantity and Quality of Exercise for Cardiorespiratory and Muscular Fitness, and Flexibility in Healthy Adults [ACSM Position Stand]. Med Sci Sport Exerc 2012; 30: 975–991

[151] Bremander A, Bergman S. Non-pharmacological management of musculoskeletal disease in primary care. Best Pract Res Clin Rheumatol 2008; 22: 563–577. doi:10.1016/j.berh.2008.01.002

[152] Stricker PR, Faigenbaum AD, McCambridge TM. Resistance training for children and adolescents. Pediatrics 2020; 145. doi:10.1542/peds.2020-1011

[153] Perales M, Santos-Lozano A, Ruiz JR, et al. Benefits of aerobic or resistance training during pregnancy on maternal health and perinatal outcomes: A systematic review. Early Hum Dev 2016; 94: 43–48. doi:10.1016/j.earlhumdev.2016.01.004

[154] Pedersen BK, Saltin B. Exercise as medicine - Evidence for prescribing exercise as therapy in 26 different chronic diseases. Scand J Med Sci Sport 2015; 25: 1–72. doi:10.1111/sms.12581

[155] Møller MB, Kjær M, Svensson RB, et al. Functional adaptation of tendon and skeletal muscle to resistance training in three patients with genetically verified classic Ehlers Danlos Syndrome. Muscles Ligaments Tendons J 2014; 4: 315–323. doi:10.11138/mltj/2014.4.3.315

[156] Magnusson SP, Julsgaard C, Aagaard P, et al. Viscoelastic properties and flexibility of the human muscle-tendon unit in benign joint hypermobility syndrome. J Rheumatol 2001; 28: 2720–2725

[157] Couppé C, Kongsgaard M, Aagaard P, et al. Habitual loading results in tendon hypertrophy and increased stiffness of the human patellar tendon. J Appl Physiol 2008; 105: 805–810. doi:10.1152/japplphysiol.90361.2008

[158] Daman M, Shiravani F, Hemmati L, et al. The effect of combined exercise therapy on knee proprioception, pain intensity and quality of life in patients with hypermobility syndrome: A randomized clinical trial. J Bodyw Mov Ther 2019; 23: 202–205. doi:10.1016/j.jbmt.2017.12.012

[159] Simmonds J V., Herbland A, Hakim A, et al. Exercise beliefs and behaviours of individuals with Joint Hypermobility syndrome/Ehlers–Danlos syndrome – hypermobility type. Disabil Rehabil 2019; 41: 445–455. doi:10.1080/09638288.2017.1398278

[160] Zabriskie HA. Rationale and Feasibility of Resistance Training in hEDS/HSD: A Narrative Review. J Funct Morphol Kinesiol 2022; 7: 1–18

[161] Remvig L, Flycht L, Christensen KB, et al. Lack of consensus on tests and criteria for generalized joint hypermobility, Ehlers-Danlos syndrome: Hypermobile type and joint hypermobility syndrome. Am J Med Genet Part A 2014; 164: 591–596. doi:10.1002/ajmg.a.36402

[162] Bloom L, Byers P, Francomano C, et al. The international consortium on the Ehlers–Danlos syndromes. Am J Med Genet Part C Semin Med Genet 2017; 175: 5–7. doi:10.1002/ajmg.c.31547

[163] Nicholson LL, Chan C. The Upper Limb Hypermobility Assessment Tool: A novel validated measure of adult joint mobility. Musculoskelet Sci Pract 2018; 35: 38–45. doi:10.1016/j.msksp.2018.02.006

[164] Johnson AP, Ward S, Simmonds J. The Lower Limb Assessment Score: A valid measure of

hypermobility in elite football? Phys Ther Sport 2019; 37: 86–90. doi:10.1016/j.ptsp.2019.03.007

[165] Palmer S, Cramp F, Lewis R, et al. Development and initial validation of the Bristol Impact of Hypermobility questionnaire. Physiother (United Kingdom) 2017; 103: 186–192. doi:10.1016/j.physio.2016.04.002

[166] Palmer S, Manns S, Cramp F, et al. Test-retest reliability and smallest detectable change of the Bristol Impact of Hypermobility (BIoH) questionnaire. Musculoskelet Sci Pract 2017; 32: 64–69. doi:10.1016/j.msksp.2017.08.007

[167] Tate RL, Perdices M. Research Note: Single-case experimental designs. J Physiother 2020; 66: 202–206. doi:10.1016/j.jphys.2020.06.004

[168] Ferrari J, Parslow C, Lim E, et al. Joint hypermobility: the use of a new assessment tool to measure lower limb hypermobility. Clin Exp Rheumatol 2005; 23: 413–420

11. Publications and conference proceedings

In the sections of publications (peer-review and non peer-review) all articles are listed, while for the congress presentations and posters only the contributions in the field of hypermobility are listed. Also, in the paragraph of supervised bachelor-thesis only the one's dealing with topics around hypermobility are listed.

Peer-reviewed publications

1. **Luder Gere**, Müller Mebes Christine, Haupt-Bertschy Bettina, Verra Martin L. Aeberli Daniel, Baeyens Jean-Pierre (2023) Krafttraining bei Frauen mit generalisierter Hypermobilität: Machbarkeit, Beschwerden und Effekte – eine pre-post Studie [Resistance training in women with generalized joint hypermobility: feasibility, symptoms, and effects – a pre-post study] Physioscience [accepted] [Included as chapter 6a and 6b]
2. Eggmann Sabrina, Irincheeva Irina, **Luder Gere**, Verra Martin L., Moser André, Bastiaenen Caroline H.G., Jakob Stephan M. (2022) Cardiorespiratory response to early rehabilitation in critically ill adults: A secondary analysis of a randomised controlled trial. PLoS One 2022 Feb 3;17(2):e0262779. doi.org/10.1371/journal.pone.0262779
3. **Luder Gere**, Aeberli Daniel, Müller Mebes Christine, Haupt-Bertschy Bettina, Verra Martin L., Baeyens Jean-Pierre (2022) Correlation of muscle and bone parameters, daily function and participation in women with generalized joint hypermobility: a descriptive evaluation. J Musculoskelet Neuronal Interact. 2022 Mar 1;22(1):15-26. [Included as chapter 5] www.ismni.org/jmni/pdf/87/jmni_22_015.pdf
4. **Luder Gere**, Aeberli Daniel, Müller Mebes Christine, Haupt-Bertschy Bettina, Baeyens Jean-Pierre, Verra Martin L. (2021) Effect of Resistance Training on Muscle Properties and Function in Women with Generalized Joint Hypermobility: A Single-Blind Pragmatic Randomized Controlled Trial. BMC Sports Science, Medicine and Rehabilitation, 13:10, doi.org/10.1186/s13102-021-00238-8 [Included as chapter 4]
5. Lehmann Isabelle, Thaler Irène, **Luder Gere**, Damm Ulrike, Wälti Charlotte, Steinheimer Saskia, Verra Martin L., Müri Rene M., Nyffeler Thomas, Vanbellingen Tim, Kamm Christian Philipp (2020) Standardized, comprehensive, hospital-based circuit training in people with multiple sclerosis (MS-FIT): results on feasibility, adherence and satisfaction of the training intervention. European Journal of Physical and Rehabilitation Medicine June;56(3):279-85. doi.org/10.23736/S1973-9087.20.06191-2
6. Eggmann Sabrina, **Luder Gere**, Verra Martin L., Irincheeva Irina, Bastiaenen Caroline H.G., Jakob Stepahn M. (2020) Functional ability and quality of life in critical illness survivors with intensive care unit acquired weakness: A secondary analysis of a randomised controlled trial. PLoS One 15(3): e0229725. doi.org/10.1371/journal.pone.0229725
7. Schmidt Leuenberger Joachim M., Hoksch Beatrix, **Luder Gere**, Schmid Ralph A., Verra Martin L., Dorn Patrick (2019). Early Assessment and Management of Dysphagia after Lung Resection: A Randomized Controlled Trial. Annals of Thoracic Surgery 108(4):1059-1064. doi.org/10.1016/j.athoracsur.2019.04.067
8. Matthias Stettler, **Gere Luder**, Stefan Schmid, Christine Mueller Mebes, Ursula Stutz, Hans-Rudolf Ziswiler, Lorenz Radlinger (2018) Passive anterior tibial translation in women with and

without joint hypermobility: an exploratory study. International Journal of Rheumatic Diseases 21(10), 1756-1762. doi.org/10.1111/1756-185X.12917

9. Eggmann Sabrina, Verra Martin L, **Luder Gere**, Takala Jukka, Jakob Stepahn M (2018) Effects of early, combined endurance and resistance training in mechanically ventilated, critically ill patients: A randomised controlled trial. PloS one 13 (11), e0207428. doi.org/10.1371/journal.pone.0207428
10. Mueller Mebes Christine, **Luder Gere**, Schmid Stefan, Stettler Matthias, Stutz Ursula, Ziswiler Hans-Rudolf, Radlinger Lorenz (2018) Symptoms in Daily Life and Activity Level of Women with and without Hypermobility. Rheumatology (Sunnyvale) 8: 241. doi.org/10.4172/2161-1149.1000241
11. Mueller Mebes Christine, **Luder Gere,** Schmid Stefan, Stettler Matthias, Stutz Ursula, Ziswiler Hans-Rudolf, Radlinger Lorenz (2016) Aspects of Isometric Contractions and Static Balance in Women with Symptomatic and Asymptomatic Joint Hypermobility. Int J Phys Med Rehabil 4:4. doi.org/10.4172/2329-9096.1000347
12. Eggmann Sabrina, Verra Martin L, **Luder Gere**, Takala Jukka, Jakob Stephan M (2016) Effects of early, combined endurance and resistance training in mechanically ventilated, critically ill patients: a study protocol for a randomised controlled trial. Trials. 17:403. doi.org/10.1186/s13063-016-1533-8.
13. **Luder Gere**, Schmid Stefan, Stettler Matthias, Mueller Mebes Christine, Stutz Ursula, Ziswiler Hans-Rudolf, Radlinger Lorenz (2015) Stair climbing - An insight and comparison between women with and without joint hypermobility: A descriptive study. J Electromyogr Kinesiol. 25 (1):161-167. doi.org/10.1016/j.jelekin.2014.07.005 [Included as chapter 3]
14. Schmid Stefan, **Luder Gere,** Mueller Mebes Christine, Stettler Matthias, Stutz Ursula, Ziswiler Hans-Rudolf, Radlinger Lorenz (2013) Neuromechanical gait adaptations in women with joint hypermobility — An exploratory study. Clinical Biomechanics 28: 1020-1025. doi.org/10.1016/j.clinbiomech.2013.09.010
15. **Luder Gere**, Bertschy Bettina, Rocourt Mariane HH, Deschner Gabriela, Radlinger Lorenz (2011) Funktionelle Defizite und Selbsteinschätzung der Leistungsfähigkeit nach chirurgischer Hüftluxation. Sportverletzung Sportschaden 25(4):201-7. doi.org/10.1055/s-0031-1299607
16. Mebes Christine, Amstutz Astrid, **Luder Gere**, Ziswiler Hans-Rudolf, Stettler Matthias, Villiger Peter, Radlinger Lorenz (2008) Isometric Rate of Force Development, Maximum Voluntary Contraction and Balance in Females With and Without Joint Hypermobility. Arthritis Care & Research 59:1665-69. doi.org/10.1002/art.24196
17. **Luder Gere**, Baumann Thomas, Jost Christoph, Schmid Stefan, Radlinger Lorenz (2007) Variabilität der Bodenreaktionskräfte von gesunden Personen beim Treppensteigen; Physioscience 3:181-187. doi.org/10.1055/s-2007-963629
18. Stacoff Alex, Kramers-de Quervain Inés A., **Luder Gerhard**, List Renate, Stüssi Edgar (2007) Ground reaction forces on stairs Part II: Knee implant patients versus normals; Gait Posture 26:48-58. doi.org/10.1016/j.gaitpost.2006.07.015
19. Stacoff Alex, Diezi Christian, **Luder Gerhard**, Stüssi Edgar, Kramers – de Quervain Inés A. (2005) Ground Reaction Forces on Stairs: Effects of Stair Inclination and Age; Gait Posture 1:24-38. doi.org/10.1016/j.gaitpost.2003.11.003

Non peer-reviewed publications

1. **Luder Gere** (2021) Wenn die Beweglichkeit zum Problem wird – Physiotherapie bei generalisierter Hypermobilität. Rheuma Schweiz 3.2021:24-31.
2. **Luder Gere** (2021) WCPT-Kongress: die Physiowelt zu Gast in der eigenen Praxis. Physioactive 3.2021:32-34.
3. **Luder Gere** (2018) Fit in die Operation. Physiomagazin 2.2018:10-12.
4. **Luder Gere** (2018) Wenn Beweglichkeit zum Problem wird – Hypermobilität aus Therapeutensicht. Physiopraxis 1.2018:24-25.
5. Verra Martin L., **Luder Gere**, Trippolini Maurizio (2018) Forschung in der Rehabilitationsmedizin. Praxis 107(4): 209–213.
6. **Luder Gere** (2016) Viel Wissen zu Muskeln und Kraft. Physioactive 6.2016:41-42.
7. **Luder Gere** (2016) Kräftige Muskeln für einen leichten Alltag. Physiomagazin 1.2016:15-17.
8. Haupt Bettina, **Luder Gere** (2016) Entlang der Referenz – Behandlung nach Schultergelenk-OP. Physiopraxis 2.2016:43-45.
9. Trippolini Maurizio, **Luder Gere,** Maguire Claire, Verra Martin (2015) Clinical Research Forum: Bericht zur 9. Ausgabe 2014 und Ausblick zum 10-Jahres-Jubiläum am 7. November. Physioscience 2015;11:127-128.
10. **Luder Gere**, Verra Martin, Winteler Balz (2015) Singapur 2015: Impressionen vom Weltkongress. Physioactive 4.2015:36-40.
11. Bertschy Bettina, Gunti Annina, **Luder Gere** (2015) Schmerzen und passive Beweglichkeit nach Schulteroperationen. Physioactive 1.20151:24-28.
12. Verra Martin, Trippolini Maurizio, **Luder Gere**, Baur Heiner (2014) 8. Clinical Research Forum am Institut für Physiotherapie des Universitätsspitals Bern. Physioscience 2014;10: 83–84..
13. Verra Martin, Trippolini Maurizio, **Luder Gere**, Baur Heiner (2014) 8. Clinical Research Forum: Forschung in der ambulanten Physiotherapie. Physiopraxis 5.2014:
14. **Luder Gere** (2014) Ausdauer – Schrittweise zu mehr Gesundheit / Gehen – älteste und einfachste Form der Bewegung. Physiomagazin 1.2014:10-12.
15. **Luder Gere** (2012) Strichzeichnung, Webplattform oder Smartphonevideo: ein Überblick zu Heimprogrammen. Physioactive 5.2012:39-43.

Oral congress presentations

1. **Luder Gere**, Meier Marion, Ernst Roger, Müller Christine, Bruins Peter (2021) Entwicklung und initiale Testung einer Smartphone App für Patientinnen mit generalisierter Hypermobilität. Kooperationskongress Physioswiss & RehaSchweiz, Online / Nottwil, Switzerland, 6./7. May 2021.
2. **Luder Gere**: Publikationsversuch eines Studienprotokolls. Clinical Research Forum, Basel, Switzerland, 4. November 2017 [Invited Lecture]
3. **Luder Gere**, Mueller Mebes Christine, Haupt-Bertschy Bettina, Verra Martin L., Aeberli Daniel, Baeyens Jean-Pierre (2017) Effect of resistance training in women with joint hypermobility – a randomized controlled trial. Kooperationskongress Physioswiss &

RehaSchweiz, Davos, Switzerland, 19. / 20. October 2017. [Abstract published in French in Kinésithérapie, la Revue 2017;17(192):34]

4. **Luder Gere**, Mueller Christine, Haupt-Bertschy Bettina, Verra Martin L., Aeberli Daniel, Baeyens Jean-Pierre (2017) Effect of resistance training in women with joint hypermobility – results of a pragmatic randomised controlled trial. 18th World Congress of Physiotherapy, Cape Town, South Africa, 2.-4. July 2017.
5. **Luder Gere**, Mueller Mebes Christine, Verra Martin L., Aeberli Daniel, Baeyens Jean-Pierre (2016) Effect of Resistance Training in Women with Joint Hypermobility – Preliminary Results of a Randomised Controlled Trial. Vortrag am hpr Symposium 2016, Interlaken, Switzerland, 25. August 2016.
6. **Luder Gere**, Schmid Stefan, Stettler Matthias, Müller Christine, Stutz Ursula, Ziswiler Hansruedi, Radlinger Lorenz (2014) Treppensteigen – Ein Vergleich zwischen Frauen mit und ohne Hypermobilität in Bezug auf Bodenreaktionskräfte und Muskelaktivität. Physioswiss Kongress, Bern, Switzerland, 13. / 14. June 2014
7. **Luder Gere**, Schmid Stefan, Stettler Matthias, Müller Christine, Stutz Ursula, Ziswiler Hansruedi, Radlinger Lorenz (2014) Bodenreaktionskräfte und Muskelaktivität beim Treppensteigen bei Frauen mit und ohne Hypermobilität. Kongress für Gesundheitsberufe, Inselspital Bern, Switzerland, 14. / 15. March 2014.
8. **Luder Gere**, Stettler Matthias, Müller Christine, Stutz Ursula, Radlinger Lorenz (2012) Bodenreaktionskräfte und Muskelaktivität beim Treppensteigen bei Frauen mit und ohne Hypermobilität. Kongress des Schweizer Physiotherapie Verbandes, Genf, Switzerland, 10. / 11. May 2012.
9. **Luder Gere**, Stutz Ursula, Mebes Christine, Amstutz Astrid, Ziswiler Hans-Rudolf, Stettler Matthias, Radlinger Lorenz (2010) Hypermobility - Influence of Active and Passive Tone. 6th Congress of the European Interdisciplinary Society for Clinical and Sports Application, St. Etienne, French, 20. / 21. May 2010.

Congress poster presentations

1. **Luder Gere**, Meier Marion, Ernst Roger, Müller Christine, Bruins Peter, Verra Martin L. (2022) Development and initial testing of a smartphone app for patients with generalised joint hypermobility. International Scientific Symposium on the Ehlers-Danlos Syndromes (EDS) & Hypermobility Spectrum Disorders (HSD), Rome, Italy, 14.- 18. September 2022.
2. **Luder Gere**, Anneler Meret, Kölliker Fabio (2022) Experienced influence of menstrual cycle in women with hypermobility spectrum disorder: a qualitative study. International Scientific Symposium on the Ehlers-Danlos Syndromes (EDS) & Hypermobility Spectrum Disorders (HSD), Rome, Italy, 14.- 18. September 2022.
3. **Luder Gere**, Meier Marion, Ernst Roger, Müller Christine, Bruins Peter, Verra Martin L. (2020) Entwicklung und initiale Testung einer Smartphone App für Patientinnen mit generalisierter Hypermobilität. Symposium Gesundheitsberufe, Bern, Switzerland, 12. March 2021.
4. **Luder Gere**, Mueller Mebes Christine, Haupt-Bertschy Bettina, Verra Martin L., Aeberli Daniel, Baeyens Jean-Pierre (2017) Krafttraining bei Frauen mit Hypermobilität: Widerstand, Belastungssteigerung und Beschwerden. Kooperationskongress Physioswiss & RehaSchweiz, Davos, Switzerland, 19. / 20. October 2017. [Abstract published in French in Kinésithérapie, la Revue 2017;17(192):15]

5. **Luder Gere**, Müller Mebes Christine, Aeberli Daniel, Verra Martin L, Baeyens Jean-Pierre (2016) Bedeutet bei hypermobilen Frauen ein grösserer Muskelquerschnitt mehr Kraft? Physioswiss-Kongress, Basel, Switzerland, 17. / 18. June 2016.
6. **Luder Gere**, Mueller Mebes Christine, Verra Martin L., Aeberli Daniel, Baeyens Jean-Pierre (2016) Effect of resistance training in women with joint hypermobility – preliminary results of a randomised controlled trial. EULAR (European League Against Rheumatism), London, United Kingdom, 8.- 11. June 2016. [Abstract accepted for publication in Annals of the Rheumatic Diseases 75 (Suppl 2):1308.1-1308]
7. **Luder Gere**, Haehni Michaela, Mueller Christine, Verra Martin L., Baeyens Jean-Pierre (2015) Joint Hypermobility - Is there a Correlation Between Muscle Cross Sectional Area and Muscle Strength? EULAR (European League against Rheumatism), Rome, Italy, 10.- 13. June 2015.
8. **Luder Gere**, Schmid Stefan, Mueller Mebes Christine, Stettler Matthias, Stutz Ursula, Ziswiler Hans-Rudolf, Radlinger Lorenz (2015) Discriminating conditional and functional factors for women with and without hypermobility - an observational study. EULAR (European League against Rheumatism), Rome, Italy, 10.- 13. June 2015.
9. **Luder Gere**, Haehni Michaela, Mueller Christine, Verra Martin L., Baeyens Jean-Pierre. Joint Hypermobility - Is there a Correlation Between Muscle Cross Sectional Area and Muscle Strength? 17th World Congress of Physiotherapy, Singapore, 1.- 4. May 2015.
10. **Luder Gere**, Schmid Stefan, Mueller Mebes Christine, Stettler Matthias, Stutz Ursula, Ziswiler Hans-Rudolf, Radlinger Lorenz. Discriminating conditional and functional factors for women with and without hypermobility - an observational study. 17th World Congress of Physiotherapy, Singapore, 1.- 4. May 2015.
11. **Luder Gere**, Schmid Stefan., Müller Christine, Stutz Ursula, Stettler Matthias, Radlinger Lorenz (2014) Stair climbing – An Insight and Comparison between Women with and without Joint Hypermobility. EULAR (European League against Rheumatism), Madrid, 12.- 15. Juni 2013.
12. **Luder Gere**, Schmid Stefan, Stettler Matthias, Müller Mebes Christine, Stutz Ursula, Ziswiler Hans-Rudolf, Radlinger Lorenz (2013) Stair climbing – An Insight and Comparison between Women with and without Joint Hypermobility. 2nd World Congress on Controversies, Debates & Consensus in Bone, Muscle & Joint Diseases (BMJD), Brussel, Belgium, 21.- 24. November 2013.
13. **Luder Gere**, Stettler Matthias, Müller Mebes Christine, Stutz Ursula, Schmid Stefan, Radlinger Lorenz (2012) Bodenreaktionskräfte und Muskelaktivität beim Treppensteigen bei Frauen mit und ohne Hypermobilität. Kongress für Gesundheitsberufe, Bern, Switzerland, 2. / 3. March 2012.
14. **Luder Gere**, Stettler Matthias, Müller Mebes Christine, Stutz Ursula, Schmid Stefan, Radlinger Lorenz (2012) Bodenreaktionskräfte und Muskelaktivität beim Treppensteigen bei Frauen mit und ohne Hypermobilität. Tag der klinischen Forschung des DKF (Departement für Klinische Forschung), Bern University, Switzerland, 2. November 2011.
15. **Luder Gere,** Stettler Matthias, Mebes Christne, Stutz Ursula, Taeymans Jan, Radlinger Lorenz (2011) Ground Reaction Forces and EMG during Stair Climbing in Women with and without Hypermobility. 16th International WCPT Congress, Amsterdam, Netherlands, 20.- 23. June 2011.

Supervised bachelor thesis

1. Michelle Nadine Morand, Nathalie Sarah Rüttimann: Praktikabilität und Interrater-Reliabilität der deutschen Übersetzung des Upper Limb Hypermobility Assessment Tool (ULHAT) Eine Reliabilitätsanalyse. 2022, Berne University of Applied Sciences, Department Health, BSc Physiotherapy [PHY19]
2. Meret Lena Anneler, Fabio Nicolas Kölliker: Einfluss des weiblichen Zyklus auf Beschwerden bei Frauen mit Hypermobilität – eine qualitative Studie. 2021, Berne University of Applied Sciences, Department Health, BSc Physiotherapy [PHY18]
3. Roger Ernst, Marion Meier: Mobile Softwareanwendungen im Gesundheitsbereich: Entwicklung einer App für hypermobile Patientinnen und Patienten. 2019, Berne University of Applied Sciences, Department Health, BSc Physiotherapy [PHY16]
4. Sarina Christa Bucher, Lisa Dohnke: Vor- und Nachteile der Hypermobilität im Sport: Ein systematisches Review. 2017, Berne University of Applied Sciences, Department Health, BSc Physiotherapy [PHY14]

Awards

1. **Research price 2012 of Reha Rheinfelden:** Bodenreaktionskräfte und Muskelaktivität beim Treppensteigen bei Frauen mit und ohne Hypermobilität. Awarded at 10. January 2013, Prize money: CHF 1500.-
2. Best oral presentation at the Congress of the Swiss Physiotherapy Association, Geneva, Switzerland, 2012: **Luder G**, Stettler M, Müller C, Stutz U, Radlinger L. Bodenreaktionskräfte und Muskelaktivität beim Treppensteigen bei Frauen mit und ohne Hypermobilität.

Appendix

Additional files to

Gere Luder, Daniel Aeberli, Christine Müller Mebes, Bettina Haupt-Bertschy, Jean-Pierre Baeyens, Martin L. Verra: Effect of Resistance Training on Muscle Properties and Function in Women with Generalized Joint Hypermobility: A Single-Blind Pragmatic Randomized Controlled Trial. BMC Sports Science, Medicine and Rehabilitation, 13:10, doi:10.1186/s13102-021-00238-8

Additional file 1: S1. Detailed description of training program.

Additional file 2: S2. Detailed description of the outcome measurements.

Additional file 3: S3. Result tables of additional parameters.

Additional file 4: S4. Basic dataset supporting the conclusions of this article

[Not included in print version. Available online at https://bmcsportsscimedrehabil.biomedcentral.com/articles/10.1186/s13102-021-00238-8#Sec19]

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE

Department of Physiotherapy
Director
Martin L. Verra, PhD, PT

Additional file S1 to **"Effect of Resistance Training on Muscle Properties and Function in Women with Generalized Joint Hypermobility: a Single-Blind Pragmatic Randomized Controlled Trial"**

by Luder Gere, Aeberli Daniel, Mueller Mebes Christine, Haupt-Bertschy Bettina, Baeyens Jean-Pierre and Verra Martin L

Description of the guided 12 week resistance training program

Key training parameters

- Two sessions weekly, resulting in a total of 24 training sessions
- Sessions of about 50 min duration, including 10 minutes warm-up
- First two weeks complex method as introduction: 2 series, 25 repetitions, resistance at 40- 50% of the 1RM, break of at least two minutes between series
- Followed by ten weeks of hypertrophy training: 3 series, 12 repetitions, resistance at 80% of 1RM, break at least 90 sec between series
- Instruction sessions were given in week 1, 3 and 6 by four experienced physiotherapists.
- All other training sessions (up to 21) were performed individually, always with a supervising physiotherapist in the training room.

Providers and place of the intervention

- The training took place in the medical training centre of the Berne University Hospital, Bern, Switzerland. The room is regularly used by the physiotherapists for exercise with patients but is also frequented by former patients or healthy people, who perform their own fitness program. All persons exercising in the fitness room have to undergo extensive instruction and regular control of their exercise. A physiotherapist is always available in the fitness room to instruct and monitor the exercises and to answer any questions the users might have. Most of the users focus mainly on resistance training, but some possibilities for endurance and balance training are also available.
- All machines for the resistance exercise and the warm-up were standard devices for medical use by Technogym (Technogym S.p.A., Cesena, Italy).
- All four providers of the instruction sessions to the study participants were qualified physio-therapists, three of whom had additional training in sports physiotherapy and exercise physiology. The fourth person served as stand-in when the others were not available and only occasionally led instruction sessions.
- Due to the nature of the intervention it was not possible to blind the instruction.
- Detailed documentation of the exercises and the instructions were provided for the physiotherapists. Since all of them also regularly instructed other people (patients and healthy) and took part in the continuous professional development and quality assurance program of all instructors in the medical fitness, no specific training for this study was offered to the physiotherapists. However, one of the study coordinators (GL) was always available for questions.

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE

Department of Physiotherapy
Director
Martin L. Verra, PhD, PT

Description of the guided 12 week resistance training program

Instruction for the resistance training

- All instruction sessions were scheduled by the responsible study coordinator
- Whenever possible all three instruction sessions were delivered by the same physiotherapist.
- The duration of the first instruction session (week 1) was 60 min, the other two sessions (weeks 3 and 6) took about 30 min. Participants were encouraged to be ready in sports clothing at the scheduled time and in session two and three to have done the warm-up before instruction.
- All instructions were performed with one physiotherapist instructing one participant.

First instruction session (60 min)

- Administrative procedure for a new patient (similar as with other persons)
- Administrative procedure for the study: training protocol sheet, box for questionnaires
- Instruction for the warm-up: depending on personal preference the warm-up was done on a cycle ergometer, on a stepper or on a cross-trainer. 10 min of warm-up were recommended, with a low to middle intensity.
- Instruction for the seven resistance exercises: leg press, knee extension and knee flexion while sitting, hip abduction, heel rise on leg press, abdominals and back extension (see below for details and pictures).
- Initial resistance was established by setting a specific weight and asking the person to do as many repetitions as possible. According to the number of possible repetitions the resistance was adapted with the aim of achieving 25 repetitions with 50% of the one repetition maximum (1RM).
- Exercises for the knee and the heel rise were performed unilaterally, doing two series for each side.
- Participants were encouraged to do at least 2 min of break between two series. Exercising the other leg or doing another exercise during the break was allowed but not compulsory.
- Finally the instructions for the notes on the training protocol were given. Actual weight and number of repetitions and series were filled in the specified boxes for each training session.
- Instruction was given to perform three training sessions with this resistance over the next ten days or until the next appointment for the second instruction.

Second and third instruction session (30 min each)

- Check current performance based on the training protocol. Ask if any problems like pain, discomfort or disability had occurred.
- Adapting the resistance for hypertrophy training (second session): Based on the resistance so far the weight was set by the physiotherapist and the number of possible repetitions evaluated. Adaptations were done till about 12 were possible, meaning a resistance of about 80% of the 1RM.
- Further increase of resistance in week 6 (third instruction session) and encouragement to further increase the resistance, whenever more than 12 repetitions were possible.
- Check the notes on the training protocol.

All other sessions

- The remaining 21 sessions were performed individually according to the instructions.
- Participants were encouraged to schedule the two sessions per week with at least two days between.
- In the training room a responsible physiotherapist was always present for support and to answer questions. Depending on daytime the room is used by 5 to 30 persons in parallel.

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE

Department of Physiotherapy
Director
Martin L. Verra, PhD, PT

Description of the guided 12 week resistance training program

Adherence and adverse events

- As already mentioned all participants had an individual training protocol for the documentation. From these the adherence to the training program was evaluated, whereby more than 80% of the permitted training sessions (i.e. 21 sessions) was rated as acceptable performance.
- Additionally, all participants filled in a short weekly questionnaire for pain and disability, including two questions about side-effects of the training or problems occurring after the training sessions.

Description of exercises

Finally, the seven exercises are illustrated here as performed by a participant. The starting and the end positions on the device and the relevant instructions for joint angles and range of motion (ROM) are shown for each exercise.

Starting position **End position**

Exercise 1: Single leg squat on leg-press, for thigh muscles, sitting position with approximately 80° of hip flexion. ROM knee from 100° flexion to 5° flexion. Performed with both legs individually.

Exercise 2: Single leg knee extension, resis-tance at ankle ,for quadriceps muscle, sitting position, approximately 120° of hip flexion. ROM knee from 130° of flexion to 10° flexion. Performed with both legs individually.

Exercise 3: Single leg knee flexion, with resistance at ankle, for hamstring muscles, standing on opposite leg, trunk lean forward approximately 40° in the hip. Range of knee motion from 10° of flexion to 100° flexion. Performed with both legs individually.

The depicted model gave consent to publish the pictures in scientific journals

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE

Department of Physiotherapy
Director
Martin L. Verra, PhD, PT

Description of the guided 12 week resistance training program

Starting position | **End position**

Exercise 4: Bilateral hip abduction in sitting position, resistance laterally at the lower half of the thigh, hip range of motion from 10° to 40° of abduction.


Exercise 5: Single leg heel rise on leg press for triceps surae, sitting position with approximately 80° of hip flexion and 90° of knee flexion. Performed with both legs individually.


Exercise 6: Back extension, resistance bilaterally at shoulder plates, sitting position. Range of hip motion from 120° to 80° of hip flexion.


Exercise 7: Abdominals, resistance at chest in a sitting position.


The depicted model gave consent to publish the pictures in scientific journals

Additional file S2 to “Effect of Resistance Training on Muscle Properties and Function in Women with Generalized Joint Hypermobility: a Single-Blind Pragmatic Randomized Controlled Trial”

by Luder Gere, Aeberli Daniel, Mueller Mebes Christine, Haupt-Bertschy Bettina, Baeyens Jean-Pierre, Verra Martin L.

Detailed description of the outcome assessments

Musculoskeletal disorders may affect an individual in several dimensions of life. According to the World Health Organisation (WHO) the impact of health problems is described on four levels: body functions, body structures, activities and participation, and environmental factors as defined in the International Classification of Functioning, Disability and Health (ICF) (World Health Organisation, 2001). The outcome assessments in this study aim to evaluate the effects of a strength training program in women with GJH in all dimensions of the ICF. In terms of body structure muscle strength was measured isometrically and muscle and bone properties by peripheral quantitative computer tomography (pQCT). Regarding body functioning, muscle activity and ground reaction force during stair climbing were measured as usual activities related to movement control. Stair climbing was also included to assess the dimension of activities and participation, and patient reported questionnaires were used to detect impairments in daily life. Some environmental factors, mainly in terms of relationship and attitudes, were included in the questionnaires. Since there was no specific questionnaire for persons with GJH available, a set of three questionnaires was used to get wide-ranging information on activities, participation and environmental factors. In detail, the following assessments with their respective analyses were used in the study:

Muscle strength: The maximum isometric strength (MVC) and the rate of force development (RFD) of the knee extensors and knee flexors were measured on a custom-built strength measurement table with a one-dimensional strain gauge (KM 1500S; Megatron, Munich, Germany) calibrated in Newton (N). The participant sat with 90° of knee and hip flexion on the table and above the ankle a sling, connected to the force transducer, was tightly attached. The participant was asked to push forward as fast and as strong as possible and to hold the highest possible force for five seconds for the measurement of extensor strength. Then the force transducer was changed to the ventral attachment and the participant was asked to pull backwards in the same way for the flexors. After familiarization and two test trials, the three measuring trials were performed with a break in between of 30 s. During strength testing the EMG of the thigh muscles was recorded in sync with the respective force signals of the transducer (as described below).

To analyse muscle strength the maximum voluntary contraction (MVC), i.e. the maximal force in Newton and rate of force development (RFD) defined as the slope of the force curve between 20% and 80% of MVC in Newton/second, were calculated for knee extensors and knee flexors. For MVC and RFD the values were normalised to body mass and the maximal value of the three trials was taken.

Muscle properties: Using a Stratec XCT 3000 scanner (Stratec Medizintechnik, Pforzheim, Germany) the muscle cross sectional area (mCSA) and the muscle mass and density at the thigh as well as the total area of the thigh were measured at 33% of femur length above the knee by peripheral quantitative computer tomography (pQCT), as previously described (Aeberli et al., 2010).

For the analysis, the muscle variables were calculated with the integrated software of the device. Main variables were the mCSA and the total CSA in mm^2 as well as the muscle mass in mg and the muscle density in mg/cm^3. Both CSA parameters were calculated in relation to body mass.

Muscle activity: The muscle activity during stair climbing of four muscles of the right leg was measured using surface EMG: vastus medialis (VM) and vastus lateralis (VL) as knee extensors and semitendinosus (ST) and biceps femoris (BF) as knee flexors. Electrode placement and measurement procedure were defined according to the recommendations of ISEK (Merletti & Torino, 1997) and SENIAM (Hermens, 2000). In detail, after marking the correct electrode positions the skin was prepared by shaving and cleaning. For each muscle two oval pre-gelled AgCl-electrodes (Ambu Blue Sensor N, Ambu A/S, Ballerup, Denmark) of 5 mm diameter were placed in parallel 2 cm apart. Additionally, a single reference electrode was placed laterally over the femoral condyle. Skin impedance for each pair of electrodes was measured by an impedance meter (Digitimer D175, Digitimer Ltd, Welwyn Garden City, UK) and had to be below 5 kΩ. Otherwise, the electrodes were removed and the procedure with shaving and cleaning was repeated. All electrodes were then connected by cable via pre-amplifiers (baseline noise<1uV RMS, input impedance>100MΩ, common mode rejection ratio>100dB, input range of +/- 10mV, base gain of 500, and a 10-500Hz bandpass filter) to a small telemetry box (TeleMyo 2400T G2, Noraxon, Scottsdale, Arizona, USA), which was worn on the participant’s back. From there the signals were transmitted to a receiver (TeleMyo 2400R G2, Noraxon, Scottsdale, Arizona, USA) and recorded at a sampling rate of 1 kHz using a 12-bit analog-digital converter (Meilhaus ME-2600i, SisNova Engineering, Zug, Switzerland) and the software package “ads” (version 1.12, uk-labs, Kempen, Germany).

Stair climbing: To measure ground reaction forces (GRF) and EMG during stair ascent and descent a custom-built wooden six-step stair-case was used (riser height 17.9 cm, tread 29 cm, inclination 30.4°, according to Stacoff et al. (Stacoff, Diezi, Luder, Stüssi, & Kramers-De Quervain, 2005)). The stair has a handrail on both sides for security reasons and ends with a platform of one meter length to allow for comfortable turning. All steps were covered with non-slippery mats. GRFs were measured using two force plates (Type 9286BA, Kistler Winterthur, Switzerland) embedded in the 3rd and 4th step of the staircase and supported by an independent heavy-weight steel frame. The vertical force signals of both force plates were transmitted via a custom-built amplifier (uk-labs, Kempen, Germany) to the recording computer. To determine the second foot contact of the stride, which was not measured on a force plate, a tri-axial accelerometer (Model 317A, Noraxon, Scottsdale, Arizona, USA) was attached to the right malleolus and connected to the EMG telemetry system as described above. These signals were then recorded in sync with the EMG and the GRF and registered together in the software package “ads” (version 1.12, uk-labs, Kempen, Germany). The participants had to climb up and down the six steps ten times at a comfortable, self-selected speed barefoot and without using the handrail.

All EMG and GRF data were processed using a custom-made MATLAB toolbox (The MathWorks, Natick, Massachusetts, USA) in accordance with previously described algorithms(Luder et al., 2015; Stacoff et al., 2005). The measurements were visually inspected and six trials selected for separate analyses of stair ascent and descent in accordance with existing recommendations (Shiavi, Frigo, & Pedotti, 1998). The EMG of the MVC measurements served as a basis for normalization calculated by RMS over 500ms using the highest value out of three trials. Dynamic EMG data was baseline corrected, fully rectified and normalised to the corresponding 100% MVC value and linear envelopes built by low pass-filtering (second-order Butterworth, cut-off 20 Hz (Hug, 2011)). Peak muscle activation during stance was calculated from the linear envelopes. The vertical force–time curves were low-pass filtered (second-order Butterworth, cut-off 30 Hz), normalised to each participant's body mass and parameterised according to previously described standard methods (Stacoff et al., 2005). Foot contact and foot off were defined as the time points when the vertical force exceeded or fell below 3% of the subject’s body mass, respectively. Foot contact at the end of the stride was determined by visual analysis of the raw accelerometer signal. The maximum force-peak during weight acceptance (Fmax) was calculated as well as the respective time after the starting point (t to Fmax) and the slope of the force curve during the loading phase (loading rate). The mean value of six trials for each subject and condition was calculated for all parameters.

General health: The Medical Outcomes Study Short Form 36-Item (SF-36) was used to measure general health status of the participants. The SF-36 is a widely used multi-item generic health survey, which is available in German. The psychometric properties are well established and normative values for many patient groups are available, including those in the field of rheumatology (Busija et al., 2011). The SF-36 was used in the first clinical trial looking at the effects of a home program on the proprioception of hypermobile persons(Ferrell et al., 2004). The questionnaire is self-administered and takes about 10 minutes to complete. The questions target eight physical and mental health domains like physical, psychological and social functioning (Busija et al., 2011). The SF-36 scores were calculated according to the standard method (Busija et al., 2011), resulting in scores for all subscales, each ranging from 0-100, with higher values indicating better health-related quality of life, and two additional sum scores.

Disability in daily life: Since there was no specific questionnaire for persons with GJH available at the time of the study preparation, the Arthritis Impact Measurement Scales 2 (AIMS-2) was chosen to evaluate disability in daily life and restrictions in participation. The AIMS-2 is an assessment of physical functioning, pain, psychological status and other domains, originally developed for patients with rheumatoid arthritis and osteoarthritis. The questionnaire has a total of 78 questions and takes about 20 minutes to complete (Gignac, Cao, McAlpine, & Badley, 2011). The AIMS-2 is available in German and the psychometric properties are well established (Rosemann & Szecsenyi, 2007). The scale was also used in one of the published clinical trials with hypermobile persons (Sahin et al., 2008). The scores for the AIMS-2 were calculated according to the described methods (Gignac et al., 2011; Rosemann & Szecsenyi, 2007), resulting in a total score of between 0- 10, with high scores indicating poor health. Scores for seven subscales (walking and bending. social activity, pain, level of tension, satisfaction, health perceptions, impact) and three component models (physical component, affect, social interaction) were calculated.

Hypermobility questionnaire (HM-Q): A simple self-developed and face-validated questionnaire for pain and disability was also used. Participants were asked to provide information about their current pain intensity and locations on five-point Likert scales. The HM-Q had 28 items, of which 16 targeted pain in different body regions and 12 questions asked about disability in daily activities like bending, stair climbing, sitting for more than one hour or carrying loads. A sum score was calculated and scaled between 20-100 with lower values indicating better health. The activities in the questionnaire were chosen based on the most frequently mentioned problem situations in a previous cross-sectional study (Mueller Mebes et al., 2018).

Conduct of assessments

All assessments were performed by a single investigator (GL), blinded to group allocation. The first assessment took place before the training or control period and the second after the end of the training or after the 12 week waiting period. The second assessment had to take place within two weeks after the last training session. Completion of all assessments took about two hours for every participant at every time point.

References

Aeberli, D., Eser, P., Bonel, H., Widmer, J., Caliezi, G., Varisco, P. A., … Villiger, P. M. (2010). Reduced trabecular bone mineral density and cortical thickness accompanied by increased outer bone circumference in metacarpal bone of rheumatoid arthritis patients: A cross-sectional study. *Arthritis Research and Therapy*, *12*(3), R119. https://doi.org/10.1186/ar3056

Busija, L., Pausenberger, E., Haines, T. P., Haymes, S., Buchbinder, R., & Osborne, R. H. (2011). Adult measures of general health and health-related quality of life. *Arthritis Care & Research*, *63*(S11), S383–S412. https://doi.org/10.1002/acr.20541

Ferrell, W. R., Tennant, N., Sturrock, R. D., Ashton, L., Creed, G., Brydson, G., & Rafferty, D. (2004). Amelioration of symptoms by enhancement of proprioception in patients with joint hypermobility syndrome. *Arthritis and Rheumatism*, *50*(10), 3323–3328. https://doi.org/10.1002/art.20582

Gignac, M. A., Cao, X., McAlpine, J., & Badley, E. M. (2011). Measures of disability. *Arthritis Care and Research*, *63*(S11), S308–S324. https://doi.org/10.1002/acr.20640

Hermens, H. J. (2000). Development of recommendations for SEMG sensors and sensor placement procedures. *Journal of Electromyography and Kinesiology*, *10*, 361–374. https://doi.org/10.1016/s1050-6411(00)00027-4

Hug, F. (2011). Can muscle coordination be precisely studied by surface electromyography? *Journal of Electromyography and Kinesiology*, *21*(1), 1–12. https://doi.org/10.1016/j.jelekin.2010.08.009

Luder, G., Schmid, S., Stettler, M., Mueller Mebes, C., Stutz, U., Ziswiler, H. R., & Radlinger, L. (2015). Stair climbing - An insight and comparison between women with and without joint hypermobility: A descriptive study. *Journal of Electromyography and Kinesiology*, *25*(1), 161–167. https://doi.org/10.1016/j.jelekin.2014.07.005

Merletti, A. R., & Torino, P. (1997). Standards for reporting EMG data. *Journal of Electromyography and Kinesiology*, *7*(2), I–II. https://doi.org/10.1016/S1050-6411(97)90001-8

Mueller Mebes, C., Luder, G., Schmid, S., Stettler, M., Stutz, U., & Radlinger, L. (2018). Symptoms in Daily Life and Activity Level of Women with and without. *Rheumatology: Current Research*, *8*(3), 1–7. https://doi.org/10.4172/2161-1149.1000241

Rosemann, T., & Szecsenyi, J. (2007). Cultural adaptation and validation of a German version of the Arthritis Impact Measurement Scales (AIMS2). *Osteoarthritis and Cartilage / OARS, Osteoarthritis Research Society*, *15*(10), 1128–1133. https://doi.org/10.1016/j.joca.2007.03.021

Sahin, N., Baskent, A., Cakmak, A., Salli, A., Ugurlu, H., & Berker, E. (2008). Evaluation of knee proprioception and effects of proprioception exercise in patients with benign joint hypermobility syndrome. *Rheumatology International*, *28*(10), 995–1000. https://doi.org/10.1007/s00296-008-0566-z

Shiavi, R., Frigo, C., & Pedotti, A. (1998). Electromyographic signals during gait: Criteria for envelope filtering and number of strides. *Medical and Biological Engineering and Computing*, *36*(2), 171–178. https://doi.org/10.1007/BF02510739

Stacoff, A., Diezi, C., Luder, G., Stüssi, E., & Kramers-De Quervain, I. A. (2005). Ground reaction forces on stairs: Effects of stair inclination and age. *Gait and Posture*, *21*(1), 24–38. https://doi.org/10.1016/j.gaitpost.2003.11.003

World Health Organisation. (2001). *International classification of functioning, disability, and health : ICF*. Geneva: World Health Organization.

Supporting Table T4. Descriptive Data of Parameters from the Vertical Ground Reaction Force During Stair Ascent and Descent Before and After Training and for the Control Group as Mean Values (Standard Deviation) and the Respective Changes as Mean Difference and 95% Confidence Interval (CI)

	Control Group (n = 24)					Training Group (n = 27)				
	Pre	Post	Mean Diff	95%CI Lower	95% CI Upper	Pre	Post	Mean Diff	95%CI Lower	95% CI Upper
Fmax Up [%bm]	109.2 (6.6)	108.9 (6.8)	-0.3	-1.6	1.0	108.9 (6.1)	107.8 (6.4)	-1.0	-2.4	0.4
t to Fmax Up [ms]	200.3 (31.4)	199.1 (27.4)	-1.1	-7.3	5.0	205.9 (29.8)	208.5 (24.4)	2.5	-6.0	11.1
Loading Rate Up [%bm/s]	122.6 (50.2)	124.4 (44.9)	1.8	-4.2	7.8	113.9 (34.1)	111.1 (30.6)	-2.8	-9.3	3.7
Contact Time Up [ms]	734.5 (89.6)	726.6 (78.5)	-7.9	-26.3	10.5	764.3 (85.1)	768.2 (73.9)	3.9	-20.6	28.5
Fmax Down [%bm]	141.4 (13.7)	142.5 (12.5)	1.1	-2.8	8.0	140.0 (13.0)	141.5 (13.8)	1.5	-2.3	5.4
t to Fmax Down [ms]	157.6 (20.5)	159.5 (17.7)	1.9	-3.9	7.6	169.7 (21.1)	168.2 (17.2)	-1.5	-8.9	5.9
Loading Rate Down [%bm/s]	170.8 (54.9)	170.2 (53.2)	-0.7	-9.5	8.2	154.0 (37.0)	153.3 (37.1)	-0.8	-9.8	8.3
Contact Time Down [ms]	701.4 (104.2)	694.4 (85.7)	-7.0	-27.4	13.4	730.3 (84.0)	731.0 (65.1)	0.9	-26.4	27.7

diff = difference, Fmax = maximal force during weight acceptance, bm = body mass, t = time

Supplorting Table T5. Descriptive Data of Maximal Muscle Activation Derived by Electromyography (EMG) During Stair Ascent and Descent Before and After Training and for the Control Group as Mean Values (Standard Deviation) and the Respective Changes as Mean Difference and 95% Confidence Interval (CI)

EMG Muscle [% MVC]	Control Group (n = 24)					Training Group (n = 27)				
	Pre	Post	Mean Diff	95%CI Lower	95% CI Upper	Pre	Post	Mean Diff	95%CI Lower	95% CI Upper
Biceps Femoris max up	16.6 (18.8)	17.9 (18.4)	1.26	-1.87	4.40	10.8 (9.2)	9.9 (7.9)	-0.89	-2.41	0.64
Semitendinosus max up	17.5 (16.0)	17.6 (19.1)	0.10	-2.17	2.36	14.1 (11.3)	11.5 (9.9)	-2.57	-5.41	0.26
Vastus Lateralis max up	44.8 (24.1)	47.8 (25.6)	2.93	-5.21	11.07	36.5 (19.2)	40.7 (24.6)	4.21	-2.34	10.75
Vastus Medialis max up	45.2 (31.6)	45.5 (37.5)	0.34	-9.84	10.52	36.5 (20.1)	48.5 (35.7)	11.95	-0.43	24.32
Biceps Femoris max down	9.7 (11.8)	7.7 (9.5)	-1.93	-3.29	-0.57	5.4 (3.9)	4.6 (3.7)	-0.76	-1.99	0.47
Semitendinosus max down	12.4 (13.6)	9.5 (10.4)	-2.97	-6.69	0.76	6.8 (6.0)	5.7 (6.0)	-1.02	-2.65	0.61
Vastus Lateralis max down	25.8 (17.6)	34.4 (30.3)	8.55	1.46	15.64	20.0 (9.6)	21.4 (17.6)	1.49	-2.56	5.55
Vastus Medialis max down	25.9 (16.9)	29.0 (25.1)	3.08	-2.12	8.27	20.3 (10.6)	27.8 (12.3)	7.56	0.83	14.24

MVC = maximal voluntary contraction

Supporting Table T6. Descriptive Data for the Eight Dimensions of the SF-36 Before and After training and for the Control Group as Mean Values (Standard Deviation) and the Respective Changes, as Mean Difference and 95% Confidence Interval (CI)

Dimension of SF-36	Control Group (n = 24)					Training Group (n = 27)				
	Pre	Post	Mean Diff	95%CI Lower	95% CI Upper	Pre	Post	Mean Diff	95%CI Lower	95% CI Upper
Physical Functioning	95.0 (11.3)	94.8 (10.1)	-0.21	-1.37	0.95	94.1 (9.9)	91.5 (12.0)	-2.59	-4.74	-0.44
Physical Role Functioning	89.6 (25.5)	91.7 (25.2)	2.08	-2.23	6.39	90.1 (24.5)	87.0 (27.2)	-3.09	-9.99	3.83
Bodily Pain	84.8 (24.2)	83.1 (20.0)	-1.67	-8.97	5.63	75.3 (18.2)	77.1 (20.4)	1.74	-3.76	7.25
General Health Perception	79.8 (16.4)	82.5 (13.5)	2.63	-1.32	6.57	75.9 (22.5)	74.1 (23.3)	-1.85	-4.56	0.85
Vitality	58.8 (19.1)	60.0 (17.4)	1.25	-3.12	5.62	53.2 (21.0)	54.3 (22.0)	1.05	-3.52	5.62
Social Role Functioning	87.0 (16.3)	90.1 (13.3)	3.13	0.32	5.93	93.1 (13.6)	92.6 (15.2)	-0.46	-5.86	4.93
Emotional Role Functioning	90.3 (20.1)	95.8 (15.0)	5.56	-1.22	12.33	95.1 (12.1)	84.0 (26.8)	-11.11	-22.68	0.45
Mental Health	73.5 (17.4)	76.5 (14.7)	3.00	-1.52	7.52	73.3 (20.8)	75.4 (19.2)	2.11	-3.31	7.54
Physical Health (sum score)	54.6 (7.3)	54.2 (7.1)	-0.41	-1.93	1.11	52.3 (7.1)	52.0 (7.9)	-0.36	-2.04	1.31
Mental Health (sum score)	49.2 (8.7)	51.2 (8.1)	2.05	-0.01	4.11	51.3 (6.8)	50.8 (8.2)	-0.54	-3.95	2.87

Scoring for individual dimensions is 0-100 with lower scores indicating poorer health, for the sum scores 50 is equivalent to the US-norm population values.

Supporting Table T7. Descriptive Data for the Dimensions of the AIMS-2 and the Hypermobility Questionnaire Before and After training and for the Control Group as Mean Values (Standard Deviation) and the Respective Changes, as Mean Difference and 95% Confidence Interval (CI)

Dimensions of AIMS-2	Control Group (n = 24)					Training Group (n = 27)				
	Pre	Post	Mean Diff	95%CI Lower	95% CI Upper	Pre	Post	Mean Diff	95%CI Lower	95% CI Upper
Walking, Bending	0.4 (0.8)	0.5 (1.2)	0.04	-0.23	0.31	0.6 (0.8)	0.8 (1.7)	0.19	-0.50	0.87
Social Activity	4.4 (1.3)	4.2 (1.4)	-0.20	-0.62	0.22	4.3 (2.0)	3.8 (2.0)	-0.48	-0.97	0.01
Pain	1.3 (1.8)	1.3 (1.7)	0.00	-0.27	0.27	1.7 (1.9)	1.3 (1.7)	-0.39	-0.75	-0.03
Level of Tension	3.4 (1.8)	3.3 (1.4)	-0.06	-0.70	0.57	3.5 (1.3)	3.4 (1.7)	-0.09	-0.62	0.43
Satisfaction	0.9 (1.5)	0.7 (0.7)	-0.24	-0.72	0.25	0.9 (1.4)	1.1 (1.2)	0.16	-0.14	0.46
Health Perceptions	2.6 (2.2)	2.6 (2.0)	0.00	-0.72	0.72	3.1 (2.3)	3.1 (2.1)	0.00	-0.64	0.64
Impact	1.9 (1.9)	2.0 (2.2)	0.12	-0.55	0.79	2.1 (2.4)	2.1 (2.4)	0.00	-0.48	0.48
Physical Component	0.3 (0.7)	0.2 (0.5)	-0.06	-0.18	0.06	0.2 (0.3)	0.2 (0.4	0.02	-0.10	0.13
Affect	2.7 (1.6)	2.6 (1.3)	-0.07	-0.65	0.50	2.8 (1.2)	2.8 (1.4)	0.04	-0.32	0.40
Social Interaction	3.2 (1.0)	3.2 (1.1)	0.01	-0.36	0.37	3.1 (1.3)	3.0 (1.1)	-0.17	-0.42	0.09
HM-Q (sum score)	29.0 (8.6)	27.1 (7.0)	-1.82	-3.73	0.08	32.6 (10.9)	31.1 (7.9)	-1.59	-3.82	0.64

AIMS-2 = Arthritis impact measurement scales 2 (scale 0-10, lower scores indicating better health), HM-Q = Hypermobility questionnaire (scale 20-100, with lower values indicating better health)