FACULTY OF MEDICINE AND HEALTH SCIENCES

MUSCLE FUNCTION AND ITS DETERMINANTS IN ADULTS WITH OSTEOGENESIS IMPERFECTA TYPE I

CROSS-SECTIONAL STUDY

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TABLE OF CONTENTS

Content

acknowledgment 4

TABLE OF CONTENTS 5

list of figures 7

list of tables 7

list of abbreviations 8

1 Abstract 10

1.1 Nederlands abstract 10

1.2 English abstract 11

2 Introduction 13

3 Method 15

3.1 Participants 15

3.2 Outcome measures 16

3.2.1 Body composition 16
3.2.2 General characteristics 16
3.2.3 Fracture history 16
3.2.4 Hypermobility 16
3.2.5 Pain characteristics 17

3.3 Muscle function parameters 17

3.4 Physical activity parameters 18

3.5 Statistical analysis 18

4 Results 20

4.1 Results outcome measures 20

4.2 Results muscle function parameters 21

4.3 Results physical activity parameters 21

4.4 Results univariate ANCOVA tests 22

5 Discussion/conclusion 26

6 populariserende samenvatting 34

7 Maatschappelijke impact en meerwaarde 35

8 bewijs van indiening bij het ethisch comité 36

8.1 Ethical Committee 36

9 Reference list 42

LIST OF FIGURES

Figure 1: Recruitment of individuals with OI

LIST OF TABLES

Table 1: Results outcome measures
Table 2: Results muscle function parameters
Table 3: Results physical activity parameters
Table 4: Results univariate ANCOVA test for 30CRT
Table 5: Results univariate ANCOVA test for HG_dom
Table 6: Results univariate ANCOVA test for HG_nondom
Table 7: Results univariate ANCOVA test for HHD_shoulder
Table 8: Results univariate ANCOVA test for HHD_hip
Table 9: Results univariate ANCOVA test for HHD_ankle

LIST OF ABBREVIATIONS

**…: Number of missing variables
[Q1-Q3]: Interquartile range

30CRT: 30 second Chair Rise Test

AG_mod_min_Dmean: ActiGraph moderate activity in minutes per day – mean

AG_MVPA_min_mean: ActiGraph moderate to vigorous activity in minutes per day – mean

AG_steps_mean: ActiGraph steps per day – mean

AG_vig_min_mean: ActiGraph vigorous activity in minutes per day – mean

AG_vvig_min_mean: ActiGraph very vigorous activity in minutes per day – mean

AG_wear_mean: ActiGraph wear time in minutes per day – mean

ANCOVA: Analysis of covariance

Beighton_total: Beighton total score

BMI: Body Mass Index

CSA: Cross-sectional Area

DXA: Dual-energy X-ray absorptiometry

Fat_subtot: Subtotal fat mass

Fract_nr: Number of fractures

Fract_nr12m: Number of fractures the last 12 months

GJH: Generalized Joint Hypermobility

hEDS: Hypermobile Ehlers-Danlos syndrome

HG: Handgrip

HG_dom: Maximal value handgrip test dominant arm

HG_end: Handgrip endurance test dominant arm

HG_nondom: Maximal value handgrip test non-dominant arm

HHD: Handheld Dynamometer

HHD_ankle: Handheld dynamometry ankle dorsiflexors

HHD_hip: Handheld dynamometry dominant hip flexors

HHD_shoulder: Handheld dynamometry shoulder abductors

HSD: Hypermobility Spectrum Disorders

ICC: Intra-class correlation coefficient

Lean_subtot_kg: Subtotal lean mass (kg)

LLAS: Lower Limb Assessment Scale

LLAS_L: Lower Limb Assessment Scale left side

LLAS_R: Lower Limb Assessment Scale right side

MET: Metabolic Equivalent of Task

MUSCLE_AREA: 66% muscle CSA of tibia

MUSCLE_DEN: 66% muscle density of tibia

OI : Osteogenesis Imperfecta

pQCT: peripheral Quantitative Computed Tomography

QoL: Quality of Life

RaMUSCLE_AREA: 66% muscle CSA of radius

RaMUSCLE_DEN: 66% muscle density of radius

SF-36: 36-Item Short Form Health Survey

SPSS: Statistical Package for Social Sciences

ULHAT: Upper Limb Hypermobility Assessment Tool

ULHAT_L: Upper Limb Hypermobility Assessment Tool left side

ULHAT_R: Upper Limb Hypermobility Assessment Tool right side

VAS: Visual Analogue Scale

VASgen: general VAS score

ZOI: Zelfhulp Osteogenesis Imperfecta

1 ABSTRACT

1.1 Nederlands abstract

Achtergrond: Osteogenesis Imperfecta (OI) of broze botten ziekte is een heterogene genetische bindweefselaandoening gekenmerkt door verminderde productie van collageen type I, wat essentieel is voor de vorming van de extracellulaire botmatrix. Het is een zeldzame erfelijke aandoening met een incidentie van 1 op 15 000/ 20 000. OI wordt gekenmerkt door extreme botfragiliteit en lage botmassa. Dit kan leiden tot botdeformaties, hogere vatbaarheid voor fracturen, pijn, groeideficiëntie en immobiliteit. Andere symptomen zoals blauwe sclera, slechthorendheid, cardiovasculaire/respiratoire afwijkingen, gewrichtshypermobiliteit en Dentinogenesis imperfecta kunnen ook optreden vanwege het uitgebreide scala aan fenotypes. Type I is het meest voorkomende en mildste type van OI met weinig tot geen misvormingen. Mutaties in COL1A1/COL1A2 liggen aan de basis van deze aandoening en kunnen resulteren in een verminderde spierkracht, wat een negatief effect kan hebben op de botmassa bij de OI-populatie. Die spier-botrelatie kan worden verklaard vanuit een biomechanisch en biochemisch aspect.

Doelstelling: De crosstalk tussen spieren en botten is bij patiënten met OI type I hetzelfde als bij gezonde personen. Een klinisch kenmerk van OI is spierzwakte die de botfragiliteit verder kan verergeren. Er is een tekort aan spiergerichte gegevens bij personen met OI. Het doel van dit onderzoek is om de spierfunctie en de bijkomende determinanten ervan te onderzoeken bij volwassenen met OI type I. Als gevolg van hun verminderde spierkracht hebben ze vaak een verminderde mobiliteit, wat kan leiden tot spieratrofie. Dit alles heeft een grote impact op de kwaliteit van leven.

Onderzoeksdesign: Cross-sectioneel onderzoek.

Methode: 45 Belgische en Australische individuen met OI type I en 45 leeftijds- en geslachtsafgestemde controlepersonen werden via verschillende kanalen gerekruteerd. Uitkomstmaten zoals lichaamssamenstelling, algemene kenmerken, fractuurgeschiedenis, hypermobiliteit en pijnkenmerken werden onderzocht alsook de spierfunctieparameters en fysieke activiteitsparameters. De statistische analyses werden uitgevoerd in SPSS 29.

Resultaten: De resultaten toonden significante verbanden aan tussen parameters van spierfunctie en specifieke determinanten bij volwassenen met OI type I. ANCOVA testen indiceerden dat fysieke activiteitsparameters, respectievelijk matige en intense fysieke activiteit, geassocieerd zijn met 30 second Chair Rise Test (30CRT) (p=0.087, p=0.099), handdynamometrie van de schouder abductoren (HHD_shoulder) (p=0.255, p=0.179) en handdynamometrie van de heup flexoren (HHD_hip) (p=0.780, p=0.741). Lengte vertoonde een verband met de handknijpkracht van de dominante zijde (HG_dom) (p=0.357), de handknijpkracht van de niet-dominante zijde (HG_nondom) (p=0.929) en handdynamometrie van de enkel dorsiflexoren (HHD_ankle) (p=0.093), terwijl de spierdichtheid geassocieerd was met HG_dom

(p=0.227), HG_nondom (p=0.151) en HHD_hip (p=0.136). Handknijpkracht-parameters toonden een link met de spierdichtheid alsook met de lengte, terwijl HHD_hip significant geassocieerd was met fysieke activiteit en spierdichtheid. Hypermobiliteit covariaten vertoonden geen significante associatie met de onderzochte parameters.

Conclusie: De resultaten van dit onderzoek tonen aan dat de parameters voor lichaamssamenstelling, spierfunctie en fysieke activiteit elk een eigen verband vertonen met de onderzochte determinanten bij volwassenen met OI type I. Deze bevindingen kunnen helpen bij het opstellen van een trainingsprogramma geschikt voor deze populatie, hoewel er meer onderzoek noodzakelijk is voor de andere typen OI.

Sleutelwoorden: Osteogenesis Imperfecta type I, volwassenen, spierfunctie, fysieke activiteit, lichaamssamenstelling

1.2 English abstract

Background: Osteogenesis Imperfecta (OI) or Brittle Bone Disease is a heterogeneous genetic connective tissue disorder characterized by reduced production of collagen type I, which is essential for the formation of the extracellular bone matrix. It is a rare heritable disorder with an incidence of 1 in 15 000/ 20 000. OI is characterized by extreme bone fragility, low bone mass and susceptibility to fractures. This can lead to deformities, pain, growth deficiency and immobility. Other symptoms include blue sclerae, hearing impairment, cardiovascular/respiratory defects, joint hypermobility and Dentinogenesis imperfecta due to its wide range of phenotypes. Type I is the most common and mildest type of OI with little to no deformities. Mutations in COL1A1/COL1A2 lie at the root of this condition and can result in reduced muscle strength, which can have a negative effect on bone mass. This muscle-bone relationship can be explained from both a biomechanical and biochemical aspect.

Objective: The muscle-bone crosstalk is equal in individuals with OI type I as in healthy people. A clinical feature of OI is muscle weakness which can further exacerbate bone fragility. There is a scarcity of muscle-focused data in people with OI. The objective of this study is to examine muscle function and its determinants in adults with OI type I. As a result of their decreased muscle strength they often have reduced mobility, which can lead to muscle atrophy and muscle disuse. This has a major impact on their quality of life (QoL).

Study Design: Cross-sectional study.

Methods: 45 Belgian and Australian individuals with OI type I and 45 gender and age matched control subjects were recruited trough different channels. Outcome measurements such as body composition, general characteristics, fracture history, hypermobility and pain characteristics were examined. The muscle function parameters and physical activity parameters were also investigated. Statistical analysis in SPSS 29 were performed.

Results: The results revealed significant associations between muscle function parameters and specific determinants among adults with OI type I. ANCOVA tests showed that physical activity parameters, respectively moderate and vigorous physical activity, are linked with 30 second Chair Rise Test (30CRT) (p=0.087, p=0.099), handheld dynamometry of the shoulder abductors (HHD_shoulder) (p=0.255, p=0.179) and handheld dynamometry of the hip flexors (HHD_hip) (p=0.780, p=0.741). Height correlated with handgrip strength of the dominant side (HG_dom) (p=0.357), handgrip strength of the non-dominant side (HG_nondom) (p=0.929) and handheld dynamometry of the ankle dorsiflexors (HHD_ankle) (p=0.093), while muscle density was associated with HG_dom (p=0.227), HG_nondom (p=0.151) and HHD_hip (p=0.136). Handgrip strength parameters had a link with both muscle density and height, whereas HHD_hip was significantly associated with physical activity and muscle density. Hypermobility covariates did not demonstrate a significant relation with any of the investigated parameters.

Conclusion: The findings of this study show that body composition parameters, muscle function parameters and physical activity parameters all have their individual association with the investigated determinants in adults with OI type I. These findings can help in creating a training program suitable for this population, although more research is necessary for other types of OI.

Keywords: Osteogenesis Imperfecta type I, adults, muscle function, physical activity, body composition

2 INTRODUCTION

Osteogenesis imperfecta (OI), also called Brittle Bone Disease, is a rare heritable connective tissue disorder of the extracellular matrix with an incidence of 1 in 15 000/ 20 000 (1). It is a heterogeneous genetic disease that is primarily characterized by low bone mass and bone fragility that causes an increased risk of fractures, skeletal dysplasia, immobility, growth deficiency and pain (1,2). Symptoms may also manifest within the function of other connective tissues due to the extensive range of phenotypes. This can lead to blue sclerae, hearing impairment, joint hypermobility, cardiovascular/respiratory defects and Dentinogenesis imperfecta (3). All these symptoms stem from impaired production of type I collagen (COL1A1 and COL1A2). Type I collagen is the major component of the extracellular bone matrix, the quantity and integrity determines bone strength (2). It is also found in the connective tissue around muscle fibers, in tendons and in ligaments, which may explain the weaker muscles and lower muscle mass found in these individuals and the difficulties in mechanotransduction: the term that explains the muscle-bone crosstalk where cells convert mechanical stimuli from muscle activity into biochemical signals leading to cellular responses promoting the formation of bone. Thus, bone formation is stimulated by muscle contraction and in reverse, bone strength influences muscle strength (1,4). According to Sillence, D. et al. (5) there are four different types of OI which vary in severity. Individuals with type I OI have no deformities, but they do have blue sclera, whereas type II is a lethal form of OI. Type III are individuals with deformities that progress over time and lastly type IV is a more severe form of OI. Genetic research provided an extension of this classification, revealing a broader spectrum of mutations and genetic variations that have led to the identification of additional subtypes of OI (6). This study, however, exclusively included individuals diagnosed with OI type I, characterized by an autosomal dominant mode of inheritance. Type I is the mildest and most common type with little to no deformities (1,2).

Muscle weakness has a huge impact on bone fragility and vice-versa. Crosstalk between bone and muscle can be explained based on different aspects (1). First, there is the biomechanical aspect including Wolff's law and Frost's mechanostat theory that show the importance of mechanical loading on bones to gain strength. By contracting the muscle, mechanical tension is send through the tendon and on to the bone which stimulates an increase of bone mass (1). This also operates reciprocally: strains created below a certain threshold stimulate the loss of bone. Secondly, biochemically speaking, myokines and osteokines amongst others provide the endocrine communication between bone and muscle (7,8). There are different myokines that play an important role in the crosstalk such as myostatin, irisin and interleukine-6 (1,9,10,11). These myokines are produced and released when muscular contractions increase, during physical exercise for example. Depending on the type of myokine involved, bone cells are influenced in either an anabolic or

catabolic manner (9). The osteokines such as osteocalcin and sclerostin are secreted by bone tissue as a result of physical activity triggering an entire signal transduction cascade (9,11). As mentioned earlier, bone tissues affect skeletal muscle mass through the crosstalk between muscle and bone, with osteokines playing a significant role in modulating this relationship. Bone formation and bone resorption, the anabolic and catabolic processes induced by osteokines and myokines, are guided by the osteocytes in the bone. Osteocytes are the most common cells in the bone matrix and they play a role in the maintaining of the skeletal homeostasis (1). Because of the many fractures and thereby the necessary immobilization, activity levels of individuals with OI could be decreased, which has an effect on their functional ability and physical fitness (12).

Furthermore, studies indicate that muscle weakness is a clinical feature of OI type I, which can further exacerbate bone fragility. In a recent study, nearly 80% of individuals with confirmed COL1A1/COL1A2 mutations and presenting an OI type I phenotype exhibited a deficit in muscle force. The muscle-bone relationship is the same in healthy people as in subjects with OI type I. And so, a lower muscle force in the OI population will have a negative effect on bone mass (13). Another study revealed that although both individuals with OI and healthy individuals exhibit similar levels of physical activity, the muscle force and muscle power was still weaker in the subjects with OI. This finding suggests that the observed muscle weakness cannot be attributed to differences in physical activity levels, as they parallel those of healthy counterparts. Instead, the root cause of muscle weakness stems from impaired collagen synthesis within the muscles and their tendons (14). Muscles and tendons rely on collagen type I within the extracellular matrix to facilitate the transmission of muscle force. However, in individuals with OI the ability of muscles to transfer contraction forces efficiently is reduced compared to those without the condition (15). This diminished efficiency can lead to reduced mechanical strength and contractility, consequently impairing the muscle function and in turn significantly impacting the quality of life (QoL) in individuals affected with OI (16). Their decreased muscle force results in reduced mobility, which in turn can exacerbate muscle disuse and atrophy, creating a vicious circle. The greater the deficit in muscle force, the lower the individual's functional capabilities become (17). It is of utmost importance to identify the root cause of their muscle strength loss and strive to counteract it. In doing so, the vicious cycle can be interrupted which can lead to preservation of their QoL to the fullest extent possible. Further research is necessary to elucidate the mechanisms driving this phenomenon.

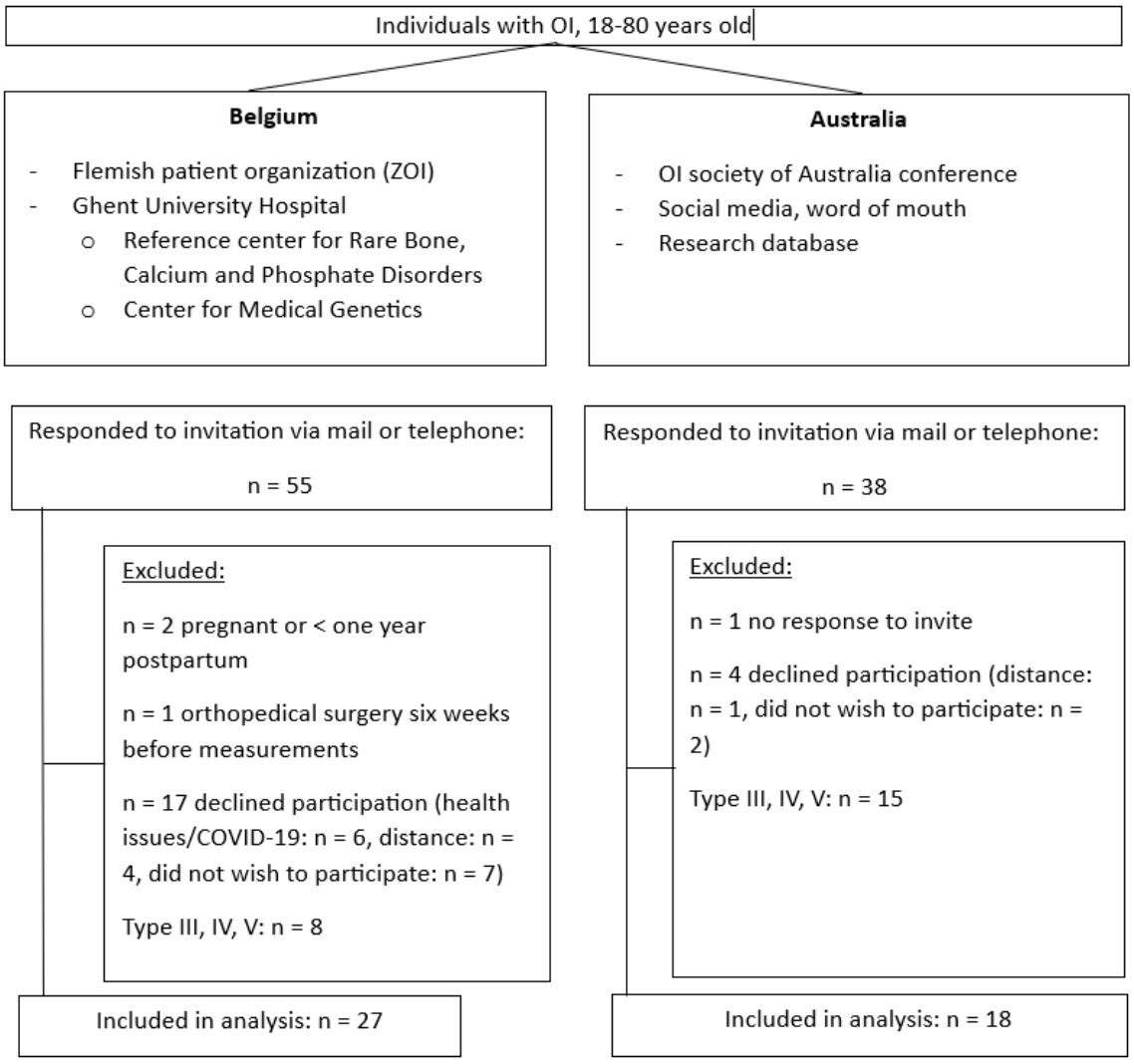
Given the scarcity of muscle-focused data in subjects with OI, the aim of this study is to examine muscle function and its determinants in adults with OI type I.

3 METHOD

3.1 Participants

This cross-sectional study included 45 individuals with OI type I and 45 age- and gender matched control subjects (± 1 year when < 30 years old, ± 3 years when ≥ 30 years old). Recruitment was done in Belgium (OI and controls both n = 27) and Australia (OI and controls both n = 18) (Figure 1). A written informed consent was obtained from all participants between October 2018 and September 2022. Healthy controls were recruited trough flyers, social media, and researcher networks. Participants with OI were recruited through the Flemish patient organization: Zelfhulp Osteogenesis Imperfecta (ZOI) and through the Ghent University hospital (Figure 1). Participants were excluded based on following exclusion criteria: [1] age < 18 years or > 80 years; [2] pregnancy or less than one year postpartum; [3] cardiac arrhythmias or failure; [4] neurological disorders not related to OI impacting balance or gait; [5] orthopedical surgery within six weeks before measurements and [6] having OI type III, IV or V.

Figure 1: Recruitment of individuals with OI



3.2 Outcome measures

3.2.1 Body composition

The individuals' height and weight were gathered as parameters. Height (m) was measured by using a stadiometer (Harpenden, Holtain Ltd) and weight (kg) was assessed using Dual-energy X-ray absorptiometry (DXA; Hologic QDR Discovery device; software version 2.3.1; Hologic, Bedford, MA, USA) in Belgium and a digital scale in Australia. Subsequently, body mass index (BMI), (kg/m^2) was calculated (18).

By using DXA, subtotal lean mass (kg; Lean_subtot_kg) and fat mass (g; Fat_subtot) were measured. Peripheral Quantitative Computed Tomography (pQCT; XCT-2000; Stratec Medizintechnik, Pforzheim, Germany) was used to assess muscle density (mg/cm^3) and muscle cross-sectional area (CSA, mm^2) of the radius and tibial shaft of the non-dominant side (if fractured or fixation materials: dominant side), using the 66% measurement site (relevant offset distance) starting from the distal end of the respective bones (18). A more detailed explanation of the measurement site used in performing pQCT can be found in the article by Whittier, D.E. et al. (19). After measuring the outer bone contours of the radius and tibia, pQCT with a 280 mg/cm^3 threshold was used to calculate the CSA (18).

3.2.2 General characteristics

Other general characteristics like age and gender were also included in the study.

3.2.3 Fracture history

Fracture history included comprehensive fracture history (total number of fractures since birth until the intake; Fract_nr) and the number of fractures within the preceding twelve months before testing (Fract_nr12m).

3.2.4 Hypermobility

To investigate joint hypermobility, the Beighton total score (Beighton_total), Lower Limb Assessment scale (LLAS) left side (LLAS_L) and right side (LLAS_R) and Upper Limb Hypermobility Assessment Tool (ULHAT) left side (ULHAT_L) and right side (ULHAT_R) were used. The Beighton score includes forward flexion of the trunk, apposition of the thumb to the forearm and hyperextension of the knees, the elbows and the fifth finger (20). Comparing the five tests left and right each time, with the exception of the first test, each test is scored with one point, resulting in a maximum of nine points with a positive Beighton score of four or more for men and women over the age of 50. In individuals under the age of 50 years old a positive Beighton score was defined as five or more. The Beighton score is considered age-related as the hypermobility decreases when getting older (21). The LLAS was used to assess the level of hypermobility of the lower limbs and the ULHAT was used

to assess the upper limbs. Both scales consist of twelve tests each and were evaluated bilaterally. A cut-off score of ≥7/12 to indicate hypermobility was established (22).

3.2.5 Pain characteristics

The assessment of the participants baseline pain levels was conducted through the utilization of two quantitative measurements. Firstly, the Visual Analogue Scale (VAS) was used, yielding scores on a scale of zero to ten. Secondly, the Margolis Pain Diagram (Margolis) employs a percentage-based representation for pain assessment. Each anatomical region is assigned a specific percentage value corresponding to the degree of pain reported by the patient. The Margolis value is then calculated as the sum of the percentage values attributed to the body parts that the patient identifies as experiencing pain (23).

3.3 Muscle function parameters

A handheld dynamometer (HHD) was applied for the hip flexors (HHD_hip), ankle dorsiflexors (HHD_ankle) and shoulder abductors (HHD_shoulder) of the dominant side using the MicroFET 2 (Hoggan Scientific, Salt Lake City, UT, USA). For measuring the hip flexors, the participant was in a seating position with the hip in a 90° angle, a relaxed knee, the contralateral side in a neutral position and with the feet supported on the ground. A 0° angle in hip, knee and ankle was necessary for the ankle dorsiflexion measurements and the position for the shoulder abduction was an extended elbow and abducted shoulder of 45° (24). For both the ankle dorsiflexion and shoulder abduction the reliability in a healthy population was excellent with an intra-class correlation coefficient (ICC) of 0.94 for the ankle dorsiflexion (25) and an ICC of 0.98 for the shoulder abduction (26). The maximal handgrip (HG) strength was tested on the dominant hand (HG_dom) and the non-dominant hand (HG_nondom). The force was measured using a Jamar hydraulic dynamometer (Sammons Preston Rolyan, Bolingbrook, IL, USA) (18). The participants sat in an upright position with feet placed flat on the floor. The shoulder, forearm and wrist were in a neutral position and the elbow was flexed at 90° (27). The intra-tester reliability in healthy people for the Jamar device had an ICC of 0.94-0.98 (28). Both the HHD and maximal HG assessments were performed three times, the highest scored attempt was selected for inclusion in the analysis. HG endurance test of the dominant hand (HG_end) was assessed by squeezing as long as possible until the force fell below half the maximum value determined during the maximal HG test.

The 30 second chair rise test (30CRT) was used to assess functional strength of the lower extremities. The individuals were asked to sit down on a chair and stand up again with arms crossed over the chest as quickly as possible within 30 seconds. The number of repetitions were counted. Each repetition should be done by standing up until the knees are fully extended, sitting down was counted when the buttocks made contact with the chair (29).

3.4 Physical activity parameters

The evaluation of the patient's physical activity level was conducted through the utilization of a tri-axial accelerometer (ActiGraph GT3X-BT, ActiGraph, Pensacola, USA). The ActiGraph was worn on the right hip (midaxillary line at the level of the iliac crest) continuously for a duration of seven consecutive days (18). Mean measurements were computed individually for the seven consecutive days the individuals wore the ActiGraph. The following parameters were examined: ActiGraph steps per day – mean (AG_steps_mean), ActiGraph wear time in minutes per day – mean (AG_wear_mean) and the duration of four intensity levels per day (quantified in minutes): ActiGraph moderate activity in minutes per day – mean (AG_mod_min_Dmean) 3.0-5.9 Metabolic Equivalent of Task (MET), ActiGraph moderate to vigorous activity in minutes per day – mean (AG_MVPA_min_mean), ActiGraph vigorous activity in minutes per day – mean (AG_vig_min_mean) $\geq$ 6 MET, ActiGraph very vigorous activity in minutes per day – mean (AG_vvig_min_mean) (30).

3.5 Statistical analysis

Statistical analyses were performed with Statistical Package for Social Sciences (SPSS, IBM Corp, Armonk, NY, USA) version 29. Firstly, normal distribution for all parameters related to the research question and that could possibly prove a relation between physical activity and its association with muscle parameters was sorted out for the two types (controls - OI type I) separately by splitting the file. By analysing the stem and leaf plot and the boxplot, outliers were detected. Afterwards, the scores were compared between the healthy participants and the participants with OI: an independent samples t-test was used for continuous parameters that were normally distributed, otherwise the Mann-Whitney U test was used. When the variables were ordinal, the two groups were compared by using the chi-square test. To describe the distribution, the mean and standard deviation are reported for normally distributed variables. For variables not normally distributed, the mean and interquartile range are provided. These findings, along with p-values considered significant when $p < 0.05$, are summarized in Table 1-3. Variables with a p-value ranging from 0.05 – 0.1 were defined as trend values. Lastly six depending variables were further examined with the control group and OI group as a fixed factor: HG_dom, HG_nondom, HHD_hip, HHD_ankle, HHD_shoulder as strength parameters and the 30CRT as a functional activity parameter. An univariate analysis of covariance (ANCOVA) test was conducted to examine if different covariates, such as height, the level of physical activity, muscle density and hypermobility, had a significant association with each of the six variables. The zero hypothesis for the ANCOVA test stated a non-significant difference between the control group and the OI group. With a p-value less than 0.05, the zero hypothesis could be rejected and so, there would be a significant difference between the groups. If the naked model (a p-value calculated only with the depending variable) of the univariate

ANCOVA test was less than 0.05 and became more than 0.05 by adding a covariate, that covariate was stated to have a big association with that depending variable.

4 RESULTS

4.1 Results outcome measures

Table 1 shows the differences in outcome measures between individuals with OI type I and controls. No significant differences were found for the following parameters: weight (p = 0.695), age (p = 0.994), gender (p = 1.000) and for the parameters with trend values: BMI (p = 0.066), Fat_subtot (p = 0.051), radius 66% muscle CSA (RaMUSCLE_AREA) (p = 0.066), the Beighton_total (p = 0.062). Height, Fract_nr, LLAS_L and LLAS_R, Margolis, and general VAS score (VASgen) showed an exceptional significant difference in the OI group in comparison with the control group (p < 0.001). A significant difference between the OI group and the control group was found in Lean_subtot_kg (p = 0.013), 66% muscle density of the tibia (MUSCLE_DEN) and radius (RaMUSCLE_DEN) (p = 0.006 and p = 0.040), 66% muscle CSA of the tibia (MUSCLE_AREA) (p = 0.001), Upper Limb Hypermobility Assessment Tool left (ULHAT_L) (p = 0.012) and right (ULHAT_R) (p = 0.021). The Fract_nr12m did not change over the course of the study.

Table 1: Results outcome measures

	OI TYPE I	CONTROLS	P-VALUE
Height (m)	1.62 ± 0.09	1.70 ± 0.10	**p < 0.001**
Weight (kg)	72.5 ± 13.8	73.6 ± 13.0	p = 0.695
BMI (kg/m2)	27.7 [23.6 – 30.8]	25.3 [22.7 – 27.4]	p = 0.066
Lean_subtot_kg (kg)	43.6 ± 9.7	50.2 ± 9.2	**p = 0.013**
Fat_subtot (g)	24260.6 ± 7232.5	20511.8 ± 6554.9	p = 0.051
MUSCLE_DEN	75.0 [73.9 – 76.4] **18	76.6 [75.2 – 78.7] **18	**p = 0.006**
MUSCLE_AREA (mm^2)	6093.5 ± 1381.3	7317.3 ± 1198.3	**p = 0.001**
RaMUSCLE_DEN	77.4 [76.6 – 79.3] **19	78.7 [77.0 – 79.9] **19	**p = 0.040**
RaMUSCLE_AREA (mm^2)	3030.7 ± 917.6	3478.3 ± 798.4	p = 0.066
Age (years)	44.8 ± 13.3	44.8 ± 12.8	p = 0.994
Gender			p = 1.000
Fract_nr	**16	**14	**p < 0.001**
Fract_nr12m	**16	**14	
Beighton_total (/9)	1.5 [0.0 – 2.0]	1.0 [0.0 – 2.0]	p = 0.062
ULHAT_L (/12)	3.7 [2.0 – 5.0] **1	2.6 [0.0 – 4.0]	**p = 0.012**
ULHAT_R (/12)	3.6 [2.0 – 5.8] **1	2.5 [1.0 – 4.0]	**p = 0.021**
LLAS_L (/12)	2.3 [1.0 – 3.5]	1.0 [0.0– 2.0]	**p < 0.001**
LLAS_R (/12)	2.6 [1.0 – 4.0]	1.0 [0.0 – 2.0]	**p < 0.001**
Margolis (%)	7.1 [1.3 – 9.3]	0.6 [0.0 – 0.0] **14	**p < 0.001**
VASgen (/10)	2.7 [0.8 – 4.0]	0.8 [0.0 – 2.0] **1	**p < 0.001**

*Normal distributed data is noted as mean ± standard deviation; Non-normal distributed data as mean [Q1-Q3]. **… = number of missing variables; **p** is a significant value. Abbreviations = BMI: Body Mass Index,*

Lean_subtot_kg (kg): Subtotal lean mass (kg), Fat_subtot: Subtotal fat mass (g) , MUSCLE_DEN: 66% muscle density of tibia, MUSCLE_AREA (mm^2): 66% muscle CSA of tibia in mm^2, RaMUSCLE_DEN: 66% muscle density of radius, RaMUSCLE_AREA (mm^2): 66% muscle CSA of radius in mm^2, Fract_nr: Number of fractures, Fract_nr12m: Number of fractures in the last 12 months, Beighton_total (/9): Beighton total score, ULHAT_L (/12): Upper Limb Hypermobility Assessment Tool left side, ULHAT_R (/12): Upper Limb Hypermobility Assessment Tool right side, LLAS_L (/12): Lower Limb Assessment scale left side, LLAS_R (12): Lower Limb Assessment scale right side, VASgen: general Visual Analogue Scale

4.2 Results muscle function parameters

The results of the muscle function parameters are presented in Table 2. All the parameters are significantly lower in the OI type I group compared to the control group except the HG_end with a p-value of 0.967.

Table 2: Results muscle function parameters

	OI TYPE I	CONTROLS	P-VALUE
HHD_hip (N)	125.8 ± 45.5 **3	169.5 ± 35.7	**p < 0.001**
HHD_ankle (N)	132.8 ± 53.6	170.4 ± 46.4**1	**p < 0.001**
HHD_shoulder (N)	98.4 ± 47.4 **1	165.2 ± 55.0 **1	**p < 0.001**
HG_dom (kg)	29.6 ± 10.0 **1	38.5 ± 11.9	**p < 0.001**
HG_nondom (kg)	28.3 ± 10.2 **2	36.5 ± 12.7	**p = 0.001**
HG_end (sec)	44.1 [29.3 – 52.8] **1	44.2 [29.5 – 53.5]	p = 0.967
30CRT	16.7 ± 7.1 **3	20.5 ± 5.6	**p = 0.006**

*Normal distributed data is noted as mean ± standard deviation; Non-normal distributed data as mean [Q1-Q3]. ** … = number of missing variables; **p** is a significant value. Abbreviations = HHD_hip (N): handheld dynamometry of the hip in N, HHD_ankle (N): handheld dynamometry of the ankle in N, HHD_shoulder (N): handheld dynamometry of the shoulder in N, HG_dom (kg): handgrip strength of the dominant side in kg, HG_nondom (kg): handgrip strength of non-dominant side in kg, HG_end (sec): handgrip endurance test dominant arm in sec, 30CRT: 30 second Chair Rise Test*

4.3 Results physical activity parameters

The comparison between OI type I and the control group for the physical activity parameters are shown in Table 3. AG_steps_mean (p = 0.020), AG_vig_min_mean (p = 0.002), AG_vvig_min_mean (p = 0.010) and AG_MVPA_min_mean (p = 0.045) were significantly higher in the control group compared to the OI group. Furthermore, AG_wear_mean (p = 0.540) showed no significant difference just like AG_mod_min_Dmean (p = 0.104).

Table 3: Results physical activity parameters

	OI TYPE I	CONTROLS	P-VALUE
AG_steps_mean	6401.4 ± 2830.4 **22	8864.1 ± 4128.5 **18	**p = 0.020**
AG_wear_mean	919.1 ± 52.5 **22	910.2 ± 48.9 **18	p = 0.540
AG_mod_min_Dmean	74.5 ± 35.5 **22	91.1 ± 35.2 **18	p = 0.104
AG_vig_min_mean	7.1 [3.9 – 10.0] **22	14.8 [8.6 – 15.0] **18	**p = 0.002**
AG_vvig_min_mean	1.6 [1.0 – 2.0] **22	2.6 [1.5 – 3.1] **18	**p = 0.010**
AG_MVPA_min_mean	83.2 ± 39.3 **22	107.8 ± 44.1 **18	**p = 0.045**

*Normal distributed data is noted as mean ± standard deviation; Non-normal distributed data as mean [Q1-Q3]. ** … = number of missing variables; **p** is a significant value. Abbreviations = AG_steps_mean: ActiGraph steps per day – mean, AG_wear_mean: ActiGraph wear time in minutes per day – mean, AG_mod_min_Dmean: ActiGraph moderate activity in minutes per day – mean, AG_vig_min_mean: ActiGraph vigorous activity in minutes per day – mean, AG_vvig_min_mean: ActiGraph very vigorous activity in minutes per day – mean, AG_MVPA_min_mean: ActiGraph moderate to vigorous activity in minutes per day – mean*

4.4 Results univariate ANCOVA tests

30CRT

The dependent variable '30CRT' was assessed in relation to covariates including height, LLAS_R, LLAS_L, AG_steps_mean, and AG_vig_min_mean, with 'Type' as the fixed factor. When only height (p = 0.011) or hypermobility factors (p = 0.004) or muscle density of the tibia (p = 0.019) were considered as covariates, p-values remained significant. However, when incorporating the level of physical activity the p-value became non-significant (p = 0.099 for vigorous physical activity and p = 0.087 for moderate physical activity). This suggests that both levels of physical activity significantly correlate with the 30CRT score, with vigorous physical activity exerting a more pronounced effect.

Table 4: Results univariate ANCOVA test for 30CRT

Naked model	p = 0.006
+ Height	p = 0.011
+ Height + LLAS_R + LLAS_L	p = 0.004
+ Height + LLAS_R + LLAS_L + MUSCLE_DEN	p = 0.019
+ Height + LLAS_R + LLAS_L + AG_steps_mean	p = 0.087
+ Height + LLAS_R + LLAS_L + AG_vig_min_mean	p = 0.099

Abbreviations: LLAS_R: Lower Limb Assessment scale right side, LLAS_L: Lower Limb Assessment scale left side, MUSCLE_DEN: 66% muscle density of tibia, AG_steps_mean: ActiGraph steps per day – mean, AG_vig_min_mean: ActiGraph vigorous activity in minutes per day – mean

HG_dom and HG_nondom

The fixed factor 'Type' was employed alongside the dependent variables 'HG_dom' and 'HG_nondom'. Adding covariates yielded similar results for both variables: height exhibited a significant impact on the p-value (p = 0.357 for HG_dom and p = 0.929 for HG_nondom), indicating a strong association between participants' HG strength and their height. Incorporating hypermobility parameters did not alter the significance level (p < 0.001 for HG_dom and p = 0.001 for HG_nondom), nor did AG_steps_mean and AG_vig_min_mean, indicating that moderate and vigorous physical activity lack a notable correlation with HG strength (p = 0.021 for HG_dom and p = 0.024 for HG_nondom for moderate activity; p = 0.031 for HG_dom and p = 0.036 for HG_nondom for vigorous activity). However, the inclusion of muscle density rendered the p-value non-significant compared to the naked model (p = 0.227 for HG_dom and p = 0.151 for HG_nondom), highlighting its importance in relation to HG strength.

Table 5: Results univariate ANCOVA test for HG_dom

Naked model	p < 0.001
+ Height	p = 0.357
+ ULHAT_R + ULHAT_L	p < 0.001
+ ULHAT_R + ULHAT_L + AG_steps_mean	p = 0.021
+ ULHAT_R + ULHAT_L + AG_steps_mean + AG_vig_min_mean	p = 0.031
+ ULHAT_R + ULHAT_L + AG_steps_mean + AG_vig_min_mean + RaMUSCLE_DEN	p = 0.227

Abbreviations: ULHAT_R: Upper Limb Hypermobility Assessment Tool right side, ULHAT_L: Upper Limb Hypermobility Assessment Tool left side, RaMUSCLE_DEN: 66% muscle density of the radius, AG_steps_mean: ActiGraph steps per day – mean, AG_vig_min_mean: ActiGraph vigorous activity in minutes per day – mean

Table 6: Results univariate ANCOVA test for HG_nondom

Naked model	p = 0.001
+ Height	p = 0.929
+ ULHAT_R + ULHAT_L	p = 0.001
+ ULHAT_R + ULHAT_L + RaMUSCLE_DEN	p = 0.151
+ ULHAT_R + ULHAT_L + AG_steps_mean	p = 0.024
+ ULHAT_R + ULHAT_L + AG_steps_mean + AG_vig_min_mean	p = 0.036

Abbreviations: ULHAT_R: Upper Limb Hypermobility Assessment Tool right side, ULHAT_L: Upper Limb Hypermobility Assessment Tool left side, RaMUSCLE_DEN: 66% muscle density of the radius, AG_steps_mean: ActiGraph steps per day – mean, AG_vig_min_mean: ActiGraph vigorous activity in minutes per day – mean

HHD_shoulder

The comparison between the fixed factor 'Type' and the dependent variable 'HHD_shoulder' revealed a statistically significant association ($p < 0.001$). Adding height, ULHAT_L, and ULHAT_R as covariates did not alter this significance level ($p < 0.001$). However, the introduction of the covariate RaMUSCLE_DEN did modify the result, though a significant association persisted ($p = 0.010$). The most substantial link was observed with the inclusion of two physical parameters. AG_steps_mean resulted in a non-significant p-value ($p = 0.255$), whereas AG_vig_min_mean yielded a slightly lower non-significant p-value ($p = 0.179$). These findings emphasize the strong association between these two physical parameters and the HHD_shoulder among individuals with OI type I.

Table 7: Results univariate ANCOVA test for HHD_shoulder

Naked model	p < 0.001
+ Height	p < 0.001
+ Height + ULHAT_L	p < 0.001
+ Height + ULHAT_L+ ULHAT_R	p < 0.001
+ Height + ULHAT_L + ULHAT_R + RaMUSCLE_DEN	p = 0.010
+ Height + ULHAT_L + ULHAT_R + AG_steps_mean	p = 0.255
+ Height + ULHAT_L + ULHAT_R + AG_vig_min_mean	p = 0.179

Abbreviations: ULHAT_L: Upper Limb Hypermobility Assessment Tool left side, ULHAT_R: Upper Limb Hypermobility Assessment Tool right side, RaMUSCLE_DEN: 66% muscle density of the radius, AG_steps_mean: ActiGraph steps per day – mean, AG_vig_min_mean: ActiGraph vigorous activity in minutes per day – mean

HHD_hip

The dependent variable 'HHD_hip' showed a strong association with the fixed factor 'Type' ($p < 0.001$). Adding height ($p < 0.001$) or hypermobility parameters ($p < 0.001$), does not alter the p-value significantly. However, upon inclusion of the covariate 'MUSCLE_DEN', the p-value became non-significant ($p = 0.136$). Thus, a strong association can be concluded between 'HHD_hip' and 'MUSCLE_DEN'. This association is not as pronounced as when incorporating physical parameters. The p-value became considerably less significant with the addition of AG_steps_mean ($p = 0.780$) and AG_vig_min_mean ($p = 0.741$). These findings underline the important association between physical activity and HHD_hip.

Table 8: Results univariate ANCOVA test for HHD_hip

Naked model	p < 0.001
+ Height	p < 0.001
+ Height + LLAS_L	p < 0.001
+ Height + LLAS_L + LLAS_R	p < 0.001
+ Height + LLAS_L + LLAS_R + MUSCLE_DEN	p = 0.136
+ Height + LLAS_L + LLAS_R + AG_Steps mean	p = 0.780
+ Height + LLAS_L + LLAS_R + AG_vig_min_mean	p = 0.741

Abbreviations: LLAS_L: Lower Limb Assessment scale left side, LLAS_R: Lower Limb Assessment scale right side, MUSCLE_DEN: 66% muscle density of tibia, AG_steps_mean: ActiGraph steps per day – mean, AG_vig_min_mean: ActiGraph vigorous activity in minutes per day – mean

HHD_ankle

With regard to the parameter 'HHD_ankle' in association with 'Type' as a fixed factor a statistically significant relationship was observed with a $p < 0.001$. Upon adjusting height as a covariate, the significance of this relationship diminished, resulting in a non-significant p-value ($p = 0.093$). Subsequently, when considering the covariate LLAS_L, a strong significant association was found ($p < 0.001$). While the covariates LLAS_R, MUSCLE_DEN, AG_steps_mean and AG_vig_min_mean also yielded significant results, their significance was less pronounced compared to LLAS_L, with corresponding p-values LLAS_R ($p = 0.010$), MUSCLE_DEN ($p = 0.003$), AG_steps_mean ($p = 0.027$) and AG_vig_min_mean ($p = 0.029$). These findings underscore the importance of height as a determining covariate when assessing the relationship with HHD_ankle in individuals with OI type I.

Table 9: Results univariate ANCOVA test for HHD_ankle

Naked model	$p < 0.001$
+ Height	$p = 0.093$
+ LLAS_L	$p < 0.001$
+ LLAS_R	$p = 0.010$
+ MUSCLE_DEN	$p = 0.003$
+ AG_steps_mean	$p = 0.027$
+ AG_vig_min_mean	$p = 0.029$

Abbreviations: LLAS_L: Lower Limb Assessment scale left side, LLAS_R: Lower Limb Assessment scale right side, MUSCLE_DEN: 66% muscle density of tibia, AG_steps_mean: ActiGraph steps per day – mean, AG_vig_min_mean: ActiGraph vigorous activity in minutes per day – mean

5 DISCUSSION/CONCLUSION

Summary of the results

The study aimed to explore muscle function and its determinants in adults with OI type I. Firstly, the healthy control group was compared to a population group diagnosed with OI type I. Height and the subtotal lean mass were significantly larger in the control group as well as the muscle density of the radius and tibia. Likewise, the muscle area was significantly higher in the control group compared to the OI group. On the other hand the number of fractures, the Margolis scale, the hypermobility parameters and the VAS score were significantly higher in the patient group. Furthermore, six dependent variables namely 30CRT, HG_dom, HG_nondom, HHD_shoulder, HHD_hip and HHD_ankle were analyzed in comparison to the control group, highlighting differences in muscle function. Associations with four covariates (height, hypermobility (LLAS_R, LLAS_L, ULHAT_R and ULHAT_L), muscle density (RaMUSCLE_DEN, MUSCLE_DEN) and physical activity (AG_steps_mean vs. AG_vig_min_mean)) were examined. Results showed significant associations between muscle function parameters and specific determinants in adults with OI type I. Physical activity parameters showed the strongest association with the 30CRT, HHD_shoulder and HHD_hip. Height emerged as the primary determinant linked with HG_dom, HG_nondom and HHD_ankle. Furthermore, muscle density showed the most pronounced association with HG_dom, HG_nondom and HHD_hip. HG strength parameters were correlated with both muscle density and height as covariates, while HHD_hip was significantly associated with physical activity and muscle density. Hypermobility covariates did not exhibit any discernible associations with the parameters that were investigated.

Physical activity and 30CRT

The results of this study indicate that physical activity parameters play a pivotal role in the performance of 30CRT, HHD_shoulder and HHD_hip in individuals diagnosed with OI type I. With vigorous physical activity showing a greater correlation with 30CRT compared to mean step count. The 30CRT serves as a valuable tool for assessing muscle strength and endurance in the lower limbs. In reviewing the literature concerning the relationship between muscle strength (given that the 30CRT serves as a measure of lower body muscle strength) and physical activity, several findings emerge. Leblanc, A. et al. (31) identified only a weak correlation between physical activity levels and lower body muscle strength ($r = -0.139$ to 0.151). Conversely, Ramsey, K.A. et al. (32) reported that increased step count, total physical activity, moderate-to-vigorous physical activity and light physical activity were all associated with enhanced lower body strength. Furthermore, intensity-based accelerometer metrics such as energy expenditure and vector magnitude units showed a positive correlation with lower body muscle strength, whereas MET did not. The study found that greater physical activity engagement and reduced sedentary behavior corresponded to improved performance on the chair stand test in community dwelling older adults. The study by Rostron, Z.P. et al. (33)

observed a positive correlation between objectively measured physical activity (using pedometers and accelerometers) and both lower limb muscle size ($r = 0.30$, $p < 0.01$) and lower limb strength ($r = 0.24$, $p < 0.01$). The study by Veilleux, L. et al. (13) tested the dynamic muscle function in 54 individuals with OI type I. The dynamic muscle function assessment consisted of three kinds of jump tests, 30CRT and the heel rise test. The results of the study indicated that participants with OI had lower average peak force and lower specific force (peak force/muscle CSA; all $p < 0.008$) compared to controls. The average peak power was lower in the OI population but not significant compared to the control group ($p > 0.54$). As previously stated, lower muscle strength is often observed in individuals with OI and represented in this study and in the study by Veilleux, L. et al. (13) by a lower score on the 30CRT compared to healthy controls. It can be suggested that greater physical activity levels are linked to increased muscle strength (31,32), resulting in a better 30CRT. This is in line with the observations in this study where vigorous physical activity had a stronger association ($p = 0.099$) with the 30CRT compared to moderate physical activity ($p = 0.087$).

Physical activity and peripheral muscle strength

Results of this study showed a significant association with moderate and vigorous physical activity, with moderate physical activity having a greater association for HHD_hip as well as HHD_shoulder, while no links were found for HHD_ankle. Not many studies have been conducted on the association between accelerometer-based physical activity and the strength of the different muscle groups (HHD_ankle, HHD_hip and HHD_shoulder). Studies mostly rely on subjective measures to assess participants' level of physical activity, rather than employing objective measures. The study by Gómez-Cabello, A. et al. (34) used a questionnaire named Physical Activity Scale for the Elderly in 1741 participants who were older than 65 years to measure the physical activity level. Significant differences for muscle strength were found in people with a higher physical activity level ($p < 0.01$) mainly in women. The HG strength measured with a hydraulic hand dynamometer (Jamar) and the muscle strength of the shoulder abductors, knee-extensors and hip flexors was investigated. Women showed a significant relationship between physical activity and strength for the shoulder ($p = 0.001$), HG strength ($p < 0.001$), hip ($p = 0.045$) and knee strength ($p < 0.001$) whereas men only showed significance for the HG strength ($p < 0.001$) and knee strength ($p < 0.001$). In contrast with Gómez-Cabello, A. et al. (34) the two aforementioned studies (32, 33) did employ objective measures to assess physical activity. Both studies reported a positive correlation between physical activity levels and measured muscle strength. However, Rostron, Z.P. et al. (33) only assessed strength in major weight-bearing muscle groups, revealing a positive correlation solely with lower limb muscle strength ($r = 0.24$, $p < 0.01$). Conversely, Ramsey, K.A. et al. (32) identified a positive relationship between both upper and lower body strength and physical activity. Notably, their measurement of upper body strength utilized arm curl exercises rather than shoulder abduction, complicating direct comparison with this study in terms of upper body muscle strength.

Physical activity and HG strength

In this study, no association was found between physical activity and HG strength. These results could be declared by a study by Kasture, S. et al. (35) which concluded that HG strength, as measured by Jamar, inadequately reflects the movement patterns observed in daily life. Therefore, relying solely on HG strength assessment is limited when evaluating overall muscle function, and consequently, assessing physical activity levels. This is in line with the analysis and results of this study, but is contradictory to the previously mentioned results by Gómez-Cabello, A. et al. (34) and Ramsey, K.A. et al. (32) who showed a significant association between HG strength and physical activity in both sexes where physical activity was measured using an accelerometer or a pedometer (32) and a questionnaire (34). In addition, the study by Silva Neto, L. S. et al. (36), found a correlation of $r = 0.35$ ($p < 0.05$) between HG strength and the physical functioning dimension of the 36-Item Short Form Health Survey (SF-36), a questionnaire that frames the health-related QoL, in a population of 56 elderly women. Same association was significant in the study of Sayer, A.A. et al. (37) who investigated 2987 community-dwelling men and women. The Jamar dynamometer was used to measure the HG strength and the participants had to fill in the SF-36 questionnaire. Lower HG strength was associated with a poor overall score on the questionnaire. To dig a little deeper, low HG strength was associated with a low score on the physical function dimension of the questionnaire in men ($p = 0.007$) and women ($p < 0.001$). This makes HG strength still a good marker for overall good health prognosis and sarcopenia prognosis in elderly. In addition to HG strength, lean mass and functional capacity all play a role in the diagnosis of sarcopenia as shown in the study of Suetta, C. et al. (38). Lean mass showed a significant association with the muscle strength of knee extensors and flexors in the study by Pisciottano, M. et al. (39) where strength of the lower limb and body composition were measured among other things in 100 women of 65 years and older. Similarly, Confortin, S.C. et al. (40) identified a noteworthy relationship between HG strength and lean mass among 2339 adolescents, even after adjusting for confounding variables like sex and age. This study did not include lean mass in its results but it is important to mention that due to the results of several studies demonstrating a significant association between lean mass and muscle strength, conclusion can be made that lean mass is also an important parameter in health and physical activity, but no study was found where patients with OI were investigated.

Height and HG strength

The findings of this study reveal a noteworthy correlation between height as covariate and the HG_dom and HG_nondom among subjects with OI type I. Other studies have also examined the importance of anthropometric measurements as influencing factor on HG strength. Chandrasekaran, B. et al. (41) revealed a positive correlation between age, height and weight with HG strength among a cohort of healthy students aged 18-23 years. Their findings suggested that this positive relationship may stem from various factors

associated with greater height, such as longer arms and an increased lever arm for force generation, thereby facilitating more efficient force production. These results are in line with the study performed by Chatterjee, S. & Chowdhuri, B.J. (42) who similarly identified a positive relation between the maximal voluntary contraction of the hands with height, weight and body surface area in men aged 7-73 years. The study conducted by Coêlho, G. et al. (43) provided insights into HG strength across different types of OI. The research revealed a notable inverse relationship between the severity of OI and HG strength, wherein individuals with more severe forms of OI (type III) exhibited significantly lower HG strength compared to those with milder forms (type I and IV), as well as when compared to age-specific reference data. Although the study did not explicitly examine the correlation between height and HG strength, the data underscored a similar association. Specifically, individuals with OI type III, characterized by greater severity, demonstrated a markedly lower height (Z-score of -5.77) compared to those with type I OI (Z-score of -2.13). This discrepancy in height corresponded to substantial differences in HG strength, with individuals with OI type III exhibiting a mean HG strength of 63.49 N, notably lower than the 171.65 N observed in individuals with OI type I. Literature showed a notable correlation between height and weight with HG strength, while the relationship with age and HG strength was variable (41, 42), which is in line with the significant association that was found between HG strength and height in this study.

Height and peripheral muscle strength

Furthermore, in this study height was observed to have a positive correlation solely with HHD_ankle and not with HHD_shoulder and HHD_hip. In regard to determining the factors that influence ankle strength the most, limited research has specifically addressed height, with predominantly focusing on variables such as weight, age and sex. Two studies did explore the impact of height on ankle dorsiflexion strength. Moraux, A. et al. (44) demonstrated that height emerged as the most significant predictor of ankle dorsiflexion strength across both adult and pediatric populations. These findings are consistent with Andrews, A.W. et al. (45) who reported a moderate to high correlation between muscle force, measured in both upper and lower body, and height (ranging from r = 0.434 to r = 0.747). Additionally, Andrews, A.W. et al. (45) reported a positive correlation between shoulder abduction on the dominant side (r = 0.692) and height, as well as height in relation to dominant side hip flexion (r = 0.672). These results are contradictory to the ones observed in this study where only HHD_ankle showed a significant association with height. Individuals with OI exhibit decreased height compared to healthy controls. This reduction in stature can lead to proportionately shorter bones, resulting in shorter muscle bellies. A shorter stature also translates to a shorter lever arm, which in conjunction with the sarcomere length-tension relationship, influences muscle force generation (46). According to this relationship, maximum isometric force is achieved when the muscle is at an intermediate length as a consequence of maximum number of cross-bridges formed between actin and myosin filaments.

At maximal extension, minimal overlap occurs, leading to fewer cross-bridges and thus lower tension. Conversely, as the muscle shortens, there is increased filament overlap, augmenting tension until reaching the optimal length. However, further shortening diminishes tension due to excessive overlap obstructing cross-bridge formation. To conclude, muscle length plays an important role in force generation via sarcomere mechanics and can be influenced by an individual's height. The same principle is applicable to upper limb strength, as demonstrated in the study by Andrews, A.W. et al. (45). In individuals with OI, the upper limb strength has predominantly been evaluated using HG strength as a measure of upper limb strength, resulting in a lack of studies evaluating shoulder abduction as a measure of upper limb strength. Due to the lack of specific literature investigating the relationship between shoulder abduction strength and height in individuals with OI, no explanation can be provided why Andrews, A.W. et al. (45) observed a significant association between shoulder abduction strength and height and this study did not.

Muscle density and peripheral muscle strength

The analysis of this research showed a significant association between muscle density and the HHD_hip as well as with HG_dom and HG_nondom. These findings are in line with the study of Wang, L. et al. (47), who examined the muscle density of 300 healthy individuals using CT scans. A positive significant association was found between muscle density and HG strength. The association was significant for men and women. The examined muscle groups were the left gluteus medius and minimus, the muscle density at the middle of the thigh and the trunk muscle at T12. A significant association was found for all muscle groups, except for the mid-thigh muscles in women. A separate investigation conducted by Laskou, F. et al. (48) did not reveal a significant correlation in males and females between forearm muscle density and HG strength, with the latter assessed bilaterally while muscle density was examined solely on the non-dominant side. These observations deviate somewhat from this study, as muscle density positively correlated with HG strength outcomes on both the dominant and the non-dominant side.

Research of Weeks, B.K. et al. (49) undertook pQCT measurements of muscle area and muscle density in healthy men and women. HG strength was measured using a Jamar hand dynamometer, while leg and thigh strengths were evaluated via an isokinetic dynamometer for ankle plantar flexors and knee extensors. Besides a weak relationship between muscle density and muscle strength of the thigh, they also noted that muscle area is more related to strength than muscle density in a healthy population, which is in contrast of the findings of the previously mentioned article of Wang, L. et al. (47) who concluded that muscle density is more associated with muscle strength than muscle size. Therefore, literature shows conflicting information about the role of muscle density on muscle strength and thus the association with hip strength and HG strength.

Hypermobility and peripheral and HG muscle strength

In this study, hypermobility had no association with one of the six variables. In individuals without an underlying condition or disease, limited research has examined the relationship between hypermobility and muscle strength, as well as hypermobility and the 30CRT. Most of the literature predominantly includes patients diagnosed with a hypermobility disorder. Based on the results of this study regarding the ULHAT and LLAS, a significant difference is seen between the control group and the group with OI type I. The literature reviewed about hypermobility can therefore only partly be compared with the population in this study, namely individuals with OI. The studies described in this part about hypermobility are therefore all about people with a hypermobility disorder. Further research is necessary about hypermobility.

Research investigating the link between hypermobility and muscle strength has yielded inconclusive findings across multiple studies (50,51,52,53,54). Juul-Kristensen, B et al. (51) examined the difference in HG strength in 36 adults and 39 children with and without Generalized Joint Hypermobility (GJH) assessed with a standardized HG dynamometer (Jamar). They found no significant differences for HG strength on the dominant arm between the people with GJH and the control group both in adults ($p = 0.93$) and in children ($p = 0.59$). These findings align with research of Massy-Westropp, N et al. (55) which similarly found no significant differences ($p > 0.05$). The study by Baert, N. et al. (56) encompassed twenty participants diagnosed with Hypermobile Ehlers-Danlos syndrome (hEDS), twenty-four subjects with Hypermobility spectrum disorders (HSD) and a control group. The study aimed to check whether there was a difference in HG strength measured with a standardized adjustable Jamar HHD in both the dominant and non-dominant arm among these three groups. The study reported no significant difference of the dominant ($p = 0.411$) and non-dominant side ($p = 0.521$). Furthermore, Scheper, M.C. et al. (57) measured the muscle strength in 36 female participants with GJH and a gender matching control. In the upper extremity, the shoulder abductors and the HG strength were determined. In the lower extremity, the ankle dorsiflexors, the knee extensors and the hip flexors were measured. Likewise, no significant differences were found between all these parameters ($p > 0.05$).

Hypermobility and 30 CRT

In contrast to this study, Baert, N. et al. (56) found that subjects with hEDS had a lower score on the 30CRT compared to the control group ($p = 0.047$). This is also reflected in the study from Scheper, M. et al. (58) who found significant differences when comparing GJH individuals and controls in performing 30CRT ($p < 0.001$). The study from Coussens, M. et al. (59) demonstrated a significantly lower score on the 30CRT in the group with hEDS ($p = 0.001$) and in the group with HSD ($p = 0.021$) compared to a control group. However, Baert, N. et al. (56) and Coussens, M. et al. (59) found no significant differences when the results were normalized for body weight with the corresponding p-values of $p = 0.131$ (hEDS vs. Controls) (56) and $p = 0.052$ (HSD vs.

controls) (59). This observation suggests that hypermobility may indeed influence the effects on muscle strength, a finding incongruent with the outcomes delineated in this study.

Strengths of the study

The strengths of this study are that the participants encompass individuals with OI type I from both Belgium and Australia, diminishing the effect of potential epigenetics. Each participant was carefully matched based on gender and age, ensuring a robust basis for comparison. The study subject remains largely unknown to many, which underscores its importance for everyday clinical practice, not only for individuals living with OI but also for healthcare professionals tasked with their care.

Limitations of the study

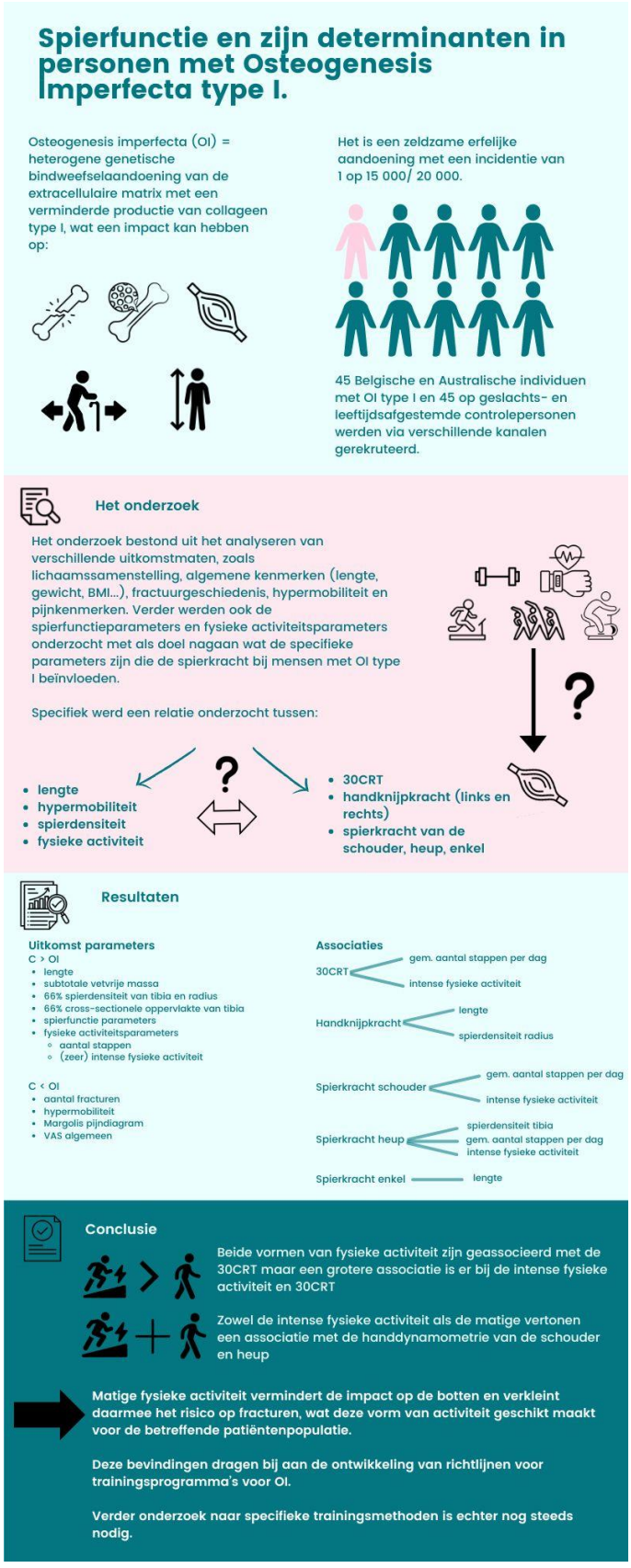
Several limitations should be acknowledged in this study. Firstly, the study exclusively focused on participants with OI type I, which does not fully represent the entire OI population. OI encompasses various types with distinct clinical manifestations and severity levels. Consequently, the findings of this study may not be applicable to individuals with other types of OI. Therefore, further research with an even larger and more diverse participant pool including different types of OI is essential to ensure that the results accurately reflect the broader OI population. Additionally, when analyzing the data, multiple parameters contained missing variables which may impact the accuracy and robustness of the analysis.

Another limitation of the study is that when conducting the univariate ANCOVA test on six different parameters, comparison between these parameters and four potential covariates was made. However, it should be noted that the covariate physical activity defined as either AG_steps_mean or AG_vig_min_mean, were solely assessed within the Belgian OI and control population. The population in Australia did not have these measurements available for analysis, which may limit the generalizability of the findings across diverse populations. Additionally, when incorporating the covariate AG_steps_mean into the analysis, the wear time of the ActiGraph was not taken into account among the individuals with OI type I and the controls. Consequently, low step counts may not accurately reflect total steps per day, as insufficient wear time (less than seven hours per day) could skew the data. This limitation highlights the potential for misrepresentation of physical activity levels. Lastly in the analysis of the parameters, outliers and extreme values were identified to ensure data accuracy, specifically checking for errors such as misplaced commas, impossible numbers. However, measures to address these outliers and extreme values were not implemented so the data analysis was performed on all values with the outliers and extreme values still included. It is important to acknowledge that outliers and extreme values can exert an influence on the results, potentially compromising the accuracy of the findings.

Conclusion

Physical activity in a population with type I OI showed an association with the 30CRT, HHD_hip and HHD_shoulder. For the latter two, there was little difference between moderate and vigorous activity, while for the 30CRT vigorous physical activity was more associated with the 30CRT score than moderate physical activity. These findings are helpful in the search of training or revalidation programs or even general physical activity for subjects with OI type I where the impact on bone must be limited, but the benefits of training must still be reflected. More research has to be done considering other types of OI and also to specify training modalities and physical activity assessments for these individuals.

6 POPULARISERENDE SAMENVATTING



7 MAATSCHAPPELIJKE IMPACT EN MEERWAARDE

Osteogenesis Imperfecta (OI) is een zeldzame aandoening die onderbelicht is in de sportwetenschappen en revalidatie, wat leidt tot veel onwetendheid bij zowel professionals als patiënten. Bestaande literatuur over OI in combinatie met sporten is vaak moeilijk toegankelijk en biedt weinig concrete richtlijnen over geschikte sporten en hun modaliteiten. Het gebrek aan informatie kan frustrerend zijn voor individuen met OI, waarbij de grens tussen voorzichtigheid en risico vaak onduidelijk is vanwege het verhoogde risico op fracturen. Dit onderzoek bestond uit het bestuderen van het effect van intensiteit bij fysieke activiteit (hoog vs. laag) op spierparameters bij individuen OI.

Onze bevindingen tonen aan dat zowel intense als matige fysieke activiteit verband houden met uithoudingsvermogen en spierkracht in de onderste ledematen (gemeten met een 30CRT). Ook vertonen ze een verband met de kracht van de schouderabductoren en heupflexoren. Intense activiteit heeft een sterker verband met de 30CRT dan matige activiteit. Voor de kracht van het schouder- en heupgewricht was er maar een klein verschil tussen de twee levels van intensiteit. Deze resultaten benadrukken het belang van matige fysieke activiteit voor mensen met OI type I aangezien dit positieve resultaten teweegbrengt en een lager fractuurrisico heeft. Deze uitkomsten brengt de gezondheidszorg een stap voorwaarts richting het opstellen van uniforme richtlijnen (belasting, frequentie, intensiteit, aantal herhalingen per set,…) voor een trainingsprogramma van individuen met OI, waarbij schade aan botten en spieren wordt vermeden.

8 BEWIJS VAN INDIENING BIJ HET ETHISCH COMITÉ

8.1 Ethical Committee

Afzender : Commissie voor medische ethiek

Prof. Dr. Fransiska Malfait
Vakgroep Voeding, Genetica en Ethologie
UGent

contact	telefoon	e-mail
Commissie voor medische ethiek	+32 (0)9 332 33 36	Ethisch.comite@uzgent.be
Aanvrager	**datum**	**pagina**
Tine Galmart	12/03/2024	1/6
Onze referentie:	**EudraCT-nr:**	**Belg. Regnr:**
BC-4151 E07		

Betreft:
Muscle function and its determinants in adults with Osteogenesis Imperfecta type I
Scriptie : Tine Galmart

Positief advies

Beste collega

De Commissie Medische Ethiek (CME) verbonden aan de Universiteit Gent (Ugent) en het Universitair Ziekenhuis Gent (UZ Gent) geeft op 08/03/2024 een gunstig advies over deze studie.

De Commissie voor Medische Ethiek beklemtoont dat een gunstig advies niet betekent dat de Commissie voor Medische Ethiek de verantwoordelijkheid voor het onderzoek op zich neemt.

De promotor en de hoofdonderzoeker dragen de verantwoordelijkheid voor het correcte ethische en wettelijke verloop van het onderzoek.

Deze studie valt niet onder de wet van 7 mei 2004 betreffende experimenten op de menselijke persoon

Ingediende documenten: zie bijlage 1
Ledenlijst: zie Bijlage 2
Aandachtspunten: zie Bijlage 3a

ALGEMENE DIRECTIE
Commissie voor Medische Ethiek

VOORZITTER:
Prof. dr. R. Peleman

SECRETARIS:
Dr. L. Goossens

INGANG 75
ROUTE 7522

Met vriendelijke groeten,
Prof. dr. Renaat Peleman
Voorzitter
Commissie voor Medische Ethiek U(Z) Gent

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Unofficial translation in English:

Positive advice

The Ethics committee (EC) of University Ghent (UGent) and Ghent University Hospital (UZ Gent) gives on 08/03/2024 a favorable opinion on this study

EC emphasizes that a favorable opinion does not mean that the Medical Ethics Committee assumes responsibility for the investigation.
The promoter and the principal investigator are responsible for the correct ethical and legal conduct of the research

This study does not fall within the scope of the law of 7 May 2004 on experiments on the human person

Submitted documents: see Annex 1
List of members: see appendix 2
Points of concern: see appendix 3b

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Bijlage 1: Documenten

Categorie: CV
- Tine Galmart, versie ontvangen dd. 23/10/2023

Alle goedgekeurde documenten van de hoofdstudie (BC-4151)

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Bijlage 2: Overzicht leden CME U(Z) Gent

voorzitter: Prof. dr. R. Peleman
Secretaris: Dr. L. Goossens

Effectief lid	Plaatsvervangend lid
Prof. dr. G. Van Lancker UZ Gent - klinisch farmacoloog, ♀	Prof. dr. S. Rottey UZ Gent - klinisch farmacoloog, ♀
Prof. dr. D. De Bacquer Ugent - statisticus, ♂	Prof. dr. P. Coorevits Ugent - statisticus, ♂
Dr. M. Cosyns Extern - huisarts, ♂	Dr. J. Matthys Extern - huisarts, ♂
Dr. J. Van Elsen Extern – huisarts ♂	Dr. J. Matthys Extern – huisarts, , ♂
Prof. dr. K. De Groote UZ Gent - kindercardioloog, ♀	Dr. P. De Bruyne UZ Gent - kinder gastro-enteroloog, ♀
Prof. dr. W. Notebaert UGent - psycholoog, ♂	Dhr. W. Schrauwen UGent - psycholoog, ♂
Mevr. R. Vrielynck UZ Gent - verpleegkundige, ♀	Mevr. A. Charles UZ Gent - verpleegkundige, ♀
Dhr. C. Demeestere UZ Gent - verpleegkundige, ♂	Dhr. G. De Smet UZ Gent - verpleegkundige, ♂
Apr. K. Kint UZ Gent - apotheker, ♀	Apr. L. Huys UZ Gent - apotheker, ♀
Dhr. B. Vanderhaegen UZ Gent - Ethicus, ♂	Dhr. K. Raus UZ Gent - Ethicus, ♂
Prof. dr. T. Goffin UGent - jurist, ♂	Mevr. V. Vanscheewijck UGent - jurist, ♀
Mevr. C. Van Caeneghem extern - patiëntvertegenwoordiger, ♀	Mevr. S. Degroote extern - patiëntvertegenwoordiger, ♀
Prof. dr. W. Van Biesen UZ Gent - nefroloog, ♂	Dr. A. Beyens UZ Gent - geneticus, ♀
Prof. dr. R. Peleman UZ Gent - internist en pneumoloog, ♂	Dr. L. Goossens UZ Gent - neonatoloog, ♀
Dr. T. Martens UZ Gent - hartchirurg, ♂	Dr. H. Eker UZ Gent - algemene en hepatobiliaire chirurg, ♂
Dr. L. Dhaenens UZ Gent - fertiliteitsarts, ♀	Dr. I. Dehaene UZ Gent - verloskunde, ♀
Dr. R. Van Der Looven UZ Gent - kinderrevalidatie, ♀	Dr. M. Neckebroek UZ Gent - anesthesist, ♀
Dr. E. Schoentjes UZ Gent - [kinder - jeugd]psychiater, ♂	Prof. dr. K. Dhondt UZ Gent - [kinder - jeugd]psychiater, ♀

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Appendix 3a: Aandachtspunten (indien van toepassing)

De CME benadrukt de verantwoordelijkheid van de PI/promotor van dit onderzoek ten aanzien van de privacy van de persoons-/patiëntgegevens in contacten met patiënten, of bij het inzien van patiëntgegevens, inclusief de juiste uitvoering daarvan door collega's en studenten. De PI/promotor is verantwoordelijk voor de uitvoering van het projectvoorstel in overeenstemming met de toepasselijke wet- en regelgeving waaronder, maar niet beperkt tot, de EU-verordening 2016/679 (Algemene Verordening Gegevensbescherming), de Belgische Wet op de patiëntenrechten van 22/ 8/2002, en het beleid van de instelling waar het onderzoek wordt uitgevoerd.

De CME verwijst op haar website naar de ICH/GCP-richtlijnen en bevestigt dat van elke onderzoeker een GCP-training vereist is. Het is de verantwoordelijkheid van de hoofdonderzoeker dat elk lid van het onderzoeksteam een geldig GCP-certificaat heeft. De conformiteit van vertaalde documenten ten opzichte van de Nederlandse documenten is de verantwoordelijkheid van de opdrachtgever.

Wij vestigen uw aandacht op het feit dat de CME verwacht dat haar eerste opmerkingen ab initio in aanmerking worden genomen bij de volgende indiening door dezelfde sponsor.

Mits er een Clinical Trial Agreement is, kan de studie pas starten wanneer de Clinical Trial Agreement werd goedgekeurd en ondertekend door de CEO van het UZ Gent (en/of door een gemachtigde vertegenwoordiger van de UGent).

Studies met geneesmiddelen voor onderzoek en bepaalde studies met "medical devices" dienen door de klant (PI of sponsor) te worden ingediend bij het FAGG (Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten).

Studies met geneesmiddelen voor onderzoek mogen enkel uitgevoerd worden op voorwaarde dat de minister (FAGG) geen bezwaar maakt binnen de wettelijke termijnen zoals beschreven in art. 13 van de Belgische wet van 7/5/2004 betreffende experimenten op de menselijke persoon en in art. 21 van de Belgische wet van 7/05/2017 betreffende klinische proeven met geneesmiddelen voor menselijk gebruik.

Bepaalde onderzoeken met medische hulpmiddelen vallen ook onder wettelijke termijnen (KB van 17/3/2009). Raadpleeg de website van het FAGG voor meer informatie: www.fagg-afmps.be .

Onderzoek op embryo's in vitro valt onder de wet van 11 mei 2003. Alvorens het onderzoeksproject kan starten, vereist dergelijk onderzoek ook een positief advies van het Federaal Comité voor medisch en wetenschappelijk onderzoek op embryo's in vitro.

Gelieve rekening te houden met de reglementen van het ziekenhuis inzake weefselbeheer en de reglementen van de wet van 19 december 2008.

Dit gunstige advies van de CME houdt niet in dat zij de geplande studie op zich neemt. U blijft verantwoordelijk voor het onderzoek. Daarnaast dient u ervoor te zorgen dat uw mening als betrokken onderzoeker wordt weergegeven in publicaties, rapporten voor de overheid etc. die het resultaat zijn van dit onderzoek. U wordt eraan herinnerd dat met betrekking tot klinische onderzoeken elke waargenomen ernstige gebeurtenis onmiddellijk moet worden gemeld aan de sponsor en de ethische commissie, zelfs als het oorzakelijk verband met de studie onduidelijk is.

De CME-goedkeuring die voor een specifiek project wordt gegeven, is één jaar geldig. Wij verzoeken u ons te informeren als het onderzoek niet wordt gestart of als het onderzoek niet binnen 1 jaar na goedkeuring start.

De CME bevestigt dat - in geval van belangenverstrengeling - betrokken leden niet deelnemen aan de stemming over het onderzoek.

Indien het onderzoek niet binnen een jaar wordt beëindigd, eist de ICH-GCP dat jaarlijks een voortgangsrapportage aan de CME wordt verstrekt.

Tot slot verzoeken wij u de (voortijdige of geplande) beëindiging van het onderzoek binnen de wettelijke termijnen te melden en het Clinical Study Report (CSR) aan de CME te bezorgen.

Houd er in het geval van een klinische proef (EudraCT) rekening mee dat de resultaten moeten worden gepubliceerd in het European Clinical Trial Register. Het rapport van deze resultaten kan als CSR naar de EC worden gestuurd.

Appendix 3b: Points of concern (if applicable)

The EC emphasizes the responsibility of the PI/promotor of this study concerning the privacy of the person/patient data in contacts with patients, or when viewing patient data, including the correct implementation thereof by coworkers and students. The PI/promotor is responsible for the implementation of the project proposal in accordance with applicable laws and regulations including, but not limited to, the EU regulation 2016/679 (General Data Protection Regulation), the Belgian Law on patients' rights of 22/8/2002, and the policy of the institution where the research will be carried out.

The EC refers to the ICH/GCP guidelines on its website, and confirms that a GCP-training is required from each investigator. It is the responsibility of the principal investigator that each member of the study team has a valid GCP-certificate.

The conformity of translated documents compared to the Dutch documents, is the responsibility of the sponsor.
We would like to draw your attention to the fact that the EC expects her initial comments to be taken into account ab initio at the next submission by the same sponsor.

*Provided that there is a **Clinical Trial Agreement**, the study can only start when the Clinical Trial Agreement has been approved and signed by the CEO of UZ Gent (and/or by an authorized representative of UGent).*

Studies with investigational medicinal products and certain studies with "medical devices" should be submitted by the client (PI or sponsor) to the FAMHP (Federal Agency for Medicines and Health Products).
Studies with investigational medicinal products are only allowed to be conducted, provided that the minister (FAMHP) does not state objections within legal deadlines as described in art. 13 of the Belgian law of 7/5/2004 concerning experiments on the human person and art. 21 of the Belgian law of 7/5/2017 concerning clinical trials with medicines for human use.

Certain studies using medical devices are also covered by legal deadlines (KB of 17/3/2009). Please consult the FAMHP website for more information: www.fagg-afmps.be.

Research on embryos in vitro is covered by the law of May 11, 2003. Before the research project can start, such research also requires a positive advice of the Federal Committee for medical and scientific research on embryos in vitro.

Please take into account the regulations of the hospital concerning tissue management and the regulations of the law of December 19, 2008.

This favorable advice of the EC does not imply that it will assume responsibility for the planned study. You will remain responsible for the study. In addition, you should ensure that your opinion as an involved researcher is reproduced in publications, reports for the government, etc. which are the result of this study. You are reminded that concerning clinical studies, any observed serious event needs to be reported immediately to the sponsor and the ethics committee, even if the causal relationship with the study is unclear.

The EC approval given for a specific project, is valid for one year. We request you to inform us if the study will not be initiated or if the study does not start within 1 year after approval.

The EC confirms that - in case of conflict of interest - involved members do not take part in the vote concerning the study.

*If the study will not be terminated within a year, the ICH-GCP demands that an **annual progress report** will be provided to the EC.*

*Finally, we request you to report the termination (early or planned) of the study within the legal deadlines and provide the **Clinical Study Report** (CSR) to the EC.*

In case of a clinical trial (EudraCT), please be informed that the results must be published in the European Clinical Trial Register. The report of these results can be sent to the EC as the CSR.

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9 REFERENCE LIST

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