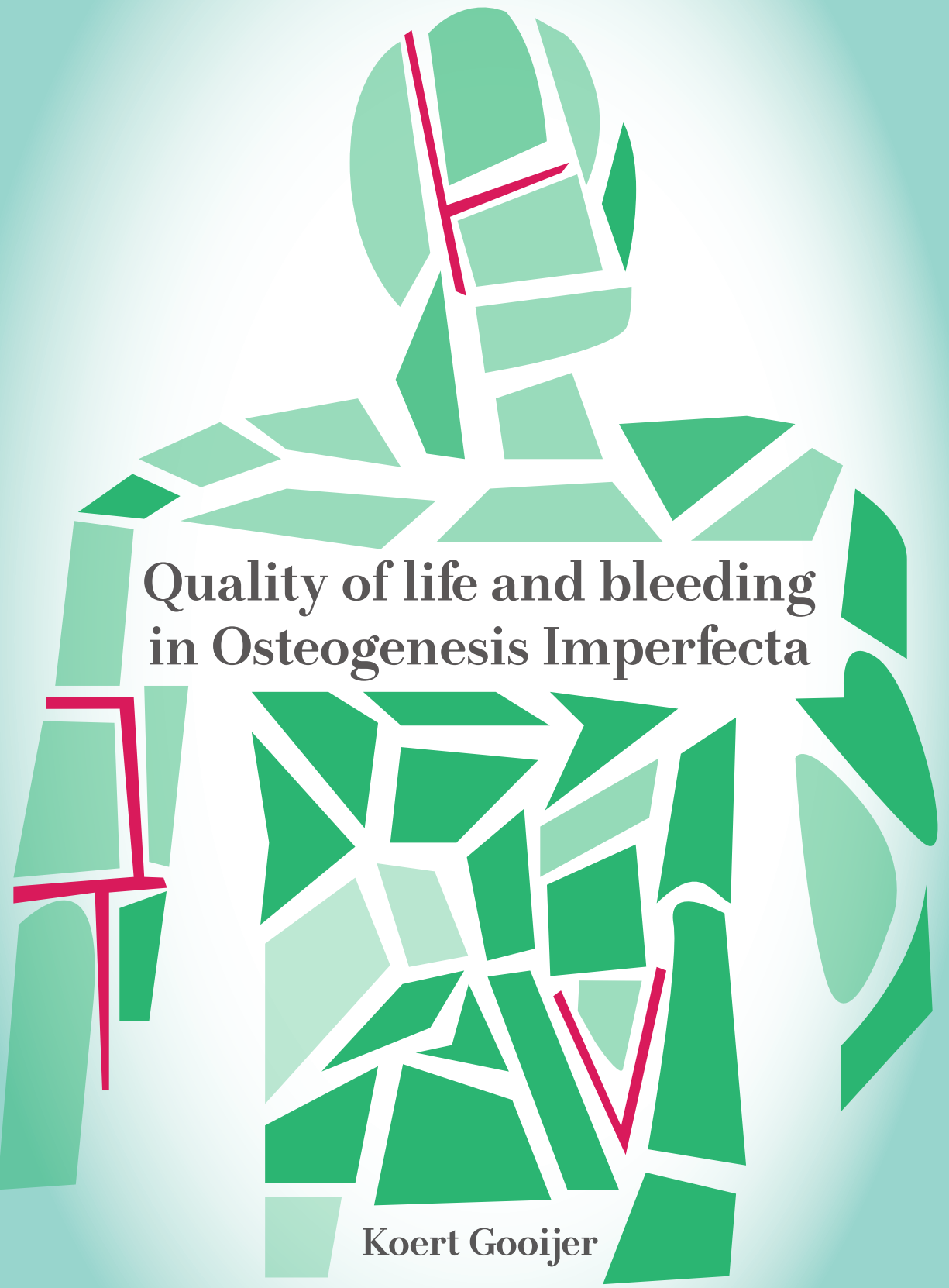

Quality of life and bleeding in Osteogenesis Imperfecta

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Chapter 1

General introduction

Introduction

Osteogenesis Imperfecta (OI) is a rare congenital connective tissue disease with a prevalence of 6.5 per 100,000 live births [1,2]. OI is often referred to as "brittle bone disease" because fragile bones and high fracture prevalence are one of its most prominent features. However, the features of OI are much broader as the underlying problem in most cases involves an abnormality in collagen type 1 production. Collagen type 1 is abundant in bones, teeth, ligaments and tendons, and to a lesser extent in sclera, blood vessels and internal organs [3]. Therefore, abnormalities and symptoms can occur in all the above-mentioned tissues and organs in OI and can affect the quality of life of people with OI in different ways [4]. This thesis addresses quality of life in OI and the bleeding tendency, one of the abnormalities that is often mentioned but scarcely investigated in OI. This introductory chapter provides background information on OI and is followed by a description of the aims and outline of the thesis.

Osteogenesis Imperfecta

Etiology of OI

The biosynthesis of collagen is a complex process in which even minor disruptions lead to a number of serious diseases. Each protein must be properly folded and modified to become functional. Basic steps in the successful production and maturation of proteins are synthesis, posttranslational modifications, folding, quality control, and transport. The collagen type 1 molecule has a triple helix structure consisting of two α1 chains and one α2 chain. Of all OI patients, approximately 85-90% have an autosomal dominant pathogenic variant in either the *COL1A1* or the *COL1A2* gene, which encodes for the collagen type 1 α1 chain and collagen type 1 α2 chain, respectively [5]. The cells that convert these mutations to proteins produce a mixture of normal and abnormal collagen [6]. Recently, recessive, dominant, and X-linked variants in several genes have been shown to cause defects in proteins responsible for transcription, synthesis, and post-translational modification. In addition, chaperone proteins, retrograde transport, extracellular processing of procollagen for bone synthesis, transport of type 1 collagen, matrix mineralization, and osteoblast differentiation are affected by pathogenic gene variants. All these genetic defects may cause OI [3,7]. The resulting phenotype can range from very mild to lethal, depending in part on which of the alpha strands is affected and the position and nature of the pathogenic variant (Table 1).

Classification

In addition to heterogeneity at the molecular level, OI is also a clinically heterogeneous disorder and several researchers have attempted to develop a useful, understandable, and comprehensive classification for it. The most widely used classification is the one developed by Sillence et al. [9] in 1979,

Table 1 *Clinical features, mutated genes, and pathways of the different OI types*

OI Type	Clinical features	Mutated gene(s)	Mode of inheritance*	Pathway
1	Mild to moderate deformation, blue sclerae, normal stature	*COL1A1/2*	AD	Genes encoding (pro) collagen chain/fibril: start of pathway
		CREB3L1	AR	ER stress response
2	Perinatal lethality	*COL1A1/2*	See type 1	
		CREB3L1	See type 1	
		CRTAP		Posttranslational modification
		KDELR2		Retrograde vesicle transport
		LEPREI		Posttranslational modification
		PPIB		Posttranslational modification
3	Progressively deforming with bowing, scoliosis and low bone density. Short stature and dentinogenesis imperfecta	*BMP1*	AR	Extracellular processing
		COL1A1/2	See type 1	
		CCDC134	AR	Regulation of MAPK
		CREB3L1	See type 1	
		CRTAP		Posttranslational modification
		IFITM5		Matrix mineralisation
		FAM46A		Unknown
		FKBP10		Posttranslational modification
		KDELR2	See type 2	
		LEPREI	See type 2	
		MBTPS2	XL	ER stress response
		MESD	AR	WNT signaling pathway
		PLOD2		Posttranslational modification
		PPIB	See type 2	
		SERPINF1		Matrix mineralisation
		SERPINH1		Posttranslational modification
		SP7		Bone cell diff. and sign
		TMEM38B		Posttranslational modification/Ca^{2+} homeostasis
		WNT1		Bone cell diff. and sign
4	Mild to moderate deformation, white sclerae, variable fracture rate.	*COL1A1/2*	See type 1	
		PLS3	XL	Actin-bundling protein
		PPIB	See type 2	
		SP7	See type 3	
		SPARC		Extracellular matrix
		WNT1	See type 3	
5	Mild deformation, calcification in interosseous membranes and hypercallus during fracture healing	*IFITM5*	AD	Matrix mineralisation
		NBAS	AD	Retrograde transport

* Autosomal dominant (AD), autosomal recessive (AR) and recessive X-linked (XL)
Table derived from van Dijk and Sillence , 2014 and Claeys et al. 2021 [7,8].

which describes four different types of OI based on clinical symptoms. In the last two decades, an attempt has been made to base the classification of OI more on its genetic causes rather than on clinical presentation [10–12]. However, the genotype-phenotype relation is still insufficiently understood (Table 1). Therefore, this expanded classification with about 20 different types has not proven to be clinically useful, and clinicians and researchers have returned to the phenotyping according to Sillence et al., with the addition of one distinguishable clinical type [8].

The phenotype of OI is thus clinically classified into five subtypes (Table 1) in which the severity ranges from barely detectable connective tissue abnormalities to lethality in the perinatal period [8]. Type 1 is the relatively mildest and most common form of OI, with a birth prevalence of about 4 per 100,000 live births [8]. OI type 1 is characterized by blue sclera, increased fracture frequency without extensive deformities, normal stature, sometimes hearing loss and sometimes dentinogenesis imperfecta. Type 2 is the most severe type and is characterized by such a lack of collagen in the bones that children die in utero during pregnancy, at birth or shortly after. This type is characterized by extensive fractures and bone deformity, micromelic bones and platyspondyly. Lethality occurs due to respiratory failure secondary to pulmonary hypoplasia as a consequence of a small thoracic cage caused by multiple rib fractures, as well as cerebral haemorrhage after vaginal delivery. In persons with type 3, there is small stature, frequent fractures with deformity of the limbs and vertebrae that increases over the years, sometimes causing respiratory insufficiency. Blue sclerae might be present or not, dentinogenesis imperfecta is usually evident. Type 4 is very similar to type 1, a difference being that there are no blue sclerae and some persons have a shorter stature. Type 5 is comparable to type 4, but persons with type 5 have a calcification of the interosseous membrane of the forearm, which restricts hand movements and can lead to secondary dislocation of the radial head. Very typically there is a greater chance of hypercalcification occurring after surgery or a fracture. Life expectancy for persons with all OI types other than type 2 is normal. In individuals with OI type 3, life expectancy may be shorter if there is severe kyphoscoliosis with restrictive pulmonary function [1,13–15].

Based on the above-mentioned prevalence data, there are approximately more than 1,100 patients with OI in the Netherlands. Storoni et al. [2] estimated the total number of patients with OI to be 850. The Expertise Center for adults with OI in Isala in Zwolle, founded in 2008, now has a cohort with over 500 adult OI patients in care. Of these 500 patients, 67% have type 1 OI, 12% type 3 and 19% type 4. Of the cohort, 2% have type 5 or other rare (recessive inherited) variants [16].

Diagnosis

The diagnosis of OI can be made on the basis of clinical and radiographic findings [8]. Fractures after mild trauma, bowing deformities of long bones, and growth deficiency are hallmark features. Specific skeletal features may include macrocephaly, flat midface and triangular facies, dentinogenesis imperfecta, chest wall deformities and scoliosis or kyphosis. Typical extra-skeletal features are blue sclerae, hearing loss and hypermobility (Table 2). Radiographic examination may reveal osteopenia, long-bone bowing and shortening, and vertebral fractures. The diagnosis of OI type 2 and the diagnosis of OI type 3 can be made prenatally based on ultrasound examination of the foetus because fractures typically occur prenatally in these types. The diagnoses of OI type 1, 4 and 5 are made postnatally on the basis of the clinical features and abnormalities on imaging examination [17]. The most common differential diagnostic consideration is nonaccidental injury, frequently in cases of suspected OI type 1 or 4 [18–20]. The diagnosis can be confirmed through molecular DNA diagnostics.

Treatment and management

No successful cure is available for OI at this moment. Although novel approaches of gene therapy are being developed [45], treatment currently focuses on management of symptoms and preferentially takes place within a multidisciplinary team. Because symptoms can be diverse, treatment also has different angles. The most obvious treatment is orthopaedic treatment of fractures and deformities. In addition, pharmacological treatment of low bone density using antiresorptive drugs (bisphosphonates, denosumab) or anabolic drugs (teriparatide, antisclerostin antibodies) in combination with calcium and vitamin D suppletion can reduce fracture incidence and improve bone density. However, medical treatment does not address the defective collagen type 1, which leads not only to reduced bone quantity, but also to abnormal bone matrix and bone.

Rehabilitation intervention (physiotherapy, occupational therapy, rehabilitation) is crucial to reduce fracture incidence and, more importantly, reduce the loss of function and improve quality of life. It is challenging for patients with brittle bones, weak muscles, and a cycle of frequent fractures followed by immobilization to maintain gross motor skills such as walking and to function independently [46]. Most patients with OI can make independent transfers, have enough skills to live independently, are well educated and participate in social life. Because of additional complaints of hearing loss, diminished lung function due to scoliosis and rib cage deformities, cardiac manifestations of OI and dentinogenesis imperfecta, the ear, nose, and throat specialist, pulmonologist, cardiologist and dentist or oral surgeon are also often involved. A periodic visit to a centre of expertise is recommended to ensure adequate surveillance [47].

Table 2 *Extra-skeletal features of the different OI types*

Features	Pathway	Prevalence
Blue sclerae	- Corneal thinning [21,22]. - Decreased light scattering by the sclera [23]. - Increased visibility of the underlying choroid and melanocytes beyond the scleral external surface [24].	Common
Glaucoma	- Thinner cornea is a risk factor in glaucoma [25].	Rare
Dentinogenesis Imperfecta	- Colour: Opalescent dentin, pigments and inclusion of remnants of blood vessels [26,27]. - Fractures: scalloping interface between dentin and the enamel is absent [28], or dentin frailty [27]. - Size and shape: defective type I collagen causes poor mineralization density and abnormal fibrillar structure [29].	Common
Cranial base anomalies: **- Platybasia** **- Basilar impression** **- Basilar invagination**	- Deformation under the strain of the brain, differential growth deficiency and bending or fractures of the skeletal cranial structures [30].	Common
Bleeding tendency	- Abnormal structure and function of the vessel wall, resulting in increased fragility and susceptibility to bleeding (Chapter 5). - Altered extracellular matrix in OI affects platelet function and activation, leading to impaired haemostasis [31-33].	Common
Skin **- Thinness, fragility and translucency** **- Elastosis perforans serpiginosa**	- The dermis has a relative increase of argyrophil and elastic fibres and a deficiency of adult collagen [34,35]. - Alteration in the elastic fibres [36,37].	Rare
Hearing loss	- Among others: Ossicular chain problems [38].	Common
Cardiovascular disease	- Collagen type 1 in myocardium and vessels [39].	Unknown
Pulmonary dysfunction	- Chest wall abnormalities [40,41]. - Pulmonary parenchymal abnormalities [41,42].	Intermediate
Muscle weakness, tendon and ligament laxity.	- Muscle: Delayed motor milestones due to severely bowed legs or fractures [43]. - Tendon and ligaments: unknown [44].	Common
Osteoarthritis and other joint problems	- Secondary to musculoskeletal concerns [44].	Common
Short stature	- Secondary to skeletal abnormalities [8].	Common

Quality of life in OI

The World Health Organization (WHO) defines quality of life as an “individual’s perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, norms and concerns” [48]. Health can have a major impact on quality of life because health is determined by the effect of illness and impairment on daily activities and behaviours, perceived health and functional status [49]. Thus, quality of life has a broad scope and is influenced by several factors. OI primarily affects bone quality, but also potentially affects all other structures containing collagen type 1. Physically measurable factors such as fractures, decreased

bone density, and scoliosis can affect quality of life, but the psychological burden of the disease such as fatigue, difficulty participating in daily life, mobility, self-care, independence, and pain can also affect the quality and are frequently reported [50,51]. These factors can result in health impairment by limiting “normal” daytime activities. The lives of persons with OI are also regularly filled with hospital checkups, given that hospital checkups in these patients are on average 1.5-2.6 times more frequent than the Dutch average [2]. People with OI sometimes describe their disease as a “full-time job”. The focus on preventing fractures in daily life sometimes limits activities, makes certain occupations impossible and makes certain homes unsuitable for living. These situational factors can also affect quality of life, in accordance with the WHO definition.

Due to the huge impact of OI on life, it is important to determine how patients with OI experience their quality of life. There are many possible negative influencing factors, but the mindset of many people with OI also results in limitations being turned into opportunities [52]. If the quality of life of people with OI is well known, the overall care in the multidisciplinary team for persons with OI can be focused on improving the worst perceived aspects. In addition, an individual patient with OI can be compared with other people with OI and more emphasis is placed on individual care needs. This underscores the importance of developing disease-specific patient-reported outcome measures (PROMs) in OI [53]. In this way, value-driven care and shared decision-making develop the care that benefits people the most.

Fatigue in OI

One of the most frequently mentioned negative influencing factors on quality of life in clinical practice is fatigue. OI is a disease with a wide range of skeletal and extra-skeletal symptoms that can cause fatigue. Fatigue of itself has a major impact on both physical and psychological domains in healthy individuals. In the physical domain, for instance, pain and painkillers can promote fatigue [54,55] and lack of energy can lead to reduced enthusiasm and endurance to perform daily tasks. In the psychological domain, fatigue can reduce satisfaction and happiness, but can also have a negative impact on thinking skills, learning ability, memory, concentration and decision-making ability [56]. The impairments on physical and psychological domains can contribute to a negative self-image or even a depression [57], and can affect social relationships and the dependence on others.

OI is a disease which already has a wide range of skeletal and extra-skeletal symptoms that can cause restrictions on the physical domains and impairments on the psychological domain. For instance, brittle bones limit mobility and physical activities, and increase dependence on others [58]. All the domains in which OI can cause impairment in itself and in which fatigue can cause additional impairment are at risk of reducing quality of life in OI.

Because each person with OI may have a different skeletal or extra-skeletal focus that causes fatigue, or in which fatigue may cause additional impairment, it is important to determine the extent of fatigue in OI compared to people without OI. Understanding the extent of fatigue in OI can be a valuable resource for quality of life interventions.

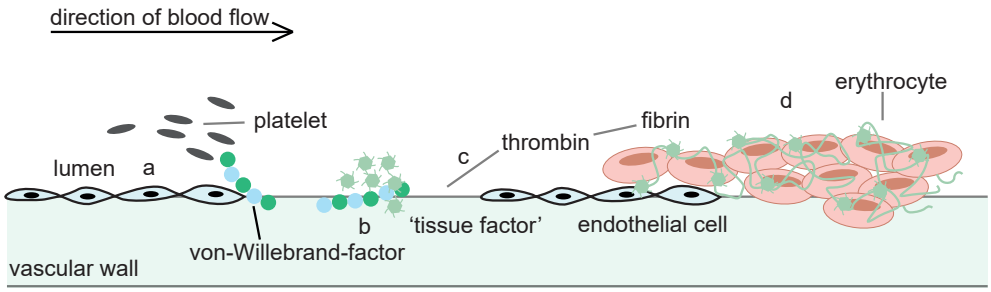
Bleeding tendency

In addition to clinically distinctive features, there are a number of complaints that are consistently mentioned by OI patients but are not clearly reflected in the literature. One notable complaint among these is frequent bruising. Frequent bruising can be a symptom of an underlying bleeding tendency [59]. In well-known coagulation disorders, such as von Willebrand disease and haemophilia, an essential part of the coagulation cascade does not function properly [60] (Figure 1). Alongside the major known coagulation abnormalities, there is also a wide range of less obvious problems that can cause a mild bleeding tendency in both the coagulation cascade and the collagen in the vessel wall [61]. Mild bleeding tendency is a well-known phenomenon in collagen disorders other than OI, such as Ehlers-Danlos. Bleeding tendency in Ehlers-Danlos is caused by a malfunction of fibrillin, which together with elastin forms an elastic fibre. These elastic fibres, together with other structures, form the basic meshwork for the connective tissue matrix [61]. This connective tissue matrix has a direct interaction with coagulation factors and also provides strength to the capillary structure, protecting it from tearing during shearing forces. A similar mechanism could be underlying in OI.
Diagnosing a mild bleeding tendency in OI can be a difficult task. In fact, bleeding problems occur frequently in the normal population without an increased bleeding tendency. Bleeding symptoms occur sequentially, sometimes with long intervals. Patients with a mild bleeding disorder may not consider the number of bleedings they experience as abnormal, as there is usually an inherited disorder at the basis of their disease. If several family members suffer from bleeding problems, it is less obvious that the bleedings are abnormal. In general practice, certain bleeding symptoms, such as heavy menstrual blood loss and epistaxis, are very common and are only recognized at a late stage as a manifestation of an underlying coagulation disorder. In coagulation disorders such as von Willebrand's disease, the time lag to diagnosis is reported to be as long as 16 years [62]. If a mild bleeding tendency is suspected, it remains extremely difficult to find an underlying explanation because not all the components of the complex coagulation cascade can be tested. This is why recent reviews emphasize the importance of a detailed bleeding history and family history [59,63].

In OI, research into bleeding tendency began in the 1950s and was aimed at finding an explanation for the frequent bruising and significant bleeding tendency in OI as was reported in various case

reports. So far, it has not yet yielded any clear answers. However, both case reports and complaints by OI patients on bleeding and bruising mentioned in clinical care are still relevant [64–69]. The early detection of bleeding problems is very important because even mild bleeding tendencies can have an impact on operations, length of hospitalization, mortality, pregnancy, birth and miscarriages. Unexplained mild bleeding tendencies can also lead to anxiety. More clarity on the underlying cause of bleeding tendency would be crucial to providing more safety in the numerous operations and interventions that patients with OI undergo.

Figure 1 *Primary haemostasis*



Primary haemostasis involves two key processes: vasoconstriction and platelet adhesion to the injured vessel wall. (a) The plasma protein von-Willebrand-factor plays a vital role in capturing platelets from the rapidly flowing blood at the site of vessel wall damage. (b) Once adhered, platelets undergo activation and aggregation. (c) Concurrently, tissue factor present in the damaged vessel wall triggers secondary haemostasis. This leads to the activation of coagulation factors on the surface of the activated platelets, resulting in the generation of thrombin. (d) Ultimately, thrombin influences the formation of a fibrin network that reinforces the haemostatic plug and acts as a trap for erythrocytes, forming a blood clot. Following clot formation, the fibrinolytic system is responsible for breaking down the blood clot [70].

Aim and outline of this thesis

The aim of this thesis is to gain insights into quality of life issues and bleeding tendency in persons with Osteogenesis imperfecta (OI). To improve patient care and guidance and to increase the diagnostic capabilities, it is important to look at OI in a broader context than just a disease with bone fragility.

Part I of this thesis focusses on the quality of life in people with OI.
The following research questions were addressed:

1. What is the quality of life in people with OI compared to control populations? **(Chapter 2)**
2. What is the impact of fatigue on daily functioning in people with OI compared to control populations? **(Chapter 3)**

In **part II** of this thesis the bleeding tendency in OI is investigated and the following research questions were formulated:

3. What is the prevalence of bleeding tendency in OI compared with a control population? **(Chapter 5)**
4. What are the clinical manifestations of bleeding tendency in OI? Is diagnostic testing for bleeding disorders indicated? **(Chapter 4 and 6)**
5. Which bleeding events are most clinically relevant in OI? What can be learned from therapeutic considerations in other mild bleeding disorders? **(Chapter 5)**

Chapter
1

References

1. Steiner RD, Basel D. COL1A1 / 2 Osteogenesis Imperfecta. GeneReviews® - NCBI Bookshelf 2005.
2. Storoni S, Treurniet S, Maugeri A, et al. Prevalence and Hospital Admissions in Patients With Osteogenesis Imperfecta in The Netherlands: A Nationwide Registry Study. Front Endocrinol (Lausanne) 2022; 13. DOI:10.3389/fendo.2022.869604.
3. Forlino A, Marini JC. Osteogenesis imperfecta. The Lancet 2016; 387: 1657–71.
4. Hald JD, Folkestad L, Harsløf T, Brixen K, Langdahl B. Health-Related Quality of Life in Adults with Osteogenesis Imperfecta. Calcif Tissue Int 2017; 101: 473–8.
5. Forlino A, Cabral WA, Barnes AM, Marini JC. New perspectives on osteogenesis imperfecta. Nat Rev Endocrinol. 2011; 7. DOI:10.1038/nrendo.2011.81.
6. Byers PH. Osteogenesis imperfecta: Perspectives and opportunities. Curr Opin Pediatr 2000; 12. DOI:10.1097/00008480-200012000-00016.
7. Claeys L, Storoni S, Eekhoff M, et al. Collagen transport and related pathways in Osteogenesis Imperfecta. Hum Genet. 2021; 140: 1121–41.
8. Van Dijk FSS, Sillence DOO. Osteogenesis imperfecta: Clinical diagnosis, nomenclature and severity assessment. Am J Med Genet A 2014; 164: 1470–81.
9. Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. J Med Genet 1979; 16: 101–16.
10. Hayat A, Hussain S, Bilal M, et al. Biallelic variants in four genes underlying recessive osteogenesis imperfecta. Eur J Med Genet 2020; 63. DOI:10.1016/j.ejmg.2020.103954.
11. Etich J, Rehberg M, Eckes B, Sengle G, Semler O, Zaucke F. Signaling pathways affected by mutations causing osteogenesis imperfecta. Cell Signal 2020; 76. DOI:10.1016/j.cellsig.2020.109789.
12. Bacon S, Crowley R. Developments in rare bone diseases and mineral disorders. Ther Adv Chronic Dis 2018; 9. DOI:10.1177/2040622317739538.
13. Yonko EA, Emanuel JS, Carter EM, Sandhaus RA, Raggio CL. Respiratory impairment impacts QOL in osteogenesis imperfecta independent of skeletal abnormalities. Arch Osteoporos 2020; 15. DOI:10.1007/s11657-020-00818-0.
14. McAllion SJ, Paterson CR. Causes of death in osteogenesis imperfecta. J Clin Pathol 1996; 49: 627–30.
15. Folkestad L, Hald JD, Canudas-Romo V, et al. Mortality and Causes of Death in Patients With Osteogenesis Imperfecta: A Register-Based Nationwide Cohort Study. Journal of Bone and Mineral Research 2016; 31: 2159–66.

16. Gooijer K, Harsevoort AGJ, van Dijk FS, Withaar H, Janus GJM, Franken AAM. A Baseline Measurement of Quality of Life in 322 Adults With Osteogenesis Imperfecta. JBMR Plus 2020; 4. DOI:10.1002/jbm4.10416.
17. Van Dijk FS, Cobben JM, Kariminejad A, et al. Osteogenesis imperfecta: A review with clinical examples. Mol Syndromol 2011; 2. DOI:10.1159/000332228.
18. Bilo RAC, Robben SGF, Van Rijn RR, Maat GJR, Huls NM. Forensic aspects of paediatric fractures: Differentiating accidental trauma from child abuse. 2010 DOI:10.1007/978-3-540-78716-7.
19. Ablin DS, Greenspan A, Reinhart M, Grix A. Differentiation of child abuse from osteogenesis imperfecta. American Journal of Roentgenology 1990; 154. DOI:10.2214/ajr.154.5.2108539.
20. Marlowe A, Pepin MG, Byers PH. Testing for osteogenesis imperfecta in cases of suspected non-accidental injury. J Med Genet 2002; 39. DOI:10.1136/jmg.39.6.382.
21. Evereklioglu C, Madenci E, Bayazit YA, Yilmaz K, Balat A, Bekir NA. Central corneal thickness is lower in osteogenesis imperfecta and negatively correlates with the presence of blue sclera. Ophthalmic and Physiological Optics 2002; 22. DOI:10.1046/j.1475-1313.2002.00062.x.
22. Chan CC, Green WR, Cruz ZC, Hillis A. Ocular Findings in Osteogenesis Imperfecta Congenita. Archives of Ophthalmology 1982; 100. DOI:10.1001/archopht.1982.01030040437014.
23. Lanting PJH, Borsboom PCF, Meerman GJ te, Kate LP ten. Decreased scattering coefficient of blue sclerae. Clin Genet 1985; 27. DOI:10.1111/j.1399-0004.1985.tb00209.x.
24. Chau FY, Wallace D, Vajaranant T, et al. Osteogenesis Imperfecta and the Eye. In: Osteogenesis Imperfecta: A Translational Approach to Brittle Bone Disease. 2013. DOI:10.1016/B978-0-12-397165-4.00031-9.
25. Viswanathan D, Goldberg I, Graham SL. Relationship of change in central corneal thickness to visual field progression in eyes with glaucoma. Graefe's Archive for Clinical and Experimental Ophthalmology 2013; 251. DOI:10.1007/s00417-013-2295-6.
26. Luder HU, Van Waes H, Raghunath M, Steinmann B. Mild dental findings associated with severe osteogenesis imperfecta due to a point mutation in the α2(I)) collagen gene demonstrate different expression of the genetic defect in bone and teeth. J Craniofac Genet Dev Biol 1996; 16.
27. Lindau B, Dietz W, Lundgren T, Storhaug K, Rgen JÈ, Nore G. Discrimination of morphological findings in dentine from osteogenesis imperfecta patients using combinations of polarized light microscopy, microradiograhpy and scanning electron microscopy. Int J Paediatr Dent 1999; 9: 253–61.

28. Levin LS, Brady JM, Melnick M. Scanning electron microscopy of teeth in dominant osteogenesis imperfecta: Support for genetic heterogeneity. Am J Med Genet 1980; 5. DOI:10.1002/ajmg.1320050213.
29. Nanci A. Development, Structure, and Function. In: Ten Cate' s Oral Histology , 9th edn. 2017.
30. Waltimo-Sirén J, Kolkka M, Pynnönen S, Kuurila K, Kaitila I, Kovero O. Craniofacial features in osteogenesis imperfecta: A cephalometric study. Am J Med Genet 2005; 133 A. DOI:10.1002/ajmg.a.30523.
31. Evensen SA, Myhre L, Stormorken H. Haemostatic studies in osteogenesis imperfecta. Scand J Haematol 1984; 33: 177–9.
32. Hathaway WE, Solomons CC, Ott JE, Ott E. Platelet Function and Pyrophosphates in Osteogenesis Imperfecta. Blood 1972; 39.
33. Estes JW. Platelet size and function in the heritable disorders of connective tissue. Ann Intern Med 1968; 68: 1237–49.
34. Hansen B, Jemec GBE. The mechanical properties of skin in osteogenesis imperfecta. Arch Dermatol 2002; 138. DOI:10.1001/archderm.138.7.909.
35. Francis MJO, Williams KJ, Sykes BC, Smith R. The relative amounts of the collagen chains α1(I), α2 and α1(III) in the skin of 31 patients with osteogenesis imperfecta. Clin Sci 1981; 60. DOI:10.1042/cs0600617.
36. Mehta RK, Burrows NP, Rowland Payne CME, Mendelsohn SS, Pope FM, Rytina E. Elastosis perforans serpiginosa and associated disorders. Clin Exp Dermatol 2001; 26. DOI:10.1046/j.1365-2230.2001.00882.x.
37. Pérez-Pérez L, Allegue F, Alfonsín N, Caeiro JL, Fabeiro JM, Zulaica A. An uncommon association: Elastosis perforans serpiginosa and osteogenesis imperfecta. Journal of the European Academy of Dermatology and Venereology 2009; 23. DOI:10.1111/j.1468-3083.2008.02751.x.
38. Pillion JP, Vernick D, Shapiro J. Hearing Loss in Osteogenesis Imperfecta: Characteristics and Treatment Considerations. Genet Res Int 2011; 2011. DOI:10.4061/2011/983942.
39. Ashournia H, Johansen FT, Folkestad L, Diederichsen ACP, Brixen K. Heart disease in patients with osteogenesis imperfecta - A systematic review. Int J Cardiol 2015; 196: 149–57.
40. LoMauro A, Pochintesta S, Romei M, et al. Rib cage deformities alter respiratory muscle action and chest wall function in patients with severe Osteogenesis imperfecta. PLoS One 2012; 7. DOI:10.1371/journal.pone.0035965.
41. Gochuico BR, Hossain M, Talvacchio SK, et al. Pulmonary function and structure abnormalities in children and young adults with osteogenesis imperfecta point to intrinsic and extrinsic lung abnormalities. J Med Genet 2023; published online May 16. DOI:10.1136/jmg-2022-109009.

42. Widmann RF, Bitan FD, Laplaza FJ, Burke SW, DiMaio MF, Schneider R. Spinal deformity, pulmonary compromise, and quality of life in osteogenesis imperfecta. Spine (Phila Pa 1976) 1999; 24: 1673–8.
43. Engelbert RH, Gulmans VA, Uiterwaal CS, Helders PJ. Osteogenesis imperfecta in childhood: Perceived competence in relation to impairment and disability. Arch Phys Med Rehabil 2001; 82. DOI:10.1053/apmr.2001.23889.
44. McKiernan FE. Musculoskeletal manifestations of mild osteogenesis imperfecta in the adult. Osteoporosis International 2005; 16: 1698–702.
45. Schindeler A, Lee LR, O'Donohue AK, Ginn SL, Munns CF. Curative Cell and Gene Therapy for Osteogenesis Imperfecta. Journal of Bone and Mineral Research 2022; 37. DOI:10.1002/jbmr.4549.
46. Montpetit K, Palomo T, Glorieux FH, Fassier F, Rauch F. Multidisciplinary Treatment of Severe Osteogenesis Imperfecta: Functional Outcomes at Skeletal Maturity. Arch Phys Med Rehabil 2015; 96. DOI:10.1016/j.apmr.2015.06.006.
47. Lafage-Proust MH, Courtois I. The management of osteogenesis imperfecta in adults: state of the art. Joint Bone Spine 2019. DOI:10.1016/j.jbspin.2019.02.001.
48. World Health Organization. WHOQOL-HIV Instrument Users Manual. SubStance 2002; : 1–13.
49. WHOQOL Group, Szabo S, Orley J, Saxena S. WHOQOL User Manual PROGRAMME ON MENTAL HEALTH. Geneve, 1997.
50. Hill, Hammond J, Sharmin M, et al. Living with osteogenesis imperfecta: A qualitative study exploring experiences and psychosocial impact from the perspective of patients, parents and professionals. Disabil Health J 2022; 15. DOI:10.1016/j.dhjo.2021.101168.
51. Vartiainen P, Heiskanen T, Sintonen H, Roine RP, Kalso E. Health-related quality of life and burden of disease in chronic pain measured with the 15D instrument. Pain 2016; 157. DOI:10.1097/j.pain.0000000000000641.
52. Wekre LL, Frøslie KF, Haugen L, Falch JA. A population-based study of demographical variables and ability to perform activities of daily living in adults with osteogenesis imperfecta. Disabil Rehabil 2010; 32. DOI:10.3109/09638280903204690.
53. Nijhuis W, Franken A, Ayers K, et al. A standard set of outcome measures for the comprehensive assessment of osteogenesis imperfecta. Orphanet J Rare Dis 2021; 16. DOI:10.1186/s13023-021-01682-y.
54. Conrad R, Geiser F, Mücke M. Pain and fatigue-a systematic review. Z Psychosom Med Psychother 2018; 64. DOI:10.13109/zptm.2018.64.4.365.

55. Cortés RM, Pastor JFS, Dolz VM. Chronic pain in adults with osteogenesis imperfecta and its relationship to appraisal, coping, and quality of life: A cross-sectional study. Medicine (United States) 2022; 101. DOI:10.1097/MD.0000000000030256.
56. Campbell RD, Bagshaw M. Human Performance and Limitations in Aviation. 2002 DOI:10.1002/9780470774472.
57. Giallo R, Gartland D, Woolhouse H, Brown S. “I didn’t know it was possible to feel that tired”: exploring the complex bidirectional associations between maternal depressive symptoms and fatigue in a prospective pregnancy cohort study. Arch Womens Ment Health 2016; 19. DOI:10.1007/s00737-014-0494-8.
58. Dogba MJ, Bedos C, Durigova M, et al. The impact of severe osteogenesis imperfecta on the lives of young patients and their parents - a qualitative analysis. BMC Pediatr 2013; 13. DOI:10.1186/1471-2431-13-153.
59. Boender J, Kruip MJHA, Leebeek FWG. A diagnostic approach to mild bleeding disorders. Journal of Thrombosis and Haemostasis 2016; 14: 1507–16.
60. Sadler JE. Biochemistry and genetics of von Willebrand factor. Annu Rev Biochem 1998; 67. DOI:10.1146/annurev.biochem.67.1.395.
61. Malfait F, Paepe A De. Bleeding in the heritable connective tissue disorders: Mechanisms, diagnosis and treatment. Blood Rev 2009; 23. DOI:10.1016/j.blre.2009.06.001.
62. Kirtava A, Crudder S, Dilley A, Lally C, Evatt B. Trends in clinical management of women with von Willebrand disease: A survey of 75 women enrolled in Haemophilia Treatment Centres in the United States. Haemophilia 2004; 10. DOI:10.1046/j.1351-8216.2003.00832.x.
63. Moenen FCJI, Nelemans PJ, Schols SEM, Schouten HC, Henskens YMC, Beckers EAM. The diagnostic accuracy of bleeding assessment tools for the identification of patients with mild bleeding disorders: A systematic review. Haemophilia. 2018; 24. DOI:10.1111/hae.13486.
64. Mayer SA, Rubin BS, Starman BJ, Byers PH. Spontaneous multivessel cervical artery dissection in a patient with a substitution of alanine for glycine (G13A) in the α1(I) chain of type I collagen. Neurology 1996; 47: 552–6.
65. Edge G, Okafor B, Fennelly ME, Ransford AO. An unusual manifestation of bleeding diathesis in a patient with osteogenesis imperfecta. Eur J Anaesthesiol 1997; 14: 215–9.
66. Kastrup M, von Heymann C, Hotz H, et al. Recombinant factor VIIa after aortic valve replacement in a patient with osteogenesis imperfecta. Ann Thorac Surg 2002; 74: 910–2.
67. Mondal RK, Mann U, Sharma M, Mondal RK, Mann U, Sharma M. Osteogenesis imperfecta with bleeding diathesis. Indian J Pediatr 2003; 70: 95–6.
68. Faqeih E, Roughley P, Glorieux FH, Rauch F. Osteogenesis imperfecta type III with intracranial hemorrhage and brachydactyly associated with mutations in exon 49 of COL1A2. Am J Med Genet A 2009; 149A: 461–5.

69. Paterson CR, Monk EA. Temporary brittle bone disease: association with intracranial bleeding. Journal of Pediatric Endocrinology and Metabolism 2013; 26: 417–26.
70. van Vulpen LFD, Wichers IM, Urbanus RT, van Galen KPM. [Diagnostics on suspicion of a bleeding disorder]. Ned Tijdschr Geneeskd 2020; 164.

Part I

Quality of life in Osteogenesis Imperfecta

Chapter 2

A baseline measurement of quality of life in 322 adults with osteogenesis imperfecta

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Abstract

Osteogenesis imperfecta (OI) is characterized by bone fragility and secondary features such as blue sclerae, dentinogenesis imperfecta, hearing loss, ligamentous laxity, and short stature. It was thought that health-related quality of life (QoL) in patients with OI mainly depends on the severity of the skeletal deformities. However, it has become clear that additional factors can affect the QoL in all patients with OI. In this study, we compare dimensions of QoL in adults with OI with a control population. The SF-36 questionnaire was distributed among 330 adult patients with different OI types. Results were compared with two control populations from the Netherlands. Age-matched comparisons were made with one of the two control populations. The results were summarized in eight domains: general and mental health, physical and social function, bodily pain, vitality, and physical and emotional role. General health and physical function in all types of OI are low compared with controls, except patients with OI type 4 aged 55+ years. Bodily pain in patients with OI appeared significantly worse than in the control population. There was no significant difference between OI types regarding pain and vitality. Vitality was only in the OI type 1 group significantly lower compared with controls. Patients with OI type 1 had a significantly reduced mental health. Social functioning appeared most effective in type 3 around 20 years of age. QoL in adult patients with OI should be an important outcome measure in every OI clinic, but the amount of baseline data on this subject is sparse. This baseline measurement study is the largest study to date investigating QoL in adult patients with OI. The mean scores indicate that people with OI generally have a significantly lower QoL than the control population. Further qualitative evaluation of QoL and its influences is important for future management.

Introduction

Osteogenesis imperfecta (OI) is an inherited connective tissue disorder primarily characterized by susceptibility to fractures. The prevalence of OI has been reported to be 6 to 7 individuals per 100,000 population [1]. OI is a clinically and genetic heterogeneous disorder. Clinically, OI is classified in five types (OI types 1 to 5) [2]. According to the clinical severity and characteristics, OI is further classified into five subtypes: nondeforming OI with blue sclerae (type 1), perinatally lethal OI (type 2), progressively deforming OI (type 3), common variable OI (type 4), and finally OI with calcification in the interosseous membranes (type 5) [2]. Patients can have blue sclerae, dentinogenesis imperfecta, hearing loss, joint hypermobility, and short stature as secondary features [3]. Symptoms such as hearing loss, physical restrictions caused by pain, bone deformation as a result of (recurrent) fractures can increase in severity with age and can affect the health-related quality of life (QoL) in patients with OI.

No cure for OI exists; treatment focuses on management of symptoms. Orthopedic and fracture treatment, physical therapy, special dental care, treatment for hearing loss, and medical treatment for low BMD are common therapies. However, there has been less attention paid to the psychosocial impact of living with OI in adults.

Today, it is commonly recognized that measuring the QoL in people with OI can provide new information to improve treatment and subsequently the QoL of patients. Here, we report on the QoL of 322 patients with a diagnosis of OI type 1, 3, and 4 in the Netherlands compared with the general Dutch population. We suspected that the QoL in patients with OI would be decreased compared with controls. To measure the QoL in a patient cohort with OI, we decided to use the validated self-reported health assessment tool, the SF-36 questionnaire [5,6], which is frequently used in international studies. The SF-36 measures QoL across eight different subscales. We compared the SF-36 subscales against the different OI-type groups and with the QoL data of two Dutch control groups, including different age categories.

Patients and Methods

Study design and population

A cross-sectional cohort study was undertaken in the National Expert Center for Adults with Osteogenesis Imperfecta, Isala Hospital, Zwolle, the Netherlands. In this center, patients with a clinical and usually confirmed molecular diagnosis of OI are assessed by the multidisciplinary OI team.

The SF-36 questionnaire [4] was provided during the first appointment. All new adult patients who attended the center from December 2007 until November 2018 were selected. Exclusion criteria were age <18 years and unavailability to fill in the questionnaire. Informed consent was obtained from each participant, and the Medical Ethics Committee of the Isala Hospital, Zwolle, the Netherlands, approved the study protocol and provided a non-WMO (Medical Research Involving Human Subjects Act) waiver.

Evaluation of quality of life in patients with OI

QoL was assessed using the validated self-reported health assessment tool, the SF-36 questionnaire [5,6], which is composed of 36 questions in eight different domains that examine aspects of physical and mental health in a 4-week timeframe. The SF-36 questionnaire is used in multiple countries to measure QoL in patients; it has been extensively tested for reliability and validity [6–10]. The four main physical domains are physical function, role limitations caused by physical health problems, bodily pain, and general health perceptions. The four main mental domains are vitality, social function, role limitations based on emotional problems, and general mental health. Each domain score is linearly converted to a 0 to 100 scale. A higher score is correlated with better mental and physical health. The physical and mental domains can be summarized in two broad scores: the physical component summary and the mental component summary. These summary scores reflect self-assessed physical and mental activity.

All patients with different types of OI were divided in age categories to compare QoL in patients with OI.

Control groups

The control values are based on two different studies. The first control was the result of a municipal screening that was carried out in 1992 by the University of Groningen, the Netherlands. It concerned a group of 1063 adults, randomly selected from the civil register of Township Emmen. The data of this control group were available according to different age ranges [11]. For the general comparison, a national randomly selected control group without age range (n = 1742) was used. Data from these individuals were generated from a study conducting a nationwide, population-based health status survey for the purpose of generating normative data for a study of patients with congenital heart defects [5].

The SF-36 questionnaire results of both control groups are presented in Figure 1.

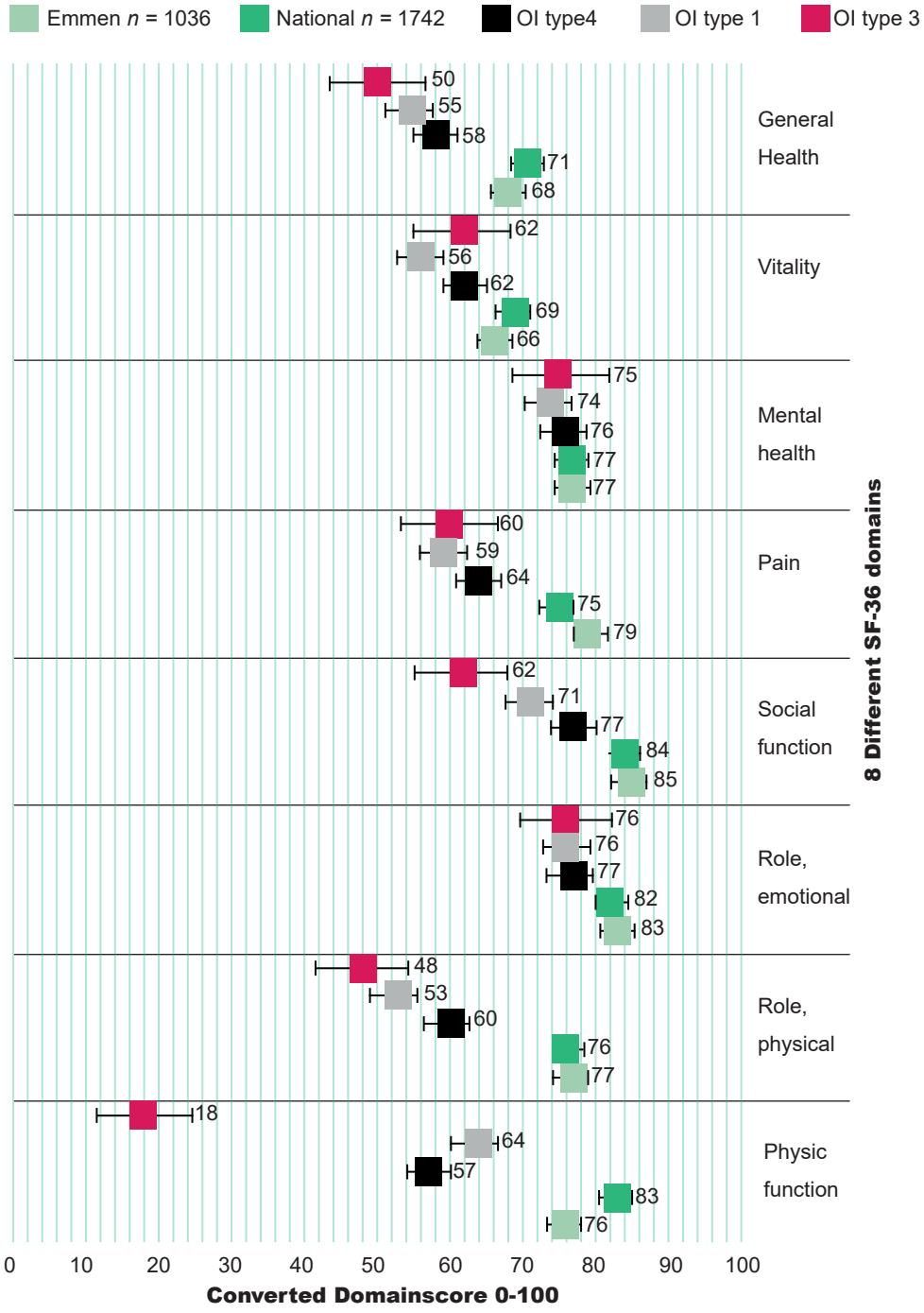

Figure 1 *Visualization of the eight different SF-36 questionnaire domains, divided per osteogenesis imperfecta type and control group*

Data and statistical analysis

In Table 1, the data of both control groups [5,11] have been combined and compared with the recruited patients with OI. Only the first control group[11] was used for the data presented in the Supplementary Appendix. For each age category, a comparison was made with the age-matched control patients to test if the null-hypothesis (no differences between OI and controls) could be rejected. Then, the OI types were reciprocally compared. To calculate a Δ score, the score of the youngest patient group was subtracted from the eldest patient group. As the oldest OI type 3 group consisted only of three individuals, the Δ score was not calculated. Given that the questionnaire score cannot be reliably estimated for participants with extreme scores, floor and ceiling effects were examined (Table 1).

Variables were tested for normal distribution with the Kolmogorov–Smirnov test, Shapiro–Wilk test, and q-q plots. Means and SDs were given for normally distributed continuous variables. Non-normally distributed continuous variables were presented as median, interquartile range (IQR). Differences in means comparing patients with OI with the controls were in normally distributed data tested using the summary independent sample *t* tests and in not normally distributed data tested with the one-sample Wilcoxon signed-rank test. Comparisons between OI types of different ages were done using ANOVA in normally distributed data, and with independent-samples Kruskal-Wallis tests with Dunn's comparison for post hoc testing in not normally distributed data. A two-sided p value of 0.05 was considered significant. Significance values for comparison between OI types have been adjusted by the Bonferroni correction for multiple testing. Significance values for comparing patients with OI with controls are presented with three decimals for adequate interpretation. Analyses were performed using SPSS 25 (SPSS, Inc., Chicago, IL, USA) for Windows.

We did not assess separately modifiers of QoL such as fracture history, scoliosis, and pulmonary function.

Results

Clinical characteristics

A total of 372 patients with OI were identified for participation in the current study. Fifty patients were excluded as their SF-36 questionnaires were unavailable. Therefore, 322 patients were available for analysis.

Table 1 *SF-36 scores in OI types and in the general population*

	Osteogenesis Imperfecta type								
Physical domains	**OI (all types) (*n* = 322)**	***P* Value**	**Type 1 (*n* = 220)**	***P* Value**	**OI type 3 (*n* = 40)**	***P* Value**	**OI type 4 (*n* = 62)**	***P* Value**	**General population (*n* = 1063 + 1742)**
PF	57 ± 31.3	.000	63.6 ± 28.6	.000	**18.4 ± 21.8**	.000	57.2 ± 28.4	.000	79.4 ± 22.8
RP	50 (0; 100)	.000	**50 (0; 100)**	.000	**50 (0; 100)**	.000	**75 (0; 100)**	.012	76.5 ± 36.3
BP	60.4 ± 27.2	.000	59.4 ± 27.8	.000	60.4 ± 25.5	.000	**64 ± 26**	.000	77.14 ± 24.4
GH	54.8 ± 20.7	.000	54.6 ± 20.4	.000	50.4 ± 23.9	.000	58.2 ± 19.3	.000	69.42 ± 21.14
PCSS	39.6 ± 11.6	.000	40.6 ± 11.8	.000	31.8 ± 9.2	.000	41 ± 10.4	.000	50 ± 10
Mental Domains									
Vitality	58 ± 20.6	.000	56.1 ± 20.5	.000	61.7 ± 20.6	.081	62.2 ± 20.4	.043	67.53 ± 19.9
SF	75 (50; 100)	.000	75 (50; 100)	.000	**62.5(37.5;87.5)**	.000	**75 (62.5; 100)**	.066	84 ± 22.3
RE	100 (66; 100)	.018	**100 (66; 100)**	.064	**100 (66; 100)**	.438	**100 (66; 100)**	.210	82.57 ± 33.3
MH	74.2 ± 18	.012	73.6 ± 18	.009	75.3 ± 18.9	.618	75.6 ± 17.7	.600	76.8 ± 17.56
MCSS	49.7 ± 11.2	.615	48.7 ± 10.9	.087	53.2 ± 11.2	.078	51 ± 11.6	.492	50 ± 10

Data shown as mean ± SD or median (interquartile range) as appropriate. *p* Values are osteogenesis imperfecta vs general population (summary independent *t* test or one-sample Wilcoxon signed-rank test).

Values indicating floor (≥15% with a score of 0) and ceiling (≥15% with a score of 100) effects are in bold face.

BP = Bodily pain; GH = general health; MCSS = mental component summary score; MH = mental health; PCSS = physical component summary score; PF = physical functioning; RE = role functioning emotional; RP = role functioning physical; SF = social functioning.

A total of 190 (59%) of the 322 patients with OI in our cohort were women; 132 (41%) were men. The mean and median age of participants with OI at the first visit were, respectively, 38 and 35.5 years (interquartile range (IQR) 27 years). Skewness and kurtosis were, respectively, 0.343 and −1.119, confirming a normal distribution with a small overrepresentation of the middle group [12]. There were 220 (66.7%) subjects who had a diagnosis of OI type 1, 40 (12.1%) were diagnosed with OI type 3, and 61 patients (18.5%) had OI type 4.

Scores of all patients with OI across eight different SF-36 subscales

Figure 1 shows the results of the eight different SF-36 subscales of the three OI types in comparison with two control groups in the Netherlands [5,11].

Individuals with OI type 1, 3 and 4 had a significantly lower mean physical function score compared with the control groups (Table 1) [5,11]. A significant difference between patients with OI and controls applied to all the subscales except for vitality in OI type 3, role limitations caused by emotional problems in OI types 3 and 4, and mental health in OI types 3 and 4 (Table 1).

Comparison of SF-36 subscale scores in different age categories

A complete overview of the results is available in the Supplementary Table S2. The comparisons have been made with the first control group [11] because in this control group participants were divided in age categories, suitable for making agematched comparisons.

Physical functioning

Physical function in the overall OI cohort was significantly lower compared with controls [5,11] in all different age categories, except for patients with OI type 4 and aged >55 years (Table 1 and Supplementary Table S2) [11]. Individuals with OI type 3 had the lowest score on physical function, (Table 1), whereas individuals with OI type 1 in the age group 18 to 24 years had the highest score on physical function. The physical function of OI type 3 was significantly lower than OI type 1 and 4 in all age categories except when compared with OI type 4 in the age group 35 to 54 years (Supplementary Table S2). The physical function of individuals with OI types 1 and 4 in the different age categories were not significantly different from each other, except in the age category 18 to 24 years (Supplementary Table S2).

In the control group [11], physical function declined during at least 30 years with 27.9 points (Δ; see Patients and Method section). The OI type 1 group followed that trend (Δ −21.72, $p < 0.05$), whereas patients with OI type 4 showed a climbing trend (Δ +18.7, $p = 0.106$), implying that several individ-

uals >55 years with OI type 4 experienced a higher physical function than patients with OI type 4 aged 18 to 24 years (Supplementary Table S1).

Role limitations caused by physical health problems

The role limitations caused by physical health problems in individuals with OI was significantly lower compared with controls [5,11] (Table 1). For patients with OI type 3, this was not significant for all age categories from 25 to 55+ years. For patients with OI type 4, this was not significant above the age of 35 years. Between OI types, there was a less-significant difference at different ages (Supplementary Table S2). Patients with OI type 4 aged 35 to 54 years (Supplementary Table S1) had the lowest score on role limitations caused by physical health problems. OI type 3 patients had the lowest score on role limitations caused by physical health problems, but the score increases until their mid-50s when the difference between OI type 3 and the controls [11] was not significant anymore (Supplementary Table S2).

The control group [11] trend over the years was decreasing slowly (Δ−15.4; Table 1). The OI type 1 group had a comparable trend (Δ –11.3), whereas patients with OI type 4 had an increasing score over the years (OI type 4: Δ +7.5). None of the OI trend values were significant.

Bodily pain

All patients with OI experienced significantly more pain than the control group [5,11] (Table 1), also within different age categories (Supplementary Table S2). On a scale from 1 to 100 points, patients with OI scored an average of 17 points lower than the control group. There was no significant difference in pain between OI types in different age categories (Supplementary Table S2). The pain in patients with OI type 1 and type 4 was higher in the oldest patient group compared with the youngest patient group (OI type 1: Δ−12.9, p = 0.101; OI type 4: Δ−7.3, p = 0.440). This was comparable to the Δ of the control group [11] (Δ−13.1). The lowest score on bodily pain was reported in patients with OI type 4 between the ages of 25 and 34 years (Supplementary Table S1).

General health perceptions

Across all the age categories, except for people with OI type 4 > 55 years, patients with OI had a significant lower general health than their controls [11] (Supplementary Table S2). There was no significant difference in health perceptions between OI types in all age categories. Health perception of patients with OI decreased less from the youngest to the eldest age group compared with healthy people [11] (Δ mean OI: –5.22, Δ mean controls: −15.88). This resulted in a statistically non-significant difference of health perception between patients with OI and controls in the age category of 55+ years.

Vitality

Only patients with OI type 1 showed a significantly lower vitality compared with the control group [5,11] (Table 1), except when >55 years [11] (Supplementary Table S2). Patients with OI types 3 and 4 did not have significantly reduced vitality compared with controls [11], except for OI type 3 in the age category of 35 to 54 years. There was no significant difference in vitality between the OI types in different age categories.

Vitality in the control group [11] slightly decreased from the youngest to the eldest age group (Δ−4.5). This was similar in the patients with OI type 1 (Δ−0.1) and OI type 4 (Δ−8.83; Supplementary Table S1).

Social functioning

Social function in patients with OI with types 1, 3, and 4 was significantly lower compared with the control group [5,11] (Table 1). However, when analyzed per age category these results were in some instances not significant [11] (Supplementary Table S2). There was one statistically significant difference in social functioning between OI types in different age categories. In age category 18 to 25 years; people with OI type 3 scored significantly lower than people with OI type 1 and OI type 4.

Role limitations caused by personal or emotional problems

Role limitations caused by personal of emotional problems of patients with OI in general were not statistically different from the control population [5,11]. Regarding the different age categories, there was a statistically significant difference between patients with OI type 4 and controls in the age category 18 to 24 years [11].

There was no significant difference regarding role limitations between the OI types in all age categories. Individuals with OI type 4 scored lowest regarding role limitations in the age category 25 to 34 years (Supplementary Table S1). Patients with OI type 4, aged 19 to 24 years, scored highest, even significantly higher than the control group [11].

Mental health

We observed—only in patients with OI type 1—a very small, but significantly reduced mental health compared with controls [5,11] (Table 1). When analyzing specific age categories in patients with OI type 1, patients with OI aged 35 to 54 years had a significant reduced mental health (Supplementary Tables S1 and S2). There was no significant difference between the OI types. The oldest and the youngest groups had similar outcomes.

Discussion

Most studies on QoL in OI have focused on children; hence, studies reporting on QoL of adult patients with OI are sparse. We used the SF-36 questionnaire to measure QoL in 322 adults with OI. The objective was to describe and compare the QoL in adults with a clinical diagnosis of OI types 1, 3, and 4 in different age categories with controls. The control group consisted of 2834 healthy Dutch adults reported in two studies [5,11], with one group divided into age categories (n = 1063) [11].

A recent online survey of 300 self-reported patients with OI, consisting of 198 adults, investigated QoL using nine patient-reported outcomes measurement information system (PROMIS) computer adaptive testing (CAT) instruments [13]. QoL has also been investigated in adults with OI using the SF-36 questionnaire. In these studies, the number of adult participants ranged from 15 to 85,[14–18] which makes the current study the largest study to date investigating QoL in adults with OI.

Our adult OI cohort reported significantly decreased psychosocial and physical QoL across multiple domains and age groups, compared with the control group(s). We identified multiple significant differences between adults with OI and the controls.

The results of physical function per OI type and age category reflect what we see in our outpatient clinics. Physical function in the overall cohort is significantly lower compared with controls, and patients with OI type 3 have the lowest physical function. Patients with OI type 1 aged 18 to 24 years have the highest physical function. This may be because it is OI type 1, which is characterized by the absence of bone deformation, and sometimes it can be mild and difficult to diagnose in the absence of a family history. Additionally, in adulthood, the fracture rate is known to decrease significantly in contrast to the childhood fracture rate. Only in patients with OI type 1 did we observe significantly reduced mental health compared with controls, probably because of the greater sample size. Mental health in the overall OI cohort compared with the control groups was significantly lower and in line with observations by Hald and colleagues [18] and Widmann and colleagues [15], where the mental domains were less affected than the physical domains in people with OI. Supplementary Table S3 provides a detailed comparison with only the study by Hald and colleagues because of their larger number of participants (n = 85) and data availability.

The relative sparing of psychosocial dimensions of QoL in patients with OI was also observed in patients with Marfan syndrome [19] and patients living with congenital heart disease [20], as well as patients with OI [18]. Perhaps the adults with OI have developed coping skills during their childhood

that allow for normal psychosocial functioning despite their physical limitations.

The difference between physical severity measured by physical function and subjective severity perception measured by general health perception illustrates that patients may perceive the disorder differently from health care professionals. This is important for health care providers to acknowledge when discussing patient reported symptoms in clinical practice. Patient reported QoL should be incorporated into clinical practice to ensure the patient's perspective is included in clinical decision-making. The mean pain in patients with OI is significantly increased compared with the control group, but between the OI types there are no significant differences. The presence of pain would imply a more-severe disease, but there is no evident association between pain and OI type in our cohort. This is comparable with observations of other studies [15,21], and has also been observed in review studies for pain in children with OI [22].

Vitality in patients with OI is only slightly lower than the control group. Some studies reported diminished vitality and social functioning abilities [23] with reduced mental health and emotional functioning compared with the adult control group [17]. In our study, only for patients with OI type 1 is vitality significantly lower than in the controls. This is important to know when seeing patients with OI with complaints about reduced vitality: Other possible causes should be excluded first, and reduced vitality should not immediately be assumed to be a feature of patients with OI.

In our cohort, there is no significant difference in social functioning between patients with OI type 1 and type 4 after the age of 25 years. There seems to be reduced social functioning in patients with OI type 3 under the age of 25 years. This improves around 25 years of age. A possible explanation could be a transitional phase where patients are becoming independent, must handle problems themselves, and acquire better social functioning skills. The large role of caretakers in daily care, frequent health care appointments, and the effort required to stay safe [24–29] are increasingly transitioned to the adults with OI giving them more control. Also, a decline in fracture rate in adults with OI compared with children with OI can play a role.

Influencing the quality of life

This study provides a baseline measurement of QoL in adults with OI. It is no surprise that the overall QoL in patients with OI is significantly lower at all age ranges and in all OI types compared with the control group. However, this baseline measurement is important because it signals which components are most affected in which health domain in which OI type at what age. It does not provide an answer for the question regarding factors that influence the different health domains of

QoL, which is why specifically designed questionnaires focused on determining factors of QoL in adults with OI are essential to improving QoL and are currently being developed.

Identifying specific outcomes that are associated with improved or decreased QoL in OI is important to guide timing and nature of interventions and to design research aimed at optimizing well-being of adults with OI [21,30]. For example, Dahan-Oliel and colleagues [21] performed a systemic review of previously mentioned studies [14–17] and concluded that for both children and adults with OI pain, scoliosis, activity limitations, and participation restrictions caused by decreased limited function are associated with lower levels of physical QoL and need to be addressed to promote QoL.

When interventions are planned, a follow-up measurement of QoL can indicate the effect of these interventions on the different health domains and as such, the impact of these interventions can be measured.

In our adult OI service we have tried to identify factors that might positively influence the QoL in people with OI. For this purpose, a value-based health care program has been developed to identify factors that we can influence in our service and that are measurable by QoL questionnaires. These aspects would be consistently monitored through the years. A very important influence on the development of a value-based health care program is the input of the OI group regarding what they consider important for their QoL.

Limitations and future plan

This study reports on baseline measurements of the QoL in 322 adult patients with OI measured by the SF-36 questionnaire. The SF-36 is a generalized, QoL questionnaire that is not specific for people with OI. This makes the data susceptible to temporary biases such as a recent fracture. However, the SF-36 is wellvalidated and widely used; therefore, it is a valid tool to evaluate QoL for patients with OI. As mentioned earlier, the development of OI-specific questionnaires is important and in progress; the results of this study can serve as basis for their development.

We compared our patient data against the data of reference populations collected more than two decades ago. Nonetheless, the reference populations were unique and representative of the Dutch population. The SF-36 is sensitive to fluctuations in health [4], which makes it suitable to measure QoL over a longer period or before and after a procedure. As such, we will aim to present a longitudinal overview of QoL in patients with OI through measurements of QoL and its influences at different time points.

Conclusion

Our study described baseline QoL measurements in the largest group of adults with different types of OI to date (n = 322) and compared outcomes with (age-matched) control groups. The mean scores indicated that people with OI generally had a significantly lower QoL than the control population, and the scores per domain gave insight into which domains at what age in which OI type were more severely affected. This is important information for aging patients with OI and their health care professionals. Longitudinal QoL measurement and further qualitative evaluation of QoL and its influences are important for future management and improvement of QoL in people with OI.

References

1. Steiner RD, Adsit J, Basel D. COL1A1/2 Osteogenesis Imperfecta. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® (Internet). Seattle (WA): University of Washington, Seattle; 2005. p. 1993–2019.
2. Van Dijk FSS, DOO S. Osteogenesis imperfecta: clinical diagnosis,nomenclature and severity assessment. Am J Med Genet A. 2014; 164(6):1470–81.
3. Starr SR, Roberts TT, Fischer PR. Osteogenesis imperfecta: primarycare. Pediatr Rev. 2010;31(8):e54–64.
4. Vander Zee K, Sanderman R, Heyink JW, de Haes H. Psychometricqualities of the RAND 36-item Health Survey 1.0: a multidimensional measure of general health status. Int J Behav Med. 1996;3:104–22.
5. Aaronson NK, Muller M, Cohen PDA, et al. Translation, validation, andnorming of the Dutch language version of the SF-36 health survey in community and chronic disease populations. J Clin Epidemiol. 1998; 51(11):1055–68.
6. Tarlov AR, Ware JE, Greenfield S, Nelson EC, Perrin E, Zubkoff M. The medical outcomes study: an application of methods for monitoring the results of medical care. JAMA. 1989;262(7):925–30.
7. Ware JE, Kosinski M, Keller SD. SF-36 Physical and mental health summary scales: a user's manual. Boston, MA: Health Institute, New England Medical Center; 1994.
8. Ware JE, Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A.Comparison of methods for the scoring and statistical analysis of SF36 health profile and summary measures: summary of results from the medical outcomes study. Med Care. 1995;33(4 Suppl):AS264–79.
9. Mc Horney CA, Ware JE Jr, Raczek AE. The MOS 36-item short-formhealth survey (sf-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993; 31(3):247–63.
10. Jenkinson C, Wright L, Coulter A. Criterion validity and reliability ofthe SF-36 in a population sample. Qual Life Res. 1994;3(1):7–12.
11. Zee KI, Sanderman R, Heyink JW, Haes H. Psychometric qualities ofthe rand 36-item health survey 1.0: a multidimensional measure of general health status. Int J Behav Med. 1996;3(2):104–22.
12. Schmider E, Ziegler M, Danay E, Beyer L, Bühner M. Is it really robust?: reinvestigating the robustness of ANOVA against violations of the normal distribution assumption. Methodology. 2010;6(4):147–51.

13. Tosi LL, Floor MK, Dollar CM, et al. Assessing disease experienceacross the life span for individuals with osteogenesis imperfecta: challenges and opportunities for patient-reported outcomes (PROs) measurement: a pilot study. Orphanet J Rare Dis. 2019;14(1):23.
14. Widmann RF, Bitan FD, Laplaza FJ, Burke SW, DiMaio MF, Schneider R.Spinal deformity, pulmonary compromise, and quality of life in osteogenesis imperfecta. Spine (Phila Pa 1976). 1999;24(16):1673–8.
15. Widmann RF, Laplaza FJ, Bitan FD, Brooks CE, Root L. Quality of life inosteogenesis imperfecta. Int Orthop. 2002;26(1):3–6.
16. Forestier-Zhang L, Watts L, Turner A, et al. Health-related quality oflife and a cost-utility simulation of adults in the UKwith osteogenesis imperfecta, X-linked hypophosphatemia and fibrous dysplasia. Orphanet J Rare Dis. 2016;11(1):1–9.
17. Balkefors V, Mattsson E, Pernow Y, Sääf M. Functioning and quality oflife in adults with mild-to-moderate osteogenesis imperfecta. Physiother Res Int. 2013;18(4):203–11.
18. Hald JD, Folkestad L, Harsløf T, Brixen K, Langdahl B. Health-relatedquality of life in adults with osteogenesis imperfecta. Calcif Tissue Int. 2017;101(5):473–8.
19. Handisides JC, Hollenbeck-Pringle D, Uzark K, et al. Health-relatedquality of life in children and young adults with Marfan syndrome. J Pediatr. 2018;204:250–5.e1.
20. Idorn L, Jensen AS, Juul K, et al. Quality of life and cognitive functionin Fontan patients, a population-based study. Int J Cardiol. 2013;168 (4):3230–5.
21. Dahan-Oliel N, Oliel S, Tsimicalis A, Montpetit K, Rauch F, Dogba MJ.Quality of life in osteogenesis imperfecta: a mixed-methods systematic review. Am J Med Genet Part A. 2016;170(1):62–76.
22. Nghiem T, Louli J, Treherne SC, et al. Pain experiences of children andadolescents with osteogenesis imperfecta: an integrative review. Clin J Pain. 2017 Mar;33(3):271–80.
23. Nicolaou N, Bowe JD, Wilkinson JM, Fernandes JA, Bell MJ. Use of theSheffield telescopic intramedullary rod system for the management of osteogenesis imperfecta: clinical outcomes at an average followup of nineteen years. J Bone Joint Surg Ser A. 2011;93(21):1994–2000.
24. Ablon J. Personality and stereotype in osteogenesis imperfecta: behavioral phenotype or response to life's hard challenges? Am J Med Genet. 2003;122A(3):201–14.
25. Wiggins S, Kreikemeier R. Bisphosphonate therapy and osteogenesisimperfecta: the lived experience of children and their mothers. J Spec Pediatr Nurs. 2017;22:e12192.
26. Arabaci LB, Bozkurt S, Vara S, Ozen S, Darcan S, Simsek DG. Difficulties experienced by caregivers of patients diagnosed with osteogenesisimperfecta (OI): example of a hospital. J Pak Med Assoc. 2015;65(7):764–70.

27. Bozkurt S, Arabaci LB, Vara S¸, Özen S, Göks¸en D, Darcan S¸. The impactof psycho-educational training on the psychosocial adjustment of caregivers of osteogenesis imperfecta patients. J Clin Res Pediatr Endocrinol. 2014;6(2):84–92.
28. dos Santos MC, Pires AF, Soares K, Barros L. Family experience withosteogenesis imperfecta type 1: the most distressing situations. Disabil Rehabil. 2018;40(19):2281–7.
29. Dogba MJ, Rauch F, Wong T, Ruck J, Glorieux FH, Bedos C. From pediatric to adult care: strategic evaluation of a transition program for patients with osteogenesis imperfecta. BMC Health Serv Res. 2014 Oct 31;14:489.
30. Wilson I, Cleary P. Linking clinical variables with health-related qualityof life. JAMA. 1995;273(1):59–65.

Table 1 *Appendix*

Age: 18-24

	OI Type 1 (*n* = 57)		OI Type 3 (*n* = 16)		OI Type 4 (*n* = 15)		Control (*n* = 135)	
	Mean	sd	Mean	sd	Mean	sd	Mean	sd
Physical functioning	75.59	25.04	12.5	15.49	47	29.75	91.7	14.3
Role functioning physical	59.21	39.42	36.76	44.3	55	39.19	86	29.2
Bodily pain	65.99	26.7	57.5	28.57	66.33	26.95	87.8	20.9
General health	61.27	22	55.29	25.7	59.33	19.17	77.1	20.6
Physical component summary score	45.09	11	30.23	9.94	37.54	9.56	50	10
Vitality	58.57	22.72	60.2	21.42	66.33	18.66	69.2	18.6
Social functioning	78.73	25.65	53.68	36.38	83.33	15.43	85.5	20.9
Role functioning emotional	79.53	37.1	72.92	40.77	93.33	18.69	81	34.4
Mental health	73.25	20.2	74.12	18.28	80.27	14.22	73.4	20.6
Mental component summary score	48.56	11.6	52.39	11.23	57	7.49	50	10

Age: 25-34

	OI Type 1 (*n* = 38)		OI Type 3 (*n* = 8)		OI Type 4 (*n* = 20)		Control (*n* = 221)	
	Mean	sd	Mean	sd	Mean	sd	Mean	sd
Physical functioning	69.61	26.97	13.96	11.61	61.78	27.23	89.5	17.8
Role functioning physical	61.84	39.3	59.38	49.89	53.75	48.17	82.5	32.4
Bodily pain	65.84	26.42	58.93	25.03	70.1	21.45	84.1	23.9
General health	52.17	19.57	56.88	25.06	59	18.96	77.5	19.7
Physical component summary score	42.28	11.07	32.21	8.32	42.9	11.9	50	10
Vitality	55.27	17.45	70	26.19	61.75	21.9	69.1	19
Social functioning	72.04	27.48	70.31	27.5	73.13	26.37	90.7	16.5
Role functioning emotional	81.58	36.92	75	38.83	65	43.9	86.8	29.6
Mental health	77.3	16.35	76.5	23.46	75.6	14.03	78.8	17.5
Mental component summary score	49.31	10.14	55.79	16.22	48.44	11.62	50	10

Underlined = Not-normally distributed

Supplemental material

Age: 35-54

	OI Type 1 (*n* = 77)		OI Type 3 (*n* = 12)		OI Type 4 (*n* = 15)		Control (*n* = 375)	
	Mean	sd	Mean	sd	Mean	sd	Mean	sd
Physical functioning	57.68	28.74	31.14	32.16	54.59	28.72	84.95	19.55
Role functioning physical	45.78	45.23	52.08	47.02	70	36.84	80.9	34.5
Bodily pain	55.18	29.05	62.59	23.61	57.82	25.86	82.15	24.2
General health	51.85	19.9	36.77	19.1	55.5	23.26	72.8	21.85
Physical component summary score	38.58	12.17	32.63	9.72	40.01	7.93	50	10
Vitality	53.18	21	55.83	15.78	62.33	18.98	67.3	19.6
Social functioning	65.58	28.4	64.58	18.34	76.67	27.49	87.05	19.7
Role functioning emotional	72.73	39.64	80.56	26.43	80	37.37	82.9	33.8
Mental health	70.44	17.36	77.67	16.58	76.8	18.15	76.8	18.8
Mental component summary score	47.43	10.2	52.58	6.09	51.96	11.21	50	10

Age: 55+

	OI Type 1 (*n* = 48)		OI Type 3 (*n* = 3)		OI Type 4 (*n* = 12)		Control (*n* = 322)	
	Mean	sd	Mean	sd	Mean	sd	Mean	sd
Physical functioning	53.87	28.2	15	10	65.65	27.36	63.85	27.98
Role functioning physical	47.92	45.2	66.67	28.87	62.5	47.07	70.58	39.9
Bodily pain	53.06	26.13	71.43	24.74	59.01	31.9	74.7	27.5
General health	53.15	17.47	60	5	58.96	16.43	61.23	22.15
Physical component summary score	37.08	11.13	35.95	6.11	43.5	11.08	50	10
Vitality	58.44	18.91	71.67	12.58	57.5	22.81	64.7	21.95
Social functioning	69.53	28	70.83	31.46	76.04	30.37	81.73	25.28
Role functioning emotional	72.46	42.34	77.78	38.49	69.7	45.84	82.28	34.5
Mental health	76.23	17.04	69.33	26.63	68.33	25.21	77.05	16.5
Mental component summary score	50.6	11.68	53.53	16.97	46.67	14.25	50	10

Table 2a Appendix *Significance (p- value) of differences between OI types and controls (data shown in Table 1 Appendix)*

Physical functioning

18-24	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.000	x	x
OI 4	0.013	0.036	x
Control	0.000	0.000	0.000

25-34	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.000	x	x
OI 4	0.830	0.000	x
Control	0.000	0.000	0.000

35-54	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.017	x	x
OI 4	1.000	0.135	x
Control	0.000	0.000	0.001

55+	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.064	x	x
OI 4	0.574	0.018	x
Control	0.022	0.003	0.827

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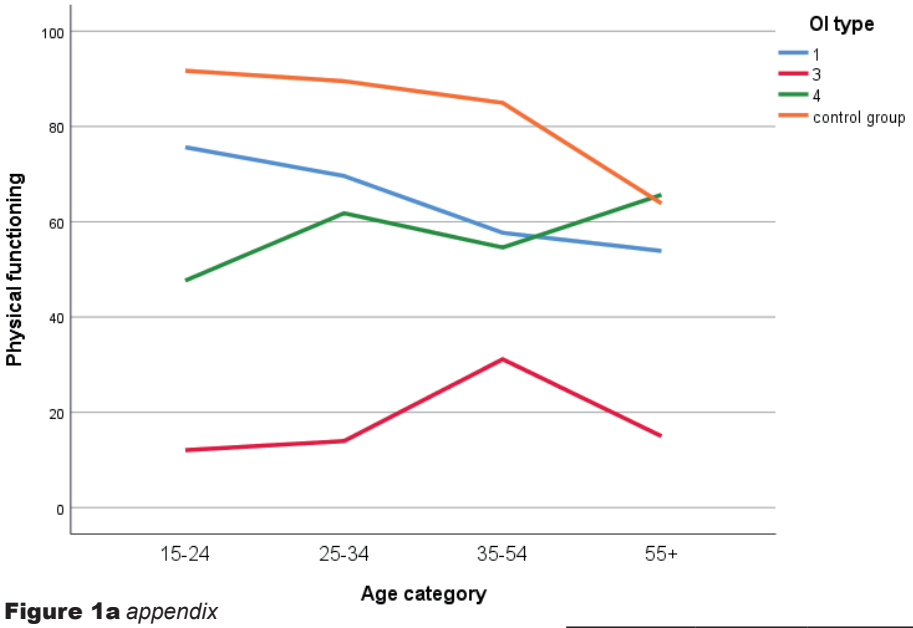

Figure 1a *appendix*
visualisation of table 1 appendix

Trend	Difference	P-value
OI 1	-21.72	0.000
OI 3	2.5	1.000
OI 4	18.65	0.563
Control	-27.85	0

Table 2b Appendix *Significance (p- value) of differences between OI types and controls (data shown in Table 1 Appendix)*

Role functioning physical

18-24	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.069	x	x
OI 4	0.747	0.157	x
Control	0.001	0.003	0.045

25-34	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.988	x	x
OI 4	0.622	0.824	x
Control	0.006	0.569	0.110

35-54	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.600	x	x
OI 4	0.069	0.381	x
Control	0.000	0.131	70

55+	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.461	x	x
OI 4	0.387	0.878	x
Control	0.002	1.000	0.811

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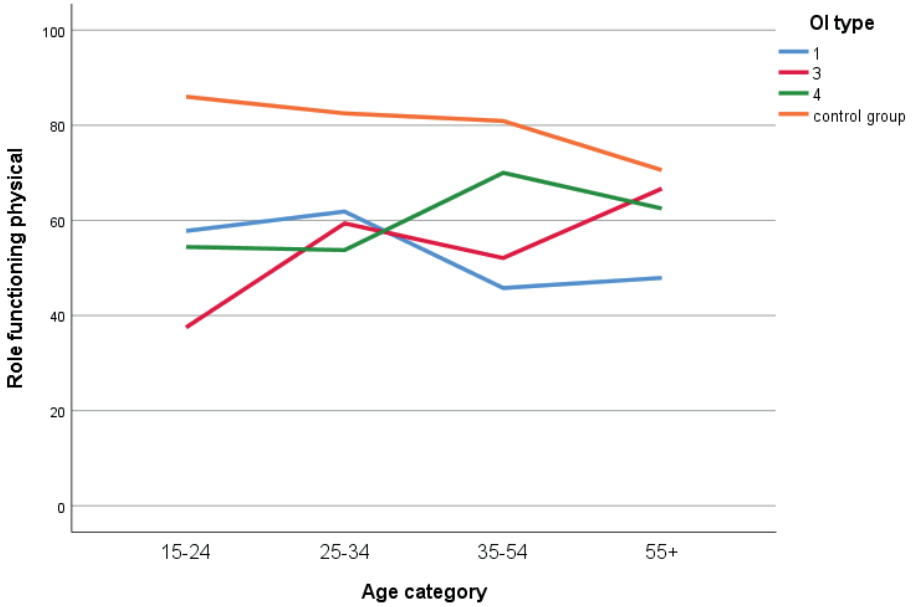

Figure 1b *appendix*
visualisation of table 1 appendix

Trend	Difference	P-value
OI 1	-11.29	0.173
OI 3	29.91	0.585
OI 4	7.5	0.799
Control	-15.42	0

Table 2c Appendix *Significance (p- value) of differences between OI types and controls (data shown in Table 1 Appendix)*

Bodily pain

18-24	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.781	x	x
OI 4	1.000	1.000	x
Control	0.000	0.000	0.000

25-34	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	1.000	x	x
OI 4	1.000	0.861	x
Control	0.000	0.004	0.012

35-54	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	1.000	x	x
OI 4	1.000	1.000	x
Control	0.000	0.006	0.000

55+	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.785	x	x
OI 4	1.000	1.000	x
Control	0.000	1.000	0.055

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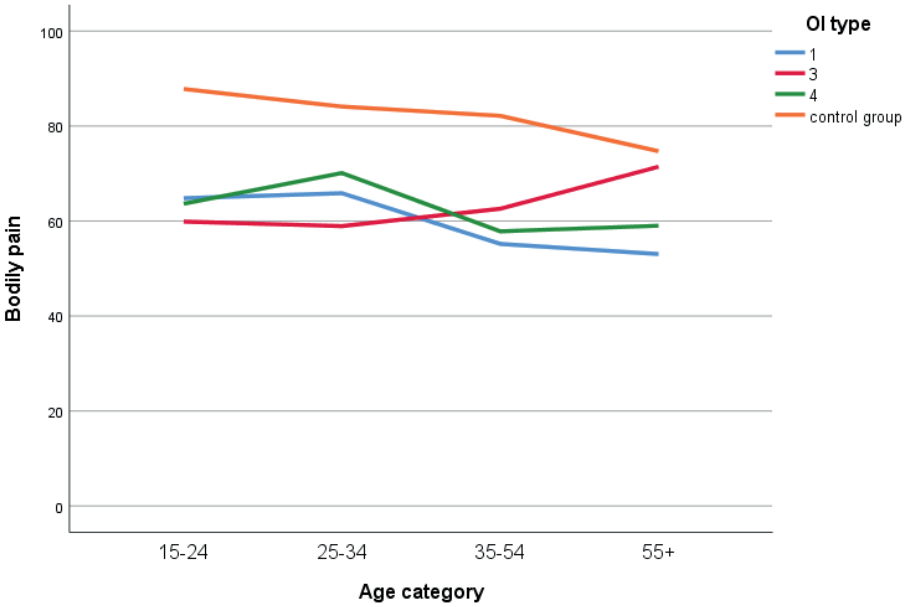

Figure 1c *appendix*
visualisation of table 1 appendix

Trend	Difference	P-value
OI 1	-12.93	0.101
OI 3	13.93	1.000
OI 4	-7.32	1.000
Control	-13.1	0

Table 2d Appendix *Significance (p- value) of differences between OI types and controls (data shown in Table 1 Appendix)*

General health

18-24	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	1.000	x	x
OI 4	1.000	1.000	x
Control	0.000	0.000	0.002

25-34	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	1.000	x	x
OI 4	0.669	1.000	x
Control	0.000	0.004	0.000

35-54	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.057	x	x
OI 4	1.000	0.058	x
Control	0.000	0.000	0.003

55+	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	1.000	x	x
OI 4	0.950	1.000	x
Control	0.005	0.723	0.726

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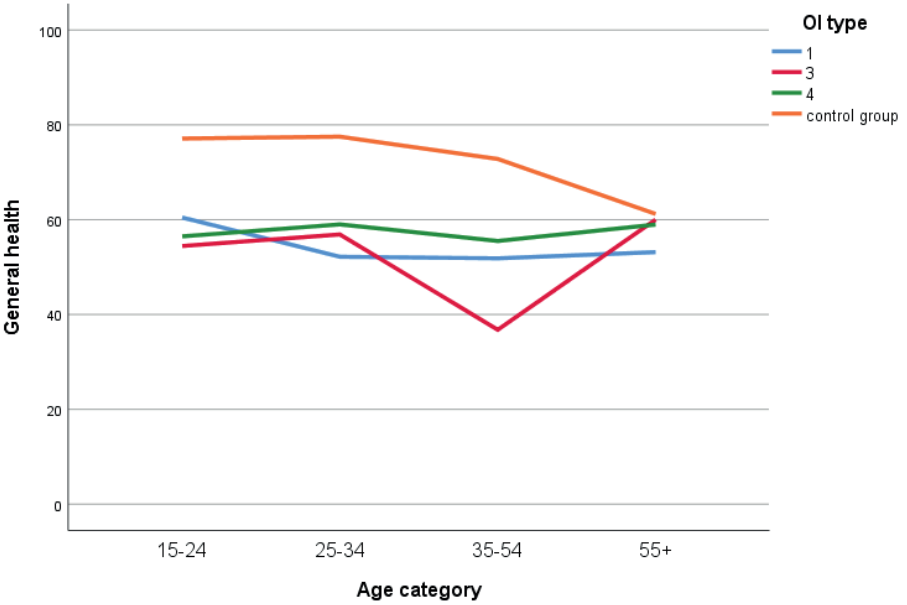

Figure 1d *appendix*
visualisation of table 1 appendix

Trend	Difference	P-value
OI 1	-8.12	0.245
OI 3	4.71	1.000
OI 4	-0.37	1.000
Control	-15.87	0

Table 2e Appendix *Significance (p- value) of differences between OI types and controls (data shown in Table 1 Appendix)*

Physical component summary score

18-24	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.000	x	x
OI 4	0.048	0.163	x
Control	0.003	0.000	0.000

25-34	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.068	x	x
OI 4	1.000	0.073	x
Control	0.000	0.000	0.000

35-54	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.289	x	x
OI 4	1.000	0.294	x
Control	0.000	0.000	0.000

55+	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	1.000	x	x
OI 4	0.226	0.874	x
Control	0.000	0.016	0.028

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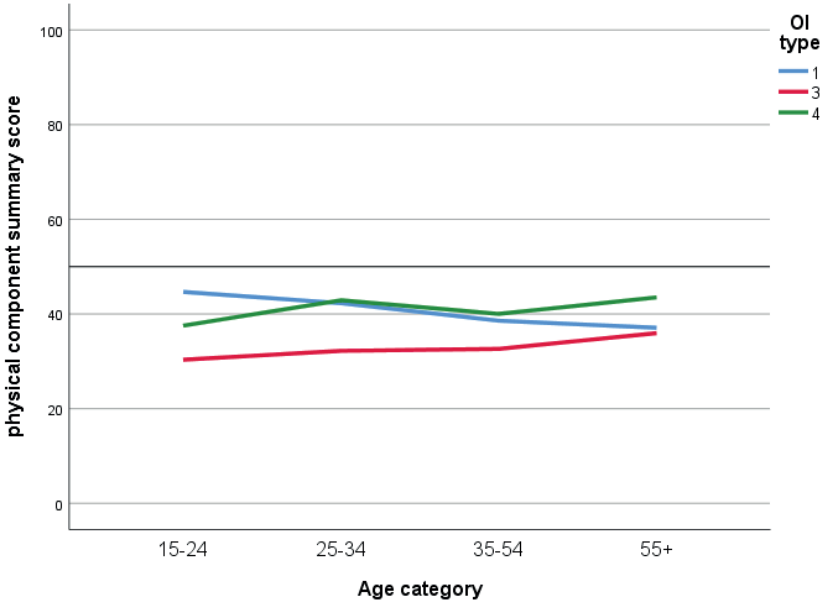

Figure 1e *appendix*
visualisation of table 1 appendix

Trend	Difference	P-value
OI 1	-8.01	0.003
OI 3	5.72	1.000
OI 4	5.96	0.852
Control	0	1

Table 2f Appendix *Significance (p- value) of differences between OI types and controls (data shown in Table 1 Appendix)*

Vitality

18-24	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	1.000	x	x
OI 4	0.673	1.000	x
Control	0.002	0.074	0.572

25-34	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.192	x	x
OI 4	0.744	0.986	x
Control	0.000	0.885	0.108

35-54	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	1.000	x	x
OI 4	0.336	1.000	x
Control	0.000	0.046	0.336

55+	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.778	x	x
OI 4	1.000	0.796	x
Control	0.062	0.584	0.266

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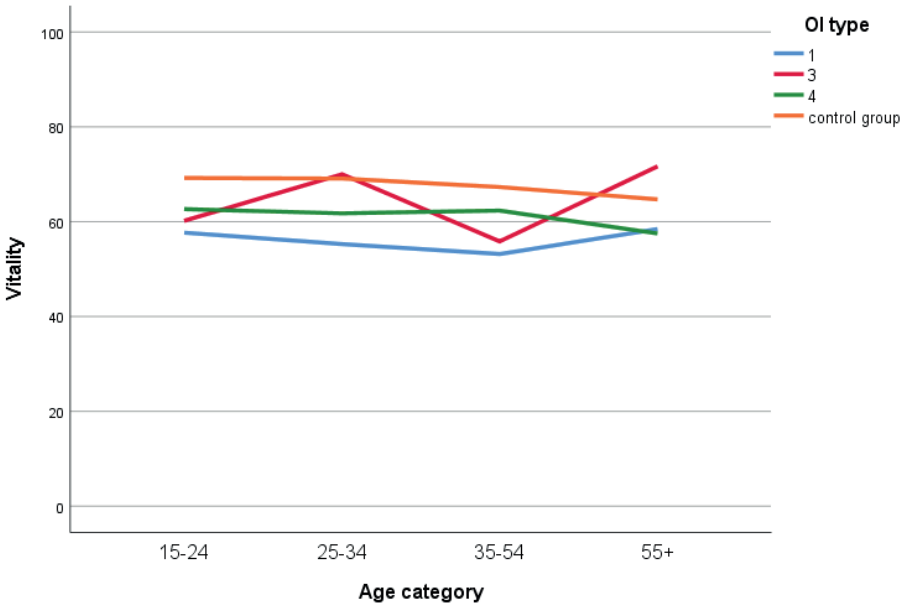

Figure 1f *appendix*
visualisation of table 1 appendix

Trend	Difference	P-value
OI 1	-0.13	1.000
OI 3	11.47	1.000
OI 4	-8.83	1.000
Control	-4.5	0.037

Table 2g Appendix *Significance (p- value) of differences between OI types and controls (data shown in Table 1 Appendix)*

Social functioning

18-24	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.010	x	x
OI 4	0.959	0.027	x
Control	0.276	0.011	0.775

25-34	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.859	x	x
OI 4	0.920	0.814	x
Control	0.000	0.068	0.004

35-54	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.701	x	x
OI 4	0.145	0.067	x
Control	0.000	0.009	0.607

55+	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.967	x	x
OI 4	0.379	0.708	x
Control	0.005	0.593	0.384

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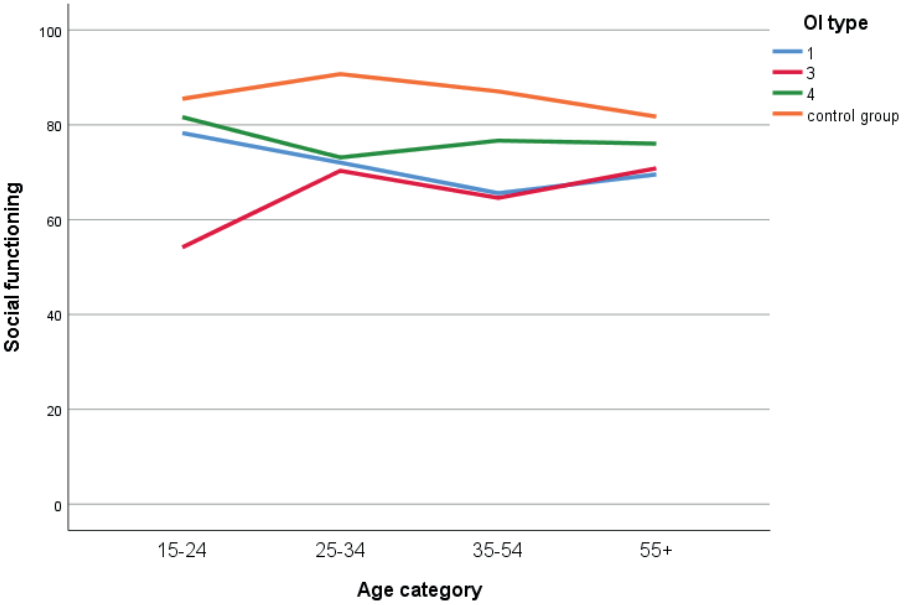

Figure 1g *appendix*
visualisation of table 1 appendix

Trend	Difference	P-value
OI 1	-9.2	0.030
OI 3	17.15	0.632
OI 4	-7.29	0.818
Control	-3.77	0.127

Table 2h Appendix *Significance (p- value) of differences between OI types and controls (data shown in Table 1 Appendix)*

Role functioning emotional

18-24	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.431	x	x
OI 4	0.233	0.105	x
Control	0.090	0.709	0.007

25-34	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.498	x	x
OI 4	0.111	0.609	x
Control	0.322	0.667	0.137

35-54	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.829	x	x
OI 4	0.488	0.641	x
Control	0.927	0.422	0.312

55+	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.86	x	x
OI 4	0.799	0.784	x
Control	0.842	1.000	0.855

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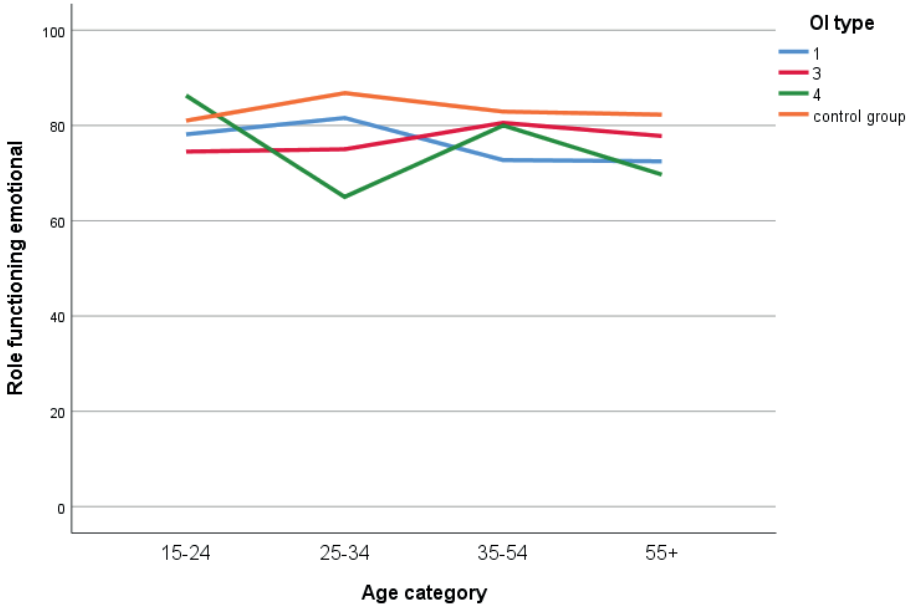

Figure 1h *appendix*
visualisation of table 1 appendix

Trend	Difference	P-value
OI 1	-7.07	0.508
OI 3	4.86	0.997
OI 4	-23.63	0.183
Control	1.28	0.717

Table 2i Appendix *Significance (p- value) of differences between OI types and controls (data shown in Table 1 Appendix)*

Mental health

18-24	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	1.000	x	x
OI 4	0.620	1.000	x
Control	0.963	0.894	0.107

25-34	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	1.000	x	x
OI 4	1.000	1.000	x
Control	0.623	0.889	0.428

35-54	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.551	x	x
OI 4	0.594	1.000	x
Control	0.006	0.874	1.000

55+	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	1.000	x	x
OI 4	0.621	1.000	x
Control	0.749	0.423	0.259

Underlined = Not-normally distributed

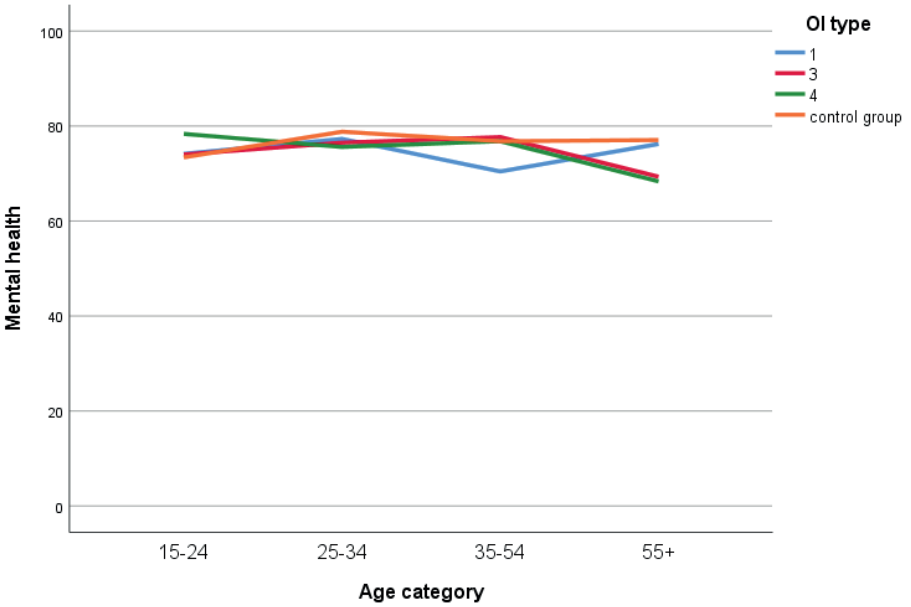

Figure 1i *appendix*
visualisation of table 1 appendix

Trend	Difference	P-value
OI 1	2.98	1.000
OI 3	-4.79	1.000
OI 4	-11.94	0.522
Control	3.65	0.046

Table 2j Appendix *Significance (p- value) of differences between OI types and controls (data shown in Table 1 Appendix)*

Mental component summary score

18-24	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.629	x	x
OI 4	0.029	0.715	x
Control	0.386	0.374	0.010

25-34	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.448	x	x
OI 4	0.769	0.386	x
Control	0.695	0.348	0.823

35-54	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	0.300	x	x
OI 4	0.334	1.000	x
Control	0.041	0.183	0.459

55+	OI 1	OI 3	OI 4
OI 1	x	x	x
OI 3	1.000	x	x
OI 4	0.991	1.000	x
Control	0.705	0.753	0.439

Underlined = Not-normally distributed

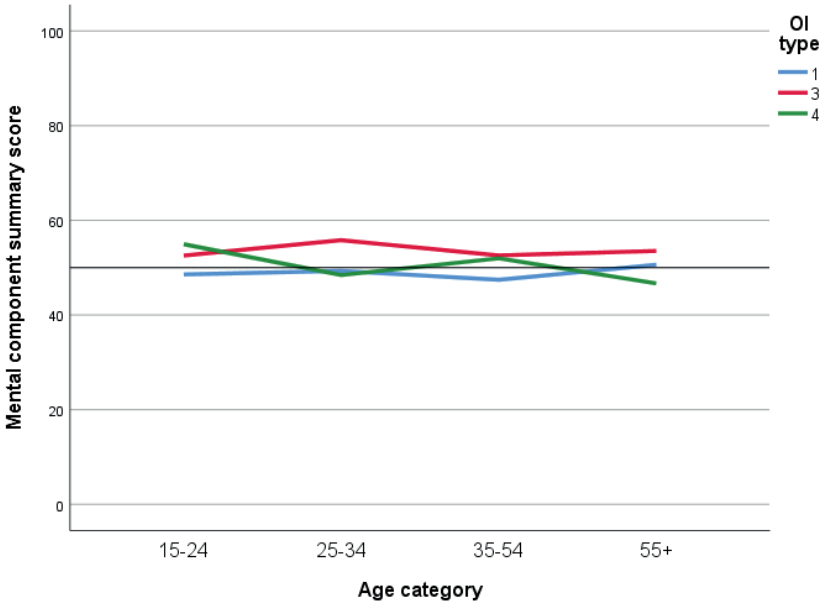

Figure 1j *appendix*
visualisation of table 1 appendix

Trend	Difference	P-value
OI 1	2.04	1.000
OI 3	1.14	1.000
OI 4	-10.33	0.127
Control	0	1.000

Table 3 *Appendix. Comparison of Current study with the study of Hald et al. 2017 per type of OI*

	Current study	Hald et al. 2017	P	Current study	Hald et al. 2017	P	Current study	Hald et al. 2017	P
	OI type 1 (*n* = 220)	OI type 1 (*n* = 58)		OI type 3 (*n* = 40)	OI type 3 (*n* = 11)		OI type 4 (*n* = 62)	OI type 4 (*n* = 15)	
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD		Mean ± SD	Mean±SD	
Physical Function	63.6 ± 28.6	72.8 ± 26.4	0.023	18.4 ± 21.8	20.9 ± 21.5	0.737	57.2 ± 28.4	64.7 ± 30.4	0.368
Role function Physical	52.5 ± 43.1	n/a	n/a	48.1 ± 45.1	n/a	n/a	59.7 ± 42.8	n/a	n/a
Bodily Pain	59.4 ± 27.8	59.3 ± 28.4	0.981	60.4 ± 25.5	60.6 ± 28.6	0.991	64 ± 26	64 ± 27.2	1.000
General Health	54.6 ± 20.4	60.4 ± 22.5	0.061	50.4 ± 23.9	63.1 ± 24.3	0.126	58.2 ± 19.3	55.5 ± 24.8	0.648
Physical Component Summary Score	40.6 ± 11.8	40.5 ± 11.5	0.954	31.8 ± 9.2	30.5 ± 9.4	0.681	41 ± 10.4	39.2 ± 11.5	0.557
Vitality	56.1 ± 20.5	59.3 ± 24.9	0.370	61.7 ± 20.6	63.2 ± 22.6	0.835	62.2 ± 20.4	55.3 ± 27.4	0.277
Social Function	70 ± 27.8	n/a	n/a	61.6 ± 29.6	n/a	n/a	77 ± 25	n/a	n/a
Role function Emotional	75 ± 39.1	n/a	n/a	76.1 ± 35	n/a	n/a	76.5 ± 17.7	n/a	n/a
Mental Health	73.6 ± 18	79.9 ± 15.9	0.016	75.3 ± 18.9	82.2 ± 10.3	0.120	75.6 ± 17.7	78.9 ± 21.5	0.537
Mental Component Summary Score	48.7 ± 10.9	52.7 ± 10.3	0.013	53.2 ± 11.2	60.6 ± 8.7	0.048	51 ± 11.6	53 ± 12.5	0.557

Chapter 3

Fatigue in adults with Osteogenesis Imperfecta

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Abstract

Background Osteogenesis Imperfecta (OI) is characterized by bone fragility, and features such as blue sclerae, dentinogenesis imperfecta, hearing loss, ligamentous laxity and short stature can be present. It has long been assumed that the functional ability and quality of life of patients with OI depends primarily on the severity of skeletal deformities. However, fatigue is often mentioned in clinic by patients with all types of OI as an important modifier of their quality of life and does not always seem to be related to their functional ability. The aim of this study is to investigate whether adults with Osteogenesis Imperfecta are significantly more fatigued than the normal population.

Methods The Fatigue Severity Scale (FSS) was distributed by mobile phone application among 151 adult patients with different OI types. Results of the FSS in the OI group were compared with two control populations from America (n = 20) and the Netherlands (n = 113).

Results Ninety-nine patients (OI type 1 (n = 72), OI type 3 (n = 13), OI type 4 (n = 14) completed the FSS questionnaire. The mean FSS score of this cohort was 4.4 and significantly higher than the control populations (2.3 / 2.9). 65% of our cohort reported at least moderate fatigue compared with 2 control populations from America and the Netherlands.

Conclusion Fatigue in patients with OI is a frequently encountered problem in our expert clinic but research into this topic is sparse. This pilot study is the largest study to date investigating fatigue in patients with OI and results have been compared with two control groups. The mean FSS score of 4.4 in the OI group indicates that people with OI are generally significantly more fatigued than the control population. Further evaluation of fatigue and its influencers in a larger group of OI patients is important for future management.

Introduction

Osteogenesis imperfecta (OI) is a rare hereditary disorder with a prevalence of 6–7:100,000 [1]. OI is primarily characterized by bone fragility. Additional features of OI include blue sclerae, dentinogenesis imperfecta, hearing loss, ligamentous laxity and short stature [2–6]. OI is known to be a clinically variable disorder with severity ranging from perinatal lethality to slightly increased fracture frequency with normal life expectancy [3]. As such, the clinical classification of OI consists of 5 different types (1–5) [6]. In approximately 90% of patients with OI, dominant mutations in the genes *COL1A1* and *COL1A2* encoding respectively the alpha1 and alpha2 chains of the protein collagen type I, are identified [6]. The functional ability of patients with OI, especially ambulation, have been historically attributed to the severity of the skeletal deformities [3, 6] and this has long been the focus of physicians involved in the care of patients with OI. However, many patients visiting our expert center for adults with OI complained about fatigue, which limits their quality of life, and asked whether this could be related to their diagnosis of OI. Previous studies indicate that the quality of life (QoL) of individuals with OI is negatively influenced by reduced function due to fatigue indicating that fatigue is an important factor when considering quality of life in OI patients [7–10]. As such, we approached a subgroup of our total group of OI patients to investigate the impact of fatigue on daily functioning compared to control populations.

Methods

Study design and population

A cross-sectional cohort study was undertaken in the national expert center for adult patients with Osteogenesis Imperfecta, Isala Hospital, Zwolle, The Netherlands. All patients who visited the expert center from December 2007 until December 2015 were selected to participate. The main exclusion criteria were unreturned questionnaires. Informed consent was obtained from each participant. The study was registered in the Isala research registry (Nr.190106) and the local Medical Ethical Committee approved the study protocol and granted an exemption because participants are not subject to procedures and are not required to follow rules of behavior.

Data collection

Many definitions of fatigue exist [11] as well as scales to measure the nature, severity and impact of fatigue in a range of clinical populations [12]. To investigate fatigue in patients with OI the Fatigue Severity Scale (FSS) was distributed among all adult patients. The FSS questionnaire is widely used and has been found valid and reliable in different patient groups [13]. It is developed to measure

the impact of fatigue on daily functioning [14] and consists of the following nine statements: 1. My motivation is lower when I am fatigued. 2. Exercise brings on my fatigue. 3. I am easily fatigued. 4. Fatigue interferes with my physical functioning. 5. Fatigue causes frequent problems for me. 6. My fatigue prevents sustained physical functioning. 7. Fatigue interferes with carrying out certain duties and responsibilities. 8. Fatigue is among my three most disabling symptoms. 9. Fatigue interferes with my work, family, or social life. The higher the score (on a scale of 1–7), the higher the impact on fatigue in daily living (1 completely disagree, to 7 completely agree.)

The questionnaire was sent to the patients in the form of an email containing a link to download a mobile application. If participants were unable to download the application, the questionnaire was sent by email or regular post. To assess how fatigue influences daily living in OI patients we analyzed the distribution of scores for the 9 separate statements. The severity of fatigue was calculated as a mean FSS score of all nine items per patient ranging from 1.0 (no fatigue) to 7.0 (maximum fatigue).

Medical records were analyzed from patients who completed the FSS to determine gender, age and the type of OI according to the updated Sillence criteria [3]. Means and standard deviation (SD) were given for normally distributed continuous variables. Differences in means comparing OI patients and separate FSS questions were tested using independent *t* tests and the mean differences were presented as the mean with 95% confidence intervals (95%CI). A two-sided p-value of 0.05 was considered significant. All data were analyzed with SPSS (statistics 24.0.)

Control populations

To evaluate the impact of fatigue on daily living in OI versus controls, we compared the FSS scores from our cohort with two previous studies that used the FSS. The first study by Krupp et al. 1989 [14] investigated fatigue in individuals with MS (multiple sclerosis) and SLE (systemic lupus erythematosus) and in a control group consisting of 20 healthy American individuals selected from volunteers unfamiliar with the study with a mean age of 39.7 years SD 9. The American control group scored a mean of 2.3 SD 0.7. The researchers determined a cut off score > 4 for severe fatigue, influencing daily living [14]. The second study concerned the study of Merkies et al. 1999 [15] which investigated fatigue in immunemediated polyneuropathies and recruited a Dutch control group (*n* = 113) from hospital personnel, companions (relatives, friends) of patients visiting their outpatient clinic, and volunteers unfamiliar with their study. These patients declared themselves to be healthy, free from any chronic medical condition, and were not taking medication that could contribute to fatigue. This

control group consisted of 54 men and 59 women with a mean age of 54.2 (range 18–83) being an average cohort out of the Dutch population and comparable to our OI cohort regarding age and gender distribution. The Dutch control group had a mean and median FSS of 2.9, SD 1.1. Severe fatigue was defined as FSS score > 5.1 (mean + 2SD) and fatigue was defined as FSS score > 4 (mean + 1SD, *n* = 113, 15).

Results

Clinical characteristics

We approached 221 OI patients who had visited the expert center to participate in this study and to fill in the questionnaire. The age range of this cohort was 18–80 years. Permission and signed informed consent were received from 151 patients. A group of 52 patients did not complete the questionnaire and was therefore excluded. Therefore, 99 patients (65.1% response rate) were available for analysis. It concerned individuals with type 1 (*n* = 72), type 3 (*n* = 13) and type 4 (*n* = 14). Sixty-one women and 38 men were included. The mean age was 45 (age range 19–80 years). These distributions are comparable to our total OI population [16].

Fatigue severity score

Participant basic characteristics and total scores

The mean and median FSS score of the individuals with OI in our cohort were respectively 4.4 and 4.8, SD 1.4 (95% CI 4.16–4.70). According to the Kolmogorov Smirnov test, the distribution of the FSS mean score was normal (*p* = 0.105). 42% (*n* = 42) of the respondents had a mean FSS score of ≥5 whilst 23.1% (*n* = 23) had a mean FSS score between 4 and 5. The man/woman distribution in the cohort was 40.5% (*n* = 17)/ 59.5% (*n* = 25).

A single sample *t* test and the Mann-Whitney U test were conducted to determine if the differences between the FSS score in the OI group versus the American and Dutch controls were statistically significant, concluding that individuals with OI in this cohort have statistically higher fatigue scores than the American control group, t (98) = (15.46), *p* = (0.000), and the Dutch control group, t (98) = (11.10), *p* = (0.000).

Statements 3 and 4 of the FSS had both higher median scores with a smaller 95% confidence interval of the mean (4.63 CI 4.27–4.99 and 4.66 CI 4.32–4.99) (significance 0.099, 0.067) compared to the other questions. Statements 6 and 8 had also a high median score (4.23, 4.67), but overall more diffuse results as can be seen in the 95% confidence interval (3.86–4.7; 4.22–5.12) (Table 1).

Gender differences

Table 1 shows that there were no significant differences per gender with regard to the total FSS score. Women scored higher (4.56 ± 1.22) than men (4.22 ± 1.57) on the total FSS score and also in all separate statements except statement 1. On statement 8 this difference was significant (w:5.03 ± 2.08, m:4.08 ± 2.42 (p = 0.048).

Table 1 *Mean score per FSS statement for the whole OI group and according to gender*

FSS Statements	Mean score	95% Confidence interval	Mean men	Mean women	Difference gender signific. *
1	5.43	5.14-5.59	5.47 ± 1.67	5.41 ± 1.38	0.837
2	4.16	3.82-4.5	4.03 ± 1.76	4.25 ± 1.69	0.538
3	4.63	4.27-4.99	4.21 ± 1.99	4.89 ± 1.63	0.069
4	4.66	4.32-4.99	4.58 ± 1.87	4.70 ± 1.56	0.719
5	3.71	3.36-4.06	3.66 ± 2	3.74 ± 1.6	0.836
6	4.23	3.86-4.7	4.16 ± 2.4	4.36 ± 1.92	0.661
7	4.14	3.75-4.53	3.89 ± 2.12	4.3 ± 1.82	0.320
8	4.67	4.22-5.12	4.08 ± 2.42	5.03 ± 2.08	0.048
9	4.19	3.77-4.62	3.87 ± 2.26	4.39 ± 2.04	0.338
Total	4.43	4.16–4.7	4.22 ± 1.57	4.56 ± 1.22	0.234

*independent *t* test

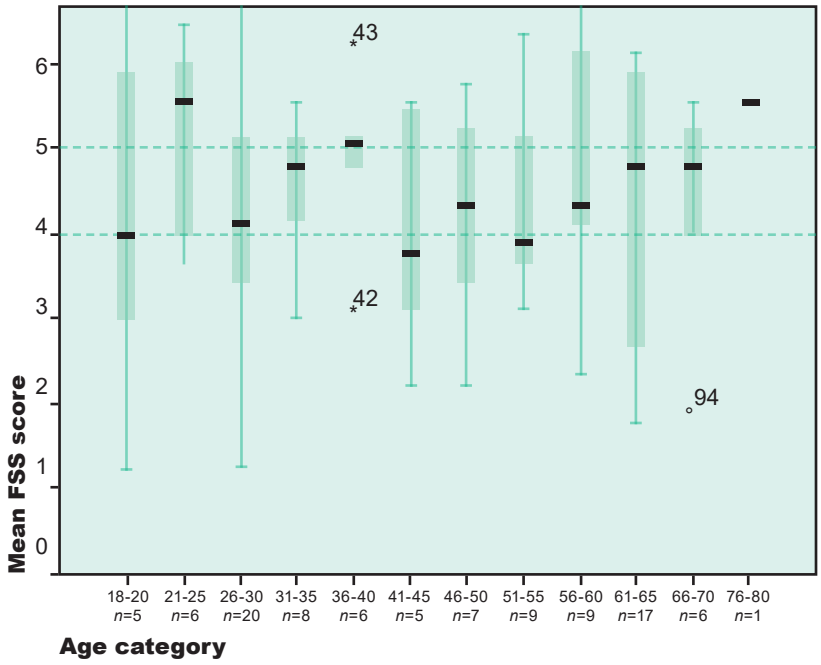
Age group distribution

A visual comparison of the separate FSS scores between the different age categories is shown in Figure 1. The FSS score for question 1 in age category 41–45 is significantly lower (2.4) than the remainder age categories in our study cohort (5.8). (independent *t* test p = 0.000). All other comparison did not reveal significantly different values.

Differences between types of OI

There were no significant differences per OI type for the mean FSS score. The FSS mean scores were in all OI types ≥4 (Table 2).

There were no significant differences per OI type for the separate FSS statements (data not shown). In the group with a mean FSS ≥5, the distributions regarding OI type were: OI type 1: 64.3% (n = 27), OI type 3: 13.4% (n = 6), OI type 4: 21.4% (n = 9). People with OI type 4 scored higher than people with OI type 3 and OI type 1 on question 3, 6 and 8.



Figuur 1 *FSS score per age with marking of moderate and high fatigue scores according to Krupp et al*

Table 2 *Mean total FSS score per OI type*

	Mean FSS score	Standard Deviation
OI type 1 (*n* = 72)	4.38	1.36
OI type 3 (*n* = 13)	4.33	1.69
OI type 4 (*n* = 14)	4.75	1.14

Discussion

Fatigue is often mentioned by individuals with OI during the clinical appointment. As the prevalence and experience of fatigue in patients with OI is largely unknown, we set out to perform a pilot study regarding occurrence and severity of fatigue in people with OI to determine whether this needs to be explored further. 99/151 patients filled in the FSS. We assessed the medical records for age, gender and type of OI. We did not analyze for any medical confounders such as recent fracture(s), cardiac or lung complications, initiated therapy, physical exertion, mobility and work. The mean and median FSS score of the individuals with OI was respectively 4.4 and 4.8.

FSS results compared to results in two control groups

The fatigue scores in our study cohort are significantly higher compared to the Dutch national control group(*n* = 113) [15] and the American control group (*n* = 20) [14]. Merkies et al. [11] define a mean FSS score ≥ 5.1 as severe fatigue, and a score > 4 and < 5 equates “borderline fatique “ [15]. When analysing the FSS results of the OI cohort according to the definitions of Merkies et al. the OI cohort experiences borderline fatigue, influencing daily living, with regard to the mean FSS score. Krupp et al. [14] defined a FSS score of > 4 as moderate to high fatigue level, influencing daily living. When analyzing the FSS results according the definition of Krupp et al. [14] it appears that 42.4% of the respondents (*n* = 42) had a mean FSS score of five or higher indicating severe fatigue. 23.1% (*n* = 23) had a score between four and five indicating borderline fatigue. When analysing the results with the definition of Merkies et al., it appears that 38.4% of the respondents (*n* = 38) had a mean FSS score of five or higher indicating severe fatigue. 27.3% (*n* = 27) had a score between 4 and 5.1, indicating borderline fatigue. These mean FSS scores are very high compared to the general population, with only 5% of the general population being severely fatigued [15]. The presence and severity of fatigue is almost equal across all OI types, which could indicate that OI type and severity of OI is not influencing fatigue. This may demonstrate that although most people with OI type 1 will have reached a higher level of daily functioning than patients with OI type 3 and 4, they still experience comparable impact of fatigue on their daily functioning. The FSS scores in the OI cohort also exceed minimal clinically important difference (MCID) values determined for other patient groups, which are for example 0.4 for SLE and 0.7 for RA (rheumatoid arthritis) [17, 18]. Given the above, there appears to be sufficient evidence for the presence of increased occurrence and severity of fatigue in OI patients in the investigated cohort

FSS results compared to one similar study involving OI patients

A comparable study was recently performed in Norway by Arponen et al. [9]. It concerned a cross-sectional study of responses of OI patients matched with healthy controls from Norway to a questionnaire, designed to evaluate levels of experienced fatigue and body pain as well as presence or absence of symptoms related to sleep disturbance or sleep apnoea. Fatigue was evaluated with, among others, the FSS questionnaire which demonstrated a FSS mean score of 5 in patients with OI (*n* = 56). Interestingly, the Norwegian control group scored a mean FSS score of 4 (*n* = 56). Arponen et al. concluded that in comparison with age and gender matched controls, adults with OI do not differ in experienced fatigue [9].

The Dutch control group [15], has a lower mean FSS score (2.9, *n* = 113) than the control group in the Norwegian study of Arponen et al (4.0, *n* = 56, 9). Compared to the American original validation [14]

who report a mean FSS of 2.3 ± 0.7 (*n* = 20) again the mean FSS score in the Norwegian control group is high.

However, there may be an explanation for the high score in the control group as a Norwegian national study investigating fatigue in the general population, [19] concluded that the high FSS scores in the general population of Norway can be due to difficulties in translation of the US-English version of the FSS into Norwegian because of lack of the concept of fatigue in Norwegian language [19]. A valid comparison between Norway, the Netherlands and the US regarding the FSS may therefore not be possible. A validation of the FSS in a Swiss control group is comparable to the Dutch and American results with a mean FSS score of 3.00 ± 1.08, (*n* = 454) [20]. As such, we can conclude that the mean FSS score of our Dutch control group is comparable with the American and Swiss control groups and that our earlier conclusion that the severity of fatigue is increased in the Dutch OI cohort still holds true.

Limitations of this study and further directions for research

There is a low response rate (151/221 gave consent and 99/151 filled in the FSS) when looked at the initially approached patients. It is difficult to speculate why this could be the case but an important factor may be that with regard to consent as well as with regard to filling in the FSS, patients were only approached once and were not sent reminder(s). Biases are difficult to avoid as it may be that the people who felt that fatigue was influencing there life significantly, were more inclined to participate but it is also possible that these patients were limited by fatigue to participate in the study.

As mentioned before, there are many scales to measure the nature, severity and impact of fatigue in a range of clinical populations and a limitation of the FSS is that it is a general questionnaire, and as such not specially developed for OI. The FSS however explores the severity of fatigue and is therefore suitable for initial screening in different clinical populations and can be used for longitudinal measurements which is important in assessing whether fatigue can increase or decrease over time and exploring possible modifiers of fatigue. Another limitation of our study lies with the control populations as both the Dutch control group and the US control group date from respectively 1999 and 1989 and trends in fatigue may change in the population over time.

Lastly, we did not investigate any factors that influence fatigue in OI patients in our study, but this is an important direction for further research into fatigue in patients with OI as fatigue may influence QOL. Other factors have been reported as well [21]. It is already known that the presence of pain,

but also educational level and employment status influence the severity of fatigue. Bathmen et al. published on fatigue in Marfan syndrome, another hereditary connective tissue disorder. The authors concluded that occurrence of chronic pain and employment status influenced the severity of fatigue [22]. Interestingly, a study in children with OI reported a decrease of the level of fatigue after a 12-week individual and supervised physical training program, and increase of the level of fatigue after the program had stopped [10, 23]. Studies in other patient groups, including people with Marfan syndrome reported good effects of physical activity on fatigue [24–26]. This is important knowledge since some OI patients or parents of OI patients tend to limit their physical activity when they become aware of the inherited bone fragility [23]. Some age categories may benefit from an individual and supervised training program.

Conclusion

In this study the influence of fatigue on daily functioning was investigated in the largest cohort of OI patients to date and compared with control groups in particular a national control group. Although, there were several limitations of our study, based on the current data, there is sufficient evidence for increased severity of fatigue in our cohort of OI patients. An important direction for future research is performing longitudinal measurements using the FSS and exploring determinants of fatigue as this may be of importance for the quality of life in OI patients.

References

1. Steiner RD, Basel D. COL1A1/2 Osteogenesis Imperfecta. (Updated 2019 Dec 12). In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® (Internet). Seattle (WA): University of Washington, Seattle; 2005. p. 1993– 2019.
2. Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. J Med Genet. 1979;16:101–16.
3. Van Dijk FSS, Sillence DOO. Osteogenesis imperfecta: clinical diagnosis, nomenclature and severity assessment. Am J Med Genet Part A. 2014;164: 1470–81.
4. Rauch F, Glorieux F. Ostegenesis Imperfecta. Lancet. 2004;363(9418):1377–85.
5. Glorieux FH. Osteogenesis imperfecta. Best Pract Res Clin Rheumatol. 2008; 22:85–100.
6. Van Dijk FS, Byers PH, Dalgleish R, Malfait F, Maugeri A, Rohrbach M, Symoens S, Sistermans EA, Pals G. EMQN best practice guidelines for the laboratory diagnosis of osteogenesis imperfecta. Eur J Hum Genet. 2012;(1): 11–9.
7. Hill CL, Baird WO, Walters SJ. Quality of life in children and adolescents with Osteogenesis Imperfecta: a qualitative interview based study. Health Qual Life Outcomes. 2014;12:54.
8. Tosi LL, Oetgen ME, Floor MK, Huber MB, Kennelly AM, McCarter RJ, Rak MF, Simmonds BJ, Simpson MD, Tucker CA, McKiernan FE. Initial report of the osteogenesis imperfecta adult natural history initiative. Orphanet J Rare Dis. 2015;10: 146.
9. Arponen H, Waltimo-Sirén J, Valta H, Mäkitie O. Fatigue and disturbances of sleep in patients with osteogenesis imperfecta - A cross-sectional questionnaire study. BMC Musculoskelet Disord. 2018;19(1):3.
10. Van Brussel M, Takken T, Uiterwaal CSPM, Pruijs HJ, Van der Net J, Helders PJM, Engelbert RHH. Physical Training in Children with Osteogenesis Imperfecta. J Pediatr. 2008;152:111–6 e1.
11. Finsterer J, Mahjoub SZ. Fatigue in healthy and diseased individuals. Am J Hosp Palliat Med. 2014;31:562–75.
12. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. J Psychosom Res. 2004;56:157–70.
13. Whitehead L. The measurement of fatigue in chronic illness: a systematic review of unidimensional and multidimensional fatigue measures. J Pain Symptom Manag. 2009;37:107–28.
14. Krupp LB, Larocca NG, Muir Nash J, Steinberg AD. The fatigue severity scale: Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989;46(10):1121–3.

15. Merkies IS, Schmitz PI, Samijn JP, van der Meché FG, van Doorn PA. Fatigue in immune-mediated polyneuropathies. European Inflammatory Neuropathy Cause and Treatment (INCAT) Group. Neurology. 1999;53(8):1648–54.
16. Scheres LJJ, van Dijk FS, Harsevoort AJ, van Dijk ATH, Dommisse AM, Janus GJM, Franken AAM. Adults with osteogenesis imperfecta: clinical characteristics of 151 patients with a focus on bisphosphonate use and bone density measurements. Bone Reports Elsevier. 2018;8:168–72.
17. Pouchot J, Kherani RB, Brant R, Lacaille D, Lehman AJ, Ensworth S, Kopec J, Esdaile JM, Liang MH. Determination of the minimal clinically important difference for seven fatigue measures in rheumatoid arthritis. J Clin Epidemiol. 2008;61(7):705–13.
18. Goligher EC, Pouchot J, Brant R, Kherani RB, Aviña-Zubieta JA, Lacaille D, Lehman AJ, Ensworth S, Kopec J, Esdaile JM, Liang MH. Minimal clinically important difference for 7 measures of fatigue in patients with systemic lupus erythematosus. J Rheumatol. 2008;35(4):635–42.
19. Lerdal A, Moum T, Wahl AK, Rustøen T, Hanestad BR. Fatigue in the general population: A translation and test of the psychometric properties of the Norwegian version of the fatigue severity scale. Scand J Public Health. 2005; 33(2):123–30.
20. Valko PO, Bassetti CL, Bloch KE, Held U, Baumann CR. Validation of the fatigue severity scale in a Swiss cohort. Sleep. 2008;31(11):1601–7.
21. Hald JD, Folkestad L, Harsløf T, Brixen K, Langdahl B. Health-related quality of life in adults with Osteogenesis Imperfecta. Calcif Tissue Int Springer US. 2017;101:473–8.
22. Bathen T, Velvin G, Rand-Hendriksen S, Robinson HS. Fatigue in adults with Marfan syndrome, occurrence and associations to pain and other factors. Am J Med Genet Part A. 2014;164A(8):1931–9.
23. Mueller B, Engelbert R, Baratta-Ziska F, Bartels B, Blanc N, Brizola E, Fraschini P, Hill C, Marr C, Mills L, Montpetit K, Pacey V, Molina MR, Schuuring M, Verhille C, de Vries O, Yeung EHK, Semler O. Consensus statement on physical rehabilitation in children and adolescents with osteogenesis imperfecta. Orphanet J Rare Dis BioMed Central. 2018;13:158.
24. Dalgas U, Stenager E, Jakobsen J, Petersen T, Hansen HJ, Knudsen C, Overgaard K. Fatigue, mood and quality of life improve in MS patients after progressive resistance training. Mult Scler. 2010;16(4):480–90.

25. Neill J, Belan I, Ried K. Effectiveness of non-pharmacological interventions for fatigue in adults with multiple sclerosis, rheumatoid arthritis, or systemic lupus erythematosus: a systematic review. J Adv Nurs. 2006;56(6):617–35.
26. Peters KF, Kong F, Horne R, Francomano CA, Biesecker BB. Living with Marfan syndrom I. Perceptions of the condition. Clin Genet. 2001;60(4):273– 82.

Part II

Bleeding and bruising in Osteogenesis Imperfecta

Chapter 4

Bleeding and bruising in Osteogenesis Imperfecta: International Society on Thrombosis and Haemostasis bleeding assessment tool and haemostasis laboratory assessment in 22 individuals

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Abstract

Osteogenesis imperfecta (OI) is characterized by susceptibility to bone fractures. Other symptoms, such as easy bruising and bleeding complications during surgery necessitating transfusions, have also been reported. The aim of the cross-sectional pilot study was to assess the bleeding and bruising tendency in OI patients and to screen for possible underlying haematological disorders. Bleeding tendency was investigated using the International Society on Thrombosis and Haemostasis bleeding assessment tool (ISTH-BAT) in 22 adult OI patients. Laboratory testing was performed to investigate for bleeding disorders or abnormal coagulation. Four patients [OI type 1(n = 3), OI type 4(n = 1)] had a bleeding score (BS) fitting with a bleeding tendency, but without test results pointing to a coagulopathy. Two patients [OI type 1(n = 1), OI type 3 (n = 1)] without a bleeding tendency according to the BS had increased fibrinolysis. This is the second largest study to date addressing bleeding tendency in OI and the first study to use ISTH-BAT and elaborate laboratory testing for coagulopathies. Four patients had an increased bleeding tendency. However, laboratory testing demonstrated no bleeding disorder or abnormal coagulation. Increased fibrinolysis was demonstrated in two patients without bleeding tendency on BS. Vascular fragility as a cause of bleeding tendency in OI has been suggested earlier. Further research on bleeding tendency in OI is important.

Introduction

Osteogenesis Imperfecta (OI) is an inherited connective tissue disorder primarily characterized by susceptibility to fractures. The prevalence of OI has been reported as 6-7 per 100,000 [1]. OI is a clinically and genetic heterogeneous disorder. Clinically, OI consists of 5 types (OI types 1-5) [2]; blue sclerae, dentinogenesis imperfecta, hearing loss, joint hypermobility and short stature can be present as secondary features [3].

Most patients with OI have a dominant pathogenic variant in either the *COL1A1* or *COL1A2* gene, which encode collagen type I alpha 1 chain and collagen type I alpha 2 chain, respectively. Collagen type I is abundant in bones, ligaments and tendons and has a triple helix structure. Dominant pathogenic variants result in decreased and/or abnormal production of collagen type 1 [4]. It is well known that the phenotype is influenced by the gene involved, the specific position of the variant and the variant type [2].

Easy bruising is commonly reported by OI patients. Earlier studies reported coagulation abnormalities: prolonged bleeding time, abnormal prothrombin consumption [5,6], abnormalities in platelet function [6], large platelets [7], decreased platelet retention and reduced factor VIII (FVIII) [8].

To our knowledge this is the second largest study after that of Evensen et al (1984), which reported on 58 clinically diagnosed OI patients [8]. In addition, six case studies reported an increased bleeding risk, without abnormal coagulation tests or further details being available. Five of these six casereports described a single patient and one reported on 20 infants aged between 1 and 6 months old [9–14]. To our knowledge, no recent studies have been performed in OI patients to identify or exclude a haematological cause. The aim of this study was firstly to investigate whether a bleeding tendency is present and, secondly, to perform haematological studies to identify or exclude coagulation disorders.

Methods

Study design and population

An observational cohort pilot study was undertaken in the Expert Centre for adults with Osteogenesis Imperfecta, Isala Hospital, Zwolle, The Netherlands. All new adult patients with a clinical diagnosis of OI who attended the centre from March 2018 until June 2018 were approached for the study

and informed consent was obtained from each participant. Exclusion criteria were: medication that could interfere with haemostasis, including bisphosphonates [15]. The Medical Ethics Committee of the Isala Hospital, Zwolle, The Netherlands, approved the study.

Data collection

Patients with OI were seen by the multidisciplinary OI team and the information retrieved was assessed and patient notes were reviewed, with specific attention to comorbidities, medication and diet. The Karnofsky index questionnaire was used to determine the general health of the patients [16].

Evaluation of bleeding tendency

The history of bleeding in OI patients was assessed using a validated bleeding assessment tool (BAT) created by the International Society on Thrombosis and Haemostasis (ISTH) [17], resulting in a bleeding score with different reference ranges for gender and age. This BAT is a merged version of 4 previous, validated BATs [18] that was primarily designed for identification of congenital disorders of haemostasis. It is mostly used for von Willebrand disease (VWD) type 1 [19], but can also be used for the diagnosis of platelet function disorders [20]. Data on epistaxis, cutaneous bleeding, minor wounds, haematuria, gastrointestinal bleeds, oral cavity bleeds, prolonged bleeding after trauma, surgeries or tooth extraction, menorrhagia, postpartum haemorrhage, muscle, joint and central nervous system bleeds were collected using an online questionnaire. Our group translated the Self-BAT version of the ISTH-BAT questionnaire [21] into Dutch so that the patients were able to complete it.

Blood sampling, laboratory methods and molecular analyses

Blood was collected by venepuncture of the cubital vein in Vacutainer blood collection tubes (Becton Dickinson; Vianen, the Netherlands) containing 3.8% sodium citrate or dipotassium ethylene diamine tetraacetic acid (K2EDTA) as anticoagulant. All tests have been standardized with defined reference ranges as criteria for pathological results. The laboratory is subject to national and international external quality assessment in the field of haemostasis and thrombosis.

A full blood count was performed on an automated modular haematology system (Sysmex XN-9000; Sysmex Europe, Etten-Leur, the Netherlands) for determination of haematocrit, and platelet count. Activated partial thromboplastin time (aPTT), prothrombin time (PT; reported as an International Normalised Ratio), fibrinogen, FVIII activity and von Willebrand factor (VWF) antigen were determined on a Sysmex CA-1500 automated analyser based on turbidimetry. VWF activity was determined by the Sanquin Diagnostic Laboratory (Amsterdam, The Netherlands) using an agglutination method.

Platelet function was tested on an automated platelet function analyser (PFA-100; Siemens Healthcare Nederland B.V. Den Haag, the Netherlands). It measures the ability of platelets to adhere and aggregate under high shear stress to a membrane covered with collagen and epinephrine or collagen and ADP.

Fibrinolysis was determined by semi-automated thromboelastometry (ROTEM delta; Werfen Netherlands, Breda, the Netherlands), which was locally calibrated as per the verification guidelines [22–24]. Clot formation and lysis was determined after addition of reagents activating the internal or external coagulation pathway. Maximum lysis (ML) was optically measured as the percentage reduction of clot firmness within 60 min. Other Rotem parameters, such as clotting time (CT), clot formation time (CFT) and maximum clot firmness (MCF) all fell within the reference ranges (Table 1) and are therefore not further discussed.

DNA was extracted from blood or saliva. Next-generation sequencing was performed for a panel of genes in which pathogenic variants are known to cause OI (*ALPL, BMP1, COL1A1/2, CREB3L1, CRTAP, FKBP10, IFITM5, P3H1, LRP5, PLOD2, PLS3, PPIB, SERPINF1, SERPINH1, SP7, TAPT1, TMEM38B, WNT1*). Identified pathogenic variants have been reported according to the Human Genome Variation Society guidelines for the nomenclature of DNA sequence variants [25].

Statistical analyses

Variables were tested for normal distribution with the Kolmogorov-Smirnov test. Means and standard deviation were given for normally distributed continuous variables. Nonnormally distributed continuous variables were presented as median, interquartile range (IQR), and categorical variables as frequencies (percentages). Differences in means comparing OI patients with the controls were tested using independent sample *t* tests and the mean differences were presented as the mean with 95% confidence intervals (95% CI). A two-sided P-value of 0.05 was considered significant. Analyses were performed using SPSS 25 for Windows (IBM Corp., Armonk, NY).

Table 1

Patients characteristics with a general overview of bleeding score and laboratory measurements

Patient (text ID)	BS	OI type	Age (years)	M/F	Bleeding symptoms	Platelet count	aPTT	FVIII	VWF antigen	VWF activity
1	3	3	24	M	Subdural bleeding	202	30	103	74	82
2	2	4	45	F	I, oral cavity bleeding	254	33	50	44	36
3 (Patient 5)	0	3	52	M		367	27	121	75	76
4	4	1	19	F	I, II, melena with consultation	269	24	154	104	101
5 (Patient 6)	0	1	18	M		163	28	116	88	135
6 (Patient 1)	6	1	51	F	I, III*, Haematochezia†, post-partum blood transfusion	180	25	209	120	185
7	1	1	56	F	Haematuria	333	23	56	91	87
8	3	1	70	M	III*, IV, haematemesis	258	28	181		
9	3	1	40	M	Epistaxis treated with cauterisation	249	27	99	74	72
10 (Patient 2)	4	1	29	M	III treated with blood transfusion	261	28	78		
11 (Patient 3)	9	4	55	F	II, V, VI, III treated with medication, VII	346	26	173		
12	0	1	33	F		290	30	97	76	79
13	1	1	30	F	I	302	29	73	64	68
14	0	1	38	F		258	28	123	78	109
15	3	1	45	F	Haematuria, spontaneous hemarthrosis	323	25	160	70	69
16	1	1	45	F	I	251	24	206	131	151
17	4	1	28	F	with iron/hormonal therapy, VIII, oral cavity bleeding	355	31	95	75	72
18	0	4	28	M		213	29	130	101	107
19 (Patient 4)	7	1	27	M	IV‡, III treated with re-surgery and blood transfusion	197	27	126	110	117
20	1	1	67	F	I	203	25	184	115	129
21	1	1	26	F	IV	394	26	222	130	143
22	1	1	53	F	II	396	28	108	84	71

Bleeding symptoms: I: menorrhagia; II: ≥5 bruises [>1 cm]; III: bleeding after surgery in <25% of the procedures; IV: bleeding after tooth extraction in <25% of all procedures; V: spontaneous epistaxis >10 min; VI: muscle haematoma after trauma; VII: bleeding umbilical stump with surgical haemostasis and blood transfusion.; VIII: >5 minor bleeds/year.
Reference ranges: aPTT: 20-35 s; EPI/ADP: 85-165 s; ExtemCFT: 34-159 s; ExtemCT: 38-79 s; ExtemMCF: 50-72 mm;Extem/IntemML: <15%;Fibrinogen: 2-4 g/l; FVIII: 60-150%; IntemCFT: 30-110 s; IntemCT: 110-240 s; IntemMCF: 50-72 mm; Platelet count: 150-400 x 109/l; PT: 09-11 s; VWF activity: 50%-150%; VWF antigen: 50%-150%. Results outside the reference ranges are marked: .

Table 1 (continued)

Patient (text ID)	EPI/ADP	Fibri-nogen	PT	Extem-CT	Extem-CFT	Extem-MCF	Extem-ML	Intem-CT	Intem-CFT	Intem-MCF	Intem-ML
1	132/107	3	1.1	75	93	64	5	167	92	62	6
2	295/177	2.4	1	68	100	59		208	98	58	
3 (Patient 5)	157/90	3.1	1.1	64	60	63	16	162	52	61	17
4	114/78	4.2	1	49	68	71	6	195	87	68	5
5 (Patient 6)	91/77	2.2	1.1	77	154	52	14	154	130	50	15
6 (Patient 1)	93/102	3	1	64	100	60	7	150	76	60	9
7	123/107	3.4	1	61	92	61	12	129	61	63	13
8		2.9	1	66	70	67	10	171	64	63	10
9	152/109	3.3	1	68	67	64	6	175	70	62	7
10 (Patient 2)	131/124	2.1	1	54	83	59	8	139	70	60	9
11 (Patient 3		3.8	1	60	46	73	8	149	43	71	7
12	112/95	2.9	1.1	72	63	66	6	172	59	64	10
13	119/113	3.2	1	79	76	67	6	195	60	65	8
14	170/92	3	1	55	77	64	5	163	62	63	5
15	168/112	2.6	1	63	66	64	11	163	51	65	11
16	95/76	2.9	1	63	71	68	3	153	68	65	4
17	128/95	2.5	1.1	67	59	70	1	187	52	70	2
18	137/109	4.2	1.1	74	118	60	8	139	96	59	8
19 (Patient 4)	103/84	2.1	1	71	97	58	3	178	107	56	4
20	129/105	3.4	1	55	71	67	2	150	50	69	3
21	95/84	3.4	1	56	59	73	4	169	48	70	10
22	162/158	2.4	1	63	58	68	4	164	53	66	5

Abbreviations: aPTT, activated partial thromboplastin time; BS, bleeding score; CFT, clot formation time; CT, clotting time; EPI/ADP, epinephrine/adenosine diphosphate; Extem, screening test for the extrinsic haemostasis system; F, female; FVII, factor VIII; EIntem, screening test for the haemostasis system; M, male; MCF, maximum clot firmness; ML, maximum lysis; OI, Osteogenesis Imperfecta; PT, prothrombin time; VWF, von Willebrand factor.
*Treatment not known,
†Without associated gastrointestinal disease,
‡Treated with re-suturing and packing.

Results

Participant characteristics

In total 23 patients were identified during the study period. One patient was excluded because laboratory testing failed as the blood samples could not be analysed within the normal timeframe. Therefore, 22 patients were available for analysis.

Fourteen of the 22 (63.6%) OI patients in our cohort were female. The mean and median age of participants with OI was 40 (IQR 28-52) According to the Kolmogorov-Smirnov test, the age distribution of this study was normal (p = 0.179). Skewness and kurtosis were 0.393 and -0.781, respectively, thus confirming the normal distribution [26]. Seventeen of the 22(77%) subjects had OI type 1, 2 (9%) type 3 and 4 patients (14%) had OI type 4. None of the patients suffered from renal or liver diseases. None of the patients reported smoking or alcohol abuse (>2 units/day). All patients were in a moderate to good condition (Karnofsky Index mean 82%, mode 80%) (Table 2).

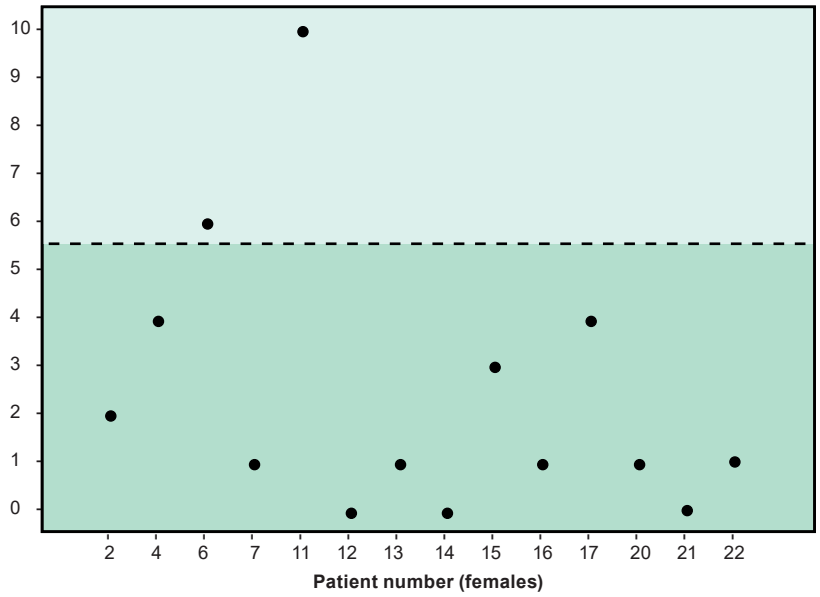
Table 2 *Overview of general patient characteristics*

Variable	OI patients	
Female, *n* (%)	14	(63.6)
Current age, years, median (IQR)	39	(28–52)
Karnofsky index, years, median (IQR)	80	(80–90)
Age at diagnosis, years, median (IQR)	4	(0–33)
OI subtype, *n* (%)		
Type 1	17	(77.3)
Type 3	2	(9.1)
Type 4	3	(13.6)
Response rate ISTH-BAT, *n* (%)	20	(91%)

Abbreviations: IQR, Interquartile range; OI, Osteogenesis imperfecta.

Bisphosphonates

Sixty percent of the patients had previously used bisphosphonates. The group who had never used bisphosphonates had a mean bleeding score of 1.38 (standard deviation, SD 1.19), whereas the group who used bisphosphonates in the past had a mean bleeding score of 3.00 (SD 3.16). The difference between these mean values is not statistically significant (p = 0.113).



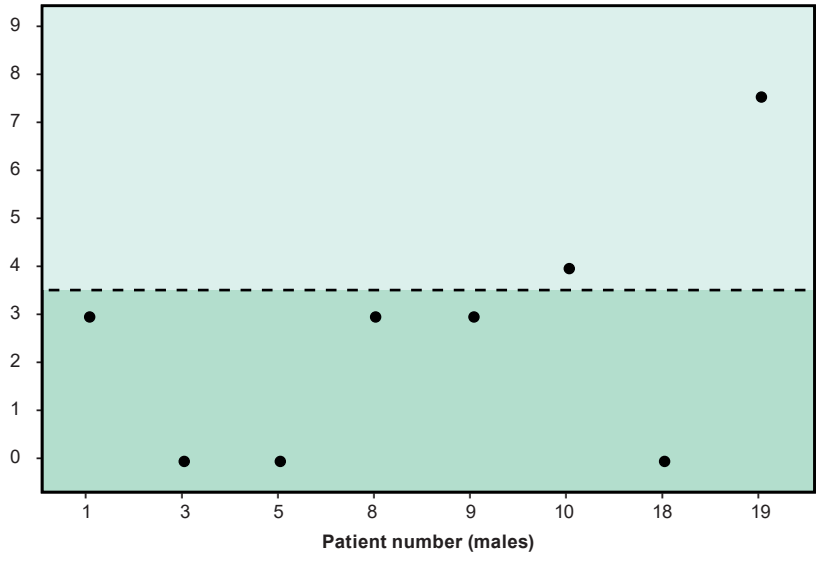


Figure 1 *Bleeding scores of the patients according to gender. ISTH-BAT: International Society on Thrombosis and Haemostasis bleeding assessment tool*

ISTH-BAT bleeding scores

Normal ISTH-BAT scores for males are <4 and <6 in females [18]. Abnormal values were found in 18% (*n* = 4) of the patients, three of whom appeared to be OI type 1, and one patient was OI type 4. We found a wide range of bleeding scores, 0-7 in males, 0-9 in females, and only 25% (*n* = 5) of the scores were 0 (Figure 1), with a median score of for males, and 1 for females. No correlations were seen between age and score within the population (Pearson correlation 0.084), or between OI type and score (Pearson correlation 0.160).

Patients 1-4 had a bleeding tendency according to the BS and reported different symptoms (Table 1). Patient 1 reported haematochezia with unknown cause, menorrhagia for which no intervention was required, excessive bleeding during surgery and bleeding after a caesarean section that required blood transfusion. She had OI type 1 due to a c.859-1G>A pathogenic variant in the *COL1A1* gene. Patient 2 reported excessive bleeding that required blood transfusion after orthopaedic surgeries. He had OI type 1 due to a c.2413G>C; p.Gly805Arg pathogenic variant in *COL1A2*. Patient 3 reported frequent spontaneous epistaxis with a bleeding episode that lasted more than 10 min, easy bruising above the score limit with 5 or more bruises (>1 cm) in exposed areas, excessive bleeding requiring procoagulant therapy after surgery, a muscle haematoma after trauma and an excessive umbilical stump bleeding after birth, for which two surgeries were required. She had OI type 4 due to a c.1171G>A; p.Gly391Ser pathogenic variant in *COL1A2*. Patient 4 reported frequent prolonged bleeding after dental extraction for which extra dental packing and stitching was necessary, as well as an excessive bleed after ear, nose and throat surgery, which required re-surgery and procoagulant therapy. He has OI type 1 due to a *COL1A1* c.3076C>T; p (Arg1026*) pathogenic variant.

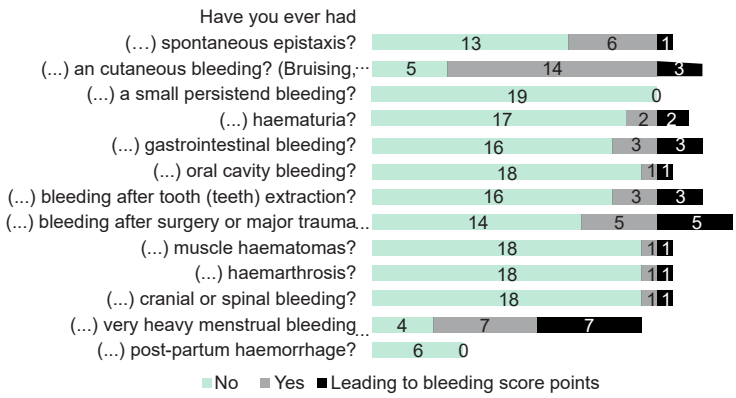


Figure 2 *Summary of the patient's answers to the International Society on Thrombosis and Haemostasis bleeding assessment tool (ISTH-BAT) questionnaire. Responses (n) shown*

Bleeding symptoms were generally mild, and most frequently consisted of easy bruising in 74% (*n* = 14), but only 16% (*n* = 3) were above the score limit with 5 or more bruises (>1 cm) in exposed areas (Fig 2.) No correlations were found between the bleeding score and VWD, FVIII, aPTT and fibrinogen values (Pearson correlation 0.117, 0.182, 0.140, 0.018, respectively) As such, none of these laboratory results were predictive for the bleeding score in this cohort. Although the platelet count was normal (>150 x 10^9/l) in all patients, 2 of the 4 patients with high bleeding scores levels had a platelet count below 200 x 10^9/l, while the mean platelet count was 275 x 10^9/l.

Platelet count, APTT, PT, Fibrinogen, VWF, FVIII

Routine coagulation parameters were analysed (Table 3). Platelet counts and PT levels were normal in all patients. Fibrinogen was abnormal in two patients; both of these patients had no other abnormalities in their blood tests or questionnaires. One patient was diagnosed with VWD type I. None of the patients had FVIII levels <50%. High FVIII activity (>150%) was found in nine patients (Table 1).

Table 3 *General coagulation findings in OI*

Test	Reference range	Abnormal findings/ Patients studied (n/N)	OI patients Mean (SD)	95% CI
aPTT	20–35 s	0/22	27.3 (2.7)	26.2–28.4
Prothrombin time	0.9–1.1	0/22	1.032 (0.0478)	1.00–1.05
Platelet count	150–400 X 10^9/l	0/22	273.6 (72.4)	245.1–306.21
Factor VIII	60–150%	9/22	128 (49.9)	108.2-152.2
Fibrinogen	2.0–4.0 g/l	2/22	3.0 (0.58)	2.8–3.3

Abbreviations: aPTT, activated partial thromboplastin time; OI, Osteogenesis imperfecta; SD, standard deviation.

PFA-100 - Platelet function

Mild platelet function disorders were found in two cases (9%), which did not correlate with the ISTH-BAT scores or the ROTEM results. However, these patients did report easy bruising. One of these patients had VWD type I. This correlated with elevated epinephrine (EPI)/ adenosine diphosphate ADP) values, as the PFA-100 analyser is very sensitive for VWD [27]. This patient had an ISTH-BAT score of only 2 and no ROTEM abnormalities (Table 1). A second patient with elevated EPI/ADP values did report family member(s) with a bleeding tendency but did not have VWD. This patient had an ISTH-BAT score of one point on the excessive bruising and no other abnormal values. There were no significant differences in laboratory values between males and females. No differences were found between the different OI types.

Fibrinolysis

The ROTEM test was performed to determine fibrinolysis in all 22 included OI patients (Table 1). One patient (Patient 5) had 17% fibrinolysis of (reference range <15%) (Figure 3); this patient had OI type 3 due to a c.2461G>A p.(Gly821Ser) pathogenic *COL1A1* variant. He had no other abnormal laboratory test results and a BS of 0. Another patient (Patient 6) had 15% fibrinolysis, OI type 1 due to a c.859-1G>A pathogenic *COL1A1*, a BS of 0 and no other abnormalities.

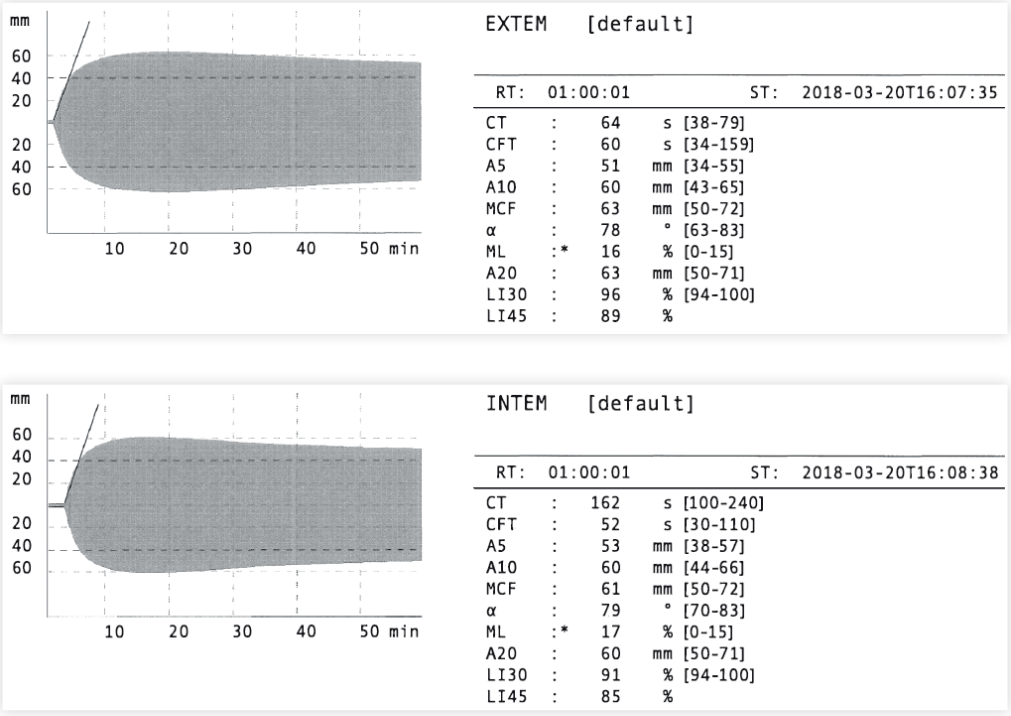


Figure 3 *ROTEM trace with increased fibrinolysis*

α: alpha angle; A5: amplitude at 5 min; A10: amplitude at 10 min; CFT, clot formation time; CT, clotting time; EXTEM, screening test for the extrinsic haemostasis system; INTEM, screening test for the haemostasis system; MCF, maximum clot firmness; ML, maximum lysis

Discussion

Bleeding tendencies have been occasionally reported in patients with OI, but detailed studies on coagulation defects in these patients are sparse. In this study we assessed the bleeding tendency with a validated questionnaire (ISTH-BAT) and investigated several laboratory parameters in all patients to identify or exclude a coagulopathy. The ISTH-BAT identified easy bruising in 74%. Five patients reported haemorrhages during surgery requiring blood transfusion and other medical interventions, such as a repeat surgery. These types of events have previously been reported in the literature in OI patients [9–14]. Interestingly, 18% of the OI patients appeared to have an elevated BS but laboratory testing did not identify a coagulopathy. Intriguingly, three patients had test results that indicated hyperfibrinolysis (*n* = 2) and VWD type 1 (*n* = 1), but these patients did not have an elevated bleeding score and the two patients with hyperfibrinolysis did not report easy bruising. VWD type 1 has a high prevalence and is most likely unrelated to OI [28].

For the patients with an elevated BS and no laboratory test abnormalities, it may be possible that the elevated BS is due to other causes. However, gender, age, OI type and the use of bisphosphonate did not point to a significant effect on bleeding tendency. Persiani et al. described a significantly higher rate of bleeding in OI type 3 patients who never used bisphosphonates and underwent femoral surgery [15]. One hypothesis for this is that the reduction and/or abnormal production of collagen type 1 may predispose to capillary fragility, as the vessel walls contain collagen type 1 [5,12,29]. However, if this hypothesis would be true, one would expect an elevated BS in all patients with OI unless there is clinical variability, ranging from slight increased propensity to bruise in the patient, to more severe clinical features resulting in elevated BS. In this scenario, the underlying genetic cause may be an important factor.

In two patients with a BS score of 0, moderately elevated fibrinolysis was measured by ROTEM®, which indicated an increased clot lysis that can lead to bleeding tendencies [30,31]. Given that fibrinolytic activity depends upon the activity of endothelial cells, cellular elements of haemostasis may possibly play a role in triggering bleeding disorders [30]. A suggestion for the possible connection between hyperfibrinolysis and OI could be a deficiency in plasminogen activator inhibitor-1 (PAI-1). PAI-1 deficiency has been reported in a patient with OI and spontaneous intraparenchymal haemorrhage [32]. There is evidence that PAI-1 also has a role in bone formation in mouse models [33–35]. PAI-1 is stabilized by vitronectin which is anchored to collagen type 1 [36]. As collagen type 1 production is reduced and/or abnormal this might influence a factor resulting in bleeding tendency in some OI

patients. Again, we hypothesize that the reduction and/or abnormal production of collagen type 1 may lead to increased fibrinolysis and, as such, is more likely to be observed in patients with OI. However, the moderately elevated fibrinolysis does not fit with a bleeding score of 0. The questionnaires might possibly have been influenced by a recall bias. Some crucial questions about duration of bleeds and bruise counts are difficult to recall, especially when a number of years have passed since a bleeding event.

Intriguingly, Patient 1, with an elevated BS, is the mother of Patient 6, who had a BS of 0 and moderately elevated fibrinolysis. Although, the younger age of Patient 6 might have affected his BS, we would have expected his mother to have abnormalities on fibrinolysis. It remains a possibility that the ISTH-BAT and fibrinolysis are good tools for identifying and/or excluding coagulopathies, but simply not suitable for diagnosing and/or excluding inherited connective tissue disorders, such as OI. We hypothesize that a frequently reported feature, such as easy bruising, might be due to capillary fragility following abnormal and/or reduced collagen type 1 production in OI patients [4,30].

Conclusions

This is the second largest study to date addressing bleeding tendency in OI and the first study to use ISTH-BAT and elaborate laboratory testing for coagulopathies. In our cohort, 74% reported easy bruising, 18% had an elevated BS on ISTH-BAT without coagulation abnormalities and 9% demonstrated slight hyperfibrinolysis with a BS of 0.

We observed no extensive bleeding disorders or evidence of abnormal coagulation in this cohort. Interestingly, two patients were found to have a slight hyperfibrinolysis, which may point to capillary fragility due to abnormal and or reduced collagen type 1 production. Another patient was diagnosed with VWD type 1, which has a high prevalence and is most likely unrelated to OI.

There is, however, no correlation between the bleeding tendency according to the BS and hyperfibrinolysis, and it is possible that the ISTH-BAT and hyperfibrinolysis are not good tools for assessing bleeding tendency in patients with OI.

Considering the rarity OI is a rare disorder, this study represents the assessment of a large group of patients. However, it is still a limited number of patients from which conclusions can be drawn. As such, it would be important to repeat the same study set-up in a large group of patients with mo-

lecularly confirmed OI in order to assess whether there is indeed an increased bleeding tendency in patients with OI. In addition, we aim to also look for evidence of easy bruising during physical examination and will investigate whether elevated BS is a consistent feature in families with OI. If an increased bleeding tendency is found to be present in a significant proportion of OI patients, the responsible mechanism will need to be further investigated.

References

1. Steiner RD, Basel D. COL1A1 / 2 Osteogenesis Imperfecta. GeneReviews® - NCBI Bookshelf 2005.
2. Van Dijk FSS, Sillence DOO. Osteogenesis imperfecta: Clinical diagnosis, nomenclature and severity assessment. Am J Med Genet A 2014; 164: 1470–81.
3. Starr SR, Roberts TT, Fischer PR. Osteogenesis Imperfecta: Primary Care. Pediatr Rev 2010; 31: e54–64.
4. Marini JC, Forlino A, Cabral WA, et al. Consortium for osteogenesis imperfecta mutations in the helical domain of type I collagen: Regions rich in lethal mutations align with collagen binding sites for integrins and proteoglycans. Hum Mutat 2007; 28: 209–21.
5. Siegel BM, Friedman IA, Schwartz SO. Hemorrhagic disease in osteogenesis imperfecta Study of platelet functional defect. Am J Med 1957.
6. Hathaway WE, Solomons CC, Ott JE, Ott E. Platelet Function and Pyrophosphates in Osteogenesis Imperfecta. Blood 1972; 39.
7. Estes JW. Platelet size and function in the heritable disorders of connective tissue. Ann Intern Med 1968; 68: 1237–49.
8. Evensen SA, Myhre L, Stormorken H. Haemostatic studies in osteogenesis imperfecta. Scand J Haematol 1984; 33: 177–9.
9. Mayer SA, Rubin BS, Starman BJ, Byers PH. Spontaneous multivessel cervical artery dissection in a patient with a substitution of alanine for glycine (G13A) in the α1(I) chain of type I collagen. Neurology 1996; 47: 552–6.
10. Edge G, Okafor B, Fennelly ME, Ransford AO. An unusual manifestation of bleeding diathesis in a patient with osteogenesis imperfecta. Eur J Anaesthesiol 1997; 14: 215–9.
11. Kastrup M, von Heymann C, Hotz H, et al. Recombinant factor VIIa after aortic valve replacement in a patient with osteogenesis imperfecta. Ann Thorac Surg 2002; 74: 910–2.
12. Mondal RK, Mann U, Sharma M, Mondal RK, Mann U, Sharma M. Osteogenesis imperfecta with bleeding diathesis. Indian J Pediatr 2003; 70: 95–6.
13. Faqeih E, Roughley P, Glorieux FH, Rauch F. Osteogenesis imperfecta type III with intracranial hemorrhage and brachydactyly associated with mutations in exon 49 of COL1A2. Am J Med Genet A 2009; 149A: 461–5.
14. Paterson CR, Monk EA. Temporary brittle bone disease: association with intracranial bleeding. Journal of Pediatric Endocrinology and Metabolism 2013; 26: 417–26.

15. Persiani P, Pesce M V., Martini L, et al. Intraoperative bleeding in patients with osteogenesis imperfecta type III treated by Fassier–Duval femoral rodding: analysis of risk factors. Journal of Pediatric Orthopaedics B 2017; : 1.
16. Karnofsky D, Burchenal J. The clinical evaluation of chemotherapeutic agents in cancer. In: In: Evaluation of chemotherapeutic agents. MacLeod CM, editor. New York: Columbia University Press; 1949. The clinical evaluation of chemotherapeutic agents in cancer; 1948: 191–205.
17. Rodeghiero F, Tosetto A, Abshire T, et al. ISTH BAT:Supplementary Material To the Official Communication of the SSC. Journal of Thrombosis and Haemostasis 2011; 8: 1–21.
18. Elbatarny M, Mollah S, Grabell J, et al. Normal range of bleeding scores for the ISTH-BAT: Adult and pediatric data from the merging project. Haemophilia 2014; 20: 831–5.
19. Tosetto A, Castaman G, Plug I, Rodeghiero F, Eikenboom J. Prospective evaluation of the clinical utility of quantitative bleeding severity assessment in patients referred for hemostatic evaluation. Journal of Thrombosis and Haemostasis 2011; 9: 1143–8.
20. Lowe GC, Lordkipanidzé M, Watson SP. Utility of the ISTH bleeding assessment tool in predicting platelet defects in participants with suspected inherited platelet function disorders. Journal of Thrombosis and Haemostasis 2013; 11: 1663–8.
21. Deforest M, Grabell J, Albert S, et al. Generation and optimization of the self-administered bleeding assessment tool and its validation as a screening test for von Willebrand disease. Haemophilia 2015; 21: e384–8.
22. Castellone DD. Establishing reference intervals in the coagulation laboratory. Int J Lab Hematol 2017; 39: 121–7.
23. CLSI. CLSI. (2008). Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition. CLSI document EP28-A3c. Wayne, PA: Clinical Laboratory Standards Institute. CLSI (2008) Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition CLSI document EP28-A3c Wayne, PA: Clinical Laboratory Standards Institute 2013.
24. Ozarda Y, Higgins V, Adeli K. Verification of reference intervals in routine clinical laboratories: Practical challenges and recommendations. Clin Chem Lab Med. 2019; 57. DOI:10.1515/cclm-2018-0059.
25. den Dunnen JT, Dalgleish R, Maglott DR, et al. HGVS Recommendations for the Description of Sequence Variants: 2016 Update. Hum Mutat 2016; 37. DOI:10.1002/humu.22981.
26. Schmider E, Ziegler M, Danay E, Beyer L, Bühner M. Is It Really Robust?: Reinvestigating the robustness of ANOVA against violations of the normal distribution assumption. Methodology 2010; 6: 147–51.

27. Akkerman ATJWN, Analyzer- PF, Voor VW, et al. Betekenis van de ‘ Platelet Function Analyzer-100 ® ’ in de dagelijkse diagnostiek. Nederlands Tijdschrift voor Hematologie 2006; 3: 133–7.
28. Sadler JE. Von Willebrand disease type 1: A diagnosis in search of a disease. Blood 2003; 101: 2089–93.
29. McAllion SJ, Paterson CR. Causes of death in osteogenesis imperfecta. J Clin Pathol 1996; 49: 627–30.
30. Alves GSA, Orsi FA, Santiago-Bassora FD, et al. Laboratory evaluation of patients with undiagnosed bleeding disorders. Blood Coagulation & Fibrinolysis 2016; : 1.
31. Hayward CPM. How I investigate for bleeding disorders. 2018; 40: 6–14.
32. Goddeau RP, Caplan LR, Alhazzani AA. Intraparenchymal hemorrhage in a patient with osteogenesis imperfecta and plasminogen activator inhibitor-1 deficiency. Arch Neurol 2010; 67: 236–8.
33. Mao L, Kawao N, Tamura Y, et al. Plasminogen Activator Inhibitor-1 Is Involved in Impaired Bone Repair Associated with Diabetes in Female Mice. 2014; 9: 3–10.
34. Moritake A, Kawao N, Okada K, et al. Plasminogen activator inhibitor-1 deficiency enhances subchondral osteopenia after induction of osteoarthritis in mice. 2017; : 1–8.
35. Jin G, Aobulikasimu A, Piao J, et al. A small-molecule PAI-1 inhibitor prevents bone loss by stimulating bone formation in a murine estrogen deficiency-induced osteoporosis model. FEBS Open Bio 2018; 8: 523–32.
36. Iris Schvartz, Dalia Seger SS. Vitronectin. The International Journal of Biochemistry & Cell Biology 31 1999; 31: 539–44.

Chapter
4

Chapter 5

Bleeding assessment in a large cohort of patients with Osteogenesis Imperfecta

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Abstract

Background Osteogenesis Imperfecta (OI) is characterised by bone fragility. Among several features, easy bruising and multiple case reports on haemorrhagic events have been reported. This paper describes the diverse manifestations of bleeding and bruising in a large cohort of 328 OI patients. The aim of this study is to provide insight in the diverse aspects and therapeutic considerations of bleedings in OI.

Methods This descriptive cohort study was conducted at the Expert Center for adults with OI in Isala, the Netherlands. Bleeding was assessed by the validated self-bleeding assessment tool (Self-BAT) The tool was distributed among 328 adults with different clinically confirmed types of OI.

Results 195 of 328 invited patients (response rate 60%) with OI type 1 (*n* =144) ,OI type 3 (*n* =17) and OI type 4 (*n* =34), aged between 18 and 82 years, completed the tool. Self-BAT scores were above the normal range in 42% of all patients. For males Self-BAT scores were increased in 37% with a mean score of 3.7, ranged between 0;18. For females the Self-BAT scores were increased in 44% with a mean of 5.4 and a range of 0;24. No statistical differences in OI subtypes were found.

Conclusions Bleeding tendency appears to be a relevant complication in OI patients as this study confirms the presumption of bleeding tendency. There are specific recommendations to clinicians who treat OI patients to consider an assessment of bleeding tendency and use potential interventions to reduce haemorrhagic complications and improve quality of life.

Introduction

Osteogenesis Imperfecta (OI), commonly defined as 'brittle bones' disease, is pathogenetically based on an hereditary collagen type I synthesis disorder, most often due to an autosomal dominant mutation in *COL1A1* or *COL1A2* genes. In addition to collagen type I genes, OI can be caused by multiple proteins connected to different parts of collagen biosynthesis [1]. Therefore it includes broader characteristics like blue sclerae, hearing loss, dental problems, ligamentous laxity and short stature [2]. The degree of impaired production of collagen type 1 is based on dominant pathogenic gene variants and results in a heterogeneous clinical expression historically classified in 5 types [3]. The prevalence of OI is about 6-7 per 100,000 [4]. Easy bruising and bleeding are prominent features of some heritable connective tissue disorders such as Ehlers-Danlos, and is also commonly reported by OI patients [5–7]. The literature for OI in relation with bleeding disorders is sparse and often dated [8–11]. Bleeding disorders in heritable disorders of the connective tissue can be a result of fragility of capillaries and perivascular connective tissue, but can also be caused by a clotting problem due to platelet dysfunction, a defect in fibrinolysis or vascular components of the haemostasis [6]. Although diagnosis of severe bleeding disorders such as moderate or severe hemophilia can be well defined, the distinction between individuals with or without a mild bleeding disorder is often difficult. The use of a bleeding assessment tool (BAT) in mild bleeding disorders can be more distinctive than a complete laboratory workup [12–14].

Since clinical appreciation of presence and severity of bleeding symptoms is a fundamental step in the evaluation of a possible bleeding disorder in OI, the aim of this study is to describe the diverse aspects of bleeding and bruising in our whole cohort of OI patients using a structured questionnaire. We also intend to provide insight in the clinical consequences and give therapeutic considerations of bleeding in OI due to surgery, tooth extraction, menstruation and obstetrics.

Methods

A nationwide descriptive cohort study was undertaken in the Expert Center for adults with OI, Isala Hospital, Zwolle, the Netherlands. All known patients in our clinic with a clinical diagnosis of OI according to the OI classification of van Dijk and Sillence [3] were invited to fill in the self-bleeding assessment tool (Self-BAT) between October 2019 and August 2020. The Medical Ethics Committee of the Isala Hospital, Zwolle, The Netherlands, confirmed that the Medical Research Involving Human Subjects Act does not apply (reference number: 190513). All patients who were invited for this study signed an informed-consent form for study participation.

Evaluation of bleeding tendency

The Self-BAT is a self-administered bleeding assessment tool validated in Canada and the Netherlands [15,16] and is based on the International Society on Thrombosis and Haemostasis Bleeding Assessment Tool (ISTH-BAT)[17,18]. The 14 Self-BAT domains cover epistaxis, cutaneous bleeding, minor wounds, haematuria, gastrointestinal bleeds, oral cavity bleeds, prolonged bleeding after trauma, surgeries or tooth extraction, menorrhagia, postpartum haemorrhage, muscle, joint and central nervous system bleeds and other bleedings. Each domain scores from 0 (absence of bleeding symptoms) to 4 (symptoms requiring extensive medical intervention). The distinction between 0 points and 1 point is of critical importance since score 1 means the symptom meets the minimal criteria defining a significant bleeding. This distinction between the different scores is described by the ISTH Scientific and Standardization Committee [19] and independently selected by 2 trained researchers (KG and HB). Different scores were reassessed and resolved by consensus. A total bleeding score is calculated by sum of scores for all BAT domains. A total bleeding score in men ≥ 4 and in women ≥ 6 was defined as an increased bleeding tendency [15,16].

Data collection

All data obtained from the Self-BAT were collected digitally and analysed using IBM SPSS Statistics Version 24. Variables were presented as numbers (n) and frequencies (%), mean and SD and median and interquartile range (IQR). Comparison of means between OI types 1, 3 and 4 was done using ANOVA with Bonferroni comparison for post-hoc testing. P values ≤ 0.05 were considered to indicate statistical significance.

Results

Of 328 invited OI patients, 225 patients (69%) returned the questionnaire. In total, 30 patients did not fully complete the questionnaire and were therefore excluded from the analysis. Therefore 195 questionnaires were available for analysis (completion rate 60%). No reasons for non-completion or signs of selective response were found.

Participant characteristics

The study population was predominantly of Dutch origin with a male/female ratio of 71/124. It concerned individuals with OI type 1 (*n* = 144), type 3 (*n* = 17) and type 4 (*n* = 34) (Table 1), with diverse genetic causes of OI. The mean age of this population at time of inclusion was 43,7 years (SD 15,6), with a median of 40 and ranged between 18 and 82 years. (Table 1) Surgery and dental extractions

were relatively common, 91% (*n* =177) of the patients had undergone surgery and 86,2% (*n* =168) had experienced a dental extractions. Of all 124 women, 91,9% (*n* =114) ever had a menstrual period and 42,7% (*n* =53) had been pregnant. Women with OI type 3 had never been pregnant. Of the women who had been pregnant, 47 had at least 1 delivery. The reason why 6 of the pregnant women did not give birth was not known. Three patients were known with von Willebrand disease (VWD). No other bleeding disorders were reported.

Table 1 *General descriptive data study population*

		OI type 1 *n* =144	OI type 3 *n* =17	OI type 4 *n* =34
Sex, *n* (%)	Male	49 (25)	7 (4)	15 (8)
	Female	95 (49)	10 (5)	19 (10)
Age in years, mean (SD)		44.7 (15.2)	31.7 (13.1)	45.4 (16.3)

Bleeding assessment

Self-BAT score

Self-BAT scores were above the normal range in 42% of all patients. For males Self-BAT scores were increased in 37% (*n* = 26) with a mean score of 3.7, ranged between 0;18. For females the Self-BAT scores were increased in 44% (*n* = 55) with a mean of 5.4 and a range of 0;24. There was no statistically significant difference between the OI types regarding severity of each bleeding symptom or total Self-BAT scores (Figure 1). The correlation between age and Self-BAT score is negligible (R^2 = 0,012).

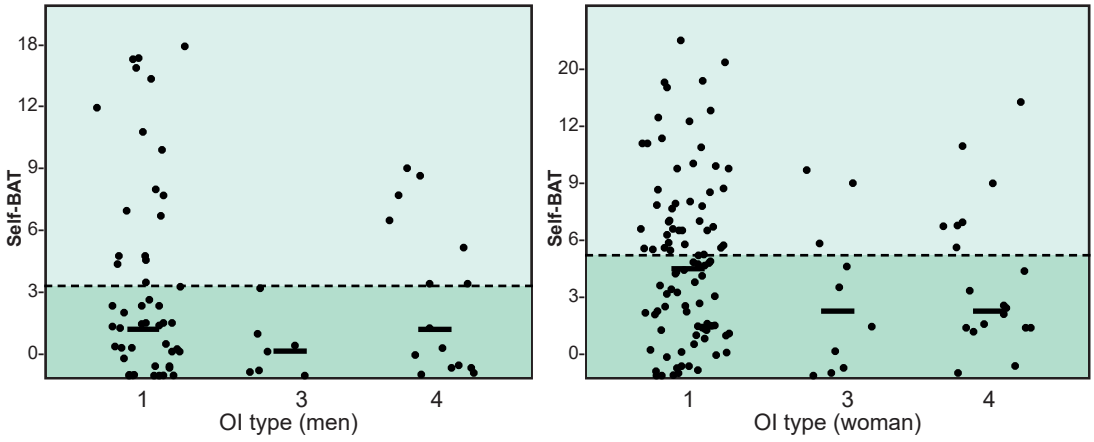


Figure 1 *Correlation between Self-BAT bleeding score and OI types. Black lines are medians. Dashed line is cut-off score for men and women*

Extensive medical intervention (a domain score of 4) was needed in 23% of the patients (*n* = 45) and mostly needed in the domains of surgery (*n* = 34), menorrhagia (*n* = 5) and dental extraction (*n* = 5). (Figure 2) 5% Of the patients (*n* = 10) required extensive medical intervention on more than 1 Self-BAT domain. The number of patients with significant bleeding per different bleeding domains is shown in Table 2. The specification of severity of bleeding symptoms (score 1-4) in the different domains are shown in supplemental Table 1. A symptom was scored as "present" if the patient indicated this in the questionnaire and scored as "significant" if the patient had a score of 1 or more on the Self-BAT for this item. Overall, the most common significant symptoms were menorrhagia (59.7% of all women) and cutaneous bleeding (50.8%). Other prevalent symptoms were postpartum hemorrhage (34%), bleeding from minor wounds (32.8%) and bleeding after surgery (30.3%). The least common symptoms were haematuria (2.1%) and cerebral bleeding (2.6%) (Table 2).

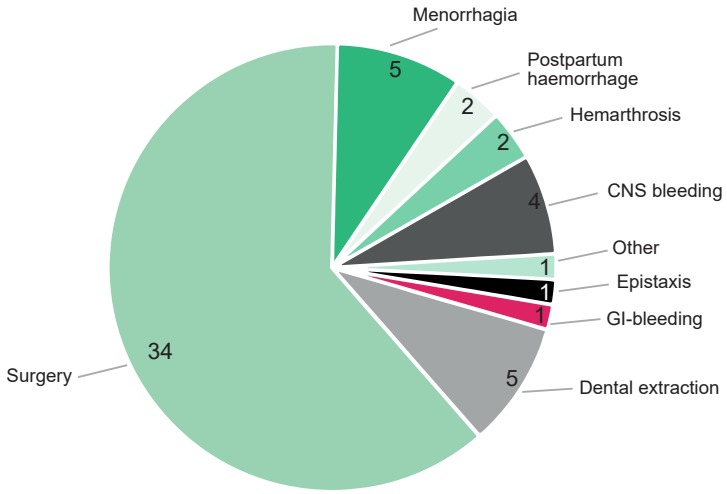
Table 2. *Analysis of the Self-BAT scores in 195 patients with OI.*

Self-BAT domains	Present* *n* (%)		Significant bleeding *n* (%)		Significant bleeding leading to increased total Self-BAT, *n* (%)	
Cutanous bleeding	171	(87.7)	99	(50.8)	58	(58.6)
Bleeding from minor wounds	184	(94.4)	64	(32.8)	45	(70.3)
Menstruation (of 124 woman women)	114/124	(91.9)	74	(59.7)	45	(60.8)
Surgery	177**	(90.8)	59	(30.3)	52	(88.1)
Dental extraction	168**	(86.2)	40	(20.5)	31	(77.5)
Epistaxis	145	(74.4)	39	(20)	26	(66.7)
Muscle hematomas	32	(16.4)	32	(16.4)	22	(68.8)
Hemarthrosis	18	(9.2)	18	(9.2)	15	(83.3)
Other bleeding	17	(8.7)	17	(8.7)	11	(64.7)
Childbirth (of 124 woman)	47/124** (37.9)		16	(34)	10	(21.3)
Oral cavity bleeding	36	(18.5)	9	(4.6)	7	(77.8)
Gastro intestinal bleeding	14	(7.2)	6	(3.1)	4	(66.7)
Central nervous system bleeding	5	(2.6)	5	(2.6)	5	(100)
Haematuria	24	(12.3)	4	(2.1)	3	(75)

* "Present" corresponds to the number of patients who experienced a cutaneous, minor wound, nose, muscle, joint, oral cavity or urinary tract bleeding regardless of significance of bleeding,

** Corresponds to the number of patients who experienced a dental extraction, surgery, women who menstruated and women who had at least 1 delivery, with or without bleeding.

Figure 2 *Distribution of bleeding symptoms needing extensive medical intervention*



Discussion

Bleeding problems are often reported by patients with OI and in case reports, but large cohort studies reporting on bleeding tendency of adult patients are not performed. Clinical appreciation of the presence and severity of bleeding symptoms is a fundamental step in the evaluation of a possible bleeding disorder in OI and therefore this study investigated bleeding tendency in a large cohort of adult OI patients using a structured BAT. In 42% of the included OI patients the Self-BAT score was increased compared to the normal range [20].

Bleeding after surgery

Surgery is frequently needed in our population. In this cohort 91% of all patients underwent surgery. Because 17% of all included patients with OI reported that they required blood transfusion after surgery, awareness of this bleeding risk is of critical importance. Identification of risk factors in OI patients before surgery can result in less bleeding incidents and reduce the need for transfusion because attention to mild bleeding symptoms can ameliorate bleeding diathesis when drugs, such as desmopressin and antifibrinolytics, are used when necessary [14,21–23]. There are several studies describing excessive bleeding due to surgery in OI patients, despite normal pre-operative haematological assessment. Wong et al. reported bleeding complications despite normal preoperative

coagulation studies in 30% of the study participants (7 out of 23) and Langness and Behnke et al. in 11% of the study participants (9 out of 80) [24,25]. A recent study of Rothschild et al. reported significant intraoperative blood loss in 17% of 205 surgeries among 83 OI patients without link to coagulation disorders [26]. Also Morton et al. (*n* = 1), Wood et al (*n* = 2), Waters et al. (*n* = 1) and Mondal (*n* = 1) describe bleeding diathesis without explanatory coagulation disorders [27–30]. Several studies try to discover a link between bleeding diathesis and laboratory abnormalities, but all were inconclusive [5,11,31–34]. The use of a structured bleeding questionnaire as is used in this study seems to be far more useful than laboratory measurements because correlation between levels of a specific factor and the severity of bleeding symptoms is usually poor. This may be because standard tests poorly reflect in vivo haemostasis. The contribution of many factors (e.g. vessel fragility or fibrinolysis) cannot be measured. Also a genomic search for the molecular basis of inherited clotting and platelet defects will not be as useful as a good questionnaire because often variability in penetrance and expressivity [35], coinheritance of haemostatic defects or superimposed genetic modifiers make the relationship between genotype and phenotype less stringent than previously appreciated [12,14]. For a mild bleeding disorder as OI a clinically driven “bleeding” diagnosis based on anamnestic risk factors can be of more benefit than preoperative laboratory investigation as is shown by Obaji et al. They applied desmopressin and/or tranexamic acid to a group of patients with a significant bleeding history with no reproducible abnormality with the standard tests of haemostasis, and found no bleeding in 90% of patients undergoing an intervention [36].

Post extraction bleeding (PEB)

21% Of the patients in this study experienced unusual bleeding due to dental extraction. PEB (Post extraction bleeding) has divergent definitions but is a well-recognized, frequently encountered complication in dental practice with an varying incidence between 0-26% [37]. Post extraction bleeding has been attributed to various factors that can be broadly classified as local and systemic. Locally soft tissue or bone bleeding can occur due to traumatic extraction leading to laceration of blood vessels. Also inflammation at the site of extraction, traumatic extraction, and failure of the patient to follow post□extraction instructions have also been associated with PEB. Systemic factors include platelet problems, coagulation disorders or excessive fibrinolysis, and inherited or acquired problems (medication induced) [38]. In the current study we did not differentiate the underlying factors that can cause bleeding and a literature review did not reveal any previous reports for bleeding risk after tooth extraction in relation to patients with OI. However, further differentiation in cause of post extraction bleeding would be very useful since patients with OI have also often dentinogenesis imperfecta [39] and are at risk of bisphosphonate related osteonecrosis of the jaw [40].

Heavy menstrual bleeding (HMB)

In our cohort 65% of the women who ever menstruated had significant abnormal bleeding during their menstruations. In 40% of all patients who menstruated, abnormal menstruation contributed to an increased total BAT score. This means that menstrual bleeding disorder in OI contributes significantly to an increased BAT score. Menorrhagia is the most frequent health problem for a woman during reproductive life, occurs in about 30% of women, is underdiagnosed and poorly treated [41]. It has a major impact on a woman's quality of life for which the NICE guideline on heavy menstrual bleeding encourages clinicians to focus their interventions on improving quality of life rather than focusing on blood loss [42]. Besides this already large problem in the general population, menorrhagia is a prominent feature of most bleeding disorders [43–45]. Among patients with moderate to severe Von Willebrand Disease in the Netherlands a prevalence of menorrhagia of nearly 80% was demonstrated [46]. No literature is available for the prevalence of menorrhagia in patients with OI, but our study suggests an increased prevalence of menorrhagia in OI compared to the general population. With regard to the major impact on quality of life and the relatively large prevalence of HMB in OI it should be noted that a substantial proportion of women with menorrhagia with abnormal laboratory haemostasis has shown to respond to therapy with desmopressin and/or tranexamic acid with decreased bleeding and improved quality of life [47]. Therefore, pro-active treatment for HMB in OI should be considered.

Postpartum haemorrhage (PPH)

In our cohort 53 female patients stated they had ever been pregnant. Of these, 47 patients reported ever having given birth. 16 Out of 47 women (34%) experienced significant PPH which is much higher than the incidence of PPH in many high-income countries [48]. Recent research on pregnancies with OI shows significant higher rates of blood transfusion compared with US normative data, a significant increase in pre-pregnancy bleeding and a non-significant increase in post-partum bleeding compared with non-OI pregnancies [49,50]. PPH though is worldwide known as a major contributor to maternal death [51] and even mild haemostatic abnormalities can be a significant risk factor for severe PPH [52]. Also previous PPH results in a much higher risk of recurrent PPH during a subsequent delivery [53,54]. The high prevalence of PPH in OI as found in this study highlights the need for awareness of possible bleeding tendency in pregnant woman with OI. Veen et al. found that PPH can be the first symptom of an inherited bleeding disorder, but also emphasises assessing the bleeding history as 75% of the women with a bleeding disorder had additional bleeding symptoms other than PPH [55]. In our cohort the percentage of women with PPH and an elevated BAT score, meaning at least 1 significant bleeding symptom other than PPH, was 63%. The use of a structured

questionnaire such as the ISTH-BAT can also be of benefit in pregnant woman with OI, especially since administration of tranexamic acid to women with post-partum haemorrhage reduces deaths due to bleeding by nearly one third, with no evidence of any adverse effects or complications [56].

Strengths and limitations

We carried out the largest nationwide study ever performed in adult patients with OI focused on bleeding assessment. With this study a lot of valuable information was obtained which gave a unique insight in the features of bleeding tendency in OI. The results of this study provide a substantial contribution to our knowledge on the symptoms of bleeding disorders in patients with OI. In addition, increased awareness of bleeding complications among health care providers involved in the care of patients with OI may contribute to improved quality of life in these patients.

Albeit the Self-BAT is a validated questionnaire for different mild bleeding disorders [15,16], it is not specially developed for OI. Due to the explorative design of this cohort study and the absence of a matched control group, no relative risk estimates could be calculated. Also the use of an self-reporting BAT has some limitations because symptoms reported by patients may be influenced by the fact that several patients are already familiar with the potential relation between OI and an increased bleeding tendence. Furthermore, recall of symptoms and treatments can be difficult, especially when the presence of bleeding symptoms spans a lifetime and might be sporadic due to a low amount of haemostatic challenges. This is also claimed by Moenen et al, who also emphasises that although an elevated BAT score increases the patients likelihood of having an mild bleeding disorder, a specific disorder cannot be diagnosed based on the BAT [57,58]. The main value of the BAT is well established in the assessment of a bleeding disorder and provides a structured, complete diagnostic anamneses. Abnormalities can justify extensive laboratory testing because a distinctive bleeding history is a prerequisite for the diagnosis of any bleeding disorder [12,59]. We used the BAT for an descriptive purpose to gain more insight in the bleeding tendency in OI. For this reason we also described the different domains of the Self-BAT, which has been done earlier [60].

Conclusions

The abundant manifestations of bleeding and bruising described in this large cohort suggests that a mild bleeding disorder should be considered in patients with OI. Despite some limitations of a self-report questionnaire, there are very likely more bleeding problems in OI compared to the normal population. Since bleedings due to surgery, tooth extraction, menstruation and obstetrics are more common and can have major clinical consequences, proactive therapy might be considered

in patients with a high bleeding tendency detected on the BAT. Many OI patients underwent multiple invasive procedures because of fractures and dentinogenesis imperfecta, possibly with a undiscovered history of bleeding. This means that patients are at risk of experiencing unnecessary and potentially debilitating haemorrhagic symptoms if a bleeding tendency is not identified. The use of a structured bleeding questionnaire as is used in this study seems to be far more useful than laboratory measurements. We recommend clinicians who treat OI patients to assess bleeding tendency with the use of a Bleeding Assessment Tool. We also recommend to consider potential interventions to reduce haemorrhagic symptoms with the use of desmopressin and/or tranexamic acid which might be sufficient to reduce haemorrhagic symptoms and (in menorrhagia) improve quality of life. These interventions had as described in literature no evidence of adverse effects, while patients might be prevented from being exposed to potential risks associated with the administration of blood products. Future studies will be required to further define the bleeding phenotype in OI and to investigate a possible correlation with genotype. Also OI specific studies into results of preventive medication on bleeding tendency and validation of reliability and feasibility of the Self-BAT in OI are important issues for future research.

References

1. Claeys L, Storoni S, Eekhoff M, et al. Collagen transport and related pathways in Osteogenesis Imperfecta. Hum Genet. 2021; 140: 1121–41.
2. Starr SR, Roberts TT, Fischer PR. Osteogenesis Imperfecta: Primary Care. Pediatr Rev 2010; 31: e54–64.
3. Van Dijk FSS, Sillence DOO. Osteogenesis imperfecta: Clinical diagnosis, nomenclature and severity assessment. Am J Med Genet A 2014; 164: 1470–81.
4. Steiner R, Adsit J, Basel D. COL1A1/2-Related Osteogenesis Imperfecta. GeneReviews. 2013. DOI:NBK1295 [bookaccession].
5. Gooijer K, Rondeel JMM, van Dijk FS, Harsevoort AGJ, Janus GJM, Franken AAM. Bleeding and bruising in Osteogenesis Imperfecta: International Society on Thrombosis and Haemostasis bleeding assessment tool and haemostasis laboratory assessment in 22 individuals. Br J Haematol 2019. DOI:10.1111/bjh.16097.
6. Malfait F, Paepe A De. Bleeding in the heritable connective tissue disorders: Mechanisms, diagnosis and treatment. Blood Rev 2009; 23. DOI:10.1016/j.blre.2009.06.001.
7. Artoni A, Bassotti A, Marinelli B, et al. Hemostatic abnormalities in patients with ehlers□danlos syndrome. 2018; : 1–7.
8. Siegel BM, Friedman IA, Schwartz SO. Hemorrhagic disease in osteogenesis imperfecta Study of platelet functional defect. Am J Med 1957.
9. Hathaway WE, Solomons CC, Ott JE, Ott E. Platelet Function and Pyrophosphates in Osteogenesis Imperfecta. Blood 1972; 39.
10. Estes JW. Platelet size and function in the heritable disorders of connective tissue. Ann Intern Med 1968; 68: 1237–49.
11. Evensen SA, Myhre L, Stormorken H. Haemostatic studies in osteogenesis imperfecta. Scand J Haematol 1984; 33: 177–9.
12. Boender J, Kruip MJHA, Leebeek FWG. A diagnostic approach to mild bleeding disorders. Journal of Thrombosis and Haemostasis 2016; 14: 1507–16.
13. Pereira J, Quiroga T, Mezzano D. Laboratory assessment of familial, nonthrombocytopenic mucocutaneous bleeding: A definitive diagnosis is often not possible. Semin Thromb Hemost. 2008; 34. DOI:10.1055/s-0028-1104544.
14. F. Rodeghiero AT and GC. How to estimate bleeding risk in mild bleeding disorders. Journal of Thrombosis and Haemostasis 2007; 5: 157–66.
15. Deforest M, Grabell J, Albert S, et al. Generation and optimization of the self-administered bleeding assessment tool and its validation as a screening test for von Willebrand disease. Haemophilia 2015; 21: e384–8.

16. Punt MC, Blaauwgeers MW, Timmer MA, Welsing PMJ, Schutgens REG, van Galen KPM. Reliability and Feasibility of the Self-Administered ISTH-Bleeding Assessment Tool. TH Open 2019; 03. DOI:10.1055/s-0039-3400483.
17. Rodeghiero F, Tosetto A, Abshire T, et al. ISTH/SSC bleeding assessment tool: A standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders. Journal of Thrombosis and Haemostasis 2010; 8: 2063–5.
18. Rydz N, James PD. The evolution and value of bleeding assessment tools. Journal of Thrombosis and Haemostasis 2012; 10. DOI:10.1111/j.1538-7836.2012.04923.x.
19. Rodeghiero F, Tosetto A, Abshire T, et al. ISTH BAT:Supplementary Material To the Official Communication of the SSC. Journal of Thrombosis and Haemostasis 2011; 8: 1–21.
20. Elbatarny M, Mollah S, Grabell J, et al. Normal range of bleeding scores for the ISTH-BAT: Adult and pediatric data from the merging project. Haemophilia 2014; 20: 831–5.
21. Oakley I, Reece LP. Anesthetic implications for the patient with osteogenesis imperfecta. AANA J 2010; 78: 47–53.
22. Federici AB, Bucciarelli P, Castaman G, et al. The bleeding score predicts clinical outcomes and replacement therapy in adults with von Willebrand disease. Blood 2014; 123. DOI:10.1182/blood-2014-02-557264.
23. Keegan MT, Whatcott BD, Harrison BA. Osteogenesis imperfecta, perioperative bleeding, and desmopressin. Anesthesiology 2002; 97. DOI:10.1097/00000542-200210000-00039.
24. Langness U, Behnke H. Klinik und Genetik der Osteogenesis imperfecta*. Deutsche Medizinische Wochenschrift 1970; 95. DOI:10.1055/s-0028-1108437.
25. Wong RS, Follis FM, Shively BK, Wernly JA. Osteogenesis imperfecta and cardiovascular diseases. Ann Thorac Surg. 1995; 60. DOI:10.1016/0003-4975(95)00706-Q.
26. Rothschild L, Goeller JK, Voronov P, Barabanova A, Smith P. Anesthesia in children with osteogenesis imperfecta: Retrospective chart review of 83 patients and 205 anesthetics over 7 years. Paediatr Anaesth 2018; 28. DOI:10.1111/pan.13504.
27. Wood SJ, Thomas J, Braimbridge M v. Mitral valve disease and open heart surgery in osteogenesis imperfecta tarda. Br Heart J 1973; 35. DOI:10.1136/hrt.35.1.103.
28. Waters DD, Clark DW, Symbas PN, Schlant RC. Aortic and mitral valve replacement in a patient with osteogenesis imperfecta. Chest 1977; 72. DOI:10.1378/chest.72.3.363.
29. Morton ME. Excessive bleeding after surgery in osteogenesis imperfecta. British Journal of Oral and Maxillofacial Surgery 1987; 25. DOI:10.1016/0266-4356(87)90144-6.
30. Mondal RK, Mann U, Sharma M, Mondal RK, Mann U, Sharma M. Osteogenesis imperfecta with bleeding diathesis. Indian J Pediatr 2003; 70: 95–6.

31. Edge G, Okafor B, Fennelly ME, Ransford AO. An unusual manifestation of bleeding diathesis in a patient with osteogenesis imperfecta. Eur J Anaesthesiol 1997; 14: 215–9.
32. Faqeih E, Roughley P, Glorieux FH, Rauch F. Osteogenesis imperfecta type III with intracranial hemorrhage and brachydactyly associated with mutations in exon 49 of COL1A2. Am J Med Genet A 2009; 149A: 461–5.
33. Kastrup M, von Heymann C, Hotz H, et al. Recombinant factor VIIa after aortic valve replacement in a patient with osteogenesis imperfecta. Ann Thorac Surg 2002; 74: 910–2.
34. Paterson CR, Monk EA. Temporary brittle bone disease: association with intracranial bleeding. Journal of Pediatric Endocrinology and Metabolism 2013; 26: 417–26.
35. Sadler JE, Budde U, Eikenboom JCJ, et al. Update on the pathophysiology and classification of von Willebrand disease: A report of the Subcommittee on von Willebrand factor. Journal of Thrombosis and Haemostasis 2006; 4. DOI:10.1111/j.1538-7836.2006.02146.x.
36. Obaji S, Alikhan R, Rayment R, Carter P, Macartney N, Collins P. Unclassified bleeding disorders: Outcome of haemostatic challenges following tranexamic acid and/or desmopressin. Haemophilia 2016; 22. DOI:10.1111/hae.12811.
37. Kataoka T, Hoshi K, Ando T. Is the HAS-BLED score useful in predicting post-extraction bleeding in patients taking warfarin? A retrospective cohort study. BMJ Open 2016; 6. DOI:10.1136/bmjopen-2015-010471.
38. Kumbargere Nagraj S, Prashanti E, Aggarwal H, et al. Interventions for treating post-extraction bleeding. Cochrane Database of Systematic Reviews. 2018; 2018. DOI:10.1002/14651858.CD011930.pub3.
39. Bailleul-Forestier I, Berdal A, Vinckier F, de Ravel T, Fryns JP, Verloes A. The genetic basis of inherited anomalies of the teeth. Part 2: Syndromes with significant dental involvement. Eur J Med Genet. 2008; 51. DOI:10.1016/j.ejmg.2008.05.003.
40. Contaldo M, Luzzi V, Ierardo G, et al. Bisphosphonate-related osteonecrosis of the jaws and dental surgery procedures in children and young people with osteogenesis imperfecta: A systematic review. J Stomatol Oral Maxillofac Surg. 2020; 121. DOI:10.1016/j.jormas.2020.03.003.
41. Fraser IS, Mansour D, Breymann C, Hoffman C, Mezzacasa A, Petraglia F. Prevalence of heavy menstrual bleeding and experiences of affected women in a European patient survey. International Journal of Gynecology and Obstetrics 2015; 128. DOI:10.1016/j.ijgo.2014.09.027.
42. National Institute for Health and Care Excellence. Heavy menstrual bleeding: assessment and management | Guidance. Nice guidelines. 2021.
43. Hayward CPM. Diagnosis and management of mild bleeding disorders. Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program 2005. DOI:10.1182/asheducation-2005.1.423.

44. El-Hemaidi I, Gharaibeh A, Shehata H. Menorrhagia and bleeding disorders. Curr Opin Obstet Gynecol. 2007; 19. DOI:10.1097/GCO.0b013e3282f1ddbe.
45. Kadir RA, Economides DL, Sabin CA, Owens D, Lee CA. Frequency of inherited bleeding disorders in women with menorrhagia. Lancet 1998; 351. DOI:10.1016/S0140-6736(97)08248-2.
46. de Wee EM, Knol HM, Mauser-Bunschoten EP, et al. Gynaecological and obstetric bleeding in moderate and severe von willebrand disease. Thromb Haemost 2011; 106. DOI:10.1160/TH11-03-0180.
47. Kouides PA, Byams VR, Philipp CS, et al. Multisite management study of menorrhagia with abnormal laboratory haemostasis: A prospective crossover study of intranasal desmopressin and oral tranexamic acid. Br J Haematol 2009; 145. DOI:10.1111/j.1365-2141.2009.07610.x.
48. Knight M, Callaghan WM, Berg C, et al. Trends in postpartum hemorrhage in high resource countries: A review and recommendations from the international postpartum hemorrhage collaborative group. BMC Pregnancy Childbirth 2009; 9. DOI:10.1186/1471-2393-9-55.
49. Ruiter-Ligeti J, Czuzoj-Shulman N, Spence AR, Tulandi T, Abenhaim HA. Pregnancy outcomes in women with osteogenesis imperfecta: A retrospective cohort study. Journal of Perinatology 2016; 36. DOI:10.1038/jp.2016.111.
50. Rao R, Cuthbertson D, Nagamani SCS, et al. Pregnancy in women with osteogenesis imperfecta: pregnancy characteristics, maternal, and neonatal outcomes. Am J Obstet Gynecol MFM 2021; 3. DOI:10.1016/j.ajogmf.2021.100362.
51. Zhang WH, Alexander S, Bouvier-Colle MH, Macfarlane A. Incidence of severe pre-eclampsia, postpartum haemorrhage and sepsis as a surrogate marker for severe maternal morbidity in a European population-based study: The MOMS-B survey. BJOG 2005; 112. DOI:10.1111/j.1471-0528.2004.00303.x.
52. Chauleur C, Cochery-Nouvellon E, Mercier E, et al. Some hemostasis variables at the end of the population distributions are risk factors for severe postpartum hemorrhages. Journal of Thrombosis and Haemostasis 2008; 6. DOI:10.1111/j.1538-7836.2008.03168.x.
53. Buzaglo N, Harlev A, Sergienko R, Sheiner E. Risk factors for early postpartum hemorrhage (PPH) in the first vaginal delivery, and obstetrical outcomes in subsequent pregnancy. Journal of Maternal-Fetal and Neonatal Medicine 2015; 28. DOI:10.3109/14767058.2014.937698.
54. Prevention and Management of Postpartum Haemorrhage: Green-top Guideline No. 52. BJOG 2017; 124. DOI:10.1111/1471-0528.14178.
55. Veen CSB, van der Reijken IS, Jansen AJG, et al. Severe postpartum haemorrhage as first presenting symptom of an inherited bleeding disorder. Haemophilia 2019; 25. DOI:10.1111/hae.13846.

56. Shakur H, Roberts I, Fawole B, et al. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. The Lancet 2017; 389. DOI:10.1016/S0140-6736(17)30638-4.
57. Moenen FCJI, Nelemans PJ, Schols SEM, Schouten HC, Henskens YMC, Beckers EAM. The diagnostic accuracy of bleeding assessment tools for the identification of patients with mild bleeding disorders: A systematic review. Haemophilia. 2018; 24. DOI:10.1111/hae.13486.
58. Quiroga T, Mezzano D. Is my patient a bleeder? A diagnostic framework for mild bleeding disorders. Hematology / the Education Program of the American Society of Hematology. American Society of Hematology. Education Program. 2012; 2012. DOI:10.1182/asheducation.v2012.1.466.3798741.
59. Rodeghiero F, Castaman G, Tosetto A, et al. The discriminant power of bleeding history for the diagnosis of type 1 von Willebrand disease: An international, multicenter study. Journal of Thrombosis and Haemostasis. 2005; 3. DOI:10.1111/j.1538-7836.2005.01663.x.
60. Biss TT, Blanchette VS, Clark DS, et al. Quantitation of bleeding symptoms in children with von Willebrand disease: Use of a standardized pediatric bleeding questionnaire. Journal of Thrombosis and Haemostasis 2010; 8. DOI:10.1111/j.1538-7836.2010.03796.x.

Chapter
5

Chapter 6

Bleeding and bruising in Osteogenesis Imperfecta: Laboratory assessment in high- and low-scoring subgroups selected by a self-administered bleeding assessment tool from a cohort of 195 individuals with Osteogenesis Imperfecta

Submitted

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Abstract

Background Osteogenesis Imperfecta (OI) is characterised by bone fragility. Its features include easy bruising and haemorrhagic events without consistent clarification. Recently we described the clinical aspects of bleeding in a large cohort of 195 OI patients. The aim of this study is to find explanatory coagulation disorders with laboratory analysis in adult OI patients with a high bleeding score compared to OI patients with a low bleeding score.

Methods This study was conducted at the Expert Center for adults with OI in Isala, the Netherlands. The self-BAT (self-administered Bleeding Assessment Tool) was distributed among 328 OI patients, 195 (60%) of whom completed the tool. Eleven OI patients with high self-BAT bleeding scores were selected and compared with a random selection of OI patients with low bleeding scores. Routine coagulation testing consisted of haematocrit and platelet count, activated partial thromboplastin time (APTT), fibrinogen, Factor VIII activity and Von Willebrand factor (VWF) antigen and activity. Additionally platelet function (PFA-200), Bleeding time (IVY method) and thromboelastometry (ROTEM) was performed.

Results Two of the 11 high-scoring OI patients showed a prolonged bleeding time. Full blood count and analysis revealed one high-scoring OI patient with low levels of fibrinogen, while two other OI patients (one with a high score and one with a low score) had abnormal Factor VIII and/or Von Willebrand factor. Four of the 11 high-scoring OI patients and two of nine low-scoring OI patients displayed platelet function deviation through the PFA-200, accounting for 30% of the entire cohort. All ROTEM results were normal or inconclusive.

Conclusion No significant differences in coagulation parameters were found between OI patients with a high bleeding score and those with a low bleeding score. A clarifying underlying mechanism for the reported bleeding problems among OI patients could not be identified. Because of the relatively high percentage of deviating platelet function OI patients, it might be useful to monitor platelet function on a larger scale, possibly extended with platelet aggregation tests.

Introduction

Although Osteogenesis Imperfecta (OI) is commonly defined as 'brittle bones' disease, it has more characteristics, like blue sclerae, hearing loss, dental problems, ligamentous laxity and short stature. OI is to the result of a hereditary defect in collagen type I synthesis. Nowadays, there are various classifications, with that of van Dijk et al. being most commonly used [1]. The prevalence of OI is estimated at about 6.5 per 100,000 live births [2].

Easy bruising and bleeding are prominent features of some heritable disorders of the connective tissue and are most prominent in Ehlers-Danlos syndrome (EDS). Heritable disorders of the connective tissue can be a result of fragility of capillaries and the perivascular connective tissue, but also of clotting or platelet dysfunction [3]. It can also be associated with a disorder of vascular haemostasis or a defect in fibrinolysis [4].

Although EDS is clearly associated with bleeding disorders [5], the literature for OI in relation to bleeding disorders and their underlying mechanism is sparse and often outdated [6–9]. The first study of OI with an association to bleeding disorders dates back to 1957 and was done by Siegel et al. [6]. Even more than 60 years later, reference is still being made to these initial articles due to limited new research.

In 2018, the Isala Expertise Centre for adults with OI in Zwolle the Netherlands, conducted research into bleeding diathesis among OI patients for the first time since 1984, using a validated self-administered bleeding questionnaire (self-BAT) and modern laboratory techniques in 22 OI patients [10]. After this pilot study, self-BAT questionnaires were distributed among a large cohort of 328 OI patients, resulting in 195 available bleeding scores [11]. In this paper we report on extensive laboratory testing among 11 OI patients from this cohort with the highest bleeding scores versus a random sample of 9 OI patients with low (normal) scores on the self-BAT.

The aim of this study was to identify or exclude coagulation disorders in OI patients with the highest bleeding tendencies based on the self-BAT questionnaire in comparison to OI patients within the normal bleeding score range.

This study provides data on laboratory results in relation to bleeding tendency in a small group of adult OI patients. However, considering the precise selection process of the data, it might be extrapolated to the presence or absence of coagulation disorders in the whole OI population. This may lead to clinical guidelines regarding the increased bleeding tendency in OI, which is highly desirable.

Materials and methods

Study design

An explorative study was undertaken in the Expert Center for adults with OI, Isala Hospital, Zwolle, the Netherlands. The Medical Ethics Committee of the Isala Hospital, Zwolle, the Netherlands, confirmed that the Medical Research Involving Human Subjects Act did not apply (reference number: 200612). All patients with a clinical diagnosis of OI who were invited to take part in this study signed informed consent for participation.

Evaluation of bleeding tendency

The self-BAT is a self-administered bleeding assessment tool validated in Canada and the Netherlands [12,13] and is based on the International Society on Thrombosis and Haemostasis Bleeding Assessment Tool (ISTH-BAT)[14,15]. The 14 self-BAT domains cover self-reported events of epistaxis, cutaneous bleeding, minor wounds, haematuria, gastrointestinal bleeds, oral cavity bleeds, prolonged bleeding after trauma, surgeries or tooth extraction, menorrhagia, postpartum haemorrhage, muscle, joint and central nervous system bleeds, and other bleedings. Each domain scores from 0 (absence of bleeding symptoms) to 4 (symptoms requiring extensive medical intervention). The distinction between zero points and 1 point is of critical importance since a score of 1 means that the symptom meets the minimal criteria defining a significant bleeding. This distinction between the different scores is described by the ISTH Scientific and Standardization Committee [16] and was independently determined by two trained researchers (KG and GM). Conflicting scores were reassessed and resolved by consensus. A total bleeding score (range 0-56) was calculated by the sum of scores for all BAT domains. A total bleeding score in men ≥ 4 and in women ≥ 6 was defined by Deforest et al. and Punt et al. as an increased bleeding tendency [12,13]. In this study, a total bleeding score of >6 was considered an increased bleeding tendency in women.

Study population and selection procedure

In total, 328 patients with a clinical diagnosis of OI, according to the classification of van Dijk and Sillence [1] known in our centre, were invited to digitally fill in the self-BAT questionnaire between October 2019 and August 2020 (Figure 1). In total, 195 of 328 (60%) questionnaires were filled in and included in the study [17].

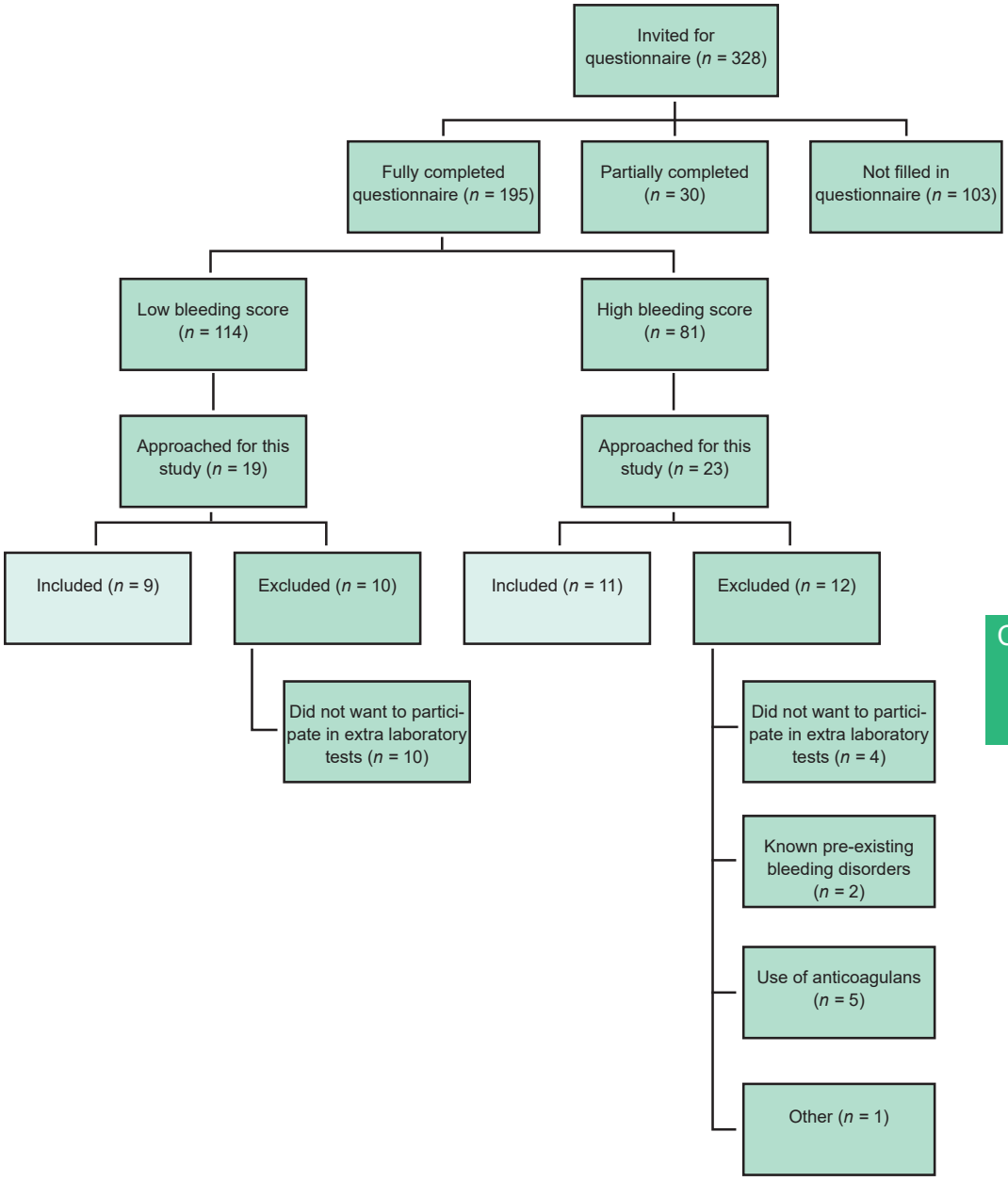

Figure 1 *Selection procedure of study participants*

From the available questionnaires, 23/81 OI patients with the highest self-BAT bleeding score were selected and invited by telephone for laboratory testing. For these additional blood tests, a separate consent was requested. For comparison purposes, a random sample was taken of 19/114 patients with a score within the normal range of the self-BAT questionnaire. Exclusion criteria were: known pre-existing bleeding diseases, renal or liver diseases, and use of medication that could interfere with haemostasis. We also excluded relatives. Since our centre has a focus on adult OI patients, we included only adult patients ≥ 18 years. Medication use (especially use of anticoagulants) was reaffirmed, as well as liver- and renal dysfunction.

Evaluation of bleeding time

The IVY method was done as additional test to assess platelet function in combination with possible vessel wall abnormalities [18]. The bleeding time test was purposely determined by the same researcher specially trained in the procedure. A fully automatic instrument (Surgicutt adult; depth: 1.0 mm and length: 5.0 mm) was used to determine the bleeding time. Furthermore, a blood pressure cuff (Speidel & Keller Stabil 3), filter paper to staunch the wound, and a timer were used. An 5mm incision was made on the volar side of the forearm lengthwise, approximately 6 cm below the elbow crease. Time was ended when there was no further bleeding after blotting. After 10 minutes of bleeding, the procedure was stopped due to a prolonged bleeding time [18].

Blood sampling and laboratory methods

Blood was collected through venepuncture of the cubital vein in Vacutainer blood collection tubes (Becton Dickinson; Vianen, the Netherlands) containing 0.109M, 3.2% trisodium citrate or dipotassium ethylene diamine tetraacetic acid (K2EDTA) as anticoagulant. All tests have been standardised using defined reference ranges as criteria for pathological results. The laboratory is subject to national and international external quality assessment in the field of haemostasis and thrombosis.

A full blood count was performed on an automated modular haematology system (Sysmex XN-9000; Sysmex Europe, Etten-Leur, the Netherlands) for determining haematocrit and platelet count. Activated partial thromboplastin time (APTT), fibrinogen, FVIII activity and von Willebrand factor (VWF) antigen and activity were determined on a Sysmex CS-2500 automated analyser based on turbidimetry.

Platelet function was tested on an automated platelet function analyser (PFA-200; Siemens Healthcare Nederland B.V. Den Haag, the Netherlands). It measures the ability of platelets to adhere and aggregate under high shear stress to a membrane covered with a collagen and epinephrine or collagen and ADP [10].

Fibrinolysis was determined through semi-automated thromboelastometry (ROTEM® sigma; Werfen Netherlands, Breda, the Netherlands). Clot formation and lysis were determined after adding reagents activating the internal or external coagulation pathway. Maximum lysis (ML) was optically measured as the percentage reduction of clot firmness within 60 minutes. Other ROTEM® parameters such as clotting time (CT), clot formation time (CFT), and maximum clot firmness (MCF) were also analysed.

Statistical analysis

Variables were tested for normal distribution using the Shapiro Wilk test and Q-Q plots. Differences in means comparing OI patients with the highest bleeding scores versus normal bleeding scores were determined for normally distributed data using the independent *t* test (CI 95%). Non-normal distributed data were tested using the Mann-Whitney test (CI 95%). All the data obtained from the bleeding time research and laboratory blood sampling were collected and analysed in SPSS 24.

Results

Clinical characteristics

Of the 23 patients with high self-BAT-scores who were invited to participate in the study, four patients did not want to participate in additional laboratory tests. Twelve patients were excluded: two patients because of known pre-existing Von Willebrand disease, five patients due to use of anticoagulants, and one patient because of a long travelling time (>5h). This resulted in 11 patients who were included in the group with the highest bleeding score on the self-BAT questionnaire. This subgroup consisted of nine females and two males, with a mean age of 44.5 years (SD 12.1). Ten patients in this group had OI type 1, one patient in this group had OI type 4.

Of the 19 patients with low bleeding scores on the self-BAT, ten did not want to participate. The subgroup of nine patients with a low bleeding score consisted of five males and four females with a mean age of 37.4 years (SD 13.8). Seven patients had OI type 1, one patient OI type 3, and one patient OI type 4 (Table 1).

The selection process resulted in laboratory tests in 20 individuals with equal male/female ratios and about the same average age compared to the total population of 195 OI patients (43.7 years; SD 15.6). All participants were of Caucasian origin.

Table 1 *Overview of participants with high versus low bleeding scores*

		OI types			Total
		1	**3**	**4**	
High score	Female	8	0	1	*11*
	Male	2	0	0	
Low score	Female	2	1	1	*9*
	Male	5	0	0	
Total		*17*	*1*	*2*	

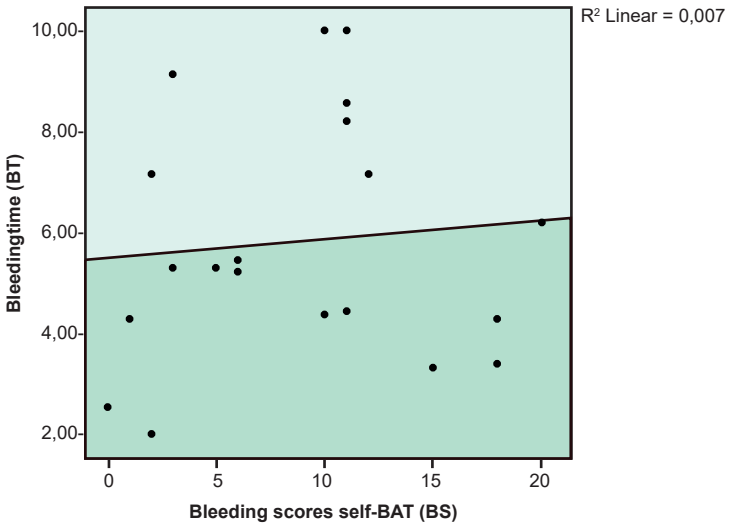

Figure 2 *Correlation between bleeding scores self-BAT and bleeding time*

Laboratory results

Bleeding time scores

The bleeding time scores of 2/20 patients were prolonged (>10 min.), in 3/20 cases the bleeding time was between 8 and 10 minutes and can be interpreted as being questionable (17) (Table 2). Correlation between self-BAT score and bleeding time was negligible (R^2 = 0.007) (Figure 2). No statistically significant difference was found between the group with the highest bleeding scores on the self-BAT versus the group with normal bleeding scores on the self-BAT.

Routine coagulation parameters

Hb, MCV, Ht, INR, Platelet count, aPTT, Fibrinogen, FVIII and VWF levels were analysed. Results of Ht, INR, platelet counts, and aPTT measurements were normal and therefore will not be discussed further. Fibrinogen was abnormal in 1/20 patient; this patient had no other abnormalities in the blood tests. High FVIII activity (>150%) was found in 3/20 patients.

FVIII, VWFag and VWFact results were greatly reduced in one case. However, after reassessment, no abnormalities were found. Low normal results for FVIII, VWFag and VWFact were found in three cases, for one of which a re-determination had to be done.

Hb levels were significantly lower for the group with the highest scores on the self-BAT (p = 0.017). Additionally, Ht levels were significantly lower for the group with the highest scores on the self-BAT (p = 0.014). But when Ht and Hb levels were corrected for gender, there was no statistical significance between both groups.

No statistically significant difference was found for MCV, INR, platelet count, aPTT, fibrinogen, FVIII, VWFag and VWFact levels between the group with the highest bleeding scores on the self-BAT versus the group with normal bleeding scores of the self-BAT.

Platelet function

Deviating platelet function was detected in 6/20 cases (30%). Of the six deviating scores, one was strongly deviated and this remained so even after re-determination. EPI levels were increased in 4/11 cases of the group with the highest self-BAT scores, no abnormalities were found in the group with normal bleeding scores on the self-BAT. ADP levels were increased in 4/11 cases of the group with the highest bleeding scores on the self-BAT and 2/9 cases of the group with the normal bleeding scores. No statistically significant difference was found for EPI and ADP levels between the group with high versus normal bleeding scores of the self-BAT.

Table 2 *(part1)*

Patient characteristics and laboratory measurements

Patient	BS		Age (years)	Gender	OI type	BT	Ht	Hb	MCV	INR	Platelet count
1	0	***low***	35	M	1	2.58	0.44	9.2	90.2	1.0	260
2	1	***low***	66	M	1	4.31	0.44	9.1	93.4	1.0	304
3	2	***low***	27	M	1	2.05	0.46	9.5	85.8	1.2	224
4	2	***low***	23	M	1	7.17	0.45	10.1	83.0	1.0	207
5	3	***low***	25	F	1	9.13	0.43	8.9	86.1	1.0	245
6	3	***low***	49	M	1	5.33	0.43	9.1	90.7	1.0	344
7	5	***low***	45	F	4	5.3	0.44	9.2	93.5	1.0	254
8	6	***low***	36	F	1	5.26	0.39	8.2	94.7	1.1	218
9	6	***low***	31	F	3	5.45	0.37	7.6	92.8	1.1	239
10	10	***high***	33	F	1	**>10**	0.4	8.6	91.8	1.0	279
11	10	***high***	33	M	1	4.41	0.44	9.7	85.5	1.0	320
12	11	***high***	34	F	1	8.23	0.37	7.5	88.8	1.0	212
13	11	***high***	47	F	4	4.45	0.41	8.1	92.6	1.0	252
14	11	***high***	60	F	1	8.57	**0.41**	8.8	92.4	1.1	195
15	11	***high***	31	F	1	**>10**	**0.34**	7.1	86.6	1.0	233
16	12	***high***	46	F	1	7.16	0.35	7.3	92.3	1.0	168
17	15	***high***	63	M	1	3.37	0.42	8.6	96.1	1.0	227
18	18	***high***	61	F	1	3.45	0.38	7.7	94.5	1.0	244
19	18	***high***	40	F	1	4.3	0.39	8.2	87.9	1.0	156
20	20	***high***	41	F	1	6.22	0.4	7.6	82.4	1.0	331

Reference ranges: aPTT: 20-35 s; BT:<10min; INR: ; Fibrinogen: 2-4 g/l; FVIII: 60-150%; Hb: 7,5 – 10 mmol/L (F), 8.5 – 11.0 mmol/L (M); Ht: 0.36 – 0.47 l/l (F), 0.41 – 0.50l/l (M); MCV: 82-100 fl; Platelet count: 150-400 x 109/l; PT: 0.9-1.1 s.
Abbreviations: aPTT, activated partial thromboplastin time; BS, bleeding score; BT, bleeding time; CT, clotting time; F, female; FVII, factor VIII; Hb, hemoglobin; Ht, hematocrit; INR, international normalized ratio; M, male; MCF, maximum clot firmness; OI, Osteogenesis Imperfecta; PFA-200, Platelet Function Analyser- 200; PT, prothrombin time; ROTEM: Thromboelastogram; VWF, von Willebrand factor.

Table 2 *(part2)*

Patient characteristics and laboratory measurements

Patient	aPTT	Fibrinogen	FVIII	VWF	PFA-200	Rotem
1	25	2.6	90	Normal	Normal	Normal
2	26	3.1	117	Normal	Normal	Normal
3	24	2.3	191	Normal	Normal	Low normal fibrinogen
4	28	2.5	**25**	Strongly reduced	Normal	CT intem prolonged
5	22	3.0	106	Normal	Normal	Normal
6	24	3.0	188	Normal	Abnormal	Normal
7	29	3.3	100	Normal	Abnormal	CT intem prolonged
8	28	**1.7**	114	Normal	Normal	Normal
9	27	2.8	145	Normal	Normal	Normal
10	30	2.5	**73**	Normal	Normal	CT intem prolonged
11	25	2.7	154	Normal	Strongly abnormal	Normal
12	25	3.1	120	Normal	Normal	Normal
13	26	3.6	112	Normal	Normal	Normal
14	25	2.8	131	Normal	Normal	Normal
15	24	2.5	114	Normal	Abnormal	Normal
16	28	4.2	178	Normal	Normal	Normal
17	28	3.2	91	Low normal	Normal	CT intem prolonged
18	26	3.9	113	Normal	Abnormal	Normal
19	27	2.5	90	Low normal	Abnormal	Normal
20	27	3.8	116	Normal	Normal	Normal

Clotting (formation) time, firmness and fibrinolysis

All Extem results for CT, CFT and MCF fell within the reference ranges. ExtemML results were abnormal in 5/20 cases.

ExtemCFT results were significantly shortened for the group with the highest bleeding scores on the self-BAT (p = 0.043). ExtemMCF results were significantly higher for the group with the highest bleeding scores on the self-BAT (p = 0.041).

Results for IntemCT were prolonged in 4/20 cases. IntemCFT results were shortened in 9/20 cases. IntemMCF results all fell within the reference ranges. IntemML results were abnormal in 3/20 cases. IntemCFT results were significantly shortened for the group with the highest bleeding scores on the self-BAT (p = 0.027). In 1/20 cases, AptemCT result was prolonged. AptemCFT results were shortened in 3/20 cases. AptemMCF results all fell within reference ranges. AptemML results were abnormal in 3/20 cases.

AptemCFT results were significantly shortened for the group with the highest bleeding scores on the self-BAT (p = 0.023). AptemMCF results were significantly higher for the group with the highest bleeding scores (p = 0.046). Signs for hyperfibrinolysis were negligible.

Discussion

Patients with OI are believed to have an increased risk of bleeding symptoms. However, an underlying clarification has not yet been found. In this study we compared 11 adult OI patients with a high bleeding score to 9 OI patients with a normal/low bleeding score. A total of 23 laboratory test variables were analysed. No significant differences between the two groups were found. A range of mild abnormalities in the total group of 20 OI patients were found, most noticeable being abnormal platelet function in 30% of the cases, regardless of the bleeding score.

The first literature on affected platelet function in OI is dated 1957 by Siegel et al. [6]. Furthermore, Estes et al. described large platelets [8] and Hathaway et al. observed abnormalities in platelet function [7]. In patients with OI, the impaired biosynthesis of collagen could potentially disrupt platelet function. Artoni et al. speculated that an altered structure of the vessel wall due to abnormal collagen biosynthesis may lead to activation and exhaustion of the platelets [5]. A comparable mechanism is decribed by Boneu et al. in 1987, describing the role of red blood cells in platelet-vessel

wall interaction and their control of bleeding time [19]. Testing of platelet function comprises a crucial element of haemostasis assessment, particularly for investigations into bleeding and/or bruising. Nowadays, the Platelet Function Assay is the most utilised primary haemostasis-screening test system available [20]. It might be useful to monitor PFA-200 results in a larger sample, possibly extended with platelet aggregation tests.

Similarly to the study of Leguillier et al.[21], we ruled out that bleeding symptoms in patients with OI are associated with VWD based on FVIII and VWF levels, and we confirmed normal levels for VWFag and VWFact in our study population. Although Leguillier et al. [21] recently found a statistical significance for VWFag and VWFact levels between children with a high versus low bleeding score, we could not identify this in our study. Their examination was based on VWF as marker of endothelial dysfunction in vascular disease [21].

Despite the thorough patient selection, this study contains several limitations regarding sample size and selection. The study sample was rather small, although the group size of 20 was expected to be sufficient in this explorative study of a rare disease. A more equal male/female distribution between the two opposite groups (low vs. high) would be preferred in future studies. Limiting the self-BAT score of the "low" control group to a maximum of two or three points should be considered. In the current study, two female participants were enrolled in the group with "low" bleeding scores while they scored six on the self-BAT. However, we believe this study still contributes to the sparse knowledge on bleeding tendency in OI patients through the results of extensive performed laboratory tests in 20 OI patients.

Conclusion

Comparing two opposite OI groups regarding their bleeding scores, both extracted from a large OI population, extensive laboratory testing did not show significant differences between the groups and did not result in finding an underlying mechanism for the reported bleeding problems in OI patients. Interestingly, PFA-200 results were abnormal in 30% of the OI patients. Monitoring PFA-200 results in a larger patient group should be considered in further studies. The results of this study are not conclusive enough to draw up guidelines for clinical practice regarding bleeding tendency in OI patients.

References

1. Van Dijk FSS, Sillence DOO. Osteogenesis imperfecta: Clinical diagnosis, nomenclature and severity assessment. Am J Med Genet A 2014; 164: 1470–81.
2. Steiner RD, Basel D. COL1A1 / 2 Osteogenesis Imperfecta. GeneReviews® - NCBI Bookshelf 2005.
3. Malfait F, Paepe A De. Bleeding in the heritable connective tissue disorders: Mechanisms, diagnosis and treatment. Blood Rev 2009; 23. DOI:10.1016/j.blre.2009.06.001.
4. Boender J, Kruip MJHA, Leebeek FWG. A diagnostic approach to mild bleeding disorders. Journal of Thrombosis and Haemostasis 2016; 14: 1507–16.
5. Artoni A, Bassotti A, Marinelli B, et al. Hemostatic abnormalities in patients with ehlers-danlos syndrome. 2018; : 1–7.
6. Siegel BM, Friedman IA, Schwartz SO. Hemorrhagic disease in osteogenesis imperfecta Study of platelet functional defect. Am J Med 1957.
7. Hathaway WE, Solomons CC, Ott JE, Ott E. Platelet Function and Pyrophosphates in Osteogenesis Imperfecta. Blood 1972; 39.
8. Estes JW. Platelet size and function in the heritable disorders of connective tissue. Ann Intern Med 1968; 68: 1237–49.
9. Evensen SA, Myhre L, Stormorken H. Haemostatic studies in osteogenesis imperfecta. Scand J Haematol 1984; 33: 177–9.
10. Gooijer K, Rondeel JMM, van Dijk FS, Harsevoort AGJ, Janus GJM, Franken AAM. Bleeding and bruising in Osteogenesis Imperfecta: International Society on Thrombosis and Haemostasis bleeding assessment tool and haemostasis laboratory assessment in 22 individuals. Br J Haematol 2019. DOI:10.1111/bjh.16097.
11. Heidsieck GM, Gooijer K, Harsevoort GJ, et al. Bleeding and bruising in Osteogenesis Imperfecta: Laboratory assessment in extreme scorings with a self bleeding assessment tool in 195 individuals with Osteogenesis Imperfecta. Submitted.
12. Deforest M, Grabell J, Albert S, et al. Generation and optimization of the self-administered bleeding assessment tool and its validation as a screening test for von Willebrand disease. Haemophilia 2015; 21: e384–8.
13. Punt MC, Blaauwgeers MW, Timmer MA, Welsing PMJ, Schutgens REG, van Galen KPM. Reliability and Feasibility of the Self-Administered ISTH-Bleeding Assessment Tool. TH Open 2019; 03. DOI:10.1055/s-0039-3400483.

14. Rodeghiero F, Tosetto A, Abshire T, et al. ISTH/SSC bleeding assessment tool: A standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders. Journal of Thrombosis and Haemostasis 2010; 8: 2063–5.
15. Rydz N, James PD. The evolution and value of bleeding assessment tools. Journal of Thrombosis and Haemostasis 2012; 10. DOI:10.1111/j.1538-7836.2012.04923.x.
16. Rodeghiero F, Tosetto A, Abshire T, et al. ISTH BAT:Supplementary Material To the Official Communication of the SSC. Journal of Thrombosis and Haemostasis 2011; 8: 1–21.
17. Gooijer K, Heidsieck G, Harsevoort Arjan, Bout D, Janus G, Franken A. Bleeding assessment in a large cohort of patients with Osteogenesis Imperfecta. Submitted.
18. Russeau AP, Vall H, Manna B. Bleeding Time. 2023.
19. Boneu B, Fernandez F. The Role of the Hematocrit in Bleeding. Transfus Med Rev 1987; 1. DOI:10.1016/S0887-7963(87)70020-0.
20. Favaloro EJ, Bonar R. An update on quality control for the PFA-100/PFA-200. Platelets 2018; 29. DOI:10.1080/09537104.2018.1475636.
21. Léguillier T, Favier R, Harroche A, et al. Assessing bleeding risk in 18 children with Osteogenesis imperfecta. Br J Haematol. 2021; 192: 785–8.

Chapter 7

Discussion with future perspectives

This chapter presents the conclusions of this thesis and discusses the key findings in a broader perspective. This thesis focuses on quality of life in Osteogenesis Imperfecta (OI) and bleeding tendency. Both topics are relatively understudied extra-skeletal features of OI. Implications for clinical care and directions for future research are outlined.

The two topics are addressed and discussed in two parts, based on the findings of this thesis and the current literature, in line with the research questions.

Part 1. Quality of life in Osteogenesis Imperfecta

What is the quality of life in people with OI?

People with OI rate their perceived general health significantly lower than the control population [1,2], as we showed in Chapter 2. This is in line with other studies investigating general health in OI [3–7]. However, perceived general health is not the same as quality of life. Quality of life is a multidimensional concept that captures broad topics such as functional status, well-being and general health assessments [8–10]. There are no agreed definitions of what dimensions should be measured when assessing quality of life, but it is well established that quality of life should be assessed by the patients themselves and that it is a multidimensional construct [11]. These various dimensions of quality of life, combined with the diversity of the different OI types, present a challenge in finding the right answer to the question “What is quality of life in OI?”. Despite these challenges, we were able to evaluate several aspects of quality of life in comparison to reference populations.

Functional status

Regardless of the type of OI, adults with OI scored significantly worse than controls on all physical domains of quality of life (Chapter 2). There was a significant difference in physical functioning between the types of OI, with physical limitations and problems being more pronounced in the severe type of OI (type 3). The significantly worse physical domains in OI compared to reference populations are confirmed by other studies on quality of life in adult OI patients [3,5,7,12,13]. Functional quality of life includes not only physical functioning, but also role-limitations due to emotional problems and social functioning. Measurements of physical function relate to limitations in daily activities such as climbing stairs, washing and dressing, or lifting groceries, while measuring role-limitations relates to limitations in work and other daily functions, and measures of social function relate to the impact on social activities.

In Chapter 2, the quality of life in OI at specific adult ages was described – for the first time in literature as far as we know. These measurements at different ages provide an opportunity to see trend lines and offer timed interventions. Instead of an increase in physical limitations at older ages, as was seen in the control group, physical limitations in OI type 3 progressively decreased to a level where there is no longer a significant difference with the healthy control group. The same trend is seen for social functioning and role-limitations due to both physical and emotional health problems. This phenomenon has also been described in previous semi-structured qualitative interviews with patients having OI and their parents on the transition from adolescence to adulthood in North America [14] and the UK [15].

This may support the theory that people with severe OI types are increasingly able to cope with their limitations in adult life, which may be beneficial for their social life, and ultimately beneficial for their mental health [3]. This highlights the need for taking physiotherapeutic and occupational therapy interventions to improve functional status, particularly at an early age.

Well-being

Well-being is a dimension of quality of life that includes pain, vitality and mental health [16]. A commonly reported symptom in OI is pain (Chapter 2). All patients with OI, regardless of the type of OI, experienced significantly more pain than the control group. On a scale of 1 to 100 points, patients with OI scored on average 17 points lower than the control group (Chapter 2). Pain can be either acute or chronic and can be caused by fractures or scoliosis [17,18]. Pain is a prominent issue in OI, having a major impact on quality of life [19–22]. Also in other connective tissue diseases pain is known to be associated with psychological problems [23,24]. Some authors state that pain and fatigue are the best predictors of quality of life in chronically ill patients [20,25]. Chapter 2 outlines that pain is significantly worse in people with OI compared to control populations, and that people with different types of OI do not differ significantly in their level of pain. This means that the type of OI does not determine whether a person has more pain, but that it varies from patient to patient. This is confirmed in other studies of adult OI patients [3–6,13], suggesting that it is helpful to assess a person's pain at regular points in time, regardless of OI type.

Among the mental dimensions of quality of life (Chapter 2), it is striking that people with OI type 1 score significantly lower than the control population [1,2]. However, this difference is small: on a scale of 1 to 100 points, patients with OI type 1 score 3.2 points lower than the control population, and type 1 patients aged 35-54 years score 6.4 points lower than the control population. For the other types of OI and other specific age groups, there was no difference in mental health between peo-

ple with OI and the control population. This suggests that disease severity and additional physical limitations do not automatically result in lower perceived mental health. Nor does a milder form of the disease lead to better mental health, as type 1 OI is considered to be relatively mild. This points to a well-known phenomenon known as the “disability paradox”, where quality of life is not entirely determined by physical limitations, but is much broader and includes, for example, one’s world view, social context, and social relationships [26,27].

There may be an increased risk of mental health problems in diseases with long-term physical limitations. In Ehlers-Danlos syndrome, a similar collagen disease with long-term physical limitations, increased anxiety and depression were found [28]. Several other long-term conditions with physical limitations have shown increased anxiety and depression [29,30].

People with OI face various challenges that may require psychological counselling and support, such as reproductive decision-making. The recurrence risk of OI in offspring is 50% for patients with autosomal dominant OI variants [31]. In rare cases of OI, with an autosomal recessive inheritance, the recurrence risk is low (but may be higher in consanguineous families). Before becoming pregnant, individuals may wish to receive genetic counselling about the risk of having a child with OI and the reproductive options available, including not having children, pre-implantation genetic testing, prenatal diagnosis (chorionic villus sampling or amniocentesis), sperm/egg donation, adoption or accepting the genetic risk [32]. Several studies have shown a positive correlation between the ability to have offspring and satisfaction with quality of life in both men and women and across different cultures [33]. Having a genetic disorder or being a carrier (couple) has a strong impact on the reproductive decisions, and if parents feel that they cannot provide adequate care and dedication to a child with OI, this may affect their desire to have children [34]. Decisions about reproductive options, such as pre-implantation genetic testing or prenatal DNA-diagnostics, are psychologically demanding and feelings of anxiety are commonly expressed [35–37]. Besides counselling on reproductive decisions, patients with OI may also want to be informed about the genetic risks for other family members.

What is the impact of fatigue on daily functioning in people with OI compared to control populations?

Fatigue is an important factor reducing functional quality of life in individuals with OI (Chapter 3). In addition, frequent fractures, reduced muscle strength [38], reduced pulmonary function [39,40] and cardiological comorbidities [41–43] can also impair functional quality of life. A wide range of interventions are available to improve functional quality of life and reduce the impact of impairing factors, even in the

milder forms of OI (types 1 and 4). The best methods to improve the physical domains of quality of life in OI have not yet been specified in detail. In general terms, physical domains of quality of life can be improved by physical training [44,45], surgery [46], rehabilitation, and occupational therapy [44,46–48]. The most appropriate intervention needs to be considered at the individual patient level.

Fatigue is often a major source of disability and is often reported as one of the most severe symptoms by patients with significant disease [49–54]. However, fatigue in OI has not been studied thoroughly. The studies that have been conducted also suggest that the quality of life of people with OI is negatively affected by functional limitations due to tiredness and fatigue [55–57].

In Chapter 3 we looked at the level of fatigue in people with OI, comparing the level of fatigue in people with OI with a healthy American and a healthy Dutch control population [58,59]. A significant difference was found between the OI group and the control population. The differences in scores between the OI cohort and the control population also exceeded the Minimal Clinically Important Difference (MCID) values that have been determined for chronic patient groups with systemic lupus erythematosus and rheumatoid arthritis [60,61]. The MCID refers to the smallest difference in a score that is considered important for the patient [62].

Part 2. Bleeding and bruising in Osteogenesis Imperfecta

Bleeding and bruising is a common complaint of OI patients, but it is not clearly addressed in the literature. Chapters 4, 5 and 6 of this thesis have attempted to objectify and clarify increased bleeding tendency and bruising in OI.

What is the prevalence of bleeding tendency in OI compared to a control population?

Chapter 5 states that 42% of patients with OI have a history of bleeding, which is more common than in the reference population [63]. This is in line with earlier estimates that persons with OI have more problems with bleeding [64,65]. In addition, potentially life-threatening bleeding occurred in 23% of the total cohort of OI patients (Chapter 5). Bleeding tendency is an umbrella term for experiencing bleeding symptoms more than normal. Severe bleeding requiring a major medical intervention, i.e. surgery to stop a bleeding, and/or a blood transfusion is called bleeding that is potentially life-threatening. Normal bleeding tendency has been established previously in studies [63,66]. A number of case report studies and a very limited number of cohort studies have reported varying degrees of bleeding in OI patients, ranging from minor bruising to life-threatening bleeding [65,67–73].

Prevalence of bleeding in a large cohort such as the one in Chapter 5 has never been studied. However, recent studies have looked at bleeding around pregnancy [74], confirming the increased risk of bleeding around pregnancy for patients with OI. An increase in the incidence of major bleeding during surgery in children has also recently been described [75].

What are the clinical manifestations of bleeding tendency in OI?

Chapter 5 shows that bleeding in OI typically occurs as spontaneous or easy bruising, prolonged bleeding after trauma or surgery, and excessive bleeding during menstruation. Post-extraction bleeding and gastrointestinal bleeding have also been reported. Spontaneous and easy bruising is a symptom of OI that is often mentioned by patients in the consulting room. This is often associated with concerns about bleeding during or after surgery. There are case reports in the literature of bleeding events with serious complications due to aneurysms [70,76–78]. These complications were not found in our study.

Chapter 5 evaluates all the different bleeding events and shows that abnormal bleeding events occur much more frequently than would be expected in a control population. The self-reported questionnaire used was analysed to identify clinically relevant bleeding symptoms. The underlying mechanism was not readily apparent from the symptoms. By focusing on clinically relevant bleeding symptoms, it was possible to estimate the severity of the bleeding tendency (Chapter 5).

Which bleeding events are most clinically relevant in OI?

The relevance of bleeding events in OI can be determined by considering the types of events that lead to bleeding. People with OI experience many events that can cause bleeding, including fractures, corrective surgeries for bone deformities, and tooth extractions due to dentinogenesis imperfecta. While this may lead to a higher number of reported bleeding events compared to the healthy population, it also raises the question of why bleeding occurs so frequently in OI. Assessing the severity of these bleeding events is key in determining whether precautions should be taken during procedures like surgery or tooth extraction.

In addition to these commonly reported bleeding events, there are also cases of intracranial bleeding after head injury that result in severe complications [79]. While these events were not reported in our study, they are highly relevant and require prompt medical attention. Based on our study outcome (Chapter 5), we recommend that individuals with OI who experience even minimal head trauma should receive a CT scan to exclude fractures and post-traumatic brain injury. Treatment for heavy menstrual bleeding might also be considered proactively with medication like desmopressin

and/or tranexamic acid to reduce bleeding and improve quality of life. Ultimately, by understanding the types of events that lead to bleeding in OI, medical professionals can take appropriate measures to prevent and treat these bleeding events.

Is diagnostic testing for bleeding disorders indicated?

The tendency to bleed is complex and can be caused by several factors. Previous studies on the tendency to bleed were not conclusive [64,80], but were also carried out during a period in which the laboratory equipment was less advanced.

Several mechanisms have been proposed to explain the bleeding tendency in OI. Our theory is that the defective collagen in OI leads to an abnormal structure and function of the vessel wall, resulting in increased fragility and susceptibility to bleeding (Chapter 5). Another hypothesis is that the altered extracellular matrix in OI affects platelet function and activation, leading to impaired haemostasis. However, these theories could not be confirmed by the studies in Chapters 4 and 6.

Diagnostic tests were performed in Chapters 4 and 6. The screening of a random cohort was first performed to objectify the bleeding tendency in Chapter 4, and later on, based on the bleeding questionnaire in the most frequent bleeders, the possible causes were investigated in the laboratory (Chapter 6). The latter was done to maximize the probability of detection. This is also reflected by the fact that we were able to pick out the people with von Willebrand disease who were expected to be found, based on the background incidence in Dutch society [81]. However, in addition to these findings (not related to OI), no specific causes were found in the laboratory that could clearly explain the bleeding tendency in OI. There is also no clear evidence in the literature that a specific laboratory test should be used for measuring the bleeding tendency in OI patients. Therefore, we believe that diagnostic testing is for now not possible.

What can be learned from therapeutic considerations in other mild bleeding disorders?

As explained in Chapter 5, there are several bleeding events that actually carry a significant risk. In surgery, pregnancy and tooth extraction, bleeding has progressed from being inconvenient to potentially life-threatening. There are many therapeutic considerations in general in the literature for controlling the bleeding in these events. However, they are not written specifically for OI, nor are they based on the underlying problems causing the increased bleeding tendency. This makes them potentially inappropriate and perhaps unnecessary. However, interventions that have little to no side effects can well be used in high-risk events for people with OI, such as the use of desmopressin or desmopressin and/or tranexamic acid for heavy menstrual bleeding (Chapter 5).

Recommendations for clinical practice

Based on the studies presented in this thesis the following recommendations were formulated:

Facilitate follow-up on quality of life using Patient-Reported Outcome Measurements (PROMS)

Chronic conditions such as Osteogenesis Imperfecta (OI) have a long-term impact on the lives of patients. In caring for people with chronic disease, quality of life is an important component as it reveals the personal experience and impact of having an incurable disability [82]. Patient-Reported Outcome Measurements (PROMS) questionnaires can be used for monitoring health, functional status and quality of life throughout the disease process. The measurements allow healthcare providers to choose the best treatment in collaboration with the patient and to monitor disease progression. PROMs can facilitate communication between patients and caregivers as well as help patients to better understand and manage their health.

For instance, at the OI Expert Centre in Isala hospital in Zwolle, the Netherlands, the results of the individual PROMS can be viewed and implemented directly in the consulting room. The results of Chapter 2 can be used to compare an individual OI patient with the entire cohort of people with OI and with a healthy control population. Through shared decision-making, so together with the patient, aspects of quality of life that need more attention can be identified and assessed (integrated care interventions).

Assess quality of life at different ages

Chapter 2 distinguishes quality of life at different ages. Adolescents who have just left their parents' home do not face the same problems as older adults with OI. For stressful events related to reproductive decisions, psychological counselling may be helpful [32,35,83]. It is important to see each patient in their unique stage of life and explore what is needed to improve quality of life [84–86]. It is also important that new treatments have a positive impact on quality of life.

Stimulate multidisciplinary treatment and (inter)national cooperation

Measuring quality of life frequently has several advantages. The knowledge gained on quality of life and how it can be improved can be used to develop guidelines and to write patient leaflets about treatment options, care and management of OI. Not only does quality of life depend on many factors, but the patients also differ from each other and have many different symptoms. It is therefore important to continue to measure quality of life at an individual level and to tailor treatment accord-

ingly with the appropriate medical specialist. This can be anticipated in a multidisciplinary approach, preferably in an OI Expert Centre.

Many patients with OI are seen in the OI Expert Centre where quality of life records are registered, therefore much knowledge has been gained about what problems may occur and what treatment is preferred. For instance, due to the high risk of intracranial bleeding after mild head injury resulting in severe complications, we recommend that individuals with OI who experience even minimal head trauma should receive a CT scan to exclude fractures and post-traumatic brain injury. By working together in a multidisciplinary team, these findings can be shared and discussed quickly. By collaborating with other centres of expertise in the Netherlands and around the whole world, as well as through European Reference Networks (ERNs), this knowledge can be used for scientific research and the development of guidelines.

Cooperation with patient organisations is of great importance. At both the national and international levels, there are several organisations that represent the voice of people with OI worldwide. They maintain networks, support research by providing ideas and funding and preferably collaborate as integral partners in projects.

Investigate bleeding tendency and consider treatment on an individual level

A work-up has been developed for bleeding diathesis in other connective tissue diseases and also to look for specific causes of mild bleeding diathesis [87,88]. We advise clinicians who have to treat OI patients at risk of bleeding to investigate the bleeding history using an ISTH-BAT questionnaire and, if abnormal, to consider a coagulation screening laboratory test to exclude inherited coagulation disorders such as von Willebrand disease. And even if these tests do not reveal coagulation disorders, clinicians should be aware of the increased risk of bleeding in OI, which may be due to vascular fragility.

Recommendations for further research

The themes in this theses offer several options for further research. Suggestions for further research are:

Develop disease-specific Patient-Reported Outcome Measures (PROMS)

Quality of life studies provide a better understanding of the functioning and health of adults with OI. This better understanding can be used to design interventions and treatment protocols that

most closely align with the domains that most affect patients with OI. Developing disease-specific Patient-Reported Outcome Measures (PROMS) to assess and follow quality of life is of importance to test the effectiveness of interventions and treatment protocols. There is a wide variation in measurement methods that examine quality of life, which sometimes limits inter-comparison with studies in the literature. Recently, an international interdisciplinary working group reached consensus on a set of PROM tools for people with OI [89]. This set will enable OI healthcare teams and systems to compare and to improve their care pathways and quality of care worldwide. Further studies are needed to implement interventions that can be evaluated by this standardized outcome set. Already, European networks and registries are being established to create larger databases.

Conduct in-depth analysis into specific sub-areas of quality of life in OI

Chapters 2 and 3 objectify different aspects of quality of life. However, the reasons why certain aspects of quality of life are less affected, or not affected (mental health) have not been investigated. There are several theories available that could explain possible outcomes. For example, joint laxity leading to fatigue [90], and deformities affecting physical functioning [91]. It is important to explore which symptoms are responsible for the low perceived general health, and in what situations people with OI become fatigued in and why.

Observational research can be used to look for causal explanations. In addition, qualitative research can be done to further explore causal relationships and assess patients' experience and needs. People with OI form an extremely heterogeneous group. This due not only to the different types of OI, which may vary in clinical presentation and associated symptoms, but also because of the different age groups and social circumstances, which may explain differences in quality of life. The use of Chapters 2 and 3 as baseline measurements of different aspects of quality of life may inspire follow-up studies in specific patient groups. Future research into the determinants of quality of life and fatigue is important in order to find interventions that will improve quality of life.

Develop treatment protocols for improving quality of life in OI

One of the findings in Chapter 2 is that patients with OI experience more pain than the control population. The fact that pain is a concrete and relevant issue that affects all different subgroups can be used to encourage researchers and clinicians to pay better attention to it during follow-up, in research, and in the consulting room. The results also provide evidence and justification for research into treatment of pain. Hypothetically, it could be that some of the pain symptoms are caused by inadequate analgesia. Given the sometimes different body surface in some types of OI, what doses of analgesia should be used in OI is a topic that needs further research. The impor-

tance of this topic for further research is clear – especially as chronic pain is an additional burden for people who already have significant impairments (Chapter 3).

Research environmental and social factors that may influence quality of life

In the Netherlands, the resources available for people with physical disabilities are widely available, perhaps more so than elsewhere in the world [92]. Another key factor is how parents raise their children who have OI. Parents who have been very overprotective indirectly cause their children to be less able to cope with adversity and to have less muscle development, which can lead to more negative symptoms of OI [15,93].

In addition to the physical limitations, there is also a psychological component in which people with OI are constantly aware of their vulnerability. For people with type 1 OI, this vulnerability is often not evident on the outside, which can actually be a burden. Fatigue from frequent hospital visits, feelings of isolation, loneliness and withdrawal can be an emotional burden. These feelings, in turn, can lead to anger and frustration. Stigma and discrimination may also play a role in perceived psychological quality of life [15]. A better understanding of environmental and social factors is needed to improve the quality of life in these areas.

Use of gene therapies to improve quality of life

Promising strategies for the future treatment of OI and other genetic bone diseases are being developed, such as stem cell transplantation, genetic engineering and the use of molecular chaperones. Unfortunately, because most of these approaches are still in the experimental phase, further research is needed to confirm their therapeutic benefits in OI [94].

Continuing the quest to unravel the bleeding tendency in OI

The findings of this study highlight the necessity for further investigation into the increased bleeding tendency in OI patients. To advance the understanding of the molecular basis of bleeding susceptibility in this population, future research should focus on analysing correlations with specific genetic mutations and the possible influence of genetic mutations on coagulation pathways, platelet function, and fibrinolysis. Moreover, systematic studies comparing bleeding tendency in different types of OI, tracking the incidence and risk factors of bleeding episodes across various age groups and clinical contexts, are recommended. It is also important to explore the possible association of bleeding complications with other comorbidities commonly found in OI patients, including dental abnormalities and cardiovascular disorders.

Investigation of efficacy and safety of therapeutic interventions on bleeding tendency

It is crucial to evaluate the efficacy and safety of various prophylactic and therapeutic interventions for bleeding in OI, including antifibrinolytic agents, desmopressin, recombinant factor replacement therapy, and platelet transfusions.

Collaboration with national and international patient networks

Finally, collaboration with patients, caregivers and patient organisations is important to better understand the impact of bleeding on their quality of life and emotional well-being and to identify priority areas for research and clinical interventions. Overall, it is essential to conduct further research to improve the diagnosis, treatment, and management of the increased bleeding tendency in OI patients.

Strengths

The studies presented in this thesis make a strong argument for further research into the quality of life and bleeding tendency in OI. These studies offer a foundation for future work, and are likely to encourage researchers to delve more deeply into these areas.

Improving quality of life and reducing complications after medical interventions are of great interest to policy makers, health- and social care providers, and above all for patients themselves. The studies on quality of life and bleeding presented in this thesis are some of the most comprehensive available, and are based on the largest cohorts of people with OI with a clinical diagnosis.

In recent years, the importance of measuring quality of life in all chronic diseases has become increasingly clear. The studies presented here provide a clear baseline for quality of life in OI, as well as highlighting areas in need of improvement. Furthermore, since bleeding tendency is an issue that has received relatively little attention in OI, it is a particularly important area of study.

As more attention is paid to these issues, studies such as these give valuable contributions to the concept of integrated care interventions for OI worldwide. Therefore, these articles provide a solid basis for further research contributing to the overall health of people with OI.

Limitations

The people included in the studies were from a cohort of people with OI who were seen by a single multidisciplinary team in one OI Expert Centre, and therefore not representative for patients who are not seen by such teams in the Netherlands or internationally. There is evidence in the literature that multidisciplinary interventions can significantly improve quality of life. Therefore, it is possible that the quality of life reported in our studies is underestimated and there was a partially biased sample. Furthermore, the validated and widely used questionnaires used to measure bleeding tendency and quality of life are not disease-specific. This has to be taken into account when interpreting the results.

Conclusions

While the quality of life in individuals with OI may be lower than in healthy reference populations especially on specific dimensions such as physical functioning, not all domains of quality of life are affected by the condition. Consequently, it is important that a multidisciplinary, individualistic, and holistic approach is used in the care for individuals with OI, and interventions need to be considered at the individual patient level. As quality of life can vary with age, it is important to assess quality of life regularly throughout the lifespan. Further research is necessary to fully understand the various dimensions of quality of life in individuals with OI. Furthermore, an increased bleeding tendency is a common complication in adults with OI and can be a significant clinical challenge. The underlying pathophysiology of this increased bleeding tendency in OI is not well understood and further research is needed. The management of bleeding episodes in people with OI requires an individualized approach, and the use of antifibrinolytics and coagulation factors may be helpful in this context.

References

1. Aaronson NK, Muller M, Cohen PDA, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998; 51: 1055–68.
2. Zee KI, Sanderman R, Heyink JW, Haes H. Psychometric qualities of the rand 36-item health survey 1.0: A multidimensional measure of general health status. Int J Behav Med 1996; 3: 104–22.
3. Hald JD, Folkestad L, Harsløf T, Brixen K, Langdahl B. Health-Related Quality of Life in Adults with Osteogenesis Imperfecta. Calcif Tissue Int 2017; 101: 473–8.
4. Orlando G, Pinedo-Villanueva R, Reeves ND, Javaid MK, Ireland A. Physical function in UK adults with osteogenesis imperfecta: a cross-sectional analysis of the RUDY study. Osteoporosis International 2021; 32: 157–64.
5. Balkefors V, Mattsson E, Pernow Y, Sääf M. Functioning and quality of life in adults with mild-to-moderate osteogenesis Imperfecta. Physiotherapy Research International 2013; 18: 203–11.
6. Nicolaou N, Bowe JD, Wilkinson JM, Fernandes JA, Bell MJ. Use of the sheffield telescopic intramedullary rod system for the management of osteogenesis imperfecta: Clinical outcomes at an average follow-up of nineteen years. Journal of Bone and Joint Surgery - Series A 2011; 93: 1994–2000.
7. Wehrli S, Rohrbach M, Landolt MA. Quality of life of pediatric and adult individuals with osteogenesis imperfecta: a meta-analysis. Orphanet J Rare Dis. 2023; 18. DOI:10.1186/s13023-023-02728-z.
8. Bullinger M. Das konzept der lebensqualität in der Medizin - Entwicklung und heutiger stellenwert. Z Evid Fortbild Qual Gesundhwes 2014; 108. DOI:10.1016/j.zefq.2014.02.006.
9. Ware JE, Kosinski M, Keller SD. SF-36 Physical and Mental Health Summary Scales : A User's Manual. 1994.
10. Zee KI Van Der, Sanderman R. Het meten van de algemene gezondheidstoestand met de RAND-36: Een handleiding, 2e druk IS. Research institute SCHARE, 2012.
11. Petrou S. Methodological issues raised by preference-based approaches to measuring the health status of children. Health Econ 2003; 12. DOI:10.1002/hec.775.
12. Murali CN, Slater B, Musaad S, et al. Health-related quality of life in adults with osteogenesis imperfecta. Clin Genet 2021; 99. DOI:10.1111/cge.13939.
13. Widmann RF, Laplaza FJ, Bitan FD, Brooks CE, Root L. Quality of life in osteogenesis imperfecta. Int Orthop 2002; 26: 3–6.

14. Dogba MJ, Bedos C, Durigova M, et al. The impact of severe osteogenesis imperfecta on the lives of young patients and their parents - a qualitative analysis. BMC Pediatr 2013; 13. DOI:10.1186/1471-2431-13-153.
15. Hill, Hammond J, Sharmin M, et al. Living with osteogenesis imperfecta: A qualitative study exploring experiences and psychosocial impact from the perspective of patients, parents and professionals. Disabil Health J 2022; 15. DOI:10.1016/j.dhjo.2021.101168.
16. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (Sf-36): I. conceptual framework and item selection. Med Care 1992; 30. DOI:10.1097/00005650-199206000-00002.
17. McKiernan FE. Musculoskeletal manifestations of mild osteogenesis imperfecta in the adult. Osteoporosis International 2005; 16: 1698–702.
18. Barlow S, Dove L, Jaggi A, Keen R, Bubbear J. The prevalence of musculoskeletal pain and therapy needs in adults with Osteogenesis Imperfecta (OI) a cross-sectional analysis. BMC Musculoskelet Disord 2022; 23. DOI:10.1186/s12891-022-05433-3.
19. Nghiem T, Chougui K, Michalovic A, et al. Pain experiences of adults with osteogenesis imperfecta: An integrative review. Canadian Journal of Pain 2018; 2. DOI:10.1080/24740527.2017.1422115.
20. Vartiainen P, Heiskanen T, Sintonen H, Roine RP, Kalso E. Health-related quality of life and burden of disease in chronic pain measured with the 15D instrument. Pain 2016; 157. DOI:10.1097/j.pain.0000000000000641.
21. Cortés RM, Pastor JFS, Dolz VM. Chronic pain in adults with osteogenesis imperfecta and its relationship to appraisal, coping, and quality of life: A cross-sectional study. Medicine (United States) 2022; 101. DOI:10.1097/MD.0000000000030256.
22. Mc Donald D, Mc Donnell T, Martin-Grace J, Mc Manus G, Crowley RK. Systematic review of health related-quality of life in adults with osteogenesis imperfecta. Orphanet J Rare Dis 2023; 18. DOI:10.1186/s13023-023-02643-3.
23. Hershenfeld SA, Wasim S, McNiven V, et al. Psychiatric disorders in Ehlers–Danlos syndrome are frequent, diverse and strongly associated with pain. Rheumatol Int 2016; 36. DOI:10.1007/s00296-015-3375-1.
24. 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. DOI:10.1007/s00296-019-04293-w.

25. Eddy L, Cruz M. The relationship between fatigue and quality of life in children with chronic health problems: A systematic review. Journal for Specialists in Pediatric Nursing. 2007; 12. DOI:10.1111/j.1744-6155.2007.00099.x.
26. Levine S. The changing terrains in medical sociology: emergent concern with quality of life. J Health Soc Behav 1987; 28: 1–6.
27. Albrecht GL, Devlieger PJ. The disability paradox: High quality of life against all odds. Soc Sci Med 1999; 48. DOI:10.1016/S0277-9536(98)00411-0.
28. Cederlöf M, Larsson H, Lichtenstein P, Almqvist C, Serlachius E, Ludvigsson JF. Nationwide population-based cohort study of psychiatric disorders in individuals with Ehlers-Danlos syndrome or hypermobility syndrome and their siblings. BMC Psychiatry 2016; 16. DOI:10.1186/s12888-016-0922-6.
29. Pinquart M, Shen Y. Depressive symptoms in children and adolescents with chronic physical illness: An updated meta-analysis. J Pediatr Psychol. 2011; 36. DOI:10.1093/jpepsy/jsq104.
30. Thabrew H, Stasiak K, Hetrick SE, et al. Psychological therapies for anxiety and depression in children and adolescents with long-term physical conditions. Cochrane Database of Systematic Reviews. 2018; 2018. DOI:10.1002/14651858.CD012488.pub2.
31. Van Dijk FSS, Sillence DOO. Osteogenesis imperfecta: Clinical diagnosis, nomenclature and severity assessment. Am J Med Genet A 2014; 164: 1470–81.
32. Zhytnik L, Simm K, Salumets A, Peters M, Märtson A, Maasalu K. Reproductive options for families at risk of Osteogenesis Imperfecta: A review. Orphanet J Rare Dis. 2020; 15. DOI:10.1186/s13023-020-01404-w.
33. Aduloju OP, Olaogun OD, Aduloju T. Quality of life in women of reproductive age: a comparative study of infertile and fertile women in a Nigerian tertiary centre. J Obstet Gynaecol (Lahore) 2018; 38. DOI:10.1080/01443615.2017.1347916.
34. Geraedts J. Healthy children without fear. EMBO Rep 2017; 18. DOI:10.15252/embr.201744253.
35. Hughes T, Bracewell-Milnes T, Saso S, et al. A review on the motivations, decision-making factors, attitudes and experiences of couples using pre-implantation genetic testing for inherited conditions. Hum Reprod Update. 2021; 27. DOI:10.1093/humupd/dmab013.
36. Boivin J, Vassena R, Costa M, et al. Tailored support may reduce mental and relational impact of infertility on infertile patients and partners. Reprod Biomed Online 2022; 44. DOI:10.1016/j.rbmo.2022.01.015.
37. Gameiro S, Boivin J, Dancet E, et al. ESHRE guideline: Routine psychosocial care in infertility and medically assisted reproduction - A guide for fertility staff. Human Reproduction. 2015; 30. DOI:10.1093/humrep/dev177.

38. Coussens M, Lapauw B, Verroken C, et al. Bone Mass, Density, Geometry, and Stress–Strain Index in Adults With Osteogenesis Imperfecta Type I and Their Associations With Physical Activity and Muscle Function Parameters. Journal of Bone and Mineral Research 2022; 37: 2456–65.
39. Khan SI, Yonko EA, Carter EM, Dyer D, Sandhaus RA, Raggio CL. Cardiopulmonary Status in Adults with Osteogenesis Imperfecta: Intrinsic Lung Disease May Contribute More Than Scoliosis. Clin Orthop Relat Res 2020; 478: 2833–43.
40. Yonko EA, Emanuel JS, Carter EM, Sandhaus RA, Raggio CL. Respiratory impairment impacts QOL in osteogenesis imperfecta independent of skeletal abnormalities. Arch Osteoporos 2020; 15. DOI:10.1007/s11657-020-00818-0.
41. Takken T, Terlingen HC, Helders PJM, Pruijs H, Van Der Ent CK, Engelbert RHH. Cardiopulmonary fitness and muscle strength in patients with osteogenesis imperfecta type I. Journal of Pediatrics 2004; 145: 813–8.
42. Radunovic Z, Steine K. Prevalence of Cardiovascular Disease and Cardiac Symptoms: Left and Right Ventricular Function in Adults With Osteogenesis Imperfecta. Canadian Journal of Cardiology 2015; 31: 1386–92.
43. Ashournia H, Johansen FT, Folkestad L, Diederichsen ACP, Brixen K. Heart disease in patients with osteogenesis imperfecta - A systematic review. Int J Cardiol 2015; 196: 149–57.
44. Mueller B, Engelbert R, Baratta-Ziska F, et al. Consensus statement on physical rehabilitation in children and adolescents with osteogenesis imperfecta. Orphanet J Rare Dis 2018; 13. DOI:10.1186/s13023-018-0905-4.
45. Van Brussel M, Takken T, Uiterwaal CSPM, et al. Physical Training in Children with Osteogenesis Imperfecta. J Pediatr 2008; 152: 111-116.e1.
46. Lafage-Proust MH, Courtois I. The management of osteogenesis imperfecta in adults: state of the art. Joint Bone Spine 2019. DOI:10.1016/j.jbspin.2019.02.001.
47. Dahan-Oliel N, Oliel S, Tsimicalis A, Montpetit K, Rauch F, Dogba MJ. Quality of life in osteogenesis imperfecta: A mixed-methods systematic review. Am J Med Genet A 2016; 170: 62–76.
48. Montpetit K, Dahan-Oliel N, Ruck-Gibis J, Fassier F, Rauch F, Glorieux F. Activities and participation in young adults with Osteogenesis Imperfecta. J Pediatr Rehabil Med 2011; 4: 13–22.
49. Shen J, Barbera J, Shapiro CM. Distinguishing sleepiness and fatigue: Focus on definition and measurement. Sleep Med Rev. 2006; 10: 63–76.
50. Shulman LM, Taback RL, Bean J, Weiner WJ. Comorbity of the nonmotor symptoms of Parkinson's disease. Movement Disorders 2001; 16. DOI:10.1002/mds.1099.
51. Karlsen K, Larsen JP, Tandberg E, Jørgensen K. Fatigue in patients with Parkinson's disease. Movement Disorders 1999; 14. DOI:10.1002/1531-8257(199903)14:2<237::aid-mds1006>3.3.co;2-o.

52. Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The Impact of Fatigue on Patients with Multiple Sclerosis. Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques 1994; 21. DOI:10.1017/S0317167100048691.
53. Pepper CM, Krupp LB, Friedberg F, Doscher C, Coyle PK. A comparison of neuropsychiatric characteristics in chronic fatigue syndrome, multiple sclerosis, and major depression. Journal of Neuropsychiatry and Clinical Neurosciences 1993; 5. DOI:10.1176/jnp.5.2.200.
54. Winningham ML, Nail LM, Burke MB, et al. Fatigue and the cancer experience: the state of the knowledge. Oncol Nurs Forum 1994; 21.
55. Hill CL, Baird WO, Walters SJ. Quality of life in children and adolescents with Osteogenesis Imperfecta: A qualitative interview based study. Health Qual Life Outcomes 2014; 12. DOI:10.1186/1477-7525-12-54.
56. Tosi LL, Floor MK, Dollar CM, et al. Assessing disease experience across the life span for individuals with osteogenesis imperfecta: challenges and opportunities for patient-reported outcomes (PROs) measurement: a pilot study. Orphanet J Rare Dis 2019; 14: 23.
57. Arponen H, Waltimo-Sirén J, Valta H, Mäkitie O. Fatigue and disturbances of sleep in patients with osteogenesis imperfecta - A cross-sectional questionnaire study. BMC Musculoskelet Disord 2018. DOI:10.1186/s12891-017-1922-5.
58. Merkies IS, Schmitz PI, Samijn JP, van der Meché FG, van Doorn PA. Fatigue in immune-mediated polyneuropathies. European Inflammatory Neuropathy Cause and Treatment (INCAT) Group. Neurology 1999.
59. Krupp LB, Larocca NG, Muir Nash J, Steinberg AD. The fatigue severity scale: Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989. DOI:10.1001/archneur.1989.00520460115022.
60. Goligher EC, Pouchot J, Brant R, et al. Minimal clinically important difference for 7 measures of fatigue in patients with systemic lupus erythematosus. Journal of Rheumatology 2008.
61. Pouchot J, Kherani RB, Brant R, et al. Determination of the minimal clinically important difference for seven fatigue measures in rheumatoid arthritis. J Clin Epidemiol 2008. DOI:10.1016/j.jclinepi.2007.08.016.
62. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of- life scores. Journal of Clinical Oncology 1998; 16. DOI:10.1200/JCO.1998.16.1.139.
63. Elbatarny M, Mollah S, Grabell J, et al. Normal range of bleeding scores for the ISTH-BAT: Adult and pediatric data from the merging project. Haemophilia 2014; 20: 831–5.
64. Hathaway WE, Solomons CC, Ott JE, Ott E. Platelet Function and Pyrophosphates in Osteogenesis Imperfecta. Blood 1972; 39.

65. Evensen SA, Myhre L, Stormorken H. Haemostatic studies in osteogenesis imperfecta. Scand J Haematol 1984; 33: 177–9.
66. Rodeghiero F, Tosetto A, Abshire T, et al. ISTH/SSC bleeding assessment tool: A standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders. Journal of Thrombosis and Haemostasis 2010; 8: 2063–5.
67. Goddeau RP, Caplan LR, Alhazzani AA. Intraparenchymal hemorrhage in a patient with osteogenesis imperfecta and plasminogen activator inhibitor-1 deficiency. Arch Neurol 2010; 67: 236–8.
68. Mondal RK, Mann U, Sharma M, Mondal RK, Mann U, Sharma M. Osteogenesis imperfecta with bleeding diathesis. Indian J Pediatr 2003; 70: 95–6.
69. Byra P, Chillag S, Petit S. Osteogenesis imperfecta and aortic dissection. American Journal of the Medical Sciences 2008; 336. DOI:10.1097/MAJ.0b013e318158e981.
70. Gaberel T, Rochey A, di Palma C, Lucas F, Touze E, Emery E. Ruptured intracranial aneurysm in patients with osteogenesis imperfecta: 2 familial cases and a systematic review of the literature. Neurochirurgie 2016; 62. DOI:10.1016/j.neuchi.2016.07.004.
71. Faqeih E, Roughley P, Glorieux FH, Rauch F. Osteogenesis imperfecta type III with intracranial hemorrhage and brachydactyly associated with mutations in exon 49 of COL1A2. Am J Med Genet A 2009; 149A: 461–5.
72. Edge G, Okafor B, Fennelly ME, Ransford AO. An unusual manifestation of bleeding diathesis in a patient with osteogenesis imperfecta. Eur J Anaesthesiol 1997; 14: 215–9.
73. Morton ME. Excessive bleeding after surgery in osteogenesis imperfecta. British Journal of Oral and Maxillofacial Surgery 1987; 25. DOI:10.1016/0266-4356(87)90144-6.
74. Rao R, Cuthbertson D, Nagamani SCS, et al. Pregnancy in women with osteogenesis imperfecta: pregnancy characteristics, maternal, and neonatal outcomes. Am J Obstet Gynecol MFM 2021; 3. DOI:10.1016/j.ajogmf.2021.100362.
75. Liang X, Chen P, Chen C, et al. Comprehensive risk assessments and anesthetic management for children with osteogenesis imperfecta: A retrospective review of 252 orthopedic procedures over 5 years. Paediatr Anaesth 2022; 32. DOI:10.1111/pan.14454.
76. Kaliaperumal C, Walsh T, Balasubramanian C, Wyse G, Fanning N, Kaar G. Osteogenesis imperfecta presenting as aneurysmal subarachnoid haemorrhage in a 53-year-old man. BMJ Case Rep 2011. DOI:10.1136/bcr.10.2011.4910.
77. Sperry K. Fatal intraopertive hemorrhage during spinal fusion surgery for osteogenesis imperfecta. American Journal of Forensic Medicine and Pathology 1989; 10. DOI:10.1097/00000433-198903000-00014.

78. Hirohata T, Miyawaki S, Mizutani A, et al. Subarachnoid hemorrhage secondary to a ruptured middle cerebral aneurysm in a patient with osteogenesis imperfecta: A case report. BMC Neurol 2014; 14. DOI:10.1186/1471-2377-14-150.
79. Yakar F, Celtikci E, Ozgural O, Eroglu U, Caglar Y. Osteogenesis Imperfecta and Extra-/Intradural Hematomas: A Case Report and Review of the Literature. J Pediatr Genet 2018; 07. DOI:10.1055/s-0038-1660826.
80. Siegel BM, Friedman IA, Schwartz SO. Hemorrhagic disease in osteogenesis imperfecta Study of platelet functional defect. Am J Med 1957.
81. Sanders Y V, de Wee EM, Meijer K, et al. [Von Willebrand disease in the Netherlands: the WiN study]. Ned Tijdschr Geneeskd 2014; 158.
82. World Health Organization. WHOQOL-HIV Instrument Users Manual. SubStance 2002; : 1–13.
83. Tong A, Jesudason S, Craig JC, Winkelmayer WC. Perspectives on pregnancy in women with chronic kidney disease: Systematic review of qualitative studies. Nephrology Dialysis Transplantation 2015; 30. DOI:10.1093/ndt/gfu378.
84. Steinberg L, Icenogle G, Shulman EP, et al. Around the world, adolescence is a time of heightened sensation seeking and immature self-regulation. Dev Sci 2018; 21. DOI:10.1111/desc.12532.
85. Patton GC, Viner R. Pubertal transitions in health. Lancet 2007; 369. DOI:10.1016/S0140-6736(07)60366-3.
86. Mendle J, Ryan RM, McKone KMP. Age at menarche, depression, and antisocial behavior in adulthood. Pediatrics 2018; 141. DOI:10.1542/peds.2017-1703.
87. Boender J, Kruip MJHA, Leebeek FWG. A diagnostic approach to mild bleeding disorders. Journal of Thrombosis and Haemostasis 2016; 14: 1507–16.
88. Moenen FCJI, Nelemans PJ, Schols SEM, Schouten HC, Henskens YMC, Beckers EAM. The diagnostic accuracy of bleeding assessment tools for the identification of patients with mild bleeding disorders: A systematic review. Haemophilia. 2018; 24. DOI:10.1111/hae.13486.
89. Nijhuis W, Franken A, Ayers K, et al. A standard set of outcome measures for the comprehensive assessment of osteogenesis imperfecta. Orphanet J Rare Dis 2021; 16. DOI:10.1186/s13023-021-01682-y.
90. Bernhoff G, Huhmar H, Käll LB. Assessment of systemic joint laxity in the clinical context: Relevance and replicability of the Beighton score in chronic fatigue. J Back Musculoskelet Rehabil 2022; 35. DOI:10.3233/BMR-210081.
91. Widmann RF, Bitan FD, Laplaza FJ, Burke SW, DiMaio MF, Schneider R. Spinal deformity, pulmonary compromise, and quality of life in osteogenesis imperfecta. Spine (Phila Pa 1976) 1999; 24: 1673–8.

92. Martin Ginis KA, van der Ploeg HP, Foster C, et al. Participation of people living with disabilities in physical activity: a global perspective. The Lancet 2021; 398. DOI:10.1016/S0140-6736(21)01164-8.
93. Suskauer SJ, Cintas HL, Marini JC, Gerber LH. Temperament and physical performance in children with osteogenesis imperfecta. Pediatrics 2003; 111. DOI:10.1542/peds.111.2.e153.
94. Botor M, Fus-Kujawa A, Uroczynska M, et al. Osteogenesis imperfecta: Current and prospective therapies. Biomolecules 2021; 11. DOI:10.3390/biom11101493.

Chapter 8

Summary

Summary

Osteogenesis imperfecta (OI) is a rare congenital connective tissue disease, also known as “brittle bone disease”, because it leads to fragile bones and a high incidence of fractures. OI is a clinically and genetically heterogeneous disorder and consists of 5 types (OI types 1-5). In most cases, brittle bones are caused by decreased and/or abnormal production of collagen type 1 production due to a dominant pathogenic variant in either the *COL1A1* or *COL1A2* gene. The phenotype is influenced by the gene involved, the specific position of the variant and the variant type.

Collagen type 1 is mainly found in bones, but also in several other structures of the human body such as teeth, ligaments and tendons, and to a lesser extent in sclera, blood vessels and internal organs. The deficiency of the collagen type 1 protein, or the synthesis of an abnormal collagen type 1, not only affects bone fragility, but can also cause other symptoms that can manifest throughout the body. These symptoms can have a negative impact on quality of life. Although other symptoms of OI, such as easy bruising and fatigue, are often mentioned, some of them have hardly been studied.

The aim of this thesis was to better understand the quality of life and bleeding tendency in individuals with OI. To improve patient care and counselling and increase therapeutic capabilities, it is important to look at OI more broadly than just a disease with bone fragility.

The following research questions were addressed:

1. What is the quality of life in people with OI compared with control populations?
2. What is the impact of fatigue on daily functioning in people with OI compared to control populations?
3. What is the prevalence of bleeding tendency in OI compared with a control population?
4. What are the clinical manifestations of bleeding tendency in OI? Is diagnostic testing for bleeding disorders indicated?
5. Which bleeding events are most clinically relevant in OI? What can be learned from therapeutic considerations in other mild bleeding disorders?

Chapter 1 is a general introduction to this thesis and provides background information on the etiology of OI, treatment, aspects of quality of life and bleeding tendency in patients with OI.

Part 1 (Chapters 2 and 3) examined quality of life in adults with OI using patient-reported questionnaires that explore different dimensions of quality of life. These dimensions describe aspects of OI commonly mentioned by patients with OI in the doctor's consultation room.

Chapter 2 examined the quality of life in adults with OI based on eight different dimensions using the validated Short Form-36 questionnaire. It assessed four physical domains and four mental domains of quality of life. The physical domains include physical functioning, role limitations in daily activities due to physical health problems, bodily pain, and general health perceptions. The four mental domains include vitality, social functioning, role limitations in daily activities due to emotional problems, and general mental health. A total of 322 OI patients were included in the study and compared to the normative data of 2,778 average Dutch individuals. An important finding was that the physical domain of quality of life among individuals with OI was significantly lower compared to the control population, while the differences in the mental domains were less pronounced. All patients were categorized into age groups, revealing age-specific challenges. Certain domains of quality of life showed trends among different age groups, suggesting areas for further investigation. Pain emerged as a significant factor among OI patients, but it has as yet received limited research attention. Chapter 2 provides a baseline measurement of quality of life that can serve as a control for future interventions, a source for improving quality of care, and an inspiration for further research.

Chapter 3 examined the prevalence and impact of fatigue on daily function in an OI cohort, involving 99 adults with OI. The results were compared to data from control populations from the United States and the Netherlands. The study showed that fatigue occurs significantly more frequently in people with OI compared to the control population, consistent with clinical observations. This study confirmed the suspicion of fatigue being an important complaint and encourages further investigation.

Part 2 (Chapters 4, 5 and 6) focused on different aspects of bleeding in persons with OI, such as the prevalence of anamnestic increased bleeding tendency and possible underlying coagulation disorders.

In **Chapter 4**, a pilot study was conducted on 22 adults with OI to explore bleeding tendencies, for the first time since 40 years. Both an extensive questionnaire (Self-BAT version of the ISTH-BAT) and laboratory blood tests were used to identify bleeding tendencies and to see whether there was an indication of underlying coagulation disorders. Four patients exhibited increased bleeding tendencies, but no underlying coagulation problems were found. Abnormal fibrinolysis was observed in two patients without a history of bleeding tendencies. This pilot study did not provide definitive evidence of increased bleeding tendencies or coagulation disorders in this group of patients with OI.

Chapter 5 examined anamnestic increased bleeding tendency in a large cohort using the self-administered ISTH-BAT (Self-BAT) questionnaire. In total, 195 questionnaires completed by persons with OI were included for analyses in this chapter to determine which bleeding symptoms were most common and which were most clinically relevant. The main finding was that 81 of 195 patients (42%) showed increased bleeding tendency, which was significantly higher than in an average population. Therefore, the main conclusion was that bleeding tendency is actually an important problem in people with OI.

Since patients with OI frequently undergo surgery and often require tooth extractions, it is essential to be alert for bleeding during these procedures. It has been noted that such procedures often require major interventions to stop bleeding. Moreover, it appears that heavy menstrual bleeding and postpartum bleeding are common. For such types of bleeding, therapies to reduce the severity of bleeding are often available. Therefore, the advice arising from this chapter was to properly identify the increased bleeding tendency in individual OI patients with a structured history (ISTH-BAT) and to apply interventions to reduce bleeding at individual bases.

In **Chapter 6**, a selection of patients was made with the highest bleeding tendencies based on the Self-BAT, as described in Chapter 5. Laboratory investigations similar to Chapter 4 were then performed in these patients. These investigations included the measurement of bleeding time, which might be the most sensitive test for the effects of collagen deficiency in the vascular wall. Of 11 selected OI patients with the highest bleeding tendency, two patients indeed had a prolonged bleeding time. In addition, abnormalities were found in fibrinogen (n =1), factor VIII (n = 2) and von Willebrand factor (n = 1). Abnormalities in platelet function were also observed (n = 6). However, all

these abnormalities were found only in nine out of 20 patients, and no clear distinction was visible between patients with a high anamnestic bleeding tendency and those with a normal anamnestic bleeding tendency.

In conclusion, no particular coagulation disorder associated with OI was found to explain bleeding tendency, but different components of coagulation may be abnormal. It is therefore advised that bleeding tendency should be explicitly asked about before surgeries, that coagulation should be monitored in the laboratory in the case of increased bleeding tendency, and that regardless of the outcome, a possible increased bleeding risks should be closely monitored.

Chapter 7 summarizes and discusses the results, providing recommendations for future research and clinical practice. It is important that a multidisciplinary, individualistic, and holistic approach is followed in the care for individuals with OI, and interventions need to be chosen in collaboration with the patient and focused on improving the quality of life. As quality of life can vary at different ages, it is important to assess quality of life regularly. Further research is necessary to fully understand the various dimensions of quality of life in individuals with OI. Furthermore, bleeding tendency is a common complication in adults with OI and can be a significant clinical challenge. The underlying pathophysiology of bleeding tendency in OI is not well understood and further research is needed. The management of bleeding episodes in OI patients requires an individualized approach, and in this context the use of antifibrinolytics and coagulation factors may be helpful.

Chapter 9

Samenvatting

Samenvatting:

Osteogenesis imperfecta (OI) is een zeldzame aangeboren bindweefselziekte die ook wel bekend staat als “broze botten ziekte”, omdat het leidt tot kwetsbare botten en een hoge incidentie van fracturen. OI is een heterogene ziekte op zowel klinisch als genetisch gebied, en wordt onderverdeeld in 5 verschillende types (OI type 1-5). In de meeste gevallen worden de broze botten veroorzaakt door een afgenomen en/of afwijkende productie van het collageen 1 op basis van een dominant pathogene variant van ofwel het *COL1A1* of het *COL1A2* gen. Het fenotype is afhankelijk van welk gen is aangedaan, de precieze locatie van de afwijking in het gen en het soort mutatie.

Collageen type 1 komt voornamelijk voor in botten, maar ook in andere structuren van het menselijk lichaam zoals de tanden, ligamenten, pezen en in mindere mate in de sclera, bloedvaten en organen. Het productieprobleem heeft niet alleen invloed op de broosheid van botten, maar kan ook symptomen veroorzaken die zich door het hele lichaam kunnen manifesteren. Deze symptomen kunnen een negatieve invloed hebben op de kwaliteit van leven. Hoewel de andere symptomen van OI, zoals vermoeidheid en een verhoogde bloedingsneiging, vaak worden genoemd, zijn sommigen ervan nog nauwelijks onderzocht.

Het doel van dit proefschrift was om meer inzicht te krijgen in de verschillende aspecten van de kwaliteit van leven en bloedingen bij personen met OI. Het is belangrijk om bij OI breder te kijken dan alleen een ziekte met botfragiliteit om de zorg en begeleiding van mensen met OI te verbeteren en de therapeutische mogelijkheden te vergroten.

De volgende onderzoeksvragen kwamen aan bod:

1. Wat is de kwaliteit van leven bij mensen met OI vergeleken met controlepopulaties?
2. Wat is de impact van vermoeidheid op het dagelijks functioneren bij mensen met OI vergeleken met controlepopulaties?
3. Wat is de prevalentie van een verhoogde bloedingsneiging bij OI vergeleken met een controlepopulatie?
4. Wat zijn de klinische manifestaties van de bloedingsneiging bij OI? Is diagnostisch onderzoek naar bloedingsstoornissen geïndiceerd?
5. Welke bloedingsgebeurtenissen zijn het meest klinisch relevant bij OI? Wat kan worden geleerd van therapeutische overwegingen bij andere milde bloedingsstoornissen?

Hoofdstuk 1 is een algemene introductie op dit proefschrift en geeft achtergrondinformatie over OI zoals de verschillende typen OI, de mogelijkheden voor behandeling, kwaliteit van leven en de verhoogde bloedingsneiging bij mensen met OI.

Deel 1 (Hoofdstukken 2 en 3) onderzocht de kwaliteit van leven bij volwassenen met OI aan de hand van vragenlijsten die verschillende dimensies van kwaliteit van leven onderzoeken. Deze dimensies beschrijven aspecten van OI die vaak worden genoemd door patiënten met OI in de spreekkamer van de arts.

In **hoofdstuk 2** is de kwaliteit van leven bij volwassenen met OI onderzocht aan de hand van acht verschillende dimensies (subschalen) met behulp van de zelfgerapporteerde gevalideerde generieke Short Form-36 vragenlijst. Hierin worden vier fysieke domeinen en vier mentale domeinen onderzocht van kwaliteit van leven. De fysieke domeinen zijn fysiek functioneren, rolbeperkingen in het dagelijks functioneren als gevolg van lichamelijke gezondheidsproblemen, pijn en algemene gezondheidsbeleving. De vier mentale domeinen zijn vitaliteit, sociaal functioneren, rolbeperkingen in het dagelijks functioneren als gevolg van emotionele problemen en algemene mentale gezondheid. In totaal werden 322 OI-patiënten meegenomen in de studie en vergeleken met de normaalwaarden in de algemene Nederlandse populatie (n = 2778). Een belangrijke bevinding is dat de kwaliteit van leven bij patiënten met OI in het fysieke domein aanzienlijk lager ligt dan bij de controlepopulatie, terwijl de verschillen in het mentale domein met de controlepopulatie minder uitgesproken waren. Alle patiënten werden verdeeld in leeftijdscategorieën, waardoor kon worden vastgesteld dat er op bepaalde leeftijden problemen kunnen zijn die op andere leeftijden minder voorkwamen. Bij het kijken naar verschillende leeftijdscategorieën vallen trends op in verschillende domeinen van kwaliteit van leven die verder onderzocht zouden kunnen worden. Pijn is een belangrijk probleem dat nadrukkelijk aanwezig is in patiënten met OI, maar waar vooralsnog weinig onderzoek naar is gedaan. Hoofdstuk 2 biedt een basismeting van de kwaliteit van leven bij mensen met OI die kan dienen als controle voor interventies, als bron voor het verbeteren van de kwaliteit van zorg en als inspiratiebron voor verder onderzoek.

Hoofdstuk 3 beschrijft de mate van vermoeidheid en de impact van vermoeidheid op het dagelijkse functioneren in een OI-cohort van 99 volwassenen met OI. De resultaten zijn vergeleken met data van controle populaties uit Amerika en Nederland. Uit het onderzoek blijkt dat vermoeidheid significant vaker voorkomt bij mensen met OI dan bij de controlepopulaties. Dit komt overeen met wat er in de spreekkamer wordt gehoord. Deze studie bevestigt het vermoeden dat vermoeidheid een belangrijke klacht is en moedigt aan tot verder onderzoek.

In **Deel 2** (Hoofdstukken 4, 5 en 6) zijn verschillende aspecten van bloedingsneiging bij mensen met OI onderzocht, waaronder de prevalentie van anamnestische verhoogde bloedingsneiging en mogelijk onderliggende stollingsstoornissen.

In **hoofdstuk 4** werd een pilotonderzoek uitgevoerd bij 22 volwassenen met OI om voor het eerst in 40 jaar bloedingsneiging nader te onderzoeken. Zowel met behulp van een uitgebreide zelf gerapporteerde ISTH-BAT vragenlijst (Self-BAT) als laboratoriumbloedonderzoek werd gezocht naar verhoogde bloedingsneiging en stollingsstoornissen. Er werden vier patiënten geïdentificeerd die een verhoogde bloedingsneiging vertoonden, maar er werden bij hen geen stollingsproblemen gevonden. Bij twee patiënten werd een afwijkende fibrinolyse vastgesteld, maar was er geen anamnestische bloedingsneiging aanwezig. Dit pilotonderzoek kon geen duidelijkheid geven over de vraag of er een verhoogde bloedingsneiging of stollingsstoornis was bij deze groep patiënten met OI.

In **hoofdstuk 5** werd in een groot cohort onderzoek gedaan naar anamnestische bloedingsneiging bij patiënten met OI aan de hand van de zelf gerapporteerde ISTH-BAT vragenlijst (Self-BAT). In totaal zijn 195 ingevulde vragenlijsten geanalyseerd. De belangrijkste bevinding was dat 42% (81/195) van alle patiënten een verhoogde bloedingsneiging meldde, wat aanzienlijk hoger was dan in een algemene populatie verwacht mag worden. De belangrijkste conclusie was dan ook dat bloedingsneiging daadwerkelijk een belangrijk symptoom is bij mensen met OI. De bloedingsneiging anamnese (Self-BAT) is geanalyseerd om te bepalen welke bloedingssymptomen het vaakst voorkomen en welke het meest klinisch relevant zijn.

Aangezien patiënten met OI vaak operaties ondergaan en vaak tandextracties nodig hebben, is het van groot belang om alert te zijn op bloedingen tijdens deze ingrepen. Bij dergelijke ingrepen zijn vaak grote interventies nodig om bloedingen te stoppen. Bovendien blijkt dat hevige menstruele bloedingen en postpartumbloedingen vaak voorkomen. Voor dergelijke bloedingen zijn vaak therapieën beschikbaar om de ernst van de bloedingen te verminderen. Het advies dat voortkomt uit dit hoofdstuk was dan ook om de bloedingsneiging bij individuele OI patiënten goed in kaart te brengen met een gestructureerde anamnese (ISTH-BAT) en om interventies op een individuele basis laagdrempelig toe te passen om bloedingen te voorkomen.

In **hoofdstuk 6** werd een selectie gemaakt van patiënten met de hoogste bloedingsneiging zoals beschreven in hoofdstuk 5. Bij deze geselecteerde patiënten werd opnieuw uitgebreid laboratoriumonderzoek uitgevoerd, vergelijkbaar met hoofdstuk 4, om eventuele stollingsproblematiek aan het licht te brengen. Hierbij werd ook de bloedingstijd gemeten, waardoor ook de mogelijke effecten van abnormaal collageen in de vaatwand werden meegenomen. Van de 11 geselecteerde patiënten met een hoge bloedingsneiging had twee patiënten inderdaad een verlengde bloedingstijd. Bovendien werden afwijkingen gevonden in het fibrinogeen (n = 1), factor VIII (n = 2) en de Von Willebrand-factor (n = 1). Ook werden afwijkingen in de trombocytenfunctie waargenomen (n = 6). Echter, al deze afwijkingen werden slechts bij negen van de 20 patiënten gevonden, en er was geen duidelijk onderscheid zichtbaar tussen patiënten met een hoge anamnestische bloedingsneiging en patiënten met een normale anamnestische bloedingsneiging.

De conclusie was dat er geen eenduidige stollingsstoornis wordt gevonden die de bloedingsneiging verklaart, maar dat er verschillende componenten van de stolling afwijkend kunnen zijn. Het wordt daarom geadviseerd om bij operaties zorgvuldig de bloedingsneiging uit te vragen, bij een verhoogde bloedingsneiging de stolling te controleren in het laboratorium, en ongeacht de uitkomst alert te blijven op een verhoogd bloedingsrisico.

In **hoofdstuk 7** worden de resultaten samengevat en bediscussieerd, en worden aanbevelingen gedaan voor toekomstig onderzoek en de klinische praktijk.

Er wordt benadrukt dat het belangrijk is dat een multidisciplinaire, individualistische en holistische benadering wordt gebruikt in de zorg voor mensen met OI. Behandelkeuzes moeten worden gemaakt in samenspraak met de individuele patiënt en gericht op het verbeteren van kwaliteit van leven. Omdat de kwaliteit van leven op verschillende leeftijden kan verschillen, is het belangrijk om de kwaliteit van leven regelmatig te beoordelen. Verder onderzoek is nodig om de verschillende dimensies van kwaliteit van leven bij mensen met OI volledig te kunnen doorgronden.

Daarnaast is een verhoogde bloedingsneiging een veel voorkomende complicatie bij volwassenen met OI en kan een aanzienlijke klinische uitdaging vormen. De onderliggende pathofysiologie van de bloedingsneiging bij OI wordt niet goed begrepen en moet verder worden onderzocht. De behandeling en preventie van bloedingen bij OI-patiënten vereist een geïndividualiseerde aanpak en het gebruik van antifibrinolytica en stollingsfactoren kan nuttig zijn.

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Met warme groeten,
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Publications

Heidsieck GM*, **Gooijer K***, Harsevoort GJ, et al. Bleeding and bruising in Osteogenesis Imperfecta: Laboratory assessment in extreme scorings with a self bleeding assessment tool in 195 individuals with Osteogenesis Imperfecta. Submitted.

Bevers MSAM, Harsevoort AGJ, **Gooijer K**, et al. Bone microarchitecture and strength in osteogenesis imperfecta using HR-pQCT: normative comparison and challenges. J Bone Miner Res. 2024 Jan 25:zjae013. DOI: 10.1093/jbmr/zjae013.

Gooijer K, Heidsieck G, Harsevoort A, Bout D, Janus G, Franken A. Bleeding assessment in a large cohort of patients with Osteogenesis Imperfecta. Orphanet J Rare Dis. 2024 Feb 12;19(1):61. DOI: 10.1186/s13023-024-03054-8.

Munk SA, Harsevoort GJ, **Gooijer K**, Edens MA, Franken AA, Janus GJM. Incidence and nonunion rates of tibial fractures in adults with osteogenesis imperfecta: a retrospective cohort study of 402 patients with 42 fractures at an expert clinic. BMC Musculoskelet Disord 2022; 23. DOI:10.1186/s12891-022-05966-7.

Gooijer K, Harsevoort AGJ, van Dijk FS, Withaar H, Janus GJM, Franken AAM. A Baseline Measurement of Quality of Life in 322 Adults With Osteogenesis Imperfecta. JBMR Plus 2020; 4. DOI:10.1002/jbm4.10416.

Harsevoort AGJ *, **Gooijer K***, Van Dijk FS, et al. Fatigue in adults with Osteogenesis Imperfecta. BMC Musculoskelet Disord 2020; 21. DOI:10.1186/s12891-019-3000-7.

Gooijer K, Rondeel JMM, van Dijk FS, Harsevoort AGJ, Janus GJM, Franken AAM. Bleeding and bruising in Osteogenesis Imperfecta: International Society on Thrombosis and Haemostasis bleeding assessment tool and haemostasis laboratory assessment in 22 individuals. Br J Haematol. 2019 DOI:10.1111/bjh.16097.

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Curriculum vitae

Koert Gooijer werd op 17 januari 1993 geboren in Zwolle. In 2011 deed hij zijn eindexamen atheneum aan het Greijdanus College in Zwolle. Na eerst 1 jaar HBO-verpleegkunde te hebben gevolgd begon hij in 2012 met zijn studie geneeskunde aan de Rijksuniversiteit Groningen. Na het behalen van zijn Bachelor geneeskunde in 2015, deed hij tijdens zijn co-schappen een onderzoeksstage naar bloedingsneiging bij Osteogenesis Imperfecta (OI) in het Expertisecentrum voor volwassenen met OI in het Isala ziekenhuis, Zwolle. Na het behalen van zijn Master geneeskunde in 2018 bleef hij parttime werken als arts-onderzoeker bij het expertisecentrum. Tegelijkertijd werkte hij gedurende 2,5 jaar als arts-assistent ouderengeneeskunde bij het woonzorg-concern IJsselheem in Zwolle. In 2021 begon hij met zijn opleiding tot specialist ouderengeneeskunde bij Gerion, onderdeel van Amsterdam UMC in Amsterdam. Hij continueerde tijdens deze opleiding het wetenschappelijk onderzoek bij het expertisecentrum voor volwassenen met OI in Zwolle, met dit proefschrift als resultaat. Gedurende zijn promotietraject presenteerde hij zijn wetenschappelijk onderzoek op verschillende wetenschapsavonden bij Isala en diverse internationale symposia en congressen. Momenteel doorloopt hij de laatste fase van zijn specialisatie tot specialist ouderengeneeskunde. Koert is in 2016 getrouwd en woont samen met zijn vrouw en 2 dochters in Kampen.