Incidence and non-union rate of tibia fractures in adults with Osteogenesis Imperfecta: a retrospective cohort study of an expert clinic of 402 patients with 42 fractures.

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Abstract

Purpose

Tibia fractures are the most common fractures seen in adults and also lead to the most non-unions. Osteogenesis Imperfecta (OI) is characterized by an increased bone fragility and a higher risk of fractures. No previous studies have been published concerning the incidence of tibia fractures and non-unions in adults with OI. This study aims to give an overview of the incidence of tibia fractures and non-unions in adult OI patients.

Methods

It is a retrospective, descriptive study where all medical charts of adult patients in the OI database of our OI expert clinic were analyzed for tibia fractures between 2008 and 2020. Tibia fracture incidence, non-union rate, treatment modality and potential risk factors were determined.

Results

The database consisted of 402 patients of which 34 patients had suffered one or more tibia fractures, resulting in 42 fractures. The incidence of a tibia fracture in OI adults is 870 per 100.000 person-years. Two out of 42 fractures led to a non-union (5%). It was not possible to adjust for risk factors or type of treatment.

Conclusion

There is a higher incidence of tibia fractures in OI patients, but a comparable non-union rate to the general population. With only 2 non-unions it is not possible to draw conclusions on the influence of risk factors or treatment of tibia fractures in OI.

Introduction

Osteogenesis Imperfecta (OI), also known as brittle bone disease, is a genetic disorder most often caused by alterations in type I collagen that encompasses a heterogenous group of inherited bone dysplasias[1]. Among other abnormalities, it impacts the quality of the bone structure, resulting in an increased risk of long bone fractures and skeletal deformation[1]. Sillence made a classification based on clinical variety including type I-IV. In 2009 type V was added to the classification. The types have a variety in bone fragility with type II being the worst and lethal prenatally, followed by type III showing skeletal deformity and type V, IV and I, being the least at risk for fractures[2].

Treatment of fractures in OI is difficult due to the porous quality of the bone and a wide range in skeletal deformities[1, 3]. Furthermore, it can lead to complications and failure because of its challenging nature[4]. Moreover, a study on femoral fractures in OI adults concluded that these fractures led to non-union after treatment in up to 20% of the fractures[5], which increases the difficulty of treatment of fractures in OI patients.

In the general population, tibia fractures are the most common long bone fractures, which also result in a non-union more often than other long bone fractures. The non-union rates in published studies are varied due to scarce existing literature and different definitions of non-union [6.8]. Up until now, as to our knowledge, there has been no research on treatment of tibia fractures and the non-union rate in OI adults.

Thus, tibia fractures already have a high risk of developing a non-union. With the knowledge of femoral fractures often leading to non-union in OI adults[5], as a consequence, we expect that tibia fractures in OI will lead to even more non-unions. This descriptive study follows Goudriaan et al.[5] in giving an overview on the incidence and non-union at our expert clinic in Zwolle, the Netherlands, but now in tibia fractures in OI adults. Furthermore, it aims to give an advice on treatment of tibia fractures in OI.

Method

Study design and setting

We performed a retrospective observational cohort study in the OI expert clinic for adults in Zwolle, the Netherlands. For this study, data were retrieved from January 2008 until February 2020.

Study population

For this study, the medical data of all OI patients above 18 years were retrieved. This resulted in 402 OI patients in the study period from 2008 to 2020. Inclusion criteria were the diagnosis of OI and being 18 years or older at the time of tibia fracture (Table 1). Exclusion criteria were the use of corticosteroids, a second genetic syndrome or primary osseous tumor or metastatic disease, since these could influence the risk of fracture and non-union[7]. Death before finishing treatment was also an exclusion criterion since union and adequacy of treatment could not be assessed (Table 1).

Data and data collection

Data collection was aided by using a medical business intelligence tool (CT/cue). The files of all patients were searched with CT/cue by using the following key words (in Dutch): lower leg fracture, tibia fracture, intramedullary pen tibia and intramedullary pen lower leg, plate fixation tibia and plate fixation lower leg.

Data

As in Goudriaan et al.[5], data selected from the patients files included demographic characteristics and the type of OI: both genetic and clinical type according to Sillence were included. Furthermore, the type of the fracture according to the AO/OTA Fracture and Dislocation Classification[9], treatment of the fracture (conservative and operative) including outcome (union, non-union) and complications (infection, malposition, failure of osteosynthesis) were recorded. In addition, potential risk factors for non-union were identified, including bisphosphonate use, smoking, nutritional deficiency, vitamin D deficiency, mobilization status, metabolic disease and endocrine pathology. Union was defined as the presence of bridging callus in at least three of four cortices, evaluated on two transverse levels on radiographic imaging. Non-union was defined as non-radiographic changes to union or the absence of bridging callus of two or more cortices, evaluated on radiographs in two transverse levels, for at least 6 months after treatment[5, 10].

In the case of missing data, patients were asked for permission to retrieve the missing documentation from other hospitals. Information was only obtained when the patients permission for requesting data for research was documented.

Table 1
In- and exclusion criteria

Inclusion	Exclusion
Tibia fracture	No tibia fracture
Age ≥18 years	Age <18 years
Osteogenesis Imperfecta	Use of corticosteroids
	Death before full healing of fracture
	A second genetic syndrome, primary osseous tumor or metastatic disease

Statistical methods

This study contains a relatively small number of subjects with too little data to analyze statistically: therefore, a descriptive study was performed. Descriptive statistics were used to analyze the results using SPSS. Categorical variables were expressed as percentage and metric variables as mean and standard deviation.

The incidence rate was calculated over all 402 patients and the 12 years of inclusion (2008 – 2020). The incidence was calculated on the amount of fractures, not individuals.

Ethics

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 (METC no. 200638). All patients had provided written consent for reading their medical records, for obtaining additional records from other institutions and use of this information for research.

Results

Of the 402 patients with OI in the database during the stated study period, 132 patients were selected with potential tibia fracture(s) using CT/cue. The remaining 270 patients were assumed not to have had a tibia fracture since none of the search terms were found in their files.

The dossiers of these 132 patients were reviewed in full by one researcher (SAM). 98 patients were excluded (Fig. 1) and 34 patients met the criteria of this study and were included. The demographics of the participants are shown in Table 2.

Six of the participants had more than one tibia fracture over time, which were included separately, resulting in a total of 42 fractures. Of these fractures, 2 resulted in non-union after treatment.

Table 2
Demographic characteristics of all subjects with one or more tibia fractures

	All subjects **N=34**
Age (years)	41 [32;61]
Gender (male, %)	17 (50)
Smoking (n, %)	10 (29)
OI type (n, %)	
I	22 (65)
III	6 (17)
IV	5 (15)
V	1 (3)
Data are presented as: median [quartile 1; quartile 3] or number of patients (percentage)	

Incidence of tibia fracture and non-union

There were 42 fractures in the cohort of 402 OI patients recorded from 2008 to 2020. This results in an incidence of tibia fractures of 870/100.000 annually. Two out of 42 fractures (5%) developed into a non-union. The incidence for non-union is 38/100.000 annually.

Influence of OI type on healing rate

Twenty-six (62%) tibia fractures were seen in Sillence type I patients and respectively 7 (17%) and 8 (19%) in type III and IV OI patients, and 1 (2%) in type V. Of the 42 analyzed fractures, 2 resulted in a nonunion (Table 3). One of these fractures was a proximal fracture in an OI type I patient, the other nonunion pertained a distal fracture in OI type III.

Influence of treatment on healing rate

For OI type I, only 1 out of 26 fractures (4%) resulted in a non-union. This proximal fracture was initially treated with a plate fixation. The other non-union was a distal tibia fracture in a type III OI patient, being 1 out of 7 fractures (14%). As treatment, a rushpen was removed and a titanium elastic nail (TEN) was implanted. With no evidence of healing, an additional cast immobilization was initiated with no result of bone healing. Since the patient is wheelchair bound and had little pain, eventually the pseudarthrosis was accepted and the patient uses a brace for support (Fig. 2).

Looking from another perspective, 1 out of 5 (20%) plate fixations for proximal tibia fractures led to a non-union. As for distal intramedullary nailing, 1 out of 3 (33%) led to a non-union. Conservative treatment alone (18 fractures) never led to a non-union, independent of location of the fracture.

Table 3
Characteristics of patients with non-unions

	Gender	Age at fracture	Type OI	Type fracture	Primary treatment
1	M	19	I	Proximal tibia	Plate fixation
2	M	22	III	Distal tibia	Intramedullary fixation

M = male

Discussion

In our study, the incidence of tibia fractures is 870/100.000 annually in OI adults where we included a total number of 42 tibia fractures in 402 patients (10%), with 2 non-unions (5%). To our knowledge, this is the first study that describes the incidence and number of non-unions in tibia fractures in adults with OI. We also aimed to draw conclusions as to whether the treatment or type of OI has any impact on the risk of non-union, but with only two non-unions with different treatments, this was not feasible.

Tibia fractures are the most common fractures in the general population. There is a recent study that estimates the incidence of tibia fractures to be between 6-101/100,000 per year in the general population [11]. The incidence of tibia fractures in this OI population is 870/100.000 per year, thus higher than the general population. However, both Hemmann et al[11] and the present study most likely give an underestimation of reality. In Hemmann they only include in-hospital patients, and in this study not all fractures of the OI population we studied might be known in our patient files: if treated elsewhere and not communicated with the expert clinic, the fracture would not have been traceable for this study. In addition the used exclusion criteria and the use of specific search terms in the selection of participants could also have led to an underestimation of incidence.

Tibia fractures are also seen with the most non-unions, even in the general population, ranging from 1% up to 23% [7, 8, 12, 13]. Our findings of 5% show a comparable non-union rate. The outcome differs from our expectation where we assumed the non-union rate would be higher in OI. Important to note is that a tibia fracture is often the result of a high energy trauma [7, 8, 13]. One study specifically on tibia shaft fractures showed the mechanism of injury and amount of soft tissue damage indeed heightened the risk on non-union[14]. In our study, the fractures were all the result of low energy trauma. Therefore, the results are not directly comparable: it might be the case that if corrected for intensity of trauma, the non-union rate would be lower than in the known literature on the general population.

Strengths and Limitations

This is a retrospective study where patient data was searched by using specific terms. Therefore, we cannot exclude the possibility of having missed fractures in the database. In addition, not all tibia fractures might be documented in our database, especially the ones that were treated successfully elsewhere. However, since Zwolle is the expert clinic on OI, it is to be expected that non-unions would have been referred to or at least discussed with our clinic and therefore would most likely be in our database.

By stating a clear definition of non-union that can objectively be measured on x-ray, there is no question on whether or not the fracture healed. With consent of all patients, it was possible to retrieve almost all missing data required to determine union.

Patient-dependent factors

With the retrospective nature of this study, we were able to include risk factors: bisphosphonate use, smoking, nutritional and vitamin D deficiency, mobilization status and other metabolic diseases. Unfortunately, data were incomplete and despite efforts made, not all data could be retrieved since often it was not documented. In addition, there were only two non-unions in the current study, making it impossible to adjust for these risk factors, even if the data would have been complete.

Conclusion

This study set out the incidence and non-union rate of tibia fractures in the adult OI population known at our expert clinic. Whereas the incidence of tibia fractures is higher in the OI population, the non-union rate is comparable to a general population, although there might be a difference if type of injury and soft tissue damage would be taken into account.

With only two non-unions, we could not draw any hard conclusions as to whether type of OI, type of treatment or risk factors influence the risk of non-union in tibia fractures.

Further research must be done to be able to make an adequate statement, preferably multicenter. With more data, it could be possible to give a useful advice on how to treat a non-union, leading to better care for the OI population.

Declarations

Funding Not applicable.

Conflict of interest SAM, GJH, KG, MAE, AAF and GJMJ declare that they have no conflict of interest.

Availability of data and material The data used and analyzed for the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Authors contributions SAM, GJH and GJMJ significantly contributed to the literature review, the writing of the manuscript, and the creation of diagrams. KG, MAE and AAF participated in the conceptual development of the manuscript and revised the article for intellectual content. All authors read and approved the final manuscript.

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Consent to participate All participants approved to use medical files and if needed additional information from other hospitals.

Consent for publication All data and images used were with consent of the participants.

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Figures

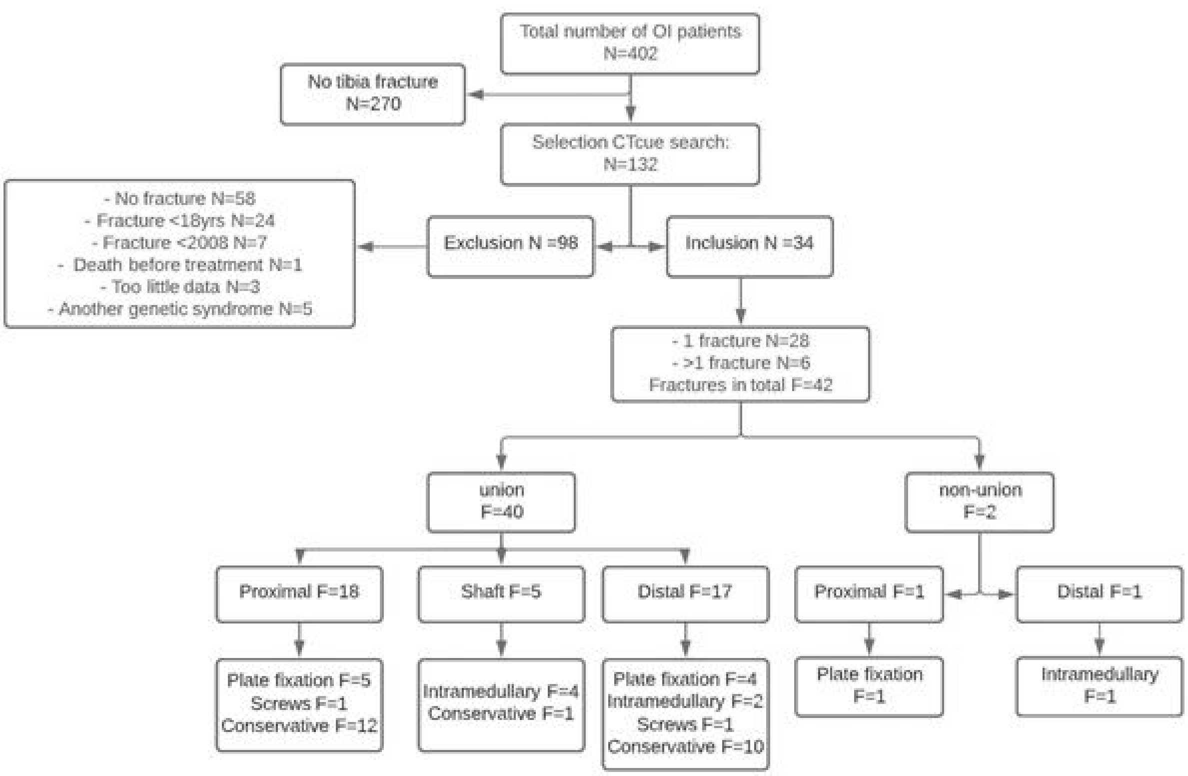

Figure 1

flowchart of participant and fracture selection, union classification and treatment of fractures

Legend: N= number of participants.   F= number of fractures

Figure 2

non-union distal tibia fracture, 2 years after initial treatment

a. AP en b. lateral view