Research Article

Prevalence and Risk Factors for Transient Osteoporosis of the Hip in Adult Osteogenesis Imperfecta Patients: A Cohort Retrospective Study

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Abstract

Purpose: Osteogenesis Imperfecta (OI) is a congenital disorder characterized by multiple fractures and a low bone mineral density (BMD). In our national OI expertise center for adults, we observed several cases of transient osteoporosis of the hip (TOH). The aim of this study was to report on the prevalence of TOH in adult OI patients, to identify possible additional risk factors and describe the natural history.

Methods: The charts of 314 adult OI patients, seen on an outpatient base between January 2008 and January 2018, were reviewed for pain in the hip region. On the basis of pain with no reported trauma a Magnetic Resonance Imaging (MRI) was performed to identify patients with TOH and exclude other diseases. Additional risk factors were evaluated.

Results: 5 of 314 (1.6%; 95% confidence interval 0.6% - 3.9%) OI patients showed TOH. There was a delay of 4-12 weeks between the start of the symptoms and the diagnosis of TOH. No additional risk factors were designated besides OI. Good clinical result by partial weight bearing in 4 patients, one patient received a total hip arthroplasty in a hospital in the surroundings of the patient.

Conclusions: The prevalence of TOH in adult OI-patients is 1.6% in a ten years cohort. Due to the high prevalence, we recommend a MRI in OI-patients with pain in the hip region suspicious of TOH and inconclusive radiographs. No additional risk factors were noticed in our patient population for the development of TOH. The natural history is favorable by off-loading of the hip during the period of pain. We hypothesize that a mild degree of trauma causing microfractures could be the reason for bone marrow edema matching the clinical entity of TOH.

Keywords: Osteogenesis imperfecta; Prevalence; Transient osteoporosis of the hip

1. Introduction

Osteogenesis Imperfecta (OI) is a rare congenital and phenotypically heterogeneous connective tissue disorder characterized primarily by increased fragility of bones and is also called "brittle bone disease". The primary defect in disturbed bone formation is in the divergent collagen type I production that leads clinically in a heterogeneous disorder with many phenotypical presentations. In the primary clinical classification by Sillence in 1979 four types were described, ranging from lethal (type II), severe (type III), moderate (type IV) to mild (type I) [1]. The original four types all have an autosomal dominant inheritance, in the last decades the detection of recessive genes also causing clinically OI generated expansion of the classification to 18 types, resembling the clinical presentation of the original type III and IV [2].

Isala Teaching Hospital in Zwolle, the Netherlands, embeds a national expertise center in OI, with a large cohort of adult OI patients. Over time we identified multiple OI patients with acute complaints of their hip region without trauma that are assigned to transient osteoporosis of the hip (TOH) after Magnetic Resonance Imaging (MRI). TOH describes a transient and self-limiting clinical entity of unknown etiology. Sudden onset hip pain in women in the last trimester of pregnancy and middle-aged men are most vulnerable for this condition [3]. The radiological term bone marrow edema (BME) is used to describe these findings on MRI. In rare cases BME may develop to avascular necrosis due to vascular compression that leads to a more incapacitating outcome [3, 4]. The acute onset hip pain is hypothesized due to the bone marrow edema. Origin of the edema is not clear causal insults as trauma, infection, inflammation, among other disorders have been described [3] Potential risk factors (secondary) as alcohol consumption, steroid usage, smoking, hypothyroidism, hypophosphatasia, low testosterone, low vitamin D, certain professions and OI are reported [5].

In OI bone marrow architecture is compromised due to an increased porosity and is thus more vulnerable for microfractures. These microfractures without an actual trauma of the hip can lead to BME, and the clinical entity of TOH. It is unclear if a microfracture is the cause or a consequence of BME [3]. We

hypothesize that due to porosity of bone in OI microfractures cause acute onset hip pain and eventually leads to bone marrow edema. The primary objective of our study is to report on the prevalence of TOH in OI patients and the secondary goal is to identify possible additional risk factors.

2. Materials and methods

2.1 Setting

Our hospital (Isala, Zwolle, the Netherlands) embeds a national expertise center for adult patients with OI. All patients with OI who visit our hospital on an outpatient base have a multidisciplinary appointment and extensive physiological investigations on their first visit. Besides baseline demographics, clinical, serological, and genetic data are collected [6]. Radiographs of pelvis and spine are made at their first visit. Follow-up is regularly on a 3-year base, but with complaints at shorter notice. The present study concerns data collected between January 2008 and January 2018 and contains data of 314 patients. Informed consent was obtained from all individual participants included in the study; the study was approved by our METC (# 181001).

2.2 Study design

This study is a descriptive study on the prevalence of TOH in the period January 2008 – January 2018. The charts of 314 consecutive adult OI-patients who visited our hospital were reviewed to assess hip pain.

2.2.1 Diagnosis of TOH: Radiographs of the pelvis of all patients were available for re-review by a musculoskeletal radiologist (MFB). For clinical indications, hip pain, MRI scans were obtained for conformation of TOH or to diagnose TOH. Both hips were imaged in one field of view on a 1.5 or 3T MR system (Philips Medical Systems, Best, The Netherlands) per protocol, which consisted of Coronal T2W TSE SPAIR, T1 TSE, T2 FFE and axial 3D WATSc sequences. Imaging criteria applied to MRI for BME are intermediate signal sequences on T1-weighted images and high-signal intensity on T2-weighted images. Of interest is that BME appears hyperintense compared with normal bone marrow on contrast-enhanced and short-tau inversion recovery imaging (STIR) [7]. The diagnosis of TOH will be advocated by a homogeneous pattern of enhancement of BME with an indistinct border, a diffuse pattern of edema with no focal defect, along with the presence of an irregular band of low signal intensity due to stress fracture and lack of subchondral changes [5].

2.3 Variables

Risk factors for TOH were extracted for all patients. These include among others pregnancy, chronic corticosteroid use, high-risk drinking, smoking, drugs, low vitamin D (25-OH Vitamin D) and injury [5]. High-risk drinking was defined as the consumption of 8 or more alcoholic drinks a week for women, and 15 or more for men [8]. Also bisphosphonate and denosumab use and biometric data were obtained. 25-OH-vitamin D is critical for bone health as deficiency can put patients at risk for developing osteoporosis. As osteogenesis imperfecta is a skeletal disorder related to calcium metabolism, vitamin D level in this high risk group is 50 nmol/L (20ng/mL) or higher [8, 9].

Dual energy x-ray absorptiometry (DXA) was used to perform measurements of lumbar spine BMD (bone mineral density), the proximal femur BMD and/or wrist BMD, expressed in T-scores. Measurements were done by means of a DXA-scan (Discovery-A,

Hologic) and were executed by the same scanner at our clinic. The coefficients of variation were 0.669% at the lumbar spine and 1.0% at the proximal femur in an age-matched normal population sample [6].

The charts of each patient with hip or groin pain on the basis of MRI-confirmed TOH were studied to extract the following additional data: presenting complaints, time from signs and symptoms to diagnosis, type of imaging test requested, trauma related pain, potential risk factors, treatment and clinical outcome.

2.4 Statistical methods

Categorical data were presented as n (%). Continuous data were presented as mean ± the standard deviation (SD) in the case of normal distribution or median (Q1 – Q3) in the case of skewed distribution or small n. Categorical data were tested using Fisher's exact test. Continuous data were tested using Mann-Whitney U test. All analyses were performed 2-tailed using alpha 5% as significance level. Analyses were performed using SPSS version 24.

3. Results

3.1 Prevalence of TOH

Five of 314 OI patients (1.6%; 95% confidence interval [0.6% - 3.9%]) were found to have MRI-confirmed TOH. All patients were diagnosed within one month after referral to our centre and within three months since the start of their symptoms of hip pain.

3.2 Subjects

(Table 1) provides patient characteristics. Of the patients with TOH four patients were classified as OI-

type I, and 1 as OI-type IV. There were 3 males and 2 females. The median age at diagnosis of TOH was 40.2 (28.5-48.5) years. All cases were atraumatic, no high-impact trauma occurred prior to their complaints. None of these patients used corticosteroids, were high-risk drinkers, suffered from co-morbidities or had other risk factors, f.e. hypophosphatasia, hypothyroidism, which could increase the risk to develop TOH.

The group without TOH consisted of 309 patients. 217 patients are classified as type I, 36 as type III, 54 as type IV, 2 as type V, there are 122 males and 187 females. The median age was 36 (24.5-52) years. Three patients used corticosteroids and 14 patients were high-risk drinkers. At entering the cohort the median T-scores of the lumbar spine and proximal femur in the TOH group was -2.4 (-2.6 – -1.0) and -0.5 (-1.7 – 0.1), respectively.

In the group without TOH there were 285 DXA scans of the lumbar spine, 278 of the hip and 18 of the wrist. The mean T-score of the lumbar spine in the group without TOH was -2.6 (± 1.4), the mean T-score of the proximal femur -1.2 (± 1.4) and the median T-score of the wrist was -2.4 (-3.7 – -1.3). There were no significant differences in T-scores of the lumbar spine and the proximal femur between groups.

In the TOH group level of vitamin D was 64.0 nmol/L (40.5-85.3 nmol/L). Vitamin D level in the non-TOH group was 69.5 ± 32.1 nmol/L; there were no significant differences between these groups.

	All (n=314)	TOH (n=5)	Non-TOH (n=309)	p-value
Age (years)	36.5 (24.5 - 52)	40.2 (28.5 – 48.5)	36 (24.5 - 52)	p=0.825
Sex (men)	125 (39.8%)	3 (60%)	122 (39.5%)	p=0.390
OI type				
− 1	221 (70.8%)	4 (80%)	217 (70%)	
− 3	36 (11.5%)	0 (0%)	36 (11.7%)	p>0.999
− 4	55 (17.6%)	1 (20%)	54 (17.6%)	
− 5	2 (0.6%)	0 (0%)	2 (0.7%)	
DXA T-Lumbar Spine	-2.6 (±1.4) $^{N=290}$	-2.4 (-2.6 - -1.0)	-2.6 (±1.4) $^{N=285}$	p=0.420
DXA T-Proximal Femur	-1.2 (±1.4) $^{N=283}$	-0.5 (-1.7 – 0.1)	-1.2 (±1.4) $^{N=278}$	p=0.246
DXA T-Wrist	-2.4 (-3.7 - -1.3) $^{N=18}$	na*	-2.4 (-3.7 - -1.3) $^{N=18}$	na*
Body Mass Index (kg/ m²)	24.1 (21.6 - 27.2) $^{N=251}$	28.4 (21.1 - 31)	24 (21.6 – 26.9) $^{N=246}$	p=0.482
25-OH-Vitamin D (nmol/L)	69.4 (±32.0) $^{N=288}$	64 (40.5 – 85.3) $^{N=4}$	69.5 (±32.1) $^{N=284}$	p=0.746
High risk alcohol (yes)	14 (7.7%) $^{N=182}$	0 (0%)	14 (7.7%) $^{N=182}$	p>0.999
Corticosteroid use (yes)	3 (1%)$^{N=314}$	0 (0%)	3 (1%)$^{N=309}$	p>0.999

*na, non applicable

Table 1: Patient characteristics.

3.3 Diagnosis

The presenting complaint was persistent hip pain for weeks in all patients who developed TOH. In cases 1,2, 3 and 5 the first investigation was a standard hip radiograph, which were all inconclusive. In case 1, a repeated radiograph six weeks after the first radiograph showed osteopenia, thereafter MRI showed edema of the proximal femur and confirmed the diagnosis. In case 2 Technetium-99m bone scintigraphy was performed 4 weeks after the radiograph, which showed a hot spot, upon which MRI confirmed the diagnosis. In case 3 MRI was made 6 weeks after the radiograph. Case 4 had a history of TOH on the contralateral side. A MRI was the first, and only investigation needed to confirm the diagnosis. In case 5, a bone scan was made when symptoms progressed after two weeks. The bone scan showed a hot spot in the femoral head, upon which a MRI was performed and confirmed the diagnosis.

MRI demonstrated intermediate signal sequences on T1-weighted images dominated by high signal on T2-weighted images at all patients. Edema was present in the femoral head and extended in all cases to the intertrochanteric region. A small amount of joint effusion could be noticed. (Figure 1 b) shows a small amount of joint effusion and a homogenous pattern of edema located at the femoral head, extended to the neck and intertrochanteric region. There are no added abnormalities matching with subchondral fractures.

3.4 Treatment

All patients were treated conservatively initially. Conservative treatment consisted of immobilization or

partial weight bearing. Treatment was prolonged or discontinued based on clinical symptoms. Case 1 immobilized for 6 weeks. Case 2 was initially treated with partial weight bearing. Due to a deterioration of pain of the hip the patient visited another hospital in the surroundings and a total hip arthroplasty was performed there. Case 3 was treated with immobilization for 4 weeks, followed by partial weight bearing for 4 weeks. Case 4 and 5 immobilized for 6 weeks followed by partial weight bearing for 6 weeks.

3.5 Outcome

All patients who were treated completely conservatively recovered with functional results as before and absence of pain. Radiological follow-up studies showed no abnormalities on plain radiography, or minimal signs of bone edema on MRI (Description of case 3, Figures 1a-c). Case 2 was

treated with a total hip arthroplasty with absence of pain after the operation.

3.6 Case description

Case 3 is a 55-year old female with OI-type 1. She experienced hip and groin pain, without any history of trauma. A hip radiograph showed no abnormalities four weeks after the first symptoms (Figure 1a). Our hospital was contacted due to persistent symptoms, six weeks after the initial radiograph. A pelvic MRI-scan was made which showed edema in the femoral head and neck (*) consistent with TOH (Figure 1b). Treatment consisted of 4 weeks immobilization, followed by 4 weeks of partial weight baring. At follow-up 14 weeks thereafter she complained of knee pain, no hip or groin pain. A pelvic MRI-scan was repeated to rule out referred pain. It showed residual bone edema in the femoral head (Figure 1c). The knee pain resolved spontaneously.

Figure 1a: Hip radiograph demonstrated no signs of TOH.
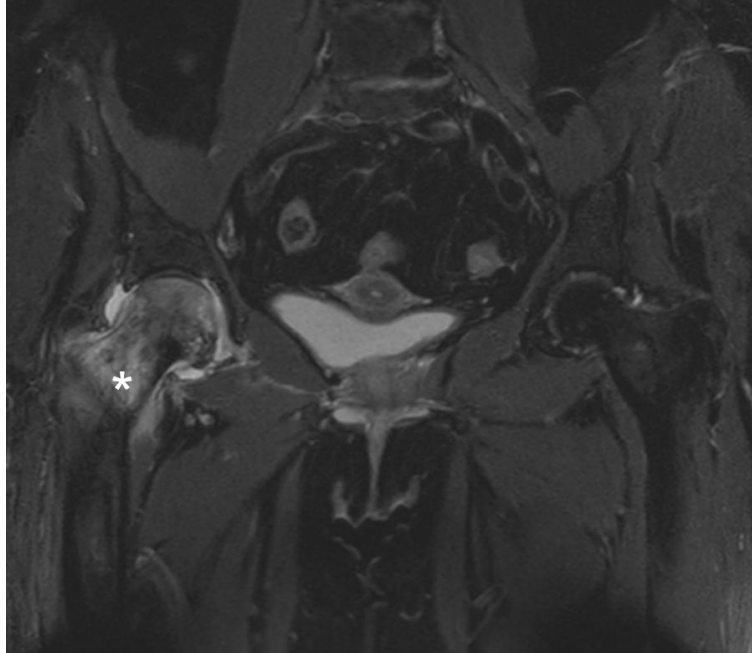
Figure 1b: Pelvic MRI (Cor T2 TSE SPAIR); bone edema of head and neck.
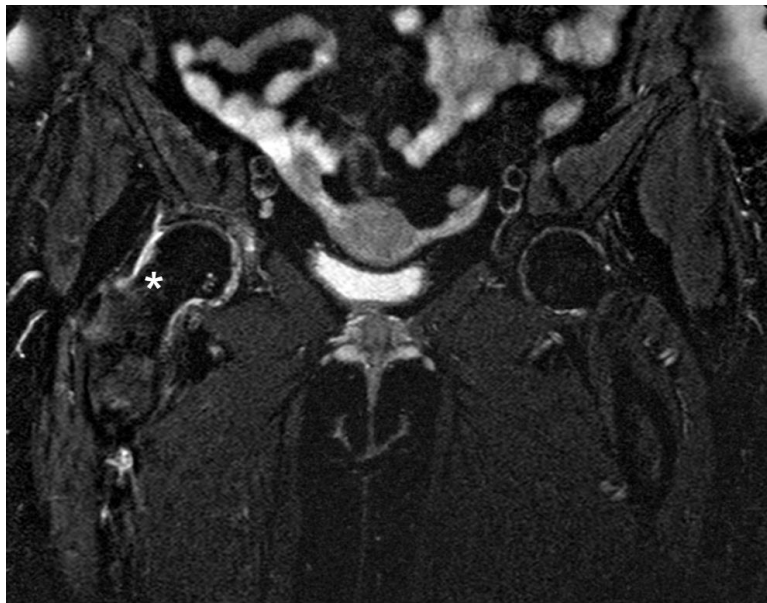
Figure 1c: Pelvic MRI (Cor T2 TSE SPAIR) after 2.5 months demonstrated diminution of bone edema in the femoral head and neck.

4. Discussion

In this study we observed a prevalence of TOH in a population of adult OI patients of 1.6% (0.6% - 3.9%) in a 10-year interval. To the best of our knowledge this is the first study in the current available literature to define the prevalence of TOH in OI-patients, no epidemiological data are available of the normal population. Patel [3] suggested that in a normal population mild cases settle spontaneously and never reach medical attention, and thus underreporting the numbers in a normal population. In the OI population the factor of importance is that patients are very alert for pain with a fracture as a possible underlying cause. Off loading the hip will lessen their pain and may affirm the clinical idea of having a fracture without noticeable trauma. As they are already limited in their activities due to the underlying disease, TOH can cause significant morbidity and pain. Swift recognition and off-loading of the limb is prognostic favorable and clinical important for this vulnerable patient category [10, 11]. For the TOH-patient is susceptible for fracture and avascular necrosis, leading to a more incapacitating outcome [3, 5, 12].

Since OI patients frequently have pain it could have been that we underestimated the true prevalence of TOH in our cohort of OI-patients. To find a more accurate estimate of the prevalence of TOH in adult OI-patients, a prospective study in which hip MRI are made in all patients in a large cohort could be done but will carry enormous financial expenses. Accurately and persistently questioning the presence of hip or groin pain is a more pragmatic solution in this high-risk group.

Although the exact pathogenesis of TOH is unclear, multiple risk factors have been described [5]. These risk factors were not present in the five patients who developed TOH in our cohort except that all patients have OI. None of the patients used corticosteroids, were high-risk drinkers, were pregnant or had any other known risk factors. Regarding studying the potential risk factors, this study is limited by the small number of patients with TOH. Within these limitations no additional risk factors could be identified.

In both our TOH and non-TOH group we found below average T-scores of the lumbar spine and the hip, reflecting a below average BMD. The below average BMD is to be expected in OI-patients. Although both groups scored below average, there were no significant differences in BMD between these groups. All cases of TOH were atraumatic, no high-impact trauma occurred. Noorda et al. [13] performed a core bone biopsy from the proximal femur of a patient with TOH. Histologic examination showed bone marrow edema, slight fibrosis and a reduced number of slender bone trabeculae. Some trabeculae demonstrated breaklines indicative of microfractures or the result of tissue processing. Due to the absence of other risk factors we hypothesize that a mild degree of trauma causing microfractures could be the only reason for bone marrow edema in OI patients matching the clinical entity of TOH, and thus affirm the hypothesis of others [12-14].

In four TOH-patients, there was a delay in diagnosis. No further investigation was done initially when the hip radiograph was inconclusive. Further investigation, by means of either a bone- or MRI-scan, was done when the symptoms persisted after 4-6 weeks. Although our conservatively treated patients recovered with no residual symptoms, earlier diagnosis and treatment might have led to a faster

recovery. The symptoms of TOH are unspecific and have a wide differential diagnosis. Diagnostic imaging is key in the diagnosis of TOH and because of plain radiography is not able to visualize changes the first weeks from the onset of symptoms [15]. MRI is the preferred imaging module [3]. It is considered as the most sensitive modality and demonstrates edema after 48 hours after the start of symptoms [16]. A bone scan had no additional value in diagnosing TOH in our patients and delayed the final diagnosis. Due to the high prevalence of TOH in OI-patients, a hip MRI should be mandatory to confirm or exclude TOH in OI-patients presenting with hip and/or groin pain and inconclusive radiography.

The etiology of TOH is not clear and OI is considered as a risk factor. In OI-patients the femoral head may more easily develop microfractures due to the inherent bone mass reduction and fragility of the bone. MRI will demonstrate BME as a result of microfractures. At the initial examination there were no significant differences in bone mineral density T-scores of the proximal femur between groups. We did not perform DXA-scans of our five patients during their period of hip pain, and were as a consequence not able to demonstrate more reduction in bone mineral density by this modality. However radiographs did not demonstrate more osteopenia compared to the original pelvic image, but as stated radiographs are not sensitive to demonstrate osteopenia in the first period of complaints. It is our opinion that the term transient, in TOH in OI patients, is more related to transitory pain and MRI-visible edema in the hip than to osteoporosis.

In conclusion, we observed a prevalence of TOH of 1.6% in our population of adult OI patients in a 10-

years period. We hypothesized that in the OI population microfractures could be the reason for development of BME, matching the clinical entity TOH. A high index of suspicion of TOH should be maintained in OI-patients presenting with hip and/or groin pain. Inconclusive radiography in adult OI-patients with hip and/or groin pain even without trauma should be followed-up by MRI.

Compliance with Ethical Standards
Declaration of Interest

None.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This was a cohort retrospective study approved by our METC (nr 181001). For this type of study, formal consent is not required.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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