Disentangling the cause of atypical femur fractures associated with the use of bisphosphonates

Published: 09-09-2013
Last updated: 24-04-2024

Primary Objective: to identify risk factors and the underlying mechanism of AFFs by:- setting up a database with detailed information to define patients* characteristics.- building a biobank with urine and blood samples from these patients. -...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Endocrine and glandular disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON46933

Source
ToetsingOnline

Brief title
Atypical femur fractures: cause and risk factors

Condition

- Endocrine and glandular disorders NEC
- Fractures

Synonym
atypical femur fracture, atypical fracture of the thigh bone

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: - Bone density conservation agents/adverse effects, - Diphosphonates/adverse effects, - Femoral fractures, - Osteoporosis

Outcome measures

Primary outcome

Potential risk factors for AFF:

1. Medication use and co-morbidity

2. Genetic predisposition

3. Femur shape

1. Medication use and co-morbidity

Cases are controls from whom medical information is already available in the ERGO study (~14.000 subjects), matched for sex, age and bisphosphonate use (none, more than five or less than five years). Controls are bisphosphonate users when they used bisphosphonates at the moment that their data were collected in the ERGO study. We will compare bone density scores, number of medication, corticosteroid use, use of proton pump inhibitors and co-morbidity between cases and controls, using the Chi-squared test and the Wilcoxon rank sum test.

2. Genetic predisposition

(Exome) sequencing can reveal a genetic predisposition. We ask all participants about the occurrence of femur fractures in the family. For genetic analysis Plink and ProABLE packages in R are used. (Exome) sequencing data are compared

to 200 controls from the ERGO study to identify genetic variants that are associated with AFF. This will be validated in the international osteoporosis consortia (GEFOS/GENOMOS).

3. Femur shape

Anatomical characteristics may predispose to an AFF. Femoral morphology and lower limb alignment can be analysed with available images (see also reference 37 en 38 in the research protocol) from patient files (DEXA scan, CT-scan, long leg X-ray). The department of Orthopaedics has material for comparison.

Secondary outcome

Patients' characteristics are described, such as risk factors for osteoporosis and data on general health. These are no primary outcomes, but can be used for future further analyses. Alcohol use, smoking and BMI can be compared to the mean values in the Dutch population (data available in CBS) using the one sample t-test. The health condition prior to the AFF will be evaluated with the EQ-5D questionnaire. Continuous data will be presented as means and categorical data as percentages. Our findings will be compared to previous findings in the medical literature.

Study description

Background summary

Osteoporosis and bisphosphonates
Osteoporosis is a common metabolic bone disease characterized by compromised bone strength predisposing individuals to an increased risk of fractures, which are associated with significant morbidity and mortality. It is estimated that

1:3 women and 1:7 men older than 60 years suffer from osteoporosis world-wide. Approximately 50% of women and 20% of men older than 50 years will sustain an osteoporosis-related fracture during their lifetime, and 20-25% of patients will die within 12 months after a hip fracture. Bisphosphonates are a key element in the treatment of osteoporosis. Randomized trials have shown that treatment with bisphosphonates substantially reduces the risk of all types of osteoporotic fractures, including vertebral fractures, non-vertebral fractures and hip fractures. Recent studies even show that bisphosphonates decrease mortality, independent of fracture reduction. Bisphosphonates are cheap now that generic forms are available and are increasingly prescribed all around the world. For instance Alendronate, a preferred bisphosphonate, was provided 320.000 times in the first six months of 2007 in the Netherlands. In the first half-year of 2000 that was 97.000 times.

Atypical femur fractures

Following the use of bisphosphonates in millions of patients in clinical practice, some unexpected possible adverse effects have been reported, including osteonecrosis of the jaw and atypical femur fractures (AFFs). After the first publication by Odvina in 2005, numerous case reports of AFFs appeared and multiple observational studies added evidence that particularly long-term use of bisphosphonates is associated with increased risk of unusal fractures of the proximal femur. Thus, AFF may be a severe side-effect of bisphosphonate use. However, a causal relationship between bisphosphonate use and AFF has not been established and the pathogenesis of AFFs remains unknown. One hypothesis is that lowering the rate of bone resorption by bisphosphonates leads to accumulation of microdamage, because fatigue bone is replaced more slowly. This phenomenon is called *frozen bone* and results in an increased fragility of the femoral cortex.

AFF has severe consequences for the patients involved. In most cases the femur breaks spontaneously or after minimal trauma. Unfortunately AFF often occur bilaterally and are associated with delayed healing or nonhealing.

The estimated incidence rate is one per 1000 long-term bisphosphonate users per year. However, the precise incidence is unknown because of a lack of diagnostic codes and adequately powered prospective studies, while observational studies are hampered by multiple sources of bias. Possibly AFFs are not always recognized as such, and therefore underdiagnosed.

Because of the attention given to this rare complication on the internet, by the treating physicians and by package inserts, patients needing bisphosphonates lose confidence in this treatment and become non-compliant. Fear of side effects is a well-known reason for non-compliance. Unfortunately patients do not realize that the medication prevents far more fractures than it causes. Even prescribing physicians fear to do more harm than good, which may result in undertreatment. The occurrence of these atypical fractures is one of the reasons that most guidelines advise not to treat patients with bisphosphonates for more than five years unless there are strong reasons to continue.

Patients* characteristics
Since bisphosphonates have been widely shown to prevent fractures, there must be individual patients* characteristics predisposing them to such an event. Besides, many patients with skeletal malignancies receiving massive doses of bisphosphonates never develop AFFs, and some patients with AFFs have never used bisphosphonates. Therefore it is plausible that factors other than bisphosphonate use contribute to the AFF.
So far these characteristics or risk factors have not been ensured. Use of co-medication such as glucocorticoids or proton-pump inhibitors was found to be associated with AFFs in some, but not all studies. In a systematic review amongst 141 cases of AFF, nearly 4 in 10 Caucasian women had used glucocorticoids. Other striking features are the relatively young age, the high number of comorbidities and non-osteoporotic bone densities described in several studies. Also, ethnicity appears to be a relevant factor. Patients of Asian descent are over-represented in some studies and AFFs may occur after a considerably shorter duration of bisphosphonates in these patients. More research is needed to identify clinical risk factors.

Genetic predisposition and femur shape analysis
Although some of the radiological features of AFFs resemble stress fractures, they appear to have their origin in the lateral cortex suggesting that they represent tensile failures of cortical bone. This may be caused by alterations to the normal pattern of collagen cross-linking. The frequent bilateral incidence of AFFs at the exact same anatomical location strongly suggests a mechanical etiology potentially related to the shape of the femur or systemic/structural bone pathology, factors that may have genetic influences. A genetic susceptibility to AFFs is also likely since various inherited metabolic bone diseases have been associated with AFFs, including X-linked hypophosphatemia, hypophosphatasia, osteopetrosis, and pycnodysostosis and Osteogenesis Imperfecta. We therefore propose that - more in general - patients who develop AFFs on bisphosphonates have an underlying genetic predisposition based on local biomechanical features related to femur shape or bone structure. Many experts in the field have stressed the importance to identify underlying causes, but so far most studies have been limited to case reports and observational data. No studies have been performed using a thorough genetic/genomic evaluation and in depth phenotyping with femur shape analysis. Femur morphology and lower limb alignment can be evaluated with medical images already available from patient files (DEXA, CT-scah, long leg X-ray).

Study objective

Primary Objective: to identify risk factors and the underlying mechanism of AFFs by:
- setting up a database with detailed information to define patients* characteristics.
- building a biobank with urine and blood samples from these patients.
- performing genetic/genomic studies in blood from these patients.

We will address these questions below:
- How is a patient with high risk at atypical femur fractures identified?
- Do our findings on patients' characteristics correspond with previous findings in medical literature?
- Does a genetic predisposition exist for atypical femur fractures?

The American Society for Bone and Mineral Research, among others, has emphasized the importance of furhter research on clinical risk factors for atypical femur fractures. A database with detailed information on patients* characteristics and genetic analysis on these patients will hopefully define risk factors and help us understand the underlying mechanisms of AFFs. Moreover a genetic analysis amongst these patients has not been performed yet in the area of medical research. This knowledge empowers medical specialists to individualize decisions on whether or not to continue bisphosphonate treatment, based on patients* risks and benefits. Confidence will be restored in treatment with bisphosphonates, compliance will increase and more fractures will be prevented. Based on the large number of patients with osteoporosis (estimated 800.000 in the Netherlands) this will lead to a substantial decrease in direct and indirect health costs, morbidity and mortality
The biobank and database will be a basis for national and international collaboration. The biobank provides blood and urine samples and thus facilitates further research, especially if new insights and/or diagnostic techniques become available.

Study design

The investigator determines whether a patient meets the inclusion criteria. A radiologist will be consulted if necessary. After written consent has been obtained, blood is drawn and subjects are requested to collect a first morning urine sample. The samples are used for biobanking and (exome) sequencing. Tests for bone turnover markers are performed only when these values have not been determined yet during routine analyses. Extensive information on a large number of variables is gathered, such as medical and family history, complete physical examination, co-morbidities, medication use and medical imaging (assessment of vertebral fractures). Also laboratory tests including bone turnover markers, vitamin D levels, liver and kidney function and bone density scores by DXA. Patient files are retrospectively viewed to obtain these data. Furthermore, questionnaires are used to obtain missing information. In case important data are lacking, the general practitioner or treating physician is contacted for further requirements. Some data are used to describe the study population and are not used for the primary outcome, though may be used for future further analyses.

This inventory is drawn up in cooperation with several hospitals in the Netherlands. Data are collected by researchers from Erasmus MC. Samples are stored in the Genetic Laboratory of Internal Medicine, Erasmus MC. The expected duration of this study is three years.

Patients* characteristics are described and compared to previous findings in the medical literature and - if possible - to the mean values in the Dutch population. Data from patients, such as bone density scores and medication use, are compared to sex- and age-matched controls from the ERGO study. Participants that use bisphosphonates will be matched with controls that use bisphosphonates as well.
A case-control study is carried out to compare genetic profiles between patients with AFF and 200 sex- and age-matched controls from the ERGO study. The genetic analysis takes place in the Genetic Laboratory of the department of Internal Medicine of Erasmus MC. For validation of genetic findings, we expect to use at least 200 cases identified in independent populations from the international osteoporosis consortia (GEFOS/GENOMOS).

Study burden and risks

For subjects involved there is no expected direct benefit. Questionnaires take approximately 20 minutes. Laboratory tests are done on a regular basis as part of the routine check for all subjects, hence the extra blood tubes and urine samples needed in this study are a minimal burden. Participation is risk-free or risks can be considered negligible, as one extra venipuncture is the only invasive procedure in this study. Preferably we will extract extra tubes of blood when subjects are at the hospital for regular monitoring. In this case, no extra venipuncture is necessary. Incapacitated adults are also included in this study, as AFF is a very rare complication and every single case of AFF is a valuable source of information.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion criteria
In order to be eligible to participate in this study, a subject must meet all of the following criteria:;- Patients must be 18 years or older.
- Patients known with a recent or past atypical femur fracture based on ASBMR criteria or suggested revised radiological criteria. ;ASBMR criteria
Two reports of a Task Force of the American Sociey for Bone and Mineral Research (ASBMR) resulted in diagnostic criteria for AFF. The fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare. Major features describe a localized periosteal or endosteal thickening of the lateral cortex at the fracture site and a fracture line with a transverse orientation that may become oblique as it progresses medially across the femur. The fracture must be non-comminuted or minimally comminuted and is associated with no or minimal trauma (fall from standing height or less). Complete fractures extend through both cortices and may be associated with a medial spike, while incomplete fractures only involve the lateral cortex. At least four out of five major features must be present. Minor features include generalized increased cortical thickness of the femoral diaphysis, prodromal pain, bilateral fracture and delayed fracture healing. ;Alternative criteria
The ASBMR criteria are internationally acknowledged, although they remain subject of debate. For instance, Feldstein et al. (Incidence and demography of femur fractures with and without atypical features, 2012) described considerable differences between patients with only major features and patients with both major and minor features. It may be that only the latter group is truly atypical. Furthermore, cortical thickness does not appear to be a relevant feature. Therefore, patients with fractures that meet criteria suggested by Schilcher et al. (Atypical femoral fractures are a separate entity, characterized by highly specific radiographic features. A comparison of 59 cases and 218 controls, 2013) are also included. According to these alternative criteria, a fracture angle between 75° and 105°, a local callus reaction and fracture location at the diaphysis are features strongly related with bisphosphonate-associated AFF.

Exclusion criteria

- The exclusion criteria as mentioned by the ASBMR Task Force consensus: fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathologic fractures associated with primary or metastatic bone tumors, periprosthetic fractures and miscellaneous bone diseases (e.g., Paget's Disease, fibrous dysplasia). ;- Patients from whom no written informed consent was obtained.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-10-2013
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	09-09-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-07-2020

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL44353.078.13