Metabolic Bone Disorders in patients attending the Fracture Liaison Service

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“Secondary Osteoporosis” revisited.

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PROEFSCHRIFT

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Feel your fingers, feel your toes
Grab your elbow, pinch your nose
Touch your ankle, tap your knees
Give your chin a little squeeze
You'll feel something hard inside
And it can not be denied
What you feel seems hard as stone
And it's something called the bone

Oh there are bones, bones, bones, bones
Bones inside of you
Bones, bones, bones, bones
More than just a few
So many you can count them
Amazing but it's true
There are bones, bones, bones, bones
Bones inside of you

There are bones inside your hand
In your feet to help you stand
In your elbow and your heel
Lots of lovely bones to feel
Though your bones are hard to see
Still you have them just like me
They are not outside but in
Yes they're underneath your skin

Yes there are bones, bones, bones, bones
Bones inside of you
Bones, bones, bones, bones
More than just a few
So many you can count them
Amazing but it's true
There are bones, bones, bones, bones
Bones inside of you

Sesame Street: The Count's Bone Song

Contents

List of abbreviations

25(OH)D	25-hydroxy vitamin D
1.25(OH)2D	1,25-dihydroxy vitamin D
ABQ	algorithm-based qualitative approach
ACE	angiotensin converting enzyme
adjRR	Adjusted relative risk
ASBMR	American society for bone and mineral research
BMD	bone mineral density
BMI	body mass index
CHF	congestive heart failure
CI	confidence interval
CKD	chronic kidney disease
CKD-MBD	chronic kidney disease–mineral bone disorder
COPD	chronic obstructive pulmonary disease
CPRD	clinical practice research datalink
CRP	C-reactive protein
CT	computed tomography
DDD	defined daily dosages
DXA	dual X-ray absorptiometry
EFFORT	European federation of national associations of orthopaedics and traumatology
eGFR	estimated glomerular filtration rate
ESR	erythrocyte sedimentation rate
EULAR	European league against Rheumatism
FHH	familial hypocalciuric hypercalcemia
FLS	fracture liaison service
FSH	follicle stimulating hormone
fT4	free tetra iodothyronine
FRAX	fracture risk assessment tool
HRT	hormone replacement therapy
IBD	inflammatory bowel disease
IL2R	interleukin 2 receptor
IOF	international osteoporosis foundation
iPTH	intact plasma PTH
IU	International unit
JIA	juvenile idiopathic arthritis
LH	luteinizing hormone
MDRD	modification of diet in renal disease

MGUS	monoclonal gammopathy of unknown significance
MRI	magnetic resonance imaging
NOF	national osteoporosis foundation
NOGG	national osteoporosis guideline group
non-VF	non vertebral fracture
OR	odds ratio
PET-scan	positron emission tomography
PHPT	primary hyperparathyroidism
PMD	pooled mean difference
PTH	parathyroid hormone
RA	rheumatoid arthritis
RCT	randomized controlled trial
RDA	recommended dietary allowances
RR	relative risk
SD	standard deviation
SECOB	secondary osteoporosis and metabolic bone diseases
SLE	systemic lupus erythematosus
SHPT	secondary hyperparathyroidism
SPSS	statistical package for the social sciences
TSH	thyroid stimulating hormone
TTG	anti-tissue transglutaminase antibody
Vit. D	Vitamin D
VF	vertebral fracture
VFA	vertebral fracture assessment
VieCuri MC	VieCuri Medical Centre
WHO	world health organisation

Chapter 1

Introduction

Fractures are a burden for patients and society, and osteoporosis is one of the risk factors for fractures. The overall incidence of fractures is high and increases with age (1), furthermore it is estimated that fracture incidence will further increase for both men and women in the near future due to aging of the population (2). In the Netherlands, patients 50 years or older are referred to the fracture liaison service (FLS) directly after their primary fracture treatment in order to evaluate and reduce the risk of subsequent fractures. However, there is a high variability in diagnostic procedures among the various FLSs, especially with regard to the evaluation of secondary osteoporosis and imaging of the spine (3). This thesis aims to provide insight in the yield and consequences of systematic implementation of diagnostic evaluation i.e. laboratory testing and spine imaging at the FLS.

The burden of fractures

Worldwide, the yearly incidence of osteoporotic fractures is high. In the year 2000, there were 9 million fractures worldwide, of which 1.6 million hip fractures, 1.7 million forearm fractures and 1.4 million clinical vertebral fractures (4). After the age of 50 years, the yearly incidence of fragility fractures, i.e. fractures occurring after a fall or lesser trauma, is highest in Caucasian women (100/10,000 patient years) and men (40/10,000 patient years), and will double worldwide between 2010 and 2040 mainly due to the expected increase in age of the population (5). At the age of 50 years, the remaining lifetime risk of fractures is reported to be >45% for women and >20% for men (6-10).

Between 2009-2011, more than 119,000 fractures occurred annually in patients of 50 years or older in The Netherlands (2, 11), 32% of them were considered osteoporosis-related. The estimation is, that in 2030 the incidence of osteoporosis related fractures will increase by 40%, and the costs by 50% (2).

Fractures are associated with increased morbidity, subsequent fracture risk and mortality risk. Pain and disability are directly related to the fracture and more than 40% of hip fracture patients do not return to their pre-fracture mobility after 1 year (12-14). The quality of life decreases after fractures, even more than in patients with diabetes mellitus, arthritis and lung diseases (15).

An initial fracture increases the risk of subsequent fractures. Within 5 years after an initial fracture, 24% of women and 20% of men sustain a subsequent fracture (16). The fracture risk is almost twice as high after an initial fracture than in the population without a history of fractures after the age of 50 years (17, 18). A prior vertebral fracture is even a stronger risk factor for sustaining a fracture than bone mineral density (BMD) (19). Timing is important. The risk of a subsequent fracture is not constant over time and is 5-10 times higher during the first years after the initial fracture than in the subsequent years after the baseline fracture, and remains elevated even 10 years after the baseline fracture (18,

20-23). This early and higher short-term risk in subsequent fracture has been described as imminent fracture risk (23-26).

About 40% of all fragility fractures in women and 24% of fragility fractures in men are subsequent fractures (27).The incidence of subsequent fractures is, both in men and in women, almost two times and in some cases even nearly four times as high as the incidence of a first fracture at any given BMD risk category (27).

Compared with those without fracture, elderly people who sustained hip, vertebral or non-hip non-vertebral fractures had a 1.5-fold to 2.0-fold increased risk of premature mortality (28). Mortality risk has been reported to be increased after any fracture, both in men and women (16, 29-31). The 5- and 10-year mortality is associated with a subsequent fracture (29, 30), 50% of women and 75% of men die within 5 years after a subsequent fracture (16, 30, 31). Other reasons for a transient increased mortality are not well known, but mortality risk has been associated with advancing age, fracture location, fracture care complications, low BMD, lower muscle strength and decreased physical activity (30, 32). Again timing is important, the highest mortality risk can be found in the first year after the fracture (29, 33).

Independent of age and BMD, the presence, number and severity of vertebral fractures are strong predictors of future fracture risk. Even more than other fractures, vertebral fractures are related to morbidity, and increased risk of subsequent fractures and mortality (17, 34-36). Although vertebral fractures are the most common fractures (37, 38), two thirds of vertebral fractures do not come to clinical attention because they do not present with clinical signs or symptoms of an acute fracture (39, 40).

The fracture liaison service

In 1999, the first initiative to facilitate case finding of patients with a recent fracture in order to provide routine assessment and, when indicated, treatment for osteoporosis, was reported in Glasgow and called: fracture liaison service (FLS) (41). Since this initial report, the organisation of post-fracture care has developed and currently FLS care has been considered as the most effective approach for evaluation and secondary fracture prevention in patients older than 50 years with a recent fracture by working groups of the American society for bone and mineral research (ASBMR), the international osteoporosis foundation (IOF) and the European league against Rheumatism/ European federation of national associations of orthopaedics and traumatology (EULAR-EFFORT) (42-44). In order to do so, patients with an initial fracture have to be identified and invited for the FLS, and evaluated at the FLS. As subsequent fracture risk and mortality risk are highest within the first year after the fracture, timing is important: patients with a recent fracture need to be assessed and treated, if indicated, as soon as possible after the fracture.

A systematic approach of secondary fracture prevention has been described as a 5-step plan (45). In the context of the FLS, the first step consists of identification and invitation of all patients 50 years or older who have had a fracture and thus could benefit from post-fracture care. The second step consists of risk evaluation, including the identification of clinical risk factors, measurement of BMD and identification of (prevalent) vertebral fractures. In the third step, differential diagnosis is performed by further evaluation of underlying disorders and medication known to be associated with osteoporosis or fracture risk, which implies anamnesis but also laboratory testing. The fourth step includes lifestyle interventions to improve bone health and to reduce both fracture and fall risk. General lifestyle interventions include stop smoking, moderation of alcohol intake, and specific lifestyle interventions focus on adequate calcium intake and vitamin D supplementation when needed. Furthermore, according to guideline recommendations specific anti-osteoporosis medication can be started in high-risk patients (11). The fifth step implies follow-up of long term treatment, including assessment of compliance, side effects and possible contra-indications (45).

Around 2004, the first Dutch FLS initiatives were reported in Groningen (46) and Maastricht (47). A FLS outpatient clinic was started at the VieCuri MC in Venlo in 2007. In 2011, the Dutch guideline on Osteoporosis and Fracture Prevention (11) advocated to systematically evaluate patients with a recent fracture. Meanwhile, an FLS has been implemented in most hospitals in the Netherlands and is part of the care for patients with a recent fracture (3).

Secondary osteoporosis

The most common method to evaluate BMD in daily practice is by using dual X-ray absorptiometry (DXA) measurement in the spine and hip. The BMD measured in a patient is compared to a healthy young reference population, and with every standard deviation decrease the fracture risk doubles (48). Osteoporosis has been defined by the WHO as a T-score of ≤ -2.5, osteopenia as a T-score between -2.5 and -1.0 and a normal BMD as a T-score ≥ -1.0 (49).

Historically, osteoporosis has been defined as primary (post-menopausal or age related) or secondary osteoporosis. Osteoporosis is considered secondary when disorders, medication or deficiencies are the underlying cause (50). However, also for “primary” osteoporosis an underlying mechanism is known, i.e. estrogen deficiency in women, or testosterone deficiency in men after the age of 70 years.

Well known examples of disorders and medications associated with secondary osteoporosis are chronic inflammatory diseases (rheumatoid arthritis (RA), inflammatory bowel disease, systemic lupus erythematosus (SLE), chronic obstructive pulmonary disease (COPD)), endocrinopathies (hyperparathyroidism, hyperthyroidism,

hypercortisolism), malabsorption (celiac disease), and medications such as glucocorticoids and anti-epileptic drugs (50). These disorders and medications decrease bone quality and increase fracture risk by influencing 1) the recruitment, activity, coupling and balance of osteoblasts, osteoclasts and osteocytes and 2) the quality of existing and newly formed bone.

Overall bone turnover is increased in primary hyperparathyroidism (51-53) and (subclinical) hyperthyroidism (54-56). More specifically, osteoclast activation is increased in inflammatory diseases such as RA, leading to lower BMD (57). The changes in bone turnover are not always reflected by BMD as measured by DXA (58). In primary hyperparathyroidism, despite an increase in bone turnover, microarchitecture of bone can be conserved, even when fracture risk is elevated (53). Other diseases associated with secondary osteoporosis lead to an increased fracture risk despite a rather normal BMD, for example type 2 diabetes mellitus (59-61).

It has been shown that fractures in patients using glucocorticosteroids occur at higher BMD than in patients who do not use glucocorticosteroids and that fractures associated with glucocorticosteroid use occur in patients without osteoporosis (62-64). Referring glucocorticosteroid use as "secondary" osteoporosis therefore is too restrictive. Whether this applies also for other "secondary" causes for osteoporosis in patients presenting with a recent fracture was unknown.

At the time that Dutch FLSs were initiated, the Dutch guideline advocated to perform laboratory testing for "secondary osteoporosis" in FLS patients only if they were diagnosed with osteoporosis (11). However, several disorders may affect bone turnover and bone quality and therefore may attribute to fracture risk in a way that is not always reflected by low BMD. Furthermore, although patients with osteoporosis have an increased risk for fractures, less than 50% of patients presenting with a fracture have osteoporosis (27, 65). Hence laboratory evaluation for metabolic bone disorders may also be useful in FLS patients without osteoporosis. As less than 50% of patients presenting with a recent fracture at the FLS was diagnosed with osteoporosis as measured by DXA and defined as a T-score of -2.5 or below, the question was raised whether and to what extent disorders that attribute to fracture risk would be present in patients with a recent fracture but without osteoporosis.

Vitamin D deficiency

Serum 25(OH)D <25-30 nmol/l leads to a decreased intestinal calcium absorption, secondary hyperparathyroidism, impaired mineralization of osteoid (osteomalacia) and extra-skeletal manifestations (66). Already at serum 25(OH)D <50 nmol/l, an increase in parathyroid hormone (PTH) can be observed (67). Although in patients with serum 25(OH)D 25-50 nmol/l intestinal calcium absorption and bone mineral deposition are

largely within normal range, secondary hyperparathyroidism can be observed, as well as increased bone turnover and accelerated bone loss (66).

In the Netherlands, the Health Council set the serum 25(OH)D level to be at least 30 nmol/l for the population 50-70 years. Vitamin D deficiency was therefore defined as a serum 25(OH)D <30 nmol/l, and an insufficiency as a 25(OH)D <50 nmol/l (68). In the general population vitamin D insufficiency and deficiency are highly prevalent (69). There was however no literature about a 25(OH)D <50 nmol/l in patients 50 years or older with a recent clinical fracture at the FLS.

Furthermore, there was a knowledge gap regarding the ideal vitamin D supplementation dose in FLS patients with a low serum 25(OH)D (70). Many factors have been reported to affect changes in serum 25(OH)D when using supplementation, for example age, gender, body mass index (BMI) and body composition, genetic factors and, more technically, variability in assays (71). We intended to answer the question whether the dose of vitamin D supplementation should be individualised according to baseline serum 25(OH)D, or whether 800IU per day would be enough for most.

Vertebral fractures

Although vertebral fractures are the most common osteoporotic fractures (37, 38), most of them occur without the acute symptoms and signs of a fracture (39, 40) and therefore are underdiagnosed. The presence of a vertebral fracture is a sensitive marker of decreased bone quality. Vertebral fractures, whether or not accompanied by an acute symptomatic episode, reflect a decrease in resistance of the bone to trauma or to mechanical loading during daily activities such as lifting objects or bending (72). The presence, number and severity of vertebral fractures are strong predictors of subsequent vertebral and non-vertebral fracture risk, independent of age and BMD (36, 73). Furthermore, as has been shown for subsequent non-vertebral fractures (21), the risk of subsequent radiographic vertebral fractures is highest within short term after an incident radiographic vertebral fracture, up to 20% within the first year (22).

Vertebral fractures can be found in patients with a recent non-vertebral fracture, and as expected patients who sustained a hip fracture, who had a spine T-score ≤-2.5 or a low BMI, or who had had more than one non-vertebral fracture are more likely to have a prevalent vertebral fracture (74, 75). However, in patients presenting with a non-vertebral fracture, vertebral fractures were also found in 19% of patients with osteopenia and 16% of patients with normal BMD (74).

Vertebral fractures can be diagnosed on X-rays, DXA, computed tomography (CT) and magnetic resonance imaging (MRI), and image analysis for the presence of vertebral fractures is referred to as vertebral fracture assessment (VFA). DXA-VFA has the

advantage of low radiation, a high negative predictive value to diagnose vertebral fractures compared to X-rays (76) and can be performed at the same time and with the same DXA device as the BMD measurement of the spine and hip. Several methods are available to evaluate the presence of vertebral fractures. The most frequently used method is the semi-quantitative method according to Genant, based on anterior, mid-vertebral or dorsal height loss (77), which can be applied to X-rays and VFA. Three different types of deformity can be distinguished, based on height loss in the anterior side (crush), posterior side (wedge), and/or middle (biconcavity) of the vertebral body. Height loss of respectively 20-24%, 25-39% or ≥40% is classified as a vertebral fracture grade 1, 2 or 3. An algorithm-based qualitative approach (ABQ) is another method that focusses on endplate fractures of vertebrae but does not take into account anterior or posterior height loss. On VFA, the ABQ methodology identifies fewer vertebral fractures compared to semi-quantitative techniques (78, 79).

As vertebral fractures are associated with an increased risk of subsequent fracture, the Dutch guideline (11) recommends evaluation of the presence of (prevalent) vertebral fracture in patients with a non-vertebral fracture and a T-score <-1.0 and furthermore to start a treatment in patients with osteopenia and a vertebral fracture grade ≥2 according to Genant (77). The clinical consequences of systematic application of VFA in all FLS patients were unknown.

Sarcoidosis

An example of a disease associated with secondary osteoporosis, is sarcoidosis. Despite the fact that BMD can be normal (80, 81) and does not change over time (82), patients with sarcoidosis have an increased risk of radiographic vertebral fractures (80, 82) and other osteoporotic fractures (83). Besides the chronic inflammation, glucocorticoid use as a current treatment for sarcoidosis could be an explanation for the increased fracture risk. Furthermore, in sarcoidosis the vitamin D metabolism is disturbed, with production of 1.25(OH)2D in granulomatous cells. High levels of 1.25(OH)2D are associated with induced bone resorption and with lower lumbar BMD in female patients with sarcoidosis (84). However, whether the risk of clinical vertebral and non-vertebral fractures is increased in patients with sarcoidosis compared to the general population, and if there is an association with glucocorticoid use, was not known.

Outline of this thesis

The overall aim of this thesis was to provide insight in the yield and consequences of systematic implementation of laboratory testing and spine imaging in patients with a recent fracture at the FLS.

In **chapter 1,** the background of post fracture FLS care and the knowledge gaps regarding diagnostic evaluation with laboratory testing and vertebral fracture assessment in the FLS population are described.

In **chapter 2**, we evaluated the prevalence of known metabolic bone disorders and evaluated to what degree a limited laboratory test set revealed previously unknown metabolic bone disorders in patients at the FLS. In addition, the prevalence of low serum 25(OH)D and low calcium intake was evaluated.

Chapter 3, we summarized the currently available literature on newly diagnosed secondary osteoporosis and metabolic bone disorders in patients with osteoporosis and in patients with a recent clinical fracture. The purpose of this review was to provide guidance to clinicians about which laboratory tests should be performed in patients with osteoporosis or with a recent fracture, regardless of BMD.

Guidelines on the need for dose adaptation of vitamin D according to baseline 25(OH)D were inconclusive. In **chapter 4**, we studied the effect of higher supplementation doses in FLS patients with lower serum 25(OH)D levels on achieved serum 25(OH)D.

In **chapter 5**, we performed a meta-regression analysis based on randomized controlled trials in adults to review the influence of supplementation-related factors (dose and duration) and patient-related factors (age and baseline serum 25(OH)D) on changes in serum levels of serum 25(OH)D.

In **chapter 6**, the proportion of patients presenting at the FLS with a recent non-vertebral fracture that had spine imaging was compared before and after implementation of the Dutch guideline. The prevalence of vertebral fractures before and after systematic implementation of VFA was compared, and the impact on the percentage of patients who were eligible for treatment.

Sarcoidosis is a chronic inflammatory disease, in which fragility fractures have been reported despite normal BMD. In **chapter 7**, we assessed whether patients with sarcoidosis have an increased risk of clinical (vertebral) fractures compared to the general population. The second objective was, to estimate their fracture risk, stratified by glucocorticoid use.

In **chapter 8**, we provide a summary of the main results of this thesis.

Finally, in **chapter 9**, we give a general discussion of our findings, including future perspectives for clinical practice and research.

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Chapter 2

Contributors to secondary osteoporosis and metabolic bone diseases in patients presenting with a clinical fracture

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Abstract

Background

Previously undetected contributors to secondary osteoporosis and metabolic bone diseases (SECOB) are frequently found in patients with osteoporosis, but the prevalence in patients at the time they present with a clinical fracture is unknown.

Methods

All consecutive patients with a recent clinical vertebral or non-vertebral fracture, who were able and willing to be investigated (n=626: 482 women, 144 men, age range 50–97 yr) had bone mineral density and laboratory investigations (serum calcium, inorganic phosphate, 25-hydroxyvitamin D, creatinine, intact PTH, TSH, free T4, serum and urine protein electrophoresis, and in men also serum testosterone).

Results

Known SECOB contributors were present in 23.0% of patients and newly diagnosed SECOB contributors in 26.5%: monoclonal proteinemia (14 of 626), renal insufficiency grade III or greater (54 of 626), primary (17 of 626) and secondary (64 of 626) hyperparathyroidism, hyperthyroidism (39 of 626), and hypogonadism in men (12 of 144). Newly diagnosed SECOBs, serum 25-hydroxy-vitamin-D less than 50 nmol/l (in 63.9%), and dietary calcium intake less than 1200 mg/d (in 90.6%) were found at any age, in both sexes, after any fracture (except SECOB in men with finger and toe fractures) and at any level of bone mineral density.

Conclusion

At presentation with a fracture, 26.5% of patients have previously unknown contributors to SECOB, which are treatable or need follow-up, and more than 90% of patients have an inadequate vitamin D status and/or calcium intake. Systematic screening of patients with a recent fracture identifies those in whom potentially reversible contributors to SECOB and calcium and vitamin D deficiency are present.

Introduction

Guidelines on osteoporosis advocate the evaluation of patients presenting with osteoporosis to exclude diseases that mimic osteoporosis and identify the cause of osteoporosis and contributory factors [National Osteoporosis Guideline Group (1, 2)] before therapy [National Osteoporosis Foundation(3)] and in patients with or without fracture [German guideline osteoporosis diagnosis and therapy (4)]. Many contributors to secondary osteoporosis and metabolic bone disease (SECOB) have been identified (3-5). If SECOB contributors are not recognized, treatment to prevent fractures may be suboptimal (6). Many contributors to SECOB are treatable [*e.g.* hyperthyroidism], need further investigation [*e.g.* idiopathic hyperparathyroidism], or need follow-up [*e.g.* monoclonal gammopathy of unknown significance (MGUS)].

In studies including various subgroups of patients with osteoporosis and/or a recent fracture, SECOB was found in 27–80%, including deficient calcium intake and vitamin D deficiency (5, 7, 8).

Therefore, we evaluated the prevalence of contributors to SECOB and low calcium intake and vitamin D deficiency separately in consecutive patients at the time they presented at the emergency unit of the hospital due to a clinical vertebral or non-vertebral fracture.

Subjects and methods

Study design and population

A prospectively planned cross-sectional chart review study was conducted among men and women presenting with a newly diagnosed clinical vertebral or non-vertebral fracture. Subjects were all consecutive patients older than 50 yr who presented at the emergency department of the VieCuri Hospital Noord-Limburg (The Netherlands) from January 2007 until September 2008. After primary fracture care, a specialized nurse invited all patients to the fracture and osteoporosis outpatient clinic of the hospital for bone mineral density (BMD) measurement and laboratory tests. Fractures were classified according to Center *et al. (9)* into hip fractures, major fractures (vertebra, pelvis, distal femur, proximal tibia, multiple rib, and humerus), minor fractures (all remaining osteoporotic fractures, except fingers and toes), and finger and toe fractures. Patients with metastatic cancer to bone, high-impact multi-trauma, osteomyelitis, or failure of a prosthesis were excluded (n=9). Patients who responded and agreed received a detailed questionnaire for evaluation of clinical risk factors for fractures, medical history, medication, previous fractures, and calcium intake and were planned for dual x-ray absorptiometry (DXA) measurement and a blood test. A visit at the outpatient clinic was scheduled after completion of these tests. At this visit height and weight were assessed,

the questionnaire was evaluated and when necessary additional questions were asked, and physical examination was performed by a physician. If laboratory results were abnormal, additional investigations were performed for detailed evaluation of newly diagnosed disorders when necessary. Depending on the BMD results, calcium intake and serum 25-hydroxyvitamin D [25(OH)D] levels, patients were treated with adequate calcium intake, vitamin D supplements, and anti-osteoporosis medication according to the Dutch guidelines for treatment of osteoporosis (10).

Data collection

The following demographic and historical data were collected from each subject 2–4 months after fracture: age, ethnicity, age at menopause, current dietary and supplemental calcium intake, vitamin D supplementation, regular exercise, history of cigarette smoking (ever smoked *vs.* never smoked), and alcohol intake (3 U/d or more *vs.* less than 3 U/d); medical and pharmacological history including previous fractures, nephrolithiasis, years of estrogen replacement use; the use of other anti-resorptive agents and diuretics; and family history (first and second degree relatives) of osteoporosis or fractures. Height, weight, and body mass index (kilograms per square meter) were recorded.

Dietary calcium intake was ascertained from a food frequency questionnaire and completed by 524 of the 626 subjects and then reviewed by the physician during the outpatient clinic visit. The questionnaire was constructed by compiling a list of foods with the highest calcium content, primarily dairy products including milk and cheese consumption, and asking the subjects to indicate their daily and weekly consumptions of these food products. Total calcium intake was calculated by adding the average daily dietary calcium intake as evaluated by long-term intake dietary records (11) to the dosage and frequency of daily calcium supplements.

Bone densitometry

BMD in the left or right hip and the lumbar spine was determined using DXA with the Hologic QDR 4500 (Hologic, Bedford, MA). Diagnosis of osteoporosis was based on the World Health Organization criteria for BMD (12), as provided by the manufacturer for women and men and which are based on the National Health and Nutrition Examination Survey III database. T-score calculations were done for women with a female and for men with a male reference population, as provided by the manufacturer. Patients were classified according to the lowest value of T-score in total hip, femoral neck, or lumbar spine: osteoporosis as a T-score of -2.5 or less, osteopenia as a T-score between -2.5 and -1.0, and normal BMD as a T-score of -1.0 or higher.

Laboratory tests and abnormalities

Basic laboratory tests included serum sodium, potassium, calcium, inorganic phosphate, albumin, creatinine, free tetraiodothyronine (fT4), TSH, serum aminotransferases (aspartate aminotransferase and alanine aminotransferase), alkaline phosphatase, intact plasma PTH (iPTH), 25(OH)D, and serum and urine protein electrophoresis for all patients. The estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease study group (MDRD) equation. The stages of chronic kidney disease (CKD) were defined according to the guidelines for CKD of the National Kidney Foundation (13). Primary hyperparathyroidism was diagnosed by hypercalcemia in the presence of inappropriately normal or elevated levels of iPTH (14, 15). Secondary hyperparathyroidism was defined as elevated plasma iPTH in combination with 25(OH)D less than 50 nmol/liter or CKD stage 3 or greater, or both. Hyperthyroidism was defined by TSH values less than 0.40 mU/liter with elevated fT4 levels and subclinical hyperthyroidism by TSH values less than 0.40 mU/liter with normal fT4 levels. Hypogonadism was defined as a clinical syndrome complex, which comprises both symptoms as well as biochemical testosterone deficiency. Testosterone deficiency was defined by a total testosterone level less than 8 nmol/liter (16). When inappropriate, additional evaluation followed. Serum and urine protein electrophoresis was performed for detection of plasma cell disorders (17, 18). The diagnosis of MGUS required a serum monoclonal protein, less than 10% bone marrow plasmacytosis, no evidence of other B-cell proliferative disorders, and no end organ damage due to the plasma cell proliferative process (*i.e.* bone lesions, hypercalcemia, renal insufficiency, anaemia) (19).

Statistics

SPSS software (version 16.0; SPSS Inc., Chicago, IL) was used for the statistical analyses. Descriptive statistics, Chi-Square, and ANOVA were used for comparing the responders with the non-responders and the participating men and women on baseline fracture locations and BMD.

To identify the possible predictors for SECOB, possible risk factors were assessed using multivariable logistic regression models. Possible risk factors included in the model were age, weight, height, BMD (normal, osteopenia, osteoporosis at any side), prior fracture after the age of 50 yr, location of current fracture, previously known SECOB, use of a walking aid, difficulties getting up from a chair, current smoking, and alcohol intake of 3 U/d or more.

Because low calcium intake and vitamin D deficiency are mentioned as the most common types of SECOB in several studies, even though they are not treated separately as such in guidelines, additional descriptive analyses are presented for patients with new SECOB, with and without secondary hyperparathyroidism, and according to a dietary calcium intake less than 1200 mg/d and 25(OH)D levels less than 50 nmol/liter.

Results

In total, 893 consecutive patients (221 men and 672 women) with a clinical vertebral or non-vertebral fracture were asked to participate in this study. Two hundred thirty-seven subjects (70 men and 167 women) did not respond to the invitation or did not agree or were not able to participate. Twenty subjects with one or more vertebral fractures (five men and 15 women) were excluded because no DXA measurement was performed. Additionally, 10 patients (two men and eight women) were excluded because laboratory results were not available. Therefore, 626 subjects (144 men and 482 women) were available for this study. Characteristics of these patients are shown in Table 1.

Table 1. Characteristics of patients presenting with a clinical vertebral or non-vertebral fracture

Variables	Men (n = 144)	Women (n = 482)
Age (yr)	66.0 ± 10.2	71.0 ± 10.6
Height (cm)	175.4 ± 7.5	162.5 ± 6.7
Weight (kg)	78.7 ± 13.2	68.5 ± 12.9
Body mass index	25.6 ± 3.8	26.0 ± 4.6
T-score lumbar spine	-1.3 ± 1.5	-1.8 ± 1.3
T-score femoral neck	-1.5 ± 1.1	-1.7 ± 1.1
T-score total hip	-1.0 ± 1.1	-1.3 ± 1.2
Dietary calcium intake (mg/day)	763 ± 301	860 ± 290
25 OH vitamin D (nmol/l)	50.7 ± 26.2	40.1 ± 22.8

The distribution of the different types of fractures in the patients who responded and were eligible for this study and non-responders are as following: the non-responders were significantly older (74.9±11.5 *vs.* 69.9±10.7 yr; $p < 0.0001$), consisted of more men (men: 29.5 *vs.* 23.0%; $p = 0.047$), and sustained significantly more hip fractures (22.8 *vs.* 8.0%; $p < 0.0001$) but significantly fewer other major fractures (26.6 *vs.* 33.1%; $p = 0.034$).

Of the fracture patients, 15.0% had normal BMD (men: 16.7% and women: 14.5%), 45.7% had osteopenia (men: 55.6% and women: 42.7%), and 39.3% had osteoporosis (men: 27.8% and women: 42.7%). Compared with patients who sustained minor and major fractures, significantly more patients with a hip fracture had low BMD ($p < 0.0001$). Osteopenia was found in 49.1% of patients with a minor fracture, in 39.1% of patients with a major fracture, and in 42.0% of patients with a hip fracture, and osteoporosis was found in 31.4% (minor fracture), 49.3% (major fracture), and 58.0% (hip fracture).

We found a total number of 207 known contributors to SECOB in 144 patients (23.0%); 58 patients had two or more known factors (Table 2).

Table 2. Prevalence of known contributors to secondary osteoporosis and metabolic bone disease at presentation with a clinical fracture

Known contributor	Number of patients (% of total)	Number of women (% of all women)	Number of men (% of all men)
History of glucocorticoid use	53 (8.5%)	42 (8.7%)	11 (7.6%)
Premature ovarian failure	25 (4.0%)	25 (5.2%)	-
History of alcoholism	16 (2.6%)	4 (0.8%)	12 (8.3%)
History of hyperthyroidism	4 (0.6%)	4 (0.8%)	0
Current anticonvulsant use	6 (1.0%)	5 (1.0%)	1 (0.7%)
History of rheumatoid arthritis or systemic lupus erythematosus	32 (5.2%)	25 (5.2%)	2 (1.4%)
History of COPD	65 (10.4%)	49 (10.2%)	16 (11.1%)
History of chronic kidney disease	3 (0.5%)	3 (0.6%)	0
History of inflammatory bowel disease or malabsorption	3 (0.5%)	2 (0.4%)	1 (0.7%)
Total (with one or more factors)[#]	144 (23.0%)	115 (23.9%)	29 (20.1%)

[#] We found a total number of 207 known contributors in 144 patients, 58 patients had 2 or more known contributors.

In 166 of the 626 patients (26.5%), 200 previously undetected disorders with a potential influence on bone or mineral metabolism were identified, 27 of them had two, two had three, and one had four new SECOBs. The frequency of various newly detected disorders is shown in Table 3. We found monoclonal proteinemia (14 of 626), renal insufficiency grade III or more (54 of 626), primary (17 of 626) and secondary (64 of 626) hyperparathyroidism, hyperthyroidism (39 of 626), and hypogonadism in men (12 of 144). Patients with vitamin D deficiency were not included in the SECOB counts unless they had secondary hyperparathyroidism. We also found eight patients with unexplained elevated iPTH levels, these were not included into the newly diagnosed SECOB group.
Additionally, in 43 patients alkaline phosphatase was elevated (≥140 IU/liter); in 27 patients it normalized after 3–4 months and therefore is most likely related to the recent fracture. In nine patients biliary problems were detected; in six patients with only slightly elevated levels (between 140 and 160 IU/liter), we have no follow-up data; and one patient had a blunt abdominal trauma with ascites. Erythrocyte sedimentation rate (ESR) was elevated in 67 patients; 20 of these patients had a confirmed pulmonary or urinary tract infection with normalization of ESR, four patients had active rheumatoid arthritis or polymyalgia rheumatica, three patients had a chronic elevated ESR of unknown origin, one patient was later diagnosed with liver cirrhosis, and one patient had a pancreatic carcinoma at follow-up.

Table 3. Newly diagnosed contributors to secondary osteoporosis and metabolic bone disease (SECOB) in men and women with a clinical fracture

Disorders	Prevalence of newly diagnosed contributors to SECOB					
	Men (n=144)		Women (n=482)		Total (n=626)	
	No	%	No	%	No	%
MGUS/myeloma	4/1	2.8/0.7	9/0	1.9/0	13/1	2.1/0.2
CKD						
Stage 3	7	4.9	45	9.3	52	8.3
Stage 4	1	0.7	1	0.2	2	0.3
Hyperparathyroidism (HPT)						
1º *	1	0.7	16	3.3	17	2.7
2º due to vit. D deficiency	11	7.6	38	7.9	49	7.8
2º due to CKD	2	1.4	4	0.8	6	1.0
2º due to vit. D deficiency and CKD	0	0	9	0.8	9	1.4
Hyperthyroidism**	8	5.6	31	6.4	39	6.2
Hypogonadism	12	8.3			12	1.9
Total number of new contributors	47		153		200	
Patients with at least one new contributor***	40	27.8	126	26.1	166	26.5

* Of the 17 patients (2.7%) with primary hyperparathyroidism, 12 (1.9%) had elevated and 5 (0.8%) inappropriately normal iPTH levels

**Of the 39 patients (6.2%) with hyperthyroidism, 30 (4.8%) were diagnosed with overt and 9 (1.4%) with subclinical hyperthyroidism

***Since there were 31 subjects (6 men and 25 women) with more than one contributor to SECOB, the total number of men and women with one or more contributors is lower than the sum of the individual contributors

1º = primary HPT, 2º = secondary HPT

MGUS = monoclonal gammopathy of unknown significance

CKD = chronic kidney disease

Newly diagnosed contributors to SECOB were found at any age, in both sexes, after any fracture (except in men with finger and toe fractures) and at any level of BMD. We found one or more new contributors in 44 patients who already had a known contributor at the moment of the fracture (30.6%). The percentage of patients with a newly detected contributor to SECOB was inversely related to BMD. In patients with a normal BMD, we found a newly diagnosed factor in 16.7% of the male and in only 7.1% of the female patients. With osteopenia we found a new factor in 23.8 and 27.7% of men and women, respectively. In the patients with osteoporosis, a new factor was diagnosed in 42.5% of men and 31.1% of women (Table 4).

Table 4. Prevalence of newly diagnosed contributors to secondary osteoporosis and metabolic bone disease (SECOB) in men and women with a fracture according to skeletal status (normal BMD, osteopenia and osteoporosis)

	Newly diagnosed contributors to SECOB			
	Men		Women	
	No (%)	Yes (%)	No (%)	Yes (%)
Normal BMD	20 (83.3%)	4 (16.7%)	65 (92.9%)	5 (7.1%)
Osteopenia	61 (76.3%)	19 (23.8%)	149 (72.3%)	57 (27.7%)
Osteoporosis	23 (57.5%)	17 (42.5%)	142 (68.9%)	64 (31.1%)
Total	104 (72.2%)	40 (27.8%)	356 (73.9%)	126 (26.1%)

Patients with vitamin D deficiency were not included unless they had secondary hyperparathyroidism

The multivariable logistic regression analysis showed that increasing age [odds ratio (OR) 1.04, confidence interval (CI) 1.02–1.06)], being male (OR 1.78, CI 1.16–2.73), having osteopenia (OR 2.67, CI 1.34–5.32), and having osteoporosis (OR 2.98, CI 1.47–6.05; normal BMD as reference) were significant risks. No interactions were found, and therefore, all risk factors are independent risk factors.

A serum 25(OH)D less than 50 nmol/liter was found in 400 patients (63.9%), 75.9% in 166 patients with a newly detected contributor to SECOB (50% with secondary hyperparathyroidism and 50% with normal PTH) and 59.6% in 460 patients without newly detected contributors to SECOB (with by definition a normal PTH). If patients with 25(OH)D less than 50 nmol/liter, regardless of the presence of secondary hyperparathyroidism, would also have been labelled as having SECOB, the number of patients with a newly diagnosed contributor to SECOB would have been 440 (70.3%). With a cut-off level of serum 25(OH)D less than 75 nmol/liter, the number of patients with newly detected SECOB would even have been 563 (89.9%).

Based on the data of 524 patients who completed the food questionnaire, only 9.4% had a dietary daily calcium intake of 1200 mg/d or greater, whereas 58.2% had a dietary daily calcium intake less than 1200 mg in combination with a 25(OH)D level less than 50 nmol/liter (see fig. 1). In combination with a vitamin D level less than 75 nmol/liter, this was even 80.3%.

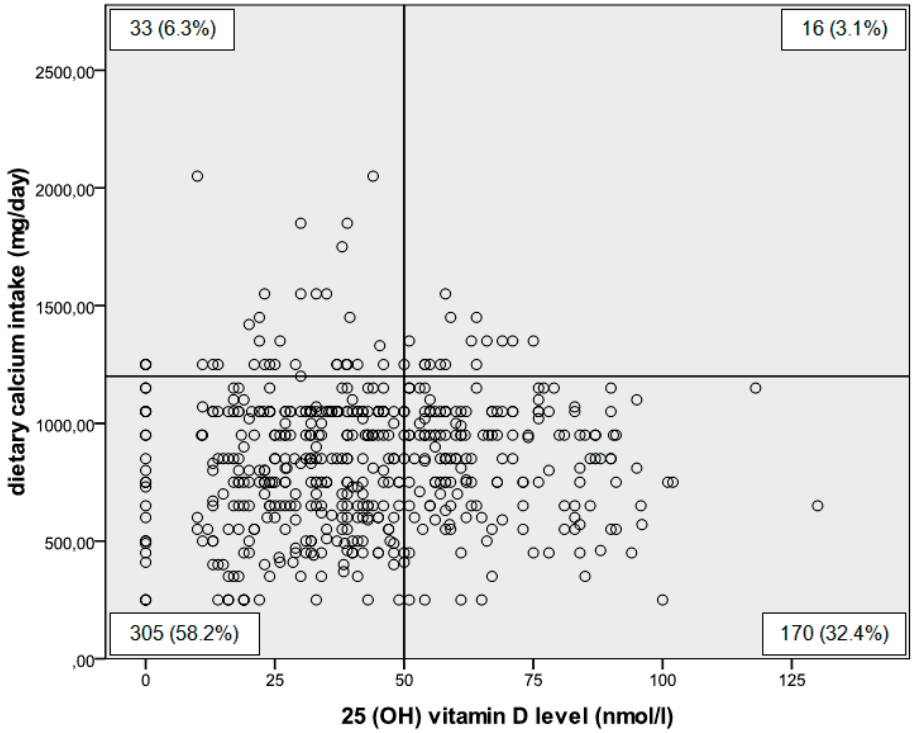

Figure 1. Serum 25(OH)D levels (x-axis) and daily calcium intake (y-axis) in 524 patients older than 50 years at the time they present with a clinical vertebral or non-vertebral fracture. Number and (%) of patients are given for the four quadrants.

In Fig. 2, the percentages of patients with a new contributor to SECOB, 25(OH)D level less than 50 nmol/liter, and a daily dietary calcium intake less than 1200 mg are presented. Newly diagnosed contributors to SECOB, serum 25(OH)D less than 50 and 75 nmol/liter, and dietary calcium less than 1200 mg/d were found in both sexes, at any age, after any fracture (except SECOB in men with finger and toe fractures) and at any level of BMD. The percentage of patients with a new contributor to SECOB was significantly different for age decades, skeletal status (both $p < 0.001$), and fracture type ($p < 0.05$) but not for sex. The percentage of patients with 25(OH)D less than 50 nmol/liter was significantly different for age decades, skeletal status (both $p < 0.001$), sex ($p < 0.01$), and fracture type ($p < 0.05$). There was no significant difference for calcium intake less than 1200 mg/d between age decades, fracture type, sex, and skeletal status.

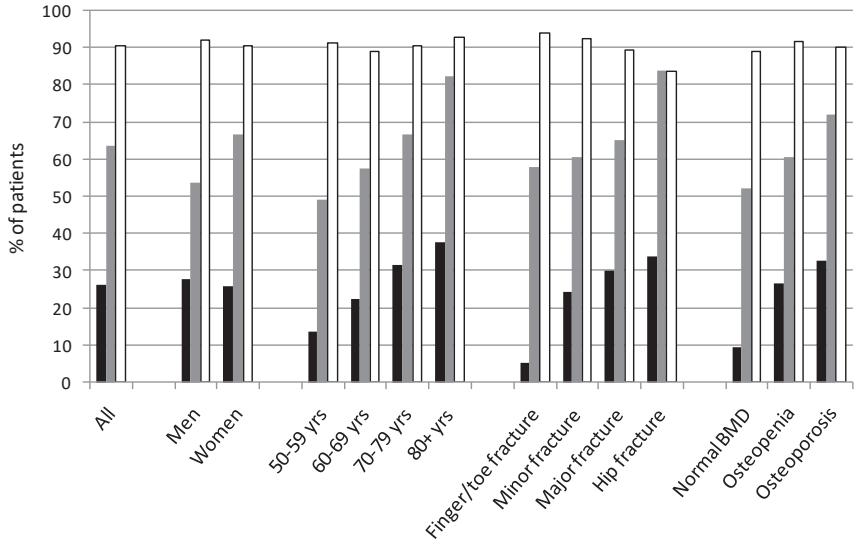

Figure 2. Percentages of patients with newly diagnosed contributors to secondary osteoporosis and metabolic bone disease (black columns), serum 25(OH)D level <50 nmol/l (grey columns) and dietary calcium intake < 1200 mg/day (white columns) according to sex, age, fracture location and BMD*.
* The percentage of patients with a new contributor to secondary osteoporosis and metabolic bone disease (SECOB) was significantly different for age decades, skeletal status (both $p<0.001$) and fracture type ($p<0.05$) but not for sex. The percentage of patients with 25(OH)D <50 nmol/l was significantly different for age decades, skeletal status (both $p<0.001$), sex ($p<0.01$) and fracture type ($p<0.05$). There was no significant difference for calcium intake <1200 mg per day between age decades, fracture type, sex and skeletal status.

Discussion

In this study we investigated the prevalence of previously undiagnosed contributors to SECOB in consecutive patients with clinical fractures. Our study indicates that undiagnosed contributors are present in 26.1% of women and 27.8% of men after the age of 50 yr presenting with a clinical fracture. When patients with already known mediators or diseases affecting bone and mineral metabolism are taken into account (*i.e.* 23.0%), a total of 42.5% of patients had one or more known or new contributors to SECOB. In addition, a high percentage of patients had deficient dietary calcium intake in combination with vitamin D deficiency, even when calculated according to the most conservative thresholds.

A remarkable finding was that newly diagnosed contributors to SECOB, serum 25(OH)D less than 50 nmol/liter, and calcium intake less than 1200 mg/d, were found in both sexes, at all ages, after all fractures (except SECOB in men with fractures of fingers and toes), and at any level of BMD. The clinical implication is that all patients at the time of a clinical vertebral or non-vertebral fracture should be evaluated for the presence of previously

unknown SECOB contributors and adequate calcium intake and vitamin D status. From a semantic point of view, we therefore extended the term “secondary osteoporosis” with the term “metabolic bone disease” into SECOB, including vitamin D deficiency with secondary hyperparathyroidism. If, in addition, all patients with serum 25(OH)D levels less than 50 nmol/liter regardless of PTH level were included, 70.3% would have been diagnosed with one or more newly diagnosed contributors to SECOB. If all patients with serum 25(OH)D level less than 75 nmol/liter were included, 89.9% of patients would have been labelled to have one or more contributors to SECOB.

Previous studies have reported the yield of laboratory screening to detect underlying disorders in patients with osteoporosis (5, 7, 20). Johnson *et al.* (20) identified previously unrecognized contributors to osteoporosis in 11% of 180 patients with osteoporosis and bone densities that were lower than expected for age, although a limited number of laboratory investigations was used. Deutschmann *et al.* (7) reported a total of known and new risk factors for osteoporosis in 63% of women and 67% of men, the largest groups of disorders being lactose malabsorption, hypercalciuria, and renal tubular acidosis type 1. Tannenbaum *et al.* (5) identified a prevalence of 32% of previously unrecognized contributors to osteoporosis in otherwise healthy postmenopausal women with osteoporosis. Although the prevalence of SECOB contributors is comparable with the results found in the present study, the disorders identified differ between both studies.

An important limitation of our study is that we did not systematically evaluate 24-h urine analysis and malabsorption, especially celiac disease. Because low vitamin D levels, secondary hyperparathyroidism, and/or low absolute urinary calcium excretion may be seen in patients with celiac disease, this can be of important influence on the results. In literature, the prevalence of celiac disease in patients with osteoporosis was reported to be 1–3% (5, 21, 22). Additionally, Tannenbaum *et al.* (5) reported that 6.4% of women with osteoporosis had low 24-h urine calcium (indicating calcium malabsorption) and 9.8% had hypercalciuria. It is possible that the unknown elevated iPTH levels in eight patients in our study could have been explained when routine 24-h urine analysis had been performed. Given these limitations, we presume that the percentage of patients with new SECOB contributors may be even higher than the 26.5% found in our study.

The routine evaluation of ESR and alkaline phosphatase did not contribute to the finding of new contributors to SECOB, and these parameters were predominantly related to postfracture infection and fracture healing, respectively, but some other diseases were detected at follow-up based on the abnormality of these parameters.

More recently, several studies reported the prevalence of SECOB in fracture patients with osteoporosis (8), elderly patients with osteoporotic fractures admitted to a hospital (23), and patients with hip fractures (24). Excluding vitamin D deficiency, Dumitrescu *et al.* (8) reported newly diagnosed SECOB contributors in approximately 10% of fracture patients with osteoporosis. In a recent study by Edwards *et al.* (24) in hip fracture patients, the

number of newly diagnosed SECOB contributors is high and seems to be comparable with the results in the patients with hip fractures in our study, although the exact number of patients with one or more SECOB contributors, excluding the patients with vitamin D deficiency, cannot be extracted from this paper.

We identified hyperthyroidism and primary hyperparathyroidism in 6.2 and 2.7% of fracture patients, respectively. Both disorders are associated with loss of BMD and increased fracture risk, and after adequate treatment, fracture risk declines (25, 26). In a recent review, it was advocated that patients with (subclinical) hyperthyroidism should be additionally tested by a BMD measurement and in case of reduced BMD should be treated with antithyroid drugs. We believe therefore that it is important to diagnose overt but also subclinical hyperthyroidism in patients with a recent clinical fracture (27). Osteopenia, osteoporosis, and fracture prevalence rates are higher in hypogonadal men of all ages, and bone density increases under testosterone substitution (16). Fracture data are not yet available, and thus, the long-term benefit of testosterone requires further investigation. The prevalence of hypogonadism found in men with fractures after the age of 50 yr in our study (8.3%) emphasizes these guides.

The finding of MGUS is relatively frequent in patients with osteoporosis or a fracture, (18, 24), and the risk of fracture appears to be increased, even before progression to myeloma (28). Screening for plasma cell disorders with serum and urine protein electrophoresis is recommended in patients with age-inappropriate bone loss, defined as fragility fractures, osteopenia, or osteoporosis in patients younger than 65 yr (17, 18). Although treatment of MGUS is not necessary, follow-up for early detection of progression to myeloma is warranted (18). Hence, evaluation for plasma cell disorder in patients with clinical fractures may be of relevance in identifying those at higher risk for future fractures and also recognition of those who require additional therapy for more progressive myeloma disease.

Newly diagnosed CKD was found in 8.6% of the patients in our study, and 28% of them had concurrent secondary hyperparathyroidism (in 16% combined with vitamin D deficiency). Two patients whose eGFR was below 30 ml/min per 1.73 m2 (stage 4 CKD) were not eligible to receive bisphosphonate therapy (< 35 ml/min per 1.73m2 for zoledronate) based on the current European Medicines Agency and Food and Drug Administration product information. In recent studies in patients with fractures and osteoporosis after the age of 50 yr, 6% of the patients were newly diagnosed with CKD (eGFR <45 ml/min per 1.73 m2) (8). In hip fracture patients, the percentage of patients with CKD stage 3 and 4 was 12 and 4%, respectively (24), and in patients with low trauma fractures, the percentage of patients with stage 3 and 4 CKD was reported to be 25.1 and 1.8%, respectively (29). Onset and severity of bone disease and abnormalities of bone mineral metabolism are related to the level of GFR; below 60 ml/min per 1.73 m2, there is a higher prevalence of abnormalities of bone metabolism (13). Furthermore, fracture

risk is increased in patients with moderate to severe CKD, especially with a eGFR less than 45 ml/min per 1.73 m2 (30). There is a significant association between hip fracture and moderate to severe degrees of CKD (31, 32). The pathophysiological alterations responsible for the renal osteodystrophy, such as increased PTH, low vitamin D status, and disorders of mineral metabolism, are evident at stage 3 of CKD. Based on these findings, we propose routine evaluation of eGFR in patients with a recent clinical vertebral or non-vertebral fracture.

Conclusion

Based on the result of our study, we propose to perform a detailed dietary questionnaire for evaluation of calcium intake in combination with a panel of laboratory tests comprising serum calcium, albumin, TSH, creatinine (with calculation of eGFR), 25(OH)D, and serum and urine protein electrophoresis in all patients presenting with a fracture after the age of 50 yr and, in men, also serum testosterone and, additionally, fT4 in patients with abnormal TSH and PTH in patients with abnormal serum calcium. Laboratory testing is not contributory in men with fractures of fingers and toes, except for serum 25(OH)D. We did not systematically perform 24-h urine analysis and malabsorption tests, especially for celiac disease, but based on the results of studies in patients with osteoporosis, these tests should also be considered in patients with a recent fracture. These analyses enable identification of previously unknown disorders related to secondary osteoporosis and metabolic bone disease that should be corrected before osteoporosis medication is started or need further follow-up and also warrant adequate individually titrated calcium and vitamin D supplementation in addition to anti-osteoporosis medication in patients with a recent fracture.

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Chapter 3

Secondary osteoporosis and metabolic bone disease in patients 50 years and older with osteoporosis or with a recent clinical fracture: a clinical perspective

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Abstract

Purpose of review

The purpose of this review is to provide guidance to clinicians about which laboratory tests should be performed in patients with osteoporosis or with a recent fracture.

Recent findings

Newly diagnosed secondary osteoporosis and other metabolic bone diseases (SECOB) have been found in 5–48% of patients with osteoporosis. In patients with a recent fracture, new SECOB is found in 10–47% of patients with osteoporosis, and in 26–51% if all patients with a fracture regardless of bone mineral density (BMD) are screened. More than one SECOB can be found in the same patient, even when they have already known SECOB. In primary hyperparathyroidism, hyperthyroidism, hypercortisolism, and multiple myeloma, both SECOB and its treatment have an impact on BMD and fractures. For other SECOBs, no treatment is available, or there are no data about the effect of treatment of the SECOB on BMD and fractures.

Summary

We recommend performing the following tests in all patients with osteoporosis or a recent clinical fracture: calcium, phosphate, creatinine, albumin, erythrocyte sedimentation rate in all patients, 24 h urine calcium in men and serum testosterone in men less than 70 years. On indication, additional tests can be performed.

Key points

- SECOB is a more adequate terminology than secondary osteoporosis, as it can be found in patients with a recent clinical fracture, regardless of BMD.
- Newly detected SECOB is highly prevalent in patients with osteoporosis and with a recent clinical fracture, and more than one SECOB can be found in the same patient.
- Systematic screening of patients with osteoporosis or a recent clinical fracture or both should focus on identification of patients with potentially reversible contributors to SECOB, which treatment has an influence on BMD and fracture risk.

Introduction

Osteoporosis has been defined as a condition characterized by a reduced bone mineral density (BMD) and altered microarchitecture, resulting in an increased fracture risk (1). The causes of osteoporosis and fractures are multifactorial (2**,3). Osteoporosis has, therefore, historically been defined as primary (postmenopausal or age related) and secondary osteoporosis (2**). Secondary osteoporosis includes diseases, use of drugs, and deficiencies leading to a decrease in BMD, or bone quality or both and an increase in fracture risk. In addition, lifestyle and fall risk factors contribute to fracture risk (2**,3–6) (Table 1).

Table 1. Overview of secondary osteoporosis and other metabolic bone diseases (SECOBs) and other factors that contribute to bone loss or fracture risk or both

Endocrine diseases
- Acromegaly
- Diabetes mellitus
- GH deficiency
- Hypercortisolism
- Hyperparathyroidism
- Hyperprolactinemia
- Hyperthyroidism
- Male hypogonadism
- Premature menopause
- Central adiposity

Gastrointestinal disorders
- Celiac disease
- Chronic biliary tract obstruction
- Gastrectomy/gastric bypass
- Inflammatory bowel disease
- Liver cirrhosis
- Malabsorption (other than celiac disease)

Rheumatic diseases
- SpondyloArthritis, including ankylosing spondylitis and psoriatic arthritis
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Systemic sclerosis

Hematologic and oncologic diseases
- Hemophilia
- Multiple myeloma
- MGUS
- Lymphoma/leukemia
- Systemic mastocytosis
- Thalassemia
- Disseminated carcinoma
- Chemotherapy

Connective tissue diseases
- Ehlers–Danlos syndrome
- Marfan's syndrome
- Osteogenesis imperfecta
- Pseudoxanthoma elasticum

Miscellaneous conditions and diseases
- AIDS/HIV
- Amyloidosis
- Chronic metabolic acidosis
- Chronic obstructive lung disease
- Congestive heart failure
- Depression
- End stage renal disease
- Muscular dystrophy
- Sarcoidosis
- Weight loss

Medication
- Glucocorticoids
- Antidepressants
- Anti-epileptic drugs
- Aromatase inhibitors
- Benzodiazepines
- Cyclosporin
- Glitazones
- Gonadotropin releasing hormone agonists
- Heparin
- Loop diuretics
- Medroxyprogesterone acetate
- Proton pump inhibitors
- Thiazolinediones
- Thyroxine (excessive)

Other
- Anorexia nervosa
- Osteomalacia

Lifestyle
- Alcohol abuse
- Smoking
- Immobilization
- Low calcium intake
- Low protein intake

In recent years, contributors to secondary osteoporosis have been integrated in fracture risk algorithms, such as FRAX (7) and osteoporosis guidelines recommend evaluating them (4–6). If these contributors are not diagnosed and managed properly, fracture

prevention may be suboptimal for several reasons (8); some contributors are treatable [e.g. hyperthyroidism, male hypogonadism, and primary hyperparathyroidism (PHPT)], are a contraindication for specific antiosteoporosis therapy (e.g. bisphosphonate therapy in renal insufficiency), or need follow-up (e.g. monoclonal gammopathy of undetermined significance, MGUS) (9).

A systematic approach for fracture prevention is recommended by the guidelines (4–6), can be organized in an osteoporosis clinic for BMD and fracture risk evaluation (10) or a Fracture Liaison Service (FLS) for secondary fracture prevention (11**,12-14), and can be approached in a five-step plan (15). The first step is case finding, that is, identifying three groups of patients with increased fracture risk: patients with a recent fracture, patients with diseases or medications that are known to increase fracture risk, and patients with other clinical risk factors. The second step is risk assessment using bone-related and fall-related clinical risk factors for fractures, including BMD measurement, and preferably also imaging of the spine. In the third step, medical history, clinical examination, and laboratory testing allow differential diagnosing of underlying causes for bone loss and fractures, the so-called secondary osteoporosis. The fourth step consists of treatment decisions: patient education, lifestyle changes, fall prevention, adequate calcium and vitamin D supplementation, and if indicated specific anti-osteoporosis treatment. The fifth step is follow-up for tolerance, compliance, efficiency, and duration of therapy.

In daily practice, the approach toward diagnosis, correction, and follow-up of secondary osteoporosis includes two scenarios. In the first scenario, in patients with osteoporosis or a recent fracture, known disorders associated with osteoporosis and fracture risk can be identified by a detailed evaluation of medical history, medication, and clinical risk factors. Furthermore, several surveys have shown that patients with osteoporosis or a recent fracture have previously unknown underlying diseases that can only be diagnosed by medical history, physical examination, and laboratory tests (2**,3). This raises the clinical challenge in which examinations for assessment of secondary osteoporosis are indicated in patients who have been diagnosed with osteoporosis based on dual energy X-ray absorptiometry (DXA) measurement, and in patients with a recent fracture, of whom the majority have no osteoporosis (16). As secondary osteoporosis is also found in patients with a recent clinical fracture who do not have osteoporosis (17-20), we recently introduced the terminology ‘secondary osteoporosis and other metabolic bone diseases’ (SECOBs) (17), which will be used in this review.

In this review, we summarize the currently available literature on newly diagnosed SECOB in patients 50 years and older, referred for DXA and diagnosed with osteoporosis or with a recent clinical fracture, regardless of BMD. Our goal is to provide some guidance to clinicians who take care of these patients in osteoporosis clinics (10) and in the FLS (11**,12–14).

Known secondary osteoporosis and other metabolic bone diseases in patients with osteoporosis or a recent clinical fracture

The prevalence of known SECOB in patients with osteoporosis or a recent clinical fracture is highly variable, ranging from 3% to 55% (10, 17-35) and depends on patient selection (reason for referral, sex), definition of osteoporosis or fracture type, and extensiveness of the assessment (Table 2).

Table 2. Prevalence of known SECOB in patients with osteoporosis or a recent clinical fracture.

Known contributor	Number of articles	Percentage of patients	Percentage of women	Percentage of men
Premature ovarian failure (women only)	4		2 – 36	
Hypogonadism (men only)	2			1 – 14.1
History of hyperthyroidism	7	1.5 – 13		
History of glucocorticoid use	12	1 – 36	2 – 12	8 – 12
History of rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis	10	0.3 – 6.1	0 – 20	0 – 1.6
History of COPD	3	10.5 – 24.5		
History of inflammatory bowel disease	4	0.5 – 8.2		
History of malabsorption	5	1.4 – 21.8		
History of chronic kidney disease	4	0.1 – 12		
History of alcoholism	10	1.5 – 38	0 – 3	1.6 – 15
Current anticonvulsant use	8	0 – 5.4		
Total (with one or more factors)[a]	18	3 – 55		

SECOB, secondary osteoporosis and other metabolic bone disease
[a]As some patients have more than one SECOB, this number is not cumulative

As a general rule, most guidelines propose to refer patients with known SECOB for measurement of BMD. In addition to treatment of low BMD, the underlying SECOB should be corrected when possible (e.g. lowest dose of medication, controlling activity of underlying disease, and adapting lifestyle). In these patients, imaging of the spine should be considered, as previously undetected vertebral fractures are frequently found in SECOB, such as rheumatoid arthritis (36,37,38*), ankylosing spondylitis (39, 40), systemic lupus erythematosus (41), inflammatory bowel disease (42), and chronic obstructive pulmonary disease (43).

Newly diagnosed secondary osteoporosis and other metabolic bone diseases in patients with osteoporosis

A major clinical challenge is whether and how unknown disorders increasing fracture risk should be evaluated in patients diagnosed with low BMD. Table 3a summarizes the prevalence of newly diagnosed SECOB in patients, referred for DXA and diagnosed with osteoporosis (22–24,29–32,44).

Any newly diagnosed SECOB was found in 5–48% of evaluated patients; the prevalence of SECOB is 5–39% in women (10,23,24,29–32) and 10–74% in men (22,30). The broad range in reported prevalence is mainly because of differences in patient selection (definition of osteoporosis, sex, and age limits) and in the number and selection of contributors to SECOB. Another point of attention is whether vitamin D deficiency was included as newly diagnosed SECOB and if so, what the definition was. For this review, we only included a vitamin D deficiency leading to secondary hyperparathyroidism as SECOB. When vitamin D deficiency would have been taken into account as SECOB, the prevalence of SECOB would have been 22–68% (10,23,30,31,44).

Newly diagnosed secondary osteoporosis and other metabolic bone diseases in patients with a recent clinical fracture

In patients with a recent clinical fracture, there are two different types of studies. In patients with a recent fracture and osteoporosis, the prevalence of SECOB is 10–30.5% (Table 3b) (19,25,27,35). In patients with a recent clinical fracture and any BMD, the prevalence of SECOB is 26–51% (17,18,20,28,33,34) (Table 3c). When including vitamin D deficiency in general, so not only a deficiency leading to secondary hyperparathyroidism, the prevalence of SECOB would have been 57% (25) and 32–70% (17,18), respectively.

Again, there was substantial heterogeneity in patient selection (sex, age, fracture location, result of DXA) and in the number and types of evaluated contributors to SECOB (see Table 3). One study (17) specified that SECOB was detected in 9.6% of patients with normal BMD, 26.6% of patients with osteopenia, and 32.9% of patients with osteoporosis. Two studies (17,22) screened for new SECOB in patients with known SECOB and detected a prevalence of 43.5–51.5%. Several studies reported more than one contributor to SECOB in 4.9–29.0% of patients (17,18,25,30,35).

Table 3. Newly diagnosed SECOB patients with A) osteoporosis on DXA, B) a recent clinical fracture and osteoporosis, C) a recent clinical fracture and any BMD

	A)Patients with osteoporosis but no clinical fracture				B)Patients with osteoporosis and a recent clinical fracture **		C)Patients with a recent clinical fracture, any BMD **	
Disorders	References	Prevalence * (total)	Prevalence (women)*	Prevalence (men)*	References	Prevalence (total)	References	Prevalence (total)
Hyperparathyroidism (HPT)	10, 21-24, 29-32, 44	All 0.5 - 35%						
PHPT	10, 21, 23, 24, 29-32, 44	0.5 - 6.1%	0.5 - 6.1%	1.2 - 1.6%	19	"yes"	17, 20, 34	0.9 - 2.7%
SHPT	10, 44	6.0 - 6.3%	6.0 - 11.1%	16.4%	25	3%		
SHPT due to vit. D deficiency							17, 20	7.8 - 21.0%
SHPT due to CKD					25	3%	17, 20	1 - 6.4%
SHPT due to vit. D deficiency and CKD							17	1.4%
Hyperthyroidism	10, 21-24, 29, 31, 44	0 - 10.1%	1 - 19.5%	0 - 8.5%	25,35	0-0.5%	17, 18, 20, 28, 34	3 - 4.7%
Hypercortisolism	21, 23, 29-32	0 - 0.6%	0	0.6%				
Hypogonadism in men	21, 22, 44			3.2 - 13.7%	25, 27, 35	0-4.5%	17, 18, 20, 28	1.9 - 40%
Prolactinoma	29, 31	0 - 0.3%	0 - 0.3%				28	6.7%
MGUS/myeloma	0				19	"Yes"	17, 20 /17, 20, 33	2.1 - 6.0% / 0.2 - 0.9%
CKD	0				19, 25	6-18%***	17, 18, 20, 28	8.6 - 18.5%
Malabsorption	10, 23, 24, 30	0.5 - 18.6%	0.5 - 18.6%				20	1.4%
Celiac disease	10, 23	0.5 - 2%	0.5 - 2%					
Calcium malabsorption	24	1.0%	1.0%				20	6.4%
Lactose	30	18.6%	18.6%	21.7%				
Other								
% of patients with at least one new SECOB	10, 21, 22, 24, 29-32	5.5 - 48.7%	5.5 - 39.6%	10.5 - 73.9%	25,35	10 - 30.5%	17, 18, 20, 34	26 - 51%
% patients with > 1 new SECOB		25.7%				52%		10%

PHPT = primary hyperparathyroidism, SHPT = secondary hyperparathyroidism, CKD = chronic kidney disease, Vit.D = vitamin D, MGUS = Monoclonal Gammopathy of undetermined significance

*As not all studies reported results for women and men separately, the percentages of men and women are not cumulative to the total percentages.

**No data available about SECOB in women and men separately

***women 9%, men 33%

Newly diagnosed secondary osteoporosis and other metabolic bone diseases, bone loss, and fracture risk

In the discussion on which contributors to SECOB should be considered for diagnosis, the clinical question is to what degree they contribute to bone loss and increased fracture risk, and whether specific treatment of SECOB improves BMD and decreases fracture risk. In Table 4, we summarized the associations of the most prevalent SECOBs with bone loss and fracture risk and the expected treatment effects.

Table 4. Newly diagnosed SECOB: association with bone loss and fracture risk and expected effect of treatment of SECOB on bone loss and fracture risk

	Association with bone loss	Association with fracture risk	Treatment improves BMD	Treatment decreases fracture risk
Primary hyperparathyroidism	Yes	yes	Yes	Yes
Secondary hyperparathyroidism				
Due to vitamin D deficiency	Not clear	yes	NA	Yes
Due to chronic kidney disease	Yes	yes	NA	NA
Familial hypocalciuric hypercalcaemia	No	yes	NA	NA
Idiopathic hypercalciuria	No	yes	Yes	Yes
Hyperthyroidism	Yes	yes	Yes	Yes
Hypercortisolism	Yes	yes	Yes	Yes
Male hypogonadism	Yes	yes	Yes	NA
MGUS	Yes	yes	NA	NA
Multiple myeloma	Yes	yes	NA	Yes
Chronic Kidney disease (CKD-MBD)	Yes	yes	NA	NA
Malabsorption	NA	yes	NA	NA
Diabetes mellitus	Yes	yes	NA	NA

MGUS = monoclonal gammopathy of undetermined significance. NA = not applicable

PHPT is associated with bone loss at cortical sites (45-47), resulting in osteoporosis predominating at the distal radius and femoral neck (48-51) and an increased risk for vertebral, forearm, hand, and lower leg fractures (52). After parathyroidectomy, BMD increases at all sites (50, 53-56) and fracture risk decreases (52).

Secondary hyperparathyroidism can result from chronic kidney disease (CKD), vitamin D deficiency or a combination of both. In patients with hypovitaminosis D and secondary hyperparathyroidism, BMD is lower, which is more prominent at the hip than at the spine (57, 58) and fracture risk is increased.

Chronic kidney disease–mineral bone disorder (CKD-MBD) includes all pathophysiological processes occurring in patients with impaired renal function, leading to secondary hyperparathyroidism. Both high and low bone turnover may result in bone loss (59, 60). BMD assessment is not recommended, as it does not predict fracture risk or type of renal osteodystrophy (60, 61). However, there may be a link between femoral BMD and cortical bone volume in patients with CKD stage 5 (61). Fracture risk is increased, independently of underlying histology (59). There are no data about the effect of treatment of metabolic complications of CKD on BMD and fractures.

PHPT should be differentiated from familial hypocalciuric hypercalcemia (FHH), which can also present with hypercalcemia and inappropriate PTH (62). In patients with FHH, BMD is comparable with controls but fracture risk is elevated (63, 64).

Hypercalciuria has many possible causes, including PHPT, hyperthyroidism, Paget's disease, myeloma, malignancy, immobility, accelerated osteoporosis, sarcoidosis, and renal tubular acidosis. There is a relationship between nephrolithiasis and increased fracture risk. Thiazide diuretics decrease hypercalciuria, improve BMD, and decrease fracture risk (65*).

Thyrotoxicosis is a risk factor for osteoporosis and fragility (66-68), hip and vertebral fractures (69-72). In patients with thyrotoxicosis, BMD returns to the normal range within 5 years after treatment irrespective of the modality of treatment (66, 73). Despite this improvement, increased fracture risk persists for at least 5 years (71). In patients with subclinical hyperthyroidism, BMD is reduced in postmenopausal women (74-76) and in men (77). Guidelines recommend treatment of subclinical hyperthyroidism in patients with osteoporosis (68).

Several guidelines recommend screening for hypercortisolism in patients with unexplained osteoporosis (78, 79). Patients with hypercortisolism sustain bone loss at trabecular sites and increased risk for mainly vertebral fractures (80). After cure of hypercortisolism, spine BMD improves (81). Fracture risk may remain high, and there might be an indication for anti-osteoporosis treatment in selected groups of patients, although there are no studies on this topic (82*).

In men with established androgen deficiency, the risk for osteoporosis and low trauma fracture is increased (83). Androgen replacement therapy leads to an increase in BMD of the spine, but it has no effect on BMD of the hip (84*). No trials are available about the effect of testosterone therapy on fragility fractures (83,84*).

In patients with MGUS, osteoporosis is more frequently diagnosed compared with healthy controls (85, 86). Patients with MGUS have more vertebral and hip fractures (85, 87). Multiple myeloma also leads to an increased fracture risk (88). In patients with multiple myeloma, treatment with clodronate (89) and zoledronic acid (90) leads to a reduction of fracture risk.

A serological diagnosis of celiac disease was established in 10% of premenopausal osteoporotic women (91). The question is whether the prevalence of celiac disease in the osteoporotic population is higher (92, 93) or similar (94, 95) compared to the general population.

Adults with type 2 diabetes have normal or high BMD (96, 97), which is possibly associated with obesity (98*), but despite this there is an increased risk of osteoporotic fractures (96,97,98*). The question is whether increased fracture risk is associated with diabetes mellitus or with age, impaired renal function, retinopathy, and other fall-related factors (98*). In patients with type 1 diabetes, BMD is decreased and fracture risk is increased (98*).

Table 5 shows an overview of laboratory tests recommended by the guidelines. On the basis of this review, we propose screening in all patients with osteoporosis or a recent clinical fracture for SECOBs, which have impact on bone loss and fracture risk and which are highly prevalent, resulting in the following panel of laboratory tests: serum calcium, phosphate, creatinine, albumin, erythrocyte sedimentation rate (ESR) in all patients, 24h urine calcium in men, and serum testosterone in men <70 years. On the basis of clinical or biochemical suspicion of hyperparathyroidism, hypercortisolism, multiple myeloma, celiac disease, or other SECOBs, additional tests may be indicated. The question is whether 25(OH)vitamin D should be measured in daily clinical practice, because most guidelines recommend supplementation of vitamin D in all patients with osteoporosis (4–6), and 800 IU is effective in most patients to raise serum levels above 50nmol/l (99*).

Discussion

The prevalence of SECOB in patients with osteoporosis or a clinical fracture or both is highly variable in the literature. For known SECOB, this variability is the result of patient selection for referral. For newly diagnosed SECOB, this variability is mainly the result of patient selection and how systematic patients are evaluated for SECOB. Furthermore, the prevalence of SECOB differs with respect to inclusion of vitamin D deficiency. Nevertheless, the prevalence of newly detected SECOB is substantial in patients with osteoporosis, and also in patients with a fracture regardless of BMD. More than one new SECOB can be detected in the same patient (17,18,25,30,35), also in patients with known SECOB (17,22). Therefore, screening for new SECOB is indicated in all patients with osteoporosis and all patients with a recent clinical fracture regardless of BMD, also when they have already known SECOB.

Screening tests should be limited to disorders associated with bone loss and fracture risk, which treatment may improve BMD and decrease fracture risk, and which have a high prevalence, as has been shown for PHPT, hyperthyroidism, and hypercalciuria.

Table 5. Panel of laboratory tests in surveys and as recommended by the guidelines

	Surveys	NOF	NOGG	CBO
ESR	Yes (21, 24, 25, 29, 34, 44)	-	+	+
Calcium	Yes (10, 17-21, 23-25, 29, 31, 44)	+	+	+
Phosphate	Yes (10, 17-21, 23, 24, 29, 31, 44)	+	+	-
Albumin	Yes (10, 17, 18, 20, 25, 29, 44)	-	+	+
Creatinine	Yes (10, 17-21, 23-25, 29-31, 44)	+	+	+
25(OH)D	Yes (10, 17, 19-23, 25, 28, 31, 44) On indication (24, 32)	+	On indication	+
PTH	Yes (10, 17, 19-23, 29-31, 44) On indication (18, 24, 32)	+	On indication	On indication
Alkaline phosphatase	Yes (10, 17-25, 29-31, 44)	+	+	+
Transaminases/liver function	Yes (10, 17, 20, 22-24, 29-31, 44)	+	+	-
TSH	Yes (17, 18, 20-23, 28-31, 34, 44) On indication (24, 32)	+	+	+
fT4	Yes (17, 23, 28-31, 34, 44) On indication (18, 24)			-
fT3	Yes (29, 30) On indication (18, 24)			
Testosterone	Yes (17, 21, 22, 28) On indication (18, 30)	+	On indication	+ (< 70y)
Serum protein electrophoresis	Yes (17, 20, 21, 23, 30, 34) On indication (24, 29, 44)	On indication	On indication	On indication
Urine Bence Jones	Yes (21, 30) On indication (24)	-	On indication	
24-h urine calcium	Yes (10, 20, 21, 23-25, 29-32, 44) On indication (17, 18, 22)	+	On indication	On indication*
Blood count	Yes (10, 18, 21-24, 29, 31, 32, 34, 44)	+	+	-
Cortisol				
Urinary	Yes (21, 23) On indication (31)	On indication	On indication	
Blood	On indication (24, 29, 32)	-	-	
+ 1 mg dexamethasone	Yes (31)	-	On indication	
FSH, LH/gonadotropins	Yes (28, 31) On indication (24, 30, 32)	In men	On indication*	
Prolactin	Yes (28) On indication (24, 30, 32)	-	On indication	
Celiac disease				
Anti-TTG	Yes (21) On indication (23)	On indication -	On indication -	On indication
Anti-gliadin	On indication (32)	-	On indication	
Anti-endomysium	On indication (32)			

*in men only

Furthermore NOF recommends on indication: Magnesium. NOGG recommends on indication: ferritin & iron, Homocystein, Tryptase, 24h urine histamine.

Furthermore on indication (each test in 1 survey only): 1,25(OH)2D, fasting blood glucose, lactose malabsorption, elastase stool, urinary spot Calcium/creatinine ratio, Xylose, bile salt malabsorption, fibroblast cultures.

Hypercortisolism and multiple myeloma have a low prevalence in patients with osteoporosis or a recent clinical fracture. For male hypogonadism treatment effect on BMD has been reported, but there are no data with regard to fracture risk. No treatment is available for MGUS and FHH, and for CKD–MBD and diabetes mellitus, there are no data about the effect of treatment of the SECOB on BMD and fractures. If it is expected that treatment of a SECOB improves BMD and reduces fracture risk, it might be considered to treat the SECOB first and only start anti-osteoporosis treatment if osteoporosis persists in spite of adequate treatment of the SECOB. As long as there are no data about the effect of SECOB itself or its treatment on BMD and fractures, treatment decisions can only be based on the classical indications (4–6).

In this review, vitamin D deficiency is only considered as SECOB if it is leading to secondary hyperparathyroidism. Although there might be discussion whether vitamin D deficiency should be considered as SECOB, supplementation of vitamin D deficiency or insufficiency is important in the treatment of patients at risk (e.g. patients with osteoporosis or a recent clinical fracture) (4–6,15).

On the basis of these considerations and the review of guidelines, the following panel of laboratory tests for screening in patients with osteoporosis or a recent clinical fracture should be considered: serum calcium, phosphate, creatinine, albumin, ESR, and in addition 24h urine calcium in men and serum testosterone in men aged under 70 years. Additional tests may be needed based on clinical and biochemistry findings in order to detect hyperparathyroidism, multiple myeloma, hypercortisolism, celiac disease, or other SECOBs. The question is whether 25(OH)D should be routinely measured. One may decide to measure serum 25(OH)D only on indication because most guidelines recommend supplementation of vitamin D in all patients with osteoporosis (4–6) and 800 IU is effective in most patients to raise serum levels above 50 nmol/l (99*).

Conclusion

Newly diagnosed SECOB is highly prevalent in patients with osteoporosis and in patients with a recent clinical fracture, regardless of the BMD outcome. This emphasizes that systematic screening of patients with osteoporosis or recent fracture or both enables identification of patients with potentially reversible contributors to SECOB. Furthermore, adequate diagnosis and treatment of a SECOB contributes to fracture risk reduction in high-risk patients in addition to calcium and vitamin D supplementation and specific anti-osteoporosis therapy.

Aknowledgements

To Caroline Wyers.

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* of special interest
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This study investigates the achieved vitamin D levels after supplementation.

Chapter 4

Suboptimal effect of different vitamin D supplementations and doses adapted to baseline serum 25(OH)D on achieved 25(OH)D levels in patients with a recent fracture: a prospective observational study

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Abstract

Objective

Guidelines on the need for dose adaptation of vitamin D3 supplementation according to baseline serum 25(OH)D are inconclusive. The effects of increasing doses of vitamin D3 at lower baseline serum 25(OH)D values on the serum 25(OH)D after 4.2 and 11 months were determined in an observational study.

Design

A prospective observational study.

Methods

Out of 1481 consecutive women and men with a recent clinical fracture, 707 had a baseline 25(OH)D level <50 nmol/l and were supplemented with increasing doses of vitamin D3 (400, 800, 1700, and ≥3500 IU/day) according to the lower baseline 25(OH)D. Final analysis was restricted to the 221 participants who had full follow-up data available for 11 months.

Results

Serum 25(OH)D ≥50 nmol/l was achieved in 57–76% of patients after 4.2 months and in 73–79% after 11 months. These percentages were similar for all doses (p=0.06 and p=0.91 respectively). The mean achieved 25(OH)D was similar for all dose groups (56.1–64.0 nmol/l after 4.2 months and 60.2–76.3 nmol/l after 11 months). With multivariate analysis, the increase in 25(OH)D (17±32.0 after 4.2 months and 24.3±34.0 nmol/l after 11 months) was dependent on the baseline 25(OH)D (p<0.001), not on supplementation dose, season, age, BMI, or gender.

Conclusions

The increase in serum 25(OH)D was significantly larger with higher vitamin D3 supplementation doses. However, this dose–effect response was mainly explained by the baseline 25(OH)D, not the supplementation dose, with a greater magnitude of response at lower baseline 25(OH)D concentrations. In 21–27% of patients, serum 25(OH)D3 levels did not reach 50 nmol/l after 11 months, at any dose. Further studies are needed to identify possible causes of suboptimal response such as non-compliance, undiagnosed malabsorption syndromes, or variability in cholecalciferol content of the vitamin D supplements.

Introduction

Serum 25(OH)D is the most widely accepted indicator of vitamin D status (1). Despite the well-documented role of vitamin D in health, there is still debate on the optimal dose of vitamin D supplements needed to achieve a desired threshold of serum 25(OH)D concentration (e.g. loading doses or a constant dose) (2). There is no universally accepted threshold, neither in the USA where the Institute of Medicine report is more in favour of 50 than 75 nmol/l, nor in Europe where it is dependent on countries' guidelines and different expert opinions (2, 3). Many factors have been reported to affect changes in serum 25(OH)D concentration using vitamin D supplements, such as sex, age, BMI, body composition, genetic factors, and variability in serum 25(OH)D assay methods (4). A dose-dependent effect of vitamin D supplements has been documented in healthy postmenopausal women with vitamin D insufficiency (serum level <50 nmol/l) and for fracture prevention (5, 6). A dose of 800 IU/day was sufficient to increase the serum level of 25(OH)D above 50 nmol/l in 98% of women (6). Other studies indicated a significant relation between baseline serum 25(OH)D and the response to vitamin D supplements, i.e. when using one dose of supplements, a higher increase is achieved when baseline levels are low than when baseline levels are normal (7). At present, there is little known about the effect of higher supplementation doses at lower baseline serum 25(OH)D levels on the increase and achieved serum 25(OH)D. We therefore conducted an observational study in patients who presented with a recent fracture and serum 25(OH)D level <50 nmol/l to assess the effect of higher supplementation doses in patients with lower 25(OH)D levels.

Subjects and methods

Study design, study population and data collection

This is a prospective, observational study designed to examine the effects of vitamin D3 supplementation on serum 25(OH)D levels in clinical practice in Caucasian patients of 50 years and older who presented with a recent clinical vertebral or non-vertebral fracture evaluated at the fracture liaison service (FLS) of the VieCuri Hospital Noord-Limburg (The Netherlands). At the FLS, after primary fracture care, a specialized nurse invited all patients to the fracture and osteoporosis outpatient clinic of the hospital for bone mineral density (BMD) measurement and laboratory tests. Fractures were classified according to Center et al. (8), into hip fractures, major fractures (vertebra, pelvis, distal femur, proximal tibia, multiple rib, and humerus), minor fractures (all remaining osteoporotic fractures, except fingers and toes), and finger and toe fractures. Patients with metastatic cancer in bone, high-impact multitrauma, osteomyelitis, or failure of prosthesis were excluded. Patients who responded and agreed received a detailed

questionnaire for the evaluation of clinical risk factors for fractures, medical history, medication, previous fractures, and calcium intake and were planned for dual X-ray absorptiometry (DXA) measurement and a blood test. A visit at the outpatient clinic was scheduled after completion of these tests. At this visit, height and weight were assessed, the questionnaire was evaluated and when necessary additional questions were asked, and physical examination was performed by a physician. If laboratory results were abnormal, additional investigations were performed for detailed evaluation of newly diagnosed disorders when necessary. Depending on the BMD results, calcium intake, and serum 25(OH)D levels, patients were treated with calcium and vitamin D3 supplements and anti-osteoporosis medication according to the Dutch guidelines for treatment of osteoporosis (9). Vitamin D3 supplementation was prescribed in all patients with a baseline 25(OH)D level <50 nmol/l. The vitamin D3 supplementation dose was based on serum 25(OH)D levels, where higher doses were started with lower serum 25(OH)D levels. Generally, patients with a 25(OH)D level between 25 and 50 nmol/l were supplemented with 800 or 400 IU vitamin D3, and those with a 25(OH)D level <25 nmol/l were supplemented with higher doses of vitamin D3, especially for patients with a level <15 nmol/l and/or secondary hyperparathyroidism.

Vitamin D3 was supplemented as liquid vitamin D3 solution (cholecalciferol, 50 000 IU/ml as intermittent weekly, monthly, or bimonthly dose), or as daily tablets 400 and 800 IU/day or as Fosavance '5600' or '2800' IU per week up to the opinion of the physician. For this study the cumulative dose of vitamin D3 supplementation per month was recalculated to equivalent daily intake of vitamin D3 for each patient. All prescribed vitamin D preparations are approved by the European Medicines Agency and delivered by registered pharmacists.

According to the local protocol at the FLS and the Dutch guidelines for osteoporosis, a follow-up visit was planned based on clinical characteristics, such as the presence of metabolic bone disease or other co-morbidity, after initiation of anti-osteoporosis medication or other reasons based on the opinion of the clinician after ~ 4 and 12 months. During the follow-up visits, clinical parameters, current dietary and supplemental calcium intake, vitamin D3 supplementation, use of other medication, and additional laboratory tests were done for all patients.

Bone densitometry

BMD in the left or right hip and the lumbar spine was determined using DXA with the Hologic QDR 4500 (Hologic, Bedford, MA, USA). Diagnosis of osteoporosis was based on the WHO criteria for BMD (10), as provided by the manufacturer's database for women and men and which was based on the National Health and Nutrition Examination Survey III. T-score calculations were done for women using a female reference population and for men using a male reference population, as provided by the manufacturer. Patients

were classified according to the lowest value of T-score at total hip, femoral neck, or lumbar spine: T-scores of <-2.5 are considered in the osteoporotic range and T-scores between -1 and -2.5 (not -1 and -2.5) are considered osteopenic.

Laboratory measurements

Blood samples were collected at study visit baseline (a mean of 2–3 months after the fracture), after a mean of 4.2 months (visit 2), and after a mean of 11 months (visit 3). Basic laboratory tests included serum sodium, potassium, calcium, inorganic phosphate, albumin, creatinine, free tetraiodothyronine (fT4), TSH, serum aminotransferases (aspartate aminotransferase and alanine aminotransferase), alkaline phosphatase, intact plasma PTH (iPTH), 25(OH)D, and serum and urine protein electrophoresis for all patients. 25(OH)D vitamin D levels in serum were determined with the Architect i2000 immunochemistry analyzer (Abbott). The analytical performance of this method in comparison with the reference method has been described in the literature (11). The estimated glomerular filtration rate was calculated using the modification of diet in renal disease study group (MDRD) equation. The stages of chronic kidney disease (CKD) were defined according to the guidelines for CKD of the National Kidney Foundation (12). Primary hyperparathyroidism was diagnosed by hypercalcemia in the presence of inappropriately normal or elevated levels of iPTH (13, 14). Secondary hyperparathyroidism was defined as elevated plasma iPTH in combination with 25(OH)D <50 nmol/l or CKD stage 3 or greater, or both. Hyperthyroidism was defined by TSH values <0.50 mU/l with elevated fT4 levels and subclinical hyperthyroidism by TSH values <0.50 mU/l with normal fT4 levels. Hypogonadism was defined as a clinical syndrome complex, which comprises both symptoms as well as biochemical testosterone deficiency. Testosterone deficiency was defined as a total testosterone level <8 nmol/l (15).When inappropriate, additional evaluation followed.

Statistical analysis

All analyses were performed using SPSS for Windows (version 18.0, SPSS, Inc.). The results are presented as means ± S.D. or percentages, if appropriate. Baseline characteristics were compared in each of the five groups (vitamin D supplementation: no dose, 400, 800, 1700, and ≥3500 IU/day) using ANOVA for continuous variables and chi-square tests for categorical variables. Box–Whisker was used to show the policy of vitamin D3 supplementation according to the baseline serum 25(OH)D. Absolute values of serum 25(OH)D were compared in each of the five groups using repeated measure ANOVA for continuous variables. Changes after 4.2 months and after 11 months were compared among vitamin D3 doses groups using both ANOVA and analysis of covariance to show the effect of confounding factors (baseline serum 25(OH)D). Serum vitamin D status was categorized based on 25(OH)D levels as being optimal (≥50 nmol/l), or having insufficiency (<50 nmol/l) to find the distribution of patients with vitamin D insufficiency.

We created a sub-group with a daily dose of 800 IU/day to test the association of changes in serum 25(OH)D and baseline serum 25(OH)D. Multiple linear regression analyses were carried out to study the predictors for the changes in serum 25(OH)D after 4.2 months and 11 months. The variables included in the model were age, gender, BMI, season, baseline serum 25(OH)D, and dose of supplementation. For all tests, a probability level <0.05 was considered statistically significant.

Results

Baseline data

A total of 1481 patients (28.1% men and 71.9% women) with a mean age of 66.1±10.4 were evaluated at the FLS. Of them, 30.6% were diagnosed with osteoporosis, 64.7% with osteopenia, and 4.8% had a normal BMD. Mean daily dietary calcium intake was 971±356 mg/day and the baseline 25(OH)D level was 50.8±25.5 nmol/l. According to the Center classification, 6.7% sustained a hip fracture, 35.6% a major fracture, 53.0% a minor fracture, and 4.7% a finger or toe fracture. Of all patients, 26.4% were diagnosed with at least one newly detected metabolic bone disease (24.7% men and 27.1% women), 9.9% with renal failure stage 3 or 4, 3.4% with subclinical or overt hyperthyroidism, 3.7% with primary hyperparathyroidism, 12.0% with secondary hyperparathyroidism due to vitamin D deficiency, 1.1% with secondary hyperparathyroidism due to renal failure, and in men 7.5% were diagnosed with hypogonadism.

Of the total group, 707 patients (47.7%; 159 men (24.9%) and 548 women (75.1%)) had a serum 25(OH)D level <50 nmol/l (Fig. 1). Vitamin D3 supplementation was started in all 707 patients (159 men and 548 women), calcium supplementation in 338 patients (86 men and 252 women) and 492 started with oral bisphosphonates. Of the total group of 1481 patients, 679 patients were evaluated after a mean of 4.2±2.2 months and 221 at the second follow-up visit after 11±4.4 months (Fig. 1). Baseline characteristics of patients that were evaluated at the initial, first, and second follow-up visit are presented in Table 1.

As vitamin D supplementation policy and serum 25(OH)D outcomes of the group that had one follow-up visit (at 4.2 months) and the group with two follow-up visits (4.2 and 11 months) were comparable at the first follow-up visit, we only present data of the 221 patients who were evaluated at all three visits during 11 months. A total of 76 patients did not receive vitamin D3 supplementation because they had a baseline 25(OH)D level ≥50 nmol/l. The vitamin D supplementation dose in patients with a baseline 25(OH)D level <50 nmol/l is shown in Fig. 2. There was a significant difference in age, serum 25(OH)D, and PTH between the different vitamin D3 dose groups (all $p<0.05$; Table 2). There was no significant difference in baseline serum 25(OH)D levels or the percentage of patients

with a 25(OH)D level <50 nmol/l between the different fracture type groups or BMD groups.

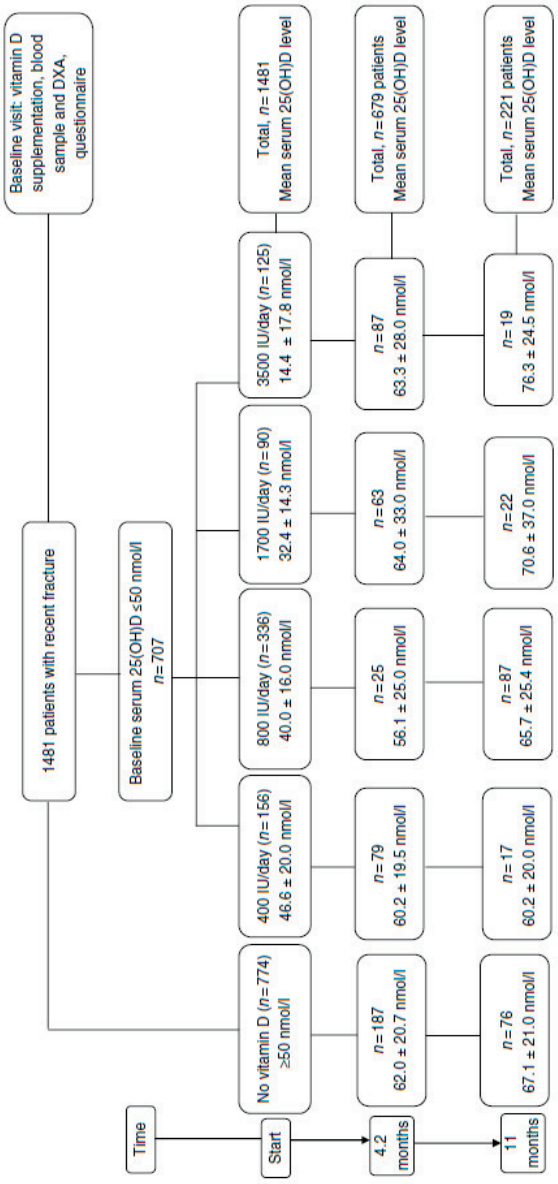

Figure 1. Study flowchart

Table 1. Baseline characteristics for three populations.

	Total group (n=1481)	Patients with one follow-up visit after 4.2 months (n=707)	Patients with two follow-up visits after 4.2 and 11 months (n=221)
Age (years)	66.1 ± 10.4	68.5 ± 10.4	69.4 ± 10.4
Male/female (%)	21.8 / 79.1	22.5 / 77.5	25.3 / 74.7
Weight (kg)	66.3 ± 10.7	68.5 ± 10.3	69.4 ± 10.5
BMI (kg/m^2)	24.0 ± 5.1	25.3 ± 5.1	25.5 ± 5.0
Calcium intake (mg/day)	970.8 ± 356.8	962.3 ± 375.5	976.6 ± 350.6
Serum 25(OH)D (nmol/l)	50.8 ± 25.5	41.5 ± 24.7	42.8 ± 22.7
Vitamin D status < 50 nmol/l (%)	48.8	65.4	65.6
Serum PTH (pmol/l)	6.6 ± 4.4	7.2 ± 4.8	6.8 ± 4.0
Serum calcium (mmol/l)	2.4 ± 0.11	2.4 ± 0.11	2.4 ± 0.1
Serum phosphate (mmol/l)	1.2 ± 0.18	1.2 ± 0.16	1.2 ± 0.17
Serum albumin (g/l)	41.0 ± 3.1	40.6 ± 3.1	40.7 ± 3.0
Serum creatinine (umol/l)	73.0 ± 17.5	72.2 ± 17.4	71.3 ± 17.0
Serum TSH (U/l)	1.8 ± 3.0	1.9 ± 3.8	1.6 ± 1.3

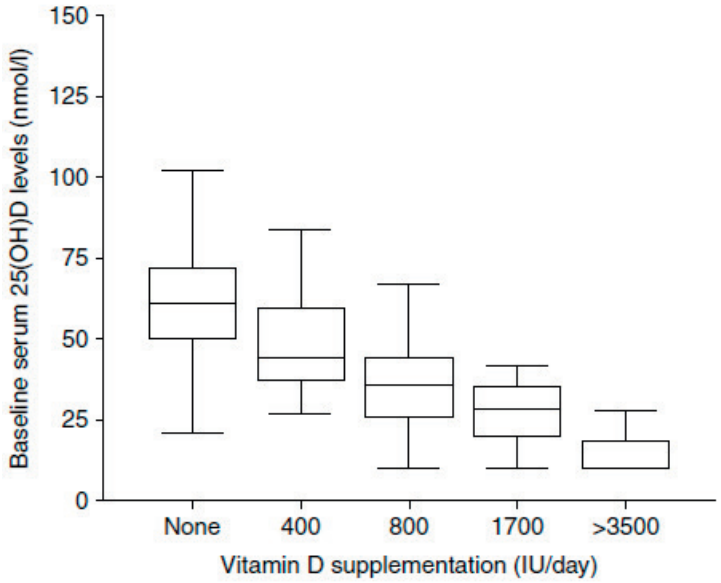

Figure 2. Vitamin D supplementation policy (IU/day) according to baseline serum 25(OH)D levels (nmol/l) in 221 patients with a recent fracture.

Table 2. Vitamin D supplementation policy, daily dietary calcium intake, laboratory results, and BMD status at baseline in 221 patients with a recent fracture who were evaluated during 11 months after starting vitamin D supplementation.

Characteristics	n=76	n=17	n=87	n=22	n=19	P-value
Vitamin D supplementation dose	No	400 IU/day	800 IU/day	1700 IU/day	≥ 3500 IU/day	
Age (years)	66.3 ± 9.8	67.0 ± 10.3	71.5 ± 10.0	71.7 ± 12.7	71.3 ± 10.5	0.013
Male/female (% of total population)	44.6 / 30.9	8.9/7.3	32.1/41.8	7.1/10.9	7.1/9.1	0.37
Weight (kg)	66.8 ± 9.8	66.3 ± 11.0	71.4 ± 9.8	71.1 ± 9.5	70.1 ± 9.6	0.07
BMI (kg/m^2)	24.1 ± 4.2	24.5 ± 5.8	26.7 ± 5.1	25.7 ± 5.7	25.8 ± 4.6	0.06
Daily dietary calcium intake (mg/day)	1030 ± 362.6	936.2 ± 380.2	947 ± 351.3	938.7 ± 303.8	966.7 ± 306.0	0.63
Serum calcium (mmol/l)	2.4 ± 0.09	2.4 ± 0.08	2.4 ± 0.09	2.4 ± 0.1	2.4 ± 0.08	0.62
Serum creatinine (umol/l)	71.3 ± 17.1	67.8 ± 17.6	71.8 ± 16.7	73.0 ± 17.6	69.3 ± 17.0	0.87
Serum 25(OH)D (nmol/l)	68.0 ± 16.4	37.6 ± 9.8	32.5 ± 10.8	26.0 ± 9.4	14.0 ± 7.4	<0.001
Serum PTH (pmol/l)	5.8 ± 2.8	6.8 ± 3.3	7.3 ± 3.9	8.8 ± 7.0	6.5 ± 3.2	0.022
% of patients with osteoporosis/osteopenia/normal BMD*	57.9/28.9/2.6	35.3/52.8/11.8	51.7/32.3/2.3	45.5/27.3/4.5	47.4/31.6/5.3	0.81

BMD, bone mineral density.
*BMD not available for all patients

Serum 25(OH)D ≥50 nmol/l was achieved in 57–76% of patients after 4.2 months and in 73–79% after 11 months (Fig. 3), and 33.9% achieved a serum 25(OH)D ≥75 nmol/l. These percentages were similar for all supplementation doses (p=0.06 and p=0.91 respectively).

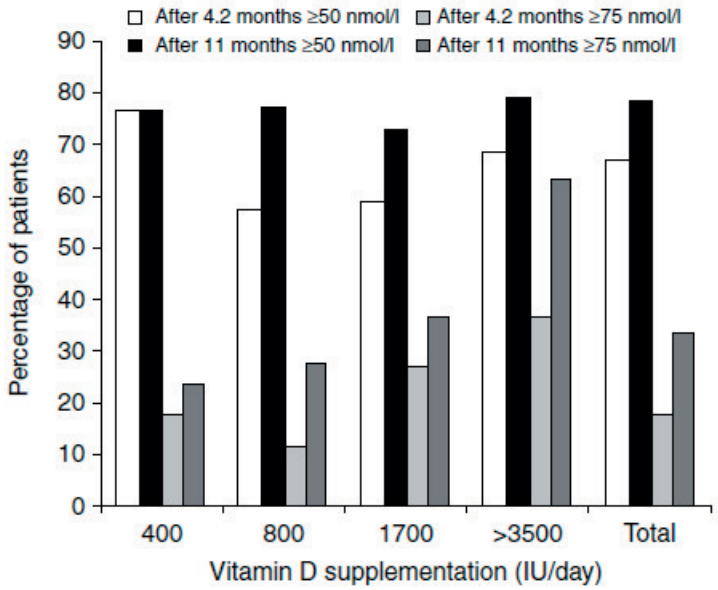

Figure 3. Percentage of patients achieving serum 25(OH)D levels ≥50 or 75 nmol/l after 4.2 and 11 months according to different vitamin D supplementation doses.

The achieved serum 25(OH)D was 60.2±19.5 nmol/l with 400 IU vitamin D3/day, 56.1±25.0 nmol/l with 800 IU/day, 64.0±33.0 nmol/l with 1700 IU/day, and 63.3±28.0 nmol/l for ≥3500 IU/day after 4.2 months and 60.2±20.0 nmol/l with 400 IU/day, 65.7±25.4 nmol/l with 800 IU/day, 70.6±37.0 nmol/l with 1700 IU/day, and 76.3±24.5 nmol/l for ≥3500 IU/day) after 11 months (Fig. 4). After 4.2 and 11 months follow-up, mean serum 25(OH)D level was not significantly different between the patients who started and did not start vitamin D supplementation (58.7±26.1 vs 62.0±20.7 nmol/l after 4.2 months (p=0.34) and 67.2±26.8 vs 67.1±21.0 nmol/l after 11 months (p=0.98), Fig. 4A). Between group comparisons in all vitamin D dose groups did not show significant differences at 4.2 and 11 months (p=0.66 and p=0.058 respectively).

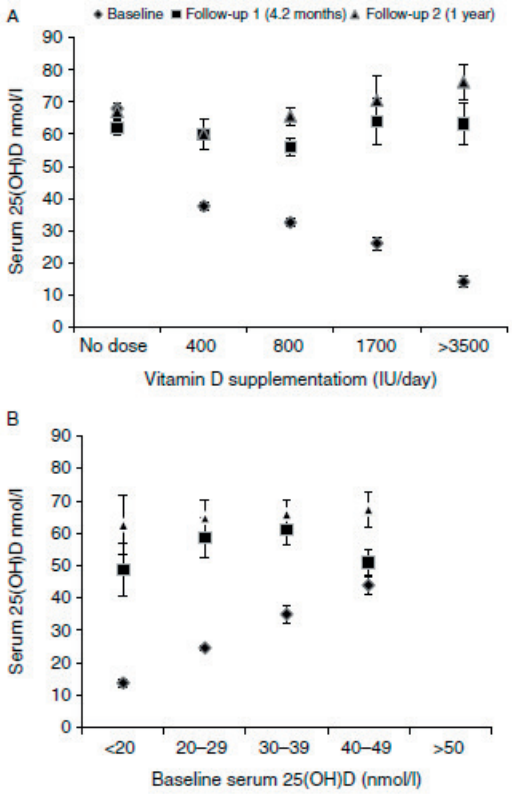

Figure 4. Serum 25(OH)D at baseline (diamonds), after 4.2 months (squares) and 11 months (triangles) follow-up in 221 (A) and 87 (B) patients with a recent fracture, according to daily vitamin D supplementation and baseline serum categories in a group with 800 IU/day vitamin D supplementation respectively.

The increase in serum 25(OH)D at 4.2 months was 22.6±20.0 nmol/l with the 400 IU vitamin D/day, 23.6±26.8 nmol/l with 800 IU/day, 38.0±37.3 nmol/l with 1700 IU/day, and 49.4±26.0 nmol/l with ≥3500 IU/day and at 11 months 22.6±18.0 nmol/l with 400 IU/day, 33.1±26.6 nmol/l with 800 IU/day, 44.6±36.7 nmol/l with 1700 IU/day, and 62.3±23.2 nmol/l with ≥3500 IU/day. Repeated measures ANOVA showed a time-related interaction between vitamin D dose groups on changes in serum 25(OH)D ($p<0.001$). Between-group comparisons in changes of serum 25(OH)D levels were significantly higher after both 4.2 and 11 months with higher supplementation dose (p for trend ≤0.001 for both time intervals). However after controlling for baseline serum 25(OH)D, there was no significant difference between supplementation dose groups in changes of 25(OH)D levels after both 4.2 and 11 months ($p=0.43$ and $p=0.31$ respectively). There was a negative correlation between the increase in serum 25(OH)D and baseline 25(OH)D levels at both 4.2 and 11 months ($r=-0.44$ and $r=-0.55$ respectively, both $p<0.001$).

To identify the predictors of 25(OH)D response after supplementation, we conducted a stepwise linear regression model. The contribution of each variable to the model is shown in Table 3. After 4.2 and 11 months, baseline serum 25(OH)D accounted 68 and 64% of variations of the change in serum 25(OH)D in the group with 221 patients. The mean increase in 25(OH)D (17±32.0 after 4.2 months and 24.3±34.0 nmol/l after 11 months) was dependent on the baseline serum 25(OH)D (R^2=0.70 and R^2=0.70, p<0.001 for both time intervals), not on supplementation dose, season, age, BMI, or gender.

Table 3. Multiple linear regression analysis for assessing the predictors of vitamin D supplementation response in 221 subjects after 4.2 and 11 months' follow-up.

	Change after 4.2 months				Change after 11 months			
	B	S.E.M.	β	p-value	B	S.E.M.	β	p-value
Constant	76.690	16.766		<0.001	45.401	18.96		0.018
Vitamin D dose (IU/day)	0.001	0.001	0.058	0.39	0.002	0.001	0.080	0.241
Baseline serum 25(OH)D (nmol/l)	-0.905	0.091	-0.68	<0.001	0.969	0.103	-0.647	<0.001
Season	0.068	1.562	0.002	0.96	2.230	1.790	0.071	0.215
Age (years)	0.453	0.300	-0.153	0.133	0.597	0.384	0.178	0.122
BMI (kg/m^2)	-0.304	0.633	-0.048	0.638	-1.426	0.865	-0.201	0.101
Gender	8.506	4.841	0.122	0.081	5.021	5.476	0.064	0.361

As many guidelines on osteoporosis advocate a daily dose of 800 IU vitamin D/day, we analyzed the patients who received 800 IU vitamin D/day (n=251) separately. As mentioned above, 32.3% achieved a serum 25(OH)D level > 50 after 4 months and 67.7% after 11 months. There was a negative correlation between the increase in serum 25(OH)D and baseline serum 25(OH)D levels (r=-0.38, p<0.001 after 4 months). After categorizing the 87 patients who were followed until 11 months into four subgroups according to the baseline serum 25(OH)D levels (<20, 20–29, 30–39, and 40–49 nmol/l), the change in serum 25(OH)D was significantly higher in patients with lower baseline levels (p=0.003). The mean achieved serum 25(OH)D levels were not significantly different between the four subgroups after 4 months (p=0.33) and after 11 months (p=0.96; Fig. 4B).

Discussion

In this prospective observational study in patients with a recent fracture who were treated in clinical practice, supplementation with higher doses of vitamin D3 in patients with lower baseline 25(OH)D levels increased serum 25(OH)D to a level ≥50 nmol/l in at

least 57% of patients after 4 months and 73% after 11 months. The increase in serum 25(OH)D was significantly larger with higher vitamin D3 supplementation doses. However, based on the multivariate analysis, this dose–effect response was mainly explained by the baseline serum 25(OH)D and not the higher supplementation dose itself. In several studies, it has been reported that a higher vitamin D supplementation dose resulted in higher serum 25(OH)D levels (16-19). However, in contrast to our study, the effect of different supplementation doses was investigated in subjects with 25(OH)D levels >50 nmol/l and in groups with equal baseline 25(OH)D levels. Our observation, that lower baseline 25(OH)D concentrations resulted in a greater magnitude of response, was also previously reported (7, 20-22). Lips et al. reported a similar negative correlation between change in 25(OH)D level after supplementation and baseline 25(OH)D levels (20, 21). The policy in our study resulted in mean achieved 25(OH)D values that were comparable after 4 and 11 months for all doses. Apparently, using our supplementation policy, baseline serum 25(OH)D is the strongest predictor for the magnitude of 25(OH)D change, not the dose itself, even when using high supplementation doses.

Using a standard supplementation dose of 800 IU/day, as advocated in many guidelines on osteoporosis and fracture prevention (23, 24), the percentage of patients reaching a serum 25(OH)D level ≥50 nmol/l were similar to using higher doses, at any baseline serum 25(OH)D. This result confirms that baseline serum 25(OH)D is the most important predictor of response to vitamin D3 supplementation. Therefore, if the aim is to achieve a serum 25(OH)D ≥50 nmol/l, as in our study, higher vitamin D supplementation doses than 800 IU/day are not needed (6, 7, 24). However, if the aim is to achieve a serum 25(OH)D ≥75 nmol/l, higher doses may be needed. Indeed, a threshold ≥75 nmol/l was only achieved in one-third of the patients taking supplementation doses of up to 1700 U/day, and in two-thirds of patients using doses of 3500 IU/day or more.

Quite surprisingly, >20% of patients in this study did not reach the threshold of 50 nmol/l, at any dose. One possibility for non-response is low compliance (25), which is a problem in many chronic diseases in clinical practice, including osteoporosis and fracture prevention (26). Another possibility is malabsorption, such as in celiac disease (27). In this study, however, we did not systematically check compliance and investigate whether patients had a malabsorption syndrome, so we do not know to what extent these aspects may have contributed to this finding. In addition, Leblanc et al. (28) have recently reported that the colecalciferol content of compounded vitamin D supplements was highly variable (23–146%), even within the same formulation and dose. Another possibility is the genetic background. Recently it has been emphasized that genetic make-up of subjects may be important with regard to the response to vitamin D supplementation or diet. This individual variability may be, at least in part, explained by vitamin D receptor polymorphisms, vitamin D-binding protein, or other genetic determinates of serum 25(OH)D (29-31). Additionally, it was reported that there are four different types of 25 hydroxylases (32). Holick et al. reported that these enzymes most

likely have different affinities for vitamin D and have different levels of negative feedback regulation by the serum 25(OH)D concentration. Thus, circulating 25(OH)D concentrations in response to vitamin D may be influenced by the baseline 25(OH)D concentration (33). Studies reported that even with good compliance, there is large variability in the response of 25(OH)D during vitamin D3 supplementation, and pointed out the prevalence of non-response patients in their populations (34), as also reported by Gallagher et al. (6). Considering the high prevalence of vitamin D deficiency in the elderly and assuming the same prevalence of 'non-responders' among the elderly population, a huge number of people may not benefit sufficiently from intake of the usually recommended amount of vitamin D. Given these considerations, follow-up measurements are helpful to detect suboptimal 25(OH)D levels and to adjust supplementation management.

Our study has several limitations. Firstly, this was an observational, non-randomized study. Secondly, we did not assess compliance. Thirdly, we did not assess baseline dietary vitamin D intake or a change in intake during the study. However, it is well documented that dietary vitamin D intake is low in The Netherlands (35). Fourthly, the various doses of vitamin D were in different formulations.

In conclusion, baseline serum 25(OH)D levels, but not supplementation dose, determined the response to vitamin D supplementation. The increase in serum 25(OH)D levels was higher in patients with lower baseline levels. In 21–27% of patients, serum 25(OH)D3 levels did not reach 50 nmol/l after 11 months, at any dose. Further studies are needed in order to identify possible causes of suboptimal response such as non-compliance, undiagnosed malabsorption syndromes, or variability in cholecalciferol content of the vitamin D supplements.

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Chapter 5

Serum 25(OH)D response to vitamin D supplementation: a meta-regression analysis

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Abstract

Objective

The aim of this study was to review factors that influence serum 25(OH)D when patients are given vitamin D supplements.

Methods

From a comprehensive search of all randomized controlled clinical trials with vitamin D3 supplementation available on PubMed up to November 2011, we selected 33 with 43 treatment arms that included at least 30 adult participants. The achieved pooled mean difference (PMD) and 95% confidence intervals (CIs) were calculated using the random-effects models. Meta-regression and subgroup analyses were performed for pre-specified factors, including dose, duration, baseline serum 25(OH)D, and age.

Results

With a mean baseline serum 25(OH)D of 50.4 nmol/L, PMD was 37 nmol/L (95% CI, 33–41) with significant heterogeneity among studies. Dose (slope: 0.006; $p < 0.001$), trial duration (slope: 0.21; $p < 0.001$), baseline serum 25(OH)D (slope: -0.19; $p < 0.001$), and age (slope: 0.42; $p < 0.001$) independently influenced vitamin D response. Similar results were found in studies with a mean baseline serum 25(OH)D <50 nmol/L. In subgroup analyses, the PMD was higher with doses ≥800 IU/d (39.3 nmol/L) after 6 to 12 months (41.7 nmol/L), with baseline 25(OH)D <50 nmol/L (39.6 nmol/L), and in adults aged >80 years (40.5 nmol/L).

Conclusion

This meta-regression indicates that a higher increase in serum levels of 25(OH)D in adults is found with a dose of ≥800 IU/d, after at least 6 to 12 months, and even when baseline 25(OH)D is low and in adults >80 years.

Introduction

Vitamin D deficiency is endemic worldwide and prevalent in all age groups and in both sexes (1). The importance of vitamin D in health is well documented in terms of its effects on bone, muscle strength, fracture and fall risk, general health, the immune system, diabetes, blood pressure, and cancer (2).

The essential question of how much vitamin D is needed for optimal bone and global health, however, remains unsolved (3-6) and public health authorities around the world recommend widely variable supplementation strategies for adults (7). The Recommended Dietary Allowances (RDA) is 400 IU/d in all children ages 0 to 12 months, 600 IU/d in males and females ages 1 to 70 years, and 800 IU/d for adults ages >70 years (8).

Additionally, the change in serum 25(OH)D levels in response to a given dose of vitamin D supplementation varies widely from person to person (9). Few studies have been conducted to identify factors responsible for serum 25(OH)D variation in response to vitamin D supplementation (9). Indeed, many factors influence the effect of vitamin D supplementation on serum levels of 25(OH)D, such as the dose (10) and duration (9), baseline 25(OH)D (9), body mass index (BMI) (9), season (9), and age (9,10).

However, there is still debate as to whether dose and duration should be based on baseline 25(OH)D (11) and whether and when serum levels should be checked during treatment (7). The Endocrine Society Task force advocated 1500 to 2000 IU/d in children and adults (12). A recent critical analysis on the basis of evidence-based medicine advocated 800 IU/d in adult or older individuals (7). The Vitamin D Council (http://www.vitamindcouncil.org), recommended an intake of 100 mg or more to achieve levels of well above 100 nmol/L. Higher doses of vitamin D supplements are also advocated in conditions that limit vitamin D absorption or alter vitamin D metabolism, such as limited sun exposition, obesity, and malabsorption (13).

Repeated measurement of serum levels of 25(OH)D is advocated in at-risk subgroups, but the best time to remeasure is unclear, as some studies already evaluated the effect soon after the start of supplementation, whereas others measured after 6 and 12 months (10).

This raises the question whether dose of vitamin D supplementation should be individualized according to baseline 25(OH)D and age and at what time after supplementation begins maximum serum levels are reached.

Therefore, we conducted a meta-regression analysis based on randomized clinical trials (RCTs) in adults to review the influence of supplementation-related factors (dose and duration) and patient-related factors (age and baseline 25[OH]D) on changes in serum levels of 25(OH)D.

Methods

Inclusion criteria

The search included RCTs that were in English and published up to November 2011. Only studies with daily vitamin D3 (cholecalciferol) supplementation were included, with a minimum of 30 participants in the vitamin D treatment and control groups and only when performed in apparently healthy individuals or in patients with no underlying reason for altered vitamin D metabolism. We excluded animal studies; cross-sectional or case–control studies; non-randomized trials; studies in children, pregnant women, and patients with conditions that affect vitamin D metabolism, such as chronic kidney disease stage 3 or higher, or hyperparathyroidism; trials that used a vitamin D preparation other than D3; and studies that included calcitriol and ergocalciferol or non-oral routes of vitamin D administration. We also excluded repeated studies and studies without a placebo or control group.

Search strategy

The papers for this review were selected through a search in PubMed using the terms vitamin D, cholecalciferol, vitamin D intake, vitamin D supplement and calcidiol. For methods (study design), the following keywords and or corresponding MeSH terms were used: randomized controlled trial and placebo. The search was done also using combinations of keywords for intervention and for method. The search for keywords in the title and in the abstract was done systematically. A manual search was done of references cited in the selected articles and in selected reviews. Titles and abstracts of the resulting articles were examined, and full-text articles were retrieved after excluding non-eligible ones.

Data extraction and quality of assessment

Data extracted from RCTs included country of origin, sample size, participant characteristics (age and sex) in every intervention group, dosage (vitamin D supplementation per day) and trial duration (months), and baseline and achieved 25(OH)D levels. Means and SDs of the baseline and final serum levels of 25(OH)D in the intervention and placebo groups were extracted. Mean difference between final values of intervention and placebo were calculated.

International units (IU) of vitamin D were used in the analysis and expressed in nmol/L. If a study had several different intervals for follow-up measurements of 25(OH)D, only the first and highest duration up to 12 months was used for analysis. If studies had subgroups such as sex, they were included in our study as a separate study. In studies with different doses we included each dose as a separate study. For some papers we had to estimate 25(OH)D levels from the figures because results were not given in the text or tables.

Authors were contacted if further study details were needed. Some of RCTs failed to provide SDs of their continuous outcome measures and therefore we used SDs from other studies in this meta-analysis (14). The Jadad scale was used to assess the methodological and reporting quality of RCTs (15).

Statistical analysis

Pooled mean difference (PMD) of achieved 25(OH)D with 95% confidence intervals (CIs) were calculated between treatment and placebo groups using a random-effects model. Cochran's Q statistic and the I^2 statistic were used to assess statistical heterogeneity in meta-analysis (16).

Potential sources of heterogeneity were also investigated in subgroup analyses with a mixed-effect model. We assessed treatment effect in prespecified subgroups: 1) dose (<800 IU, 800 IU, and >800 IU), 2) duration (<6 months, 6–12 months, and >12 months), 3) baseline 25(OH)D (<50 or ≥50 nmol/L), and 4) age (<69, 70–79 and >80 years).

The random-effect meta-regression was used to analyze which factors within a trial best explained the variance in PMD. Using meta-regression we analyzed the contribution of daily dose, duration, baseline 25(OH)D, and age on PMD.

We performed ancillary analyses including curve estimation models for weighted mean difference of serum levels of 25(OH)D according to dose and duration as continuous variables.

The chi-square test was used to analyze the distribution of populations who reached 25(OH)D ≥50 nmol/L.

Publication bias was analyzed by funnel plot analysis and Egger's regression asymmetry test (17). All tests were two-tailed. For all tests, a probability level <0.05 was considered statistically significant. Statistics were performed using Comprehensive Meta-Analysis (Version V2.0) and SPSS version 18.

Results

A flow chart showing the number of RCTs assessed and included in the review is shown in Fig. 1. The primary search was conducted in November 2011 and disclosed 2860 articles, of which 33 RCTs fulfilled the inclusion and exclusion criteria (18-51).

All studies were RCTs, but in 16 studies, the method of randomization was not clearly mentioned (18-32). Of those, eight studies were not blinded (18, 21, 26, 30, 31, 49-51). Four studies did not report data on dropouts (26, 41, 50). Six studies scored <3 on the Jadad scale (18, 21, 26, 30, 31, 50).

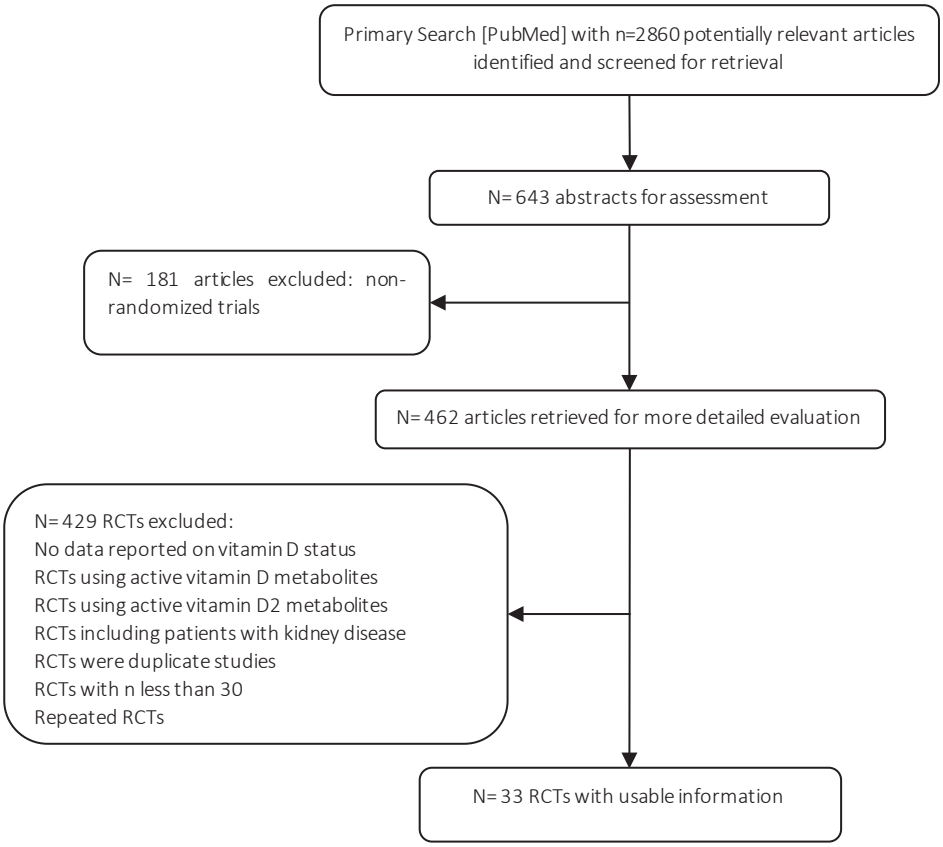

Figure 1. Flow chart of the selection procedure of 2860 potentially relevant articles in this study

The 33 RCTs selected included 43 treatment arms with 3659 treated participants and 3491 placebo-treated individuals. The mean age was 65.8 years. The daily oral cholecalciferol supplementation dose varied from 200 to 4000 IU (Table 1). The duration of supplementation varied between 1 and 36 months. Most of the patients were supplemented with 800 IU (28.6%) for 12 months (35.7%), 14.3% of the studies included only men, 45.2% only women, and 40.5% men and women combined.

Mean baseline 25(OH)D varied between 18.3 and 97.0 nmol/L with an average of 50.4 nmol/L. In 21 (47.7%) of 44 study arms, mean baseline serum 25(OH)D was <50 nmol/L. Mean achieved 25(OH)D varied between 46 and 123 nmol/L with an average of 81.3 nmol/L. In 19 of 21 study arms with a mean baseline 25(OH)D below 50 nmol/L, these mean levels were >50 nmol/L.

Table 1. Study and participant summary

Author	Country	Year	Participants	Sex	(n)	Age	Dose (IU/Day)	Trial Duration (months)	Mean difference (nmol/L)
Dawson-Hughes	U.S.	1991	Elderly Women	2	124	61.9	500	12.0	31.50
Chapuy 2	France	1992	Elderly People	2	73	84	800	12.0	80.00
Ooms	The Netherlands	1995	Elderly Women	2	177	80.1	400	24.0	39.00
Dawson-Hughes1	U.S.	1997	Elderly	1	86	70	700	36.0	81.08
Dawson-Hughes2	U.S.	1997	Elderly	2	101	71	700	36.0	86.80
Krieg1	Switzerland	1999	Elderly Institutionalized Women	2	34	84	880	12.0	53.75
Hunter3	U.K.	2000	Women	2	79	59.2	800	24.0	26.32
Pfeifer	Germany	2001	Older Women	2	74	74.8	800	2.0	20.48
Chapuy2 #	France	2002	Elderly Women	2	199	84.9	800	12.0	63.70
Chapuy6 §	France	2002	Elderly Women	2	194	84.9	800	12.0	68.70
Meyer	Norway	2002	The Elderly	3	34	84.4	400	12.0	18.00
Kenny	U.S.	2003	Men	1	33	76	1000	6.0	30.00
Grados	France	2003	Ambulatory Elderly Women	2	95	74.2	800	12.0	68.35
Bischoff-Ferrari	Switzerland	2003	Elderly Women	2	45	84.9	800	3.0	37.00
Larsen2	Denmark	2004	Elderly Community-Dwelling Residents	3	58	75.2	400	24.0	9.00
Brazier	France	2005	Elderly Women	2	95	74.2	800	12.0	45.10
Bischoff-Ferrari1	Switzerland	2006	Women 65 Years Or Older	2	121	71	700	36.0	36.00
Bischoff-Ferrari2	Switzerland	2006	Men ≥ 65y	1	98	70	700	36.0	33.50
Schleithoff	Germany	2006	Patients With CHF	3	42	57	2000	9.0	55.70
Talwar2	U.S.	2007	Healthy Black Postmenopausal Women	2	104	59.9	2000	24.0	24.30
Lappe	U.S.	2007	Community-Dwelling Women	2	403	66.7	1000	12.0	24.90
Smedshaug	Norway	2007	Elderly People	3	32	82.8	400	12.0	20.40
Blum	U.S.	2008	Healthy, Ambulatory Men And Women	1	132	72	700	12.0	42.70
Björkman1	Finland	2008	Bedridden Older Patients	2	63	83.9	1200	6.0	48.20
Björkman2	Finland	2008	Bedridden Older Patients	2	60	84.2	400	6.0	22.70

Author	Country	Year	Participants	Sex	(n)	Age	Dose (IU/Day)	Trial Duration (months)	Mean difference (nmol/L)
Cashman1	U.K.	2008	Healthy Young	3	53	29.9	600	5.5	31.60
Cashman2	U.K.	2008	Healthy Young	3	57	29.9	400	5.5	22.60
Cashman3	U.K.	2008	Healthy Young	3	48	29.9	200	5.5	12.30
Nelson	U.K.	2009	Premenopausal women	2	55	22	800	5.0	24.70
Pfeifer	Germany	2009	Community-Dwelling Seniors	3	121	76	800	12.0	27.00
Kuwabara #	Japan	2009	Institutionalized Elderly	3	32	83.8	800	1.0	19.55
Li -Ng		2009	Ambulatory Adults	3	78	59.3	2000	3.0	27.60
Islam1*	Bangladesh	2010	Apparently Healthy Subjects	3	40	22.1	400	12.0	34.70
Islam2**	Bangladesh	2010	Apparently Healthy Subjects	3	40	22.1	400	12.0	33.70
Kärkkäinen	Finland	2010	Elderly Women	2	287	67.4	800	36.0	18.60
Krishnamoorthy	India	2010	Adults With New-Onset Epilepsy	3	32	23.6	400	3.0	29.40
Laaksi	Finland	2010	Acute Respiratory Tract Infection	1	58	23	400	3.0	20.30
Von Hurst	New Zealand	2010	Women	2	42	41.8	4000	6.0	51.00
Seamans1	U.K.	2010	Healthy Adults	3	53	70.7	600	5.5	32.20
Seamans2	U.K.	2010	Healthy Adults	3	57	70.7	400	5.5	27.90
Seamans3	U.K.	2010	Healthy Adults	3	48	70.7	200	5.5	11.60
Pilz	Germany	2011	Non-diabetic Subjects	1	31	49.4	3332	12.0	50.90
Dean	Australia	2011	Young Adults	3	63	21.5	5000	1.5	22.60

CHF, congestive heart failure

1 = men, 2 = women, 3 = men and women

Ca–D3 fixed combination.

§ Ca+D3 separate combination.

* Supplementation with vitamin D.

** Supplementation with vitamin D-calcium.

Meta-analysis

The weighted mean change of 25(OH)D from baseline was +34.1 nmol/L (-7 to +73 nmol/L) in the treated group.

Vitamin D supplementation resulted in a PMD of 37 nmol/L (95% CI, 33–41; $p < 0.001$) (Fig. 2). There was significant heterogeneity between studies (test for heterogeneity: $p < 0.001$; I^2=95.8%). Influence analysis showed that no particular trial affected the pooled effect size (Fig. 3) and cumulative analysis indicated consistency from the year 2006 (Fig. 4). Egger's regression analysis showed that there was no publication bias (p=0.78; Fig. 5).

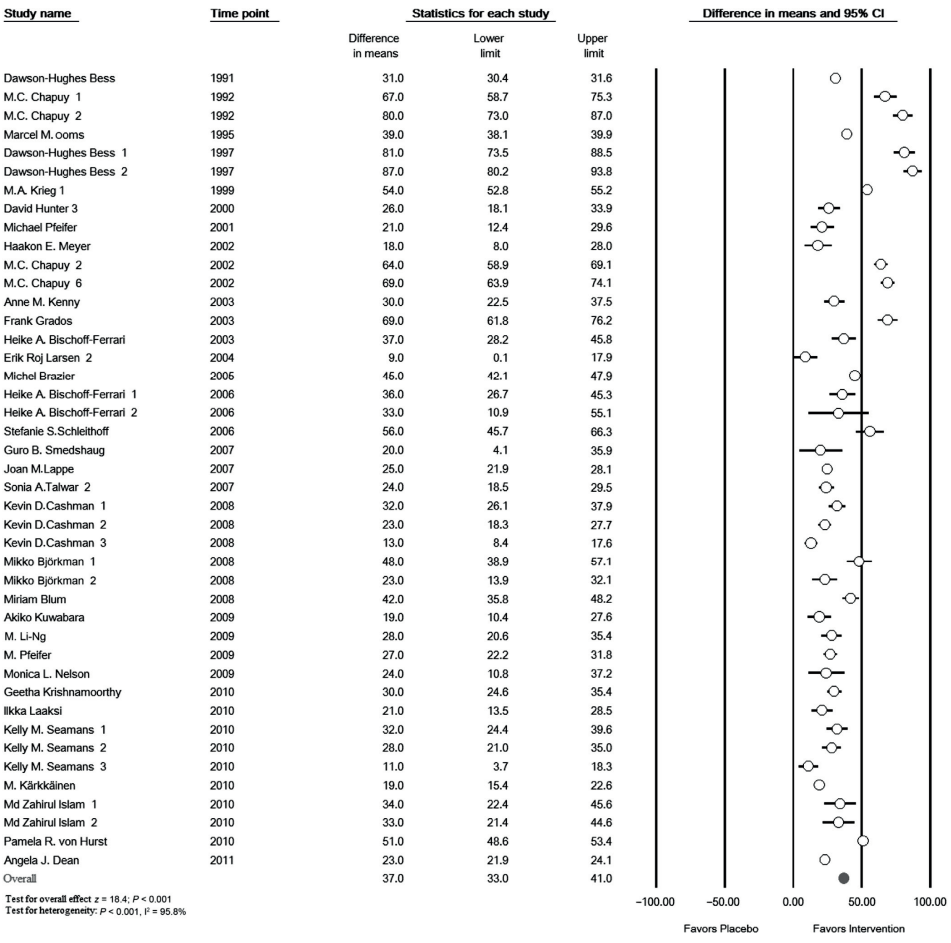

Figure 2. Effect of vitamin D supplementation on the mean difference of 25(OH)D levels compared with placebo in 33 randomized control trials.

Study name	Time point	Point	Lower limit	Upper limit
Dawson-Hughes Bess	1991	37.1	32.3	41.9
M.C. Chapuy 1	1992	36.3	32.3	40.3
M.C. Chapuy 2	1992	36.0	32.0	39.9
Marcel M. ooms	1995	36.9	32.3	41.5
Dawson-Hughes Bess 1	1997	36.0	32.0	39.9
Dawson-Hughes Bess 2	1997	35.8	31.9	39.7
M.A. Krieg 1	1999	36.6	33.0	40.2
David Hunter 3	2000	37.3	33.2	41.3
Michael Pfeifer	2001	37.4	33.4	41.4
Haakon E. Meyer	2002	37.4	33.4	41.5
M.C. Chapuy 2	2002	36.3	32.4	40.3
M.C. Chapuy 6	2002	36.2	32.3	40.2
Anne M. Kenny	2003	37.2	33.1	41.2
Frank Grados	2003	36.2	32.2	40.2
Heike A. Bischoff-Ferrari	2003	37.0	33.0	41.1
Erik Roj Larsen 2	2004	37.7	33.6	41.7
Michel Brazier	2005	36.8	32.7	40.9
Heike A. Bischoff-Ferrari 1	2006	37.0	33.0	41.1
Heike A. Bischoff-Ferrari 2	2006	37.1	33.1	41.1
Stefanie S Schleithoff	2006	36.6	32.6	40.6
Guro B. Smedshaug	2007	37.3	33.3	41.4
Joan M.Lappe	2007	37.3	33.3	41.4
Sonia A.Talwar 2	2007	37.3	33.3	41.4
Kevin D.Cashman 1	2008	37.1	33.1	41.2
Kevin D.Cashman 2	2008	37.4	33.3	41.4
Kevin D.Cashman 3	2008	37.6	33.6	41.6
Mikko Björkman 1	2008	36.8	32.7	40.8
Mikko Björkman 2	2008	37.3	33.3	41.4
Miriam Blum	2008	36.9	32.8	40.9
Akiko Kuwabara	2009	37.4	33.4	41.5
M. Li-Ng	2009	37.2	33.2	41.3
M. Pfeifer	2009	37.3	33.2	41.3
Monica L. Nelson	2009	37.3	33.2	41.3
Geetha Krishnamoorthy	2010	37.2	33.1	41.2
Ilkka Laaksi	2010	37.4	33.4	41.4
Kelly M. Seamans 1	2010	37.1	33.1	41.2
Kelly M. Seamans 2	2010	37.2	33.2	41.3
Kelly M. Seamans 3	2010	37.6	33.6	41.7
M. Kärkkäinen	2010	37.5	33.4	41.5
Md Zahirul Islam 1	2010	37.1	33.0	41.1
Md Zahirul Islam 2	2010	37.1	33.1	41.1
Pamela R. von Hurst	2010	36.7	32.6	40.7
Angela J. Dean	2011	37.4	33.3	41.4
Overall		37.0	33.0	41.0

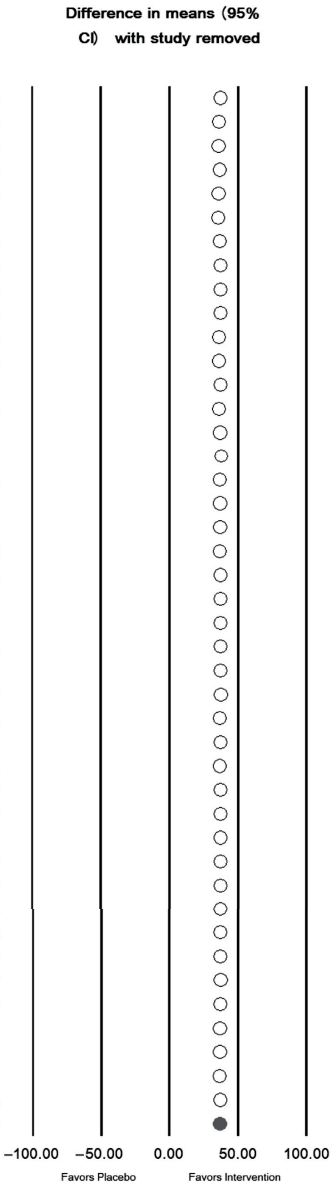

Figure 3. Influence analysis

Study name	Time point	Cumulative statistics		
		Point	Lower limit	Upper limit
Dawson-Hughes Bess	1991.000	31.0	30.4	31.6
M.C. Chapuy 1	1992.000	48.8	13.5	84.0
M.C. Chapuy 2	1992.000	59.2	24.0	94.4
Marcel M. ooms	1995.000	52.3	44.1	60.4
Dawson-Hughes Bess 1	1997.000	58.0	49.7	66.4
Dawson-Hughes Bess 2	1997.000	63.1	54.3	71.9
M.A. Krieg 1	1999.000	62.0	52.5	71.5
David Hunter 3	2000.000	57.7	48.7	66.6
Michael Pfeifer	2001.000	53.8	45.4	62.2
Haakon E. Meyer	2002.000	50.5	42.5	58.5
M.C. Chapuy 2	2002.000	51.8	44.0	59.6
M.C. Chapuy 6	2002.000	53.2	45.6	60.9
Anne M. Kenny	2003.000	51.5	44.1	58.8
Frank Grados	2003.000	52.7	45.5	59.9
Heike A. Bischoff-Ferrari	2003.000	51.7	44.8	58.6
Erik Roj Larsen 2	2004.000	49.1	42.4	55.9
Michel Brazier	2005.000	48.9	42.5	55.3
Heike A. Bischoff-Ferrari 1	2006.000	48.2	42.0	54.5
Heike A. Bischoff-Ferrari 2	2006.000	47.7	41.6	53.9
Stefanie S. Schleithoff	2006.000	48.1	42.1	54.1
Guro B. Smedshaug	2007.000	47.0	41.2	52.9
Joan M.Lappe	2007.000	46.0	40.3	51.7
Sonia A.Talwar 2	2007.000	45.0	39.4	50.5
Kevin D.Cashman 1	2008.000	44.4	39.0	49.8
Kevin D.Cashman 2	2008.000	43.5	38.2	48.8
Kevin D.Cashman 3	2008.000	42.2	37.0	47.5
Mikko Björkman 1	2008.000	42.4	37.3	47.6
Mikko Björkman 2	2008.000	41.8	36.7	46.8
Miriam Blum	2008.000	41.8	36.8	46.7
Akiko Kuwabara	2009.000	41.0	36.2	45.9
M. Li-Ng	2009.000	40.6	35.8	45.4
M. Pfeifer	2009.000	40.2	35.5	44.8
Monica L. Nelson	2009.000	39.7	35.1	44.3
Geetha Krishnamoorthy	2010.000	39.4	34.9	44.0
Ilkka Laaksi	2010.000	38.9	34.5	43.4
Kelly M. Seamans 1	2010.000	38.7	34.3	43.1
Kelly M. Seamans 2	2010.000	38.4	34.1	42.7
Kelly M. Seamans 3	2010.000	37.7	33.4	42.0
M. Kärkkäinen	2010.000	37.2	32.9	41.4
Md Zahirul Islam 1	2010.000	37.1	32.9	41.3
Md Zahirul Islam 2	2010.000	37.0	32.9	41.1
Pamela R. von Hurst	2010.000	37.4	33.3	41.4
Angela J. Dean	2011.000	37.0	33.0	41.0
Overall		37.0	33.0	41.0

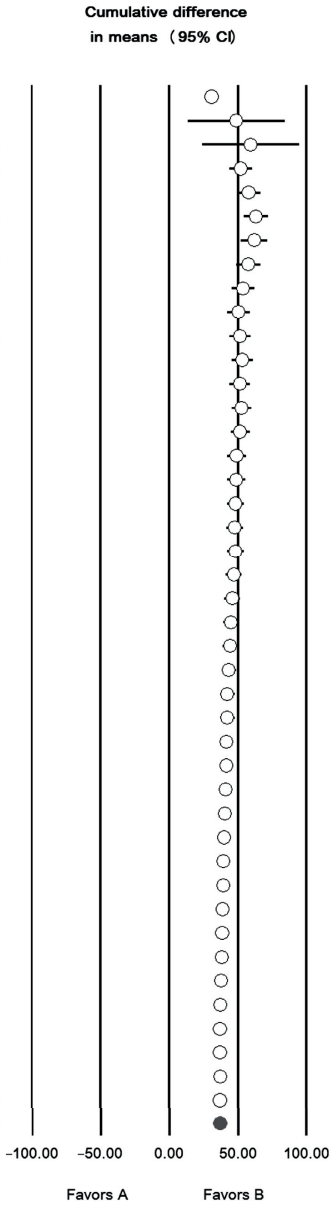

Figure 4. Cumulative analysis

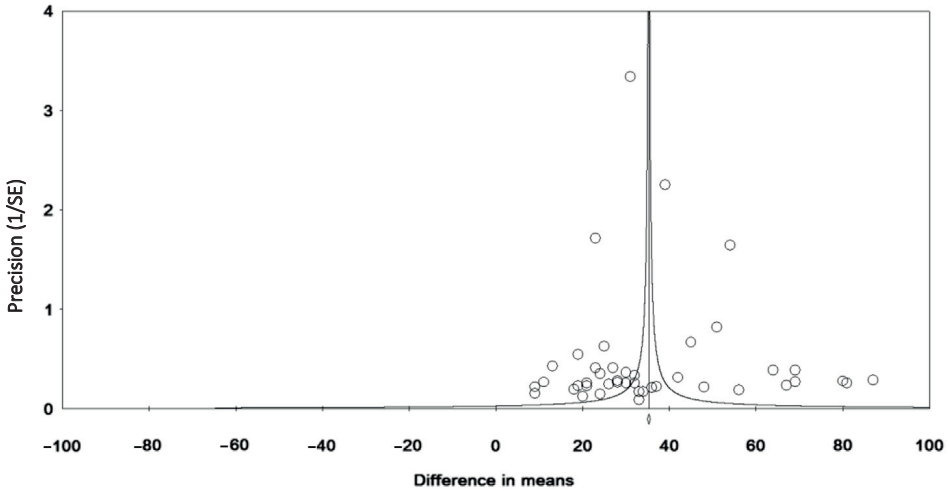

Figure 5. Funnel plot to assess publication bias

Subgroup analysis

Each of the prespecified factors significantly affected PMD (Table 2). PMD was higher with vitamin D doses of 800 IU/d (39.3 nmol/L) than with doses <800 IU/d (32.5 nmol/L). PMD increased significantly with duration (25.6 nmol/L within <6 months, 41.7 nmol/L during 6–12 months, and 39.5 after 12 months). Individuals with baseline 25(OH)D <50 nmol/L had higher PMD (39.6 nmol/L) than those with baseline >50 nmol/L (30.8 nmol/L). PMD in individuals older than 80 years (40.5 nmol/L) was significantly higher than in those <69 years (28.4 nmol/L).

Meta-regression

Meta-regression analysis indicated that each of the factors just discussed (dose, duration, baseline 25(OH)D, and age) were significantly and independently related to PMD (Table 3; Fig. 6): Dose (slope: 0.006; $p < 0.001$), duration (slope: 0.21; $p < 0.001$), baseline 25(OH)D3 (slope: -0.19; $p < 0.001$), and age (slope: 0.42; $p < 0.001$).

Ancillary analyses

Curve estimation regression showed a significant logarithmic correlation between PMD and dose ($R^2 = 0.11$; $P = 0.032$) and between PMD and duration ($R^2 = 0.13$; $P = 0.015$), flattening from a dose of 800 IU/d on and after 6 months, without reaching a plateau with increasing dose or duration (Fig. 7). Individuals with baseline 25(OH)D <50 nmol/L had a logarithmic dose dependent increase in PMD that was not found in those with baseline 25(OH)D ≥50 nmol/L. They also had a logarithmically quicker and sustained higher PMD during follow-up than individuals with baseline 25(OH)D ≥50 nmol/L, which reached a

plateau at 6 months, whereas in participants with baseline 25(OH)D ≥50 nmol/L, PMD progressively increased over time (data not shown).

Table 2: Subgroup analysis for mean difference (MD) from baseline of serum 25(OH)D

	MD	95%CI	P-value
Vitamin D dose			
<800 IU/d	32.5	28.1-37.0	<0.001
800 IU/d	39.3	42.4-57.4	
>800 IU/d	34.2	32.6-43.2	
Duration			
<6 months	25.6	18.1-33.1	<0.001
6-12 months	41.7	33.8-49.5	
>12 months	39.5	36.5-52.5	
Baseline serum 25(OH)D			
≤50 nmol/L	39.6	34.0-45.2	<0.001
>50 nmol/L	30.8	25.6-36.0	
Age			
<69y	28.4	23.6-33.2	<0.001
70-79y	35.5	28.1-51.0	
>80y	40.5	32.0-49.0	

Table 3: Summary of multiple regressions between PMD of serum 25(OH)D and dose, trial duration, baseline levels of serum 25(OH)D and age

	Slope	(95%CI)	P-value
Dose (IU/d)	0.006	0.005-0.007	<0.001
Trial duration (months)	0.21	0.14-0.27	<0.001
Baseline serum 25(OH)D (nmol/l)	-0.19	-0.21 to -0.18	<0.001
Age (y)	0.42	0.40-0.46	<0.001

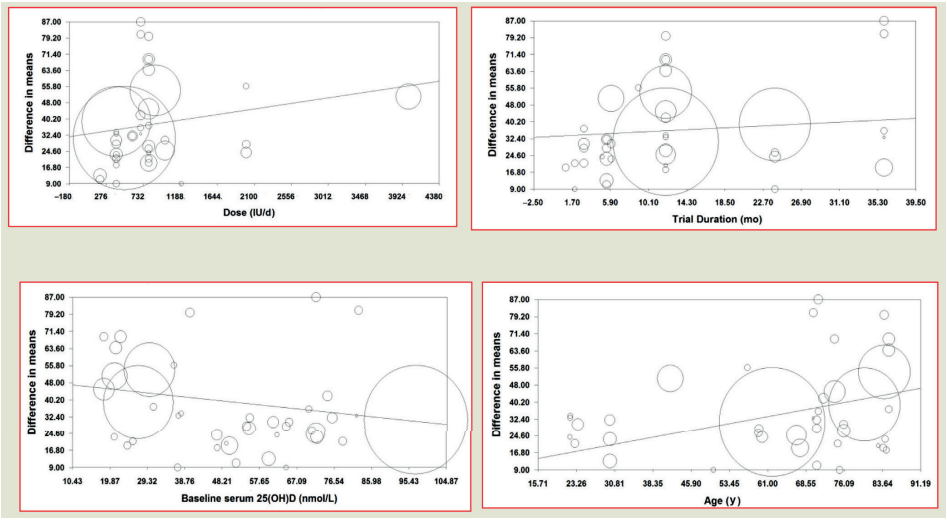

Figure 6. Meta-Regression analysis of differences in means of serum 25(OH)D versus age, baseline levels of serum 25(OH)D, dosage of vitamin D and trial duration

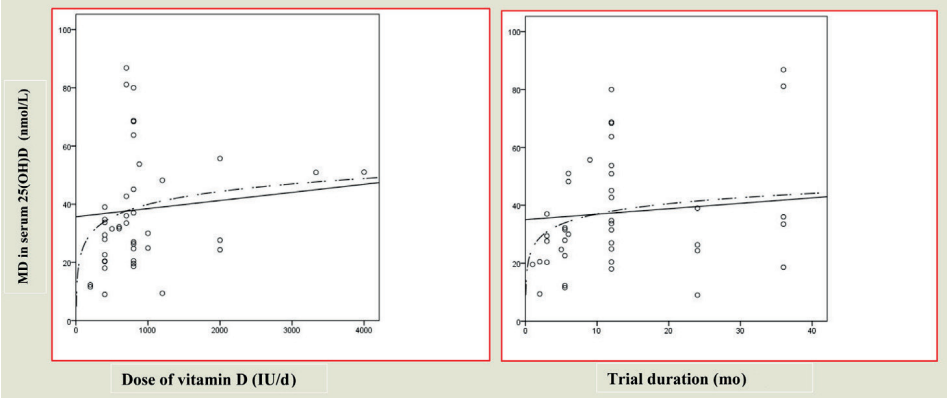

Figure 7. Correlation of mean difference (MD) in 25(OH)D levels with dose of vitamin D (IU/d) and trial duration (months).

Discussion

In the present meta-regression analysis of 33 RCTs in adults with a mean baseline 25(OH)D of 50 nmol/L, vitamin D3 supplementation significantly increased 25(OH)D with a PMD of 37 nmol/L. This increase was heterogeneous and dependent on dose, duration, baseline 25(OH)D, and age.

Effect of dose

We found a dose-dependent increase in PMD, which was curvilinear with flattening from a dose of 800 IU/d, with only a slight increase with higher doses. This is in contrast with the first dose to response in older white women found in an earlier study. The study found a dose-dependent effect on achieved serum levels reaching a plateau around 4000 IU/d in patients with low baseline levels of 25(OH)D [10]. However, until November 2011, only one valid RCT was available for inclusion in our study with doses >2000 IU/d, so that a dose response at higher doses could not be studied adequately. The study results also demonstrated that a dose of 800 IU/d resulted in 97.5% of participants reaching levels >50 nmol/L.

In another study, a meta-regression analysis from RCTs that started in the winter at latitudes higher than 49.5°N were used to create a model to calculate the need of vitamin D supplements (52). That study reported that a total daily dose of 930 IU is needed to achieve a serum 25(OH)D of 50 nmol/L, taking into account the variability of response, which is in line with our results. However, in this analysis, the effect of high doses of vitamin D3 was not examined.

The nonlinear response of 25(OH)D to dose of vitamin D3 intake also has been shown in other studies (8, 53, 54). Apparently, there is a homeostatic control system that regulates 25(OH)D and buffers variability in vitamin D supply (55).

Interestingly, it was confirmed, in a pooled analysis, that supplementation of vitamin D ≥800 IU/d reduced the risk for hip and any non-vertebral fracture in individuals ages ≥65 years (56).

Most guidelines suggest a fixed daily dose such as 800 or 1000 IU vitamin D. However, our results indicated that a fixed dose is not sufficient for all patients. There was large variability in response of 25(OH)D during vitamin D supplementation in studies. If the aim of treatment is to achieve so-called optimal levels of serum 25(OH)D (≥75 nmol/L), individuals will need higher doses of vitamin D3 supplements than the dose needed to achieve 50 nmol/L (57, 58).

We only studied daily doses due to problems observed in earlier studies (59). An increase of serum 25(OH)D was reported with 100 000 IU every 4 months (equivalent to 800 IU/d).

However, they concluded that this dosage might be too low (44). One explanation could be that intermittent supplements are less effective than daily doses.

Although higher doses of supplementation resulted in higher serum values, it has been shown on the basis of bone density measurements and fall and fracture prevention in the elderly the beneficial amount is likely to be 800 to 1000 IU/d (60, 61). These studies also included calcium supplements.

Effect of duration

Another important finding was the increase in serum 25(OH)D over time. An immediate increase in PMD was found in patients with baseline <50 nmol/L reaching a plateau after 6 months. This suggests that a measurement of 25(OH)D after 6 months reflects the maximum attained 25(OH)D level period. Similar findings were reported previously (10). In contrast, individuals with a baseline 25(OH)D >50 nmol/L required a longer duration to determine an accurate effect of supplementation. In a recently published prospective observational study (62), we found that supplementation with higher doses of vitamin D3 in patients with lower baseline 25(OH)D concentration increased serum 25(OH)D to a level ≥50 nmol/L in at least 57% of patients after 4 months and 73% after 11 months, indicating that measurement of serum 25(OH)D after 4 months does not reflect the maximum achievable level.

Effect of baseline 25(OH)D levels

Based on the findings in the present study, higher increases of 25(OH)D are achieved with lower baseline 25(OH)D concentrations. This finding is consistent with that of previous studies (62-65). Possible explanations could be cholecalciferol stores in the body or genetic background (58, 66).

It has been shown that genetic background may play a role with regard to the response to vitamin D supplementation or diet, such as polymorphisms of the vitamin D receptor, vitamin D-binding protein, or other genetic determinates of serum 25(OH)D (66-68).

Effect of age

Interestingly, older participants demonstrated a better response to vitamin D3 intake, independent of baseline 25(OH)D. Several studies have suggested that the greater effect could be contributed to the high prevalence of vitamin D deficiency in this population (69, 70). Our results indicate that other age-related factors also play a role.

Limitations

There are limitations to this meta-regression. First, our search was limited to published studies. We did not search for unpublished trials and did not have access to individual

patient data. Second, we could not adjust for BMI according to lack of access to individual data and data of BMI in studies. Third, we could not correct for seasonal influences, sun exposure, and dietary intake of vitamin D and calcium because not all studies reported these data. However, using PMD, effects of season or diet were corrected. Additionally, both sunlight and dietary sources are reflected in the baseline 25(OH)D concentrations (71). Fourth, the use of different assay types may have influenced the validity of the study outcomes. Fifth, we did not explore the effect of sex because most studies included participants from only one sex and the other studies did not report results separately by sex. Therefore, analysis by sex was not feasible. However, a meta-analysis of the effect of vitamin D supplements (700–1000 U/d) on fall prevention did not show an effect of sex (72).

Finally, the influence of ethnic diversity was not studied. Most participants in this meta-analysis were white. It was reported by the Dietary Recommended Intakes committee that South Asian and Middle Eastern immigrant groups require more vitamin D (73). National surveys in the United States and Canada show that poor vitamin D status is more prevalent in non-white than white individuals (74, 75).

Conclusion

In conclusion, this meta-regression indicates that a higher increase in serum levels of 25(OH)D in adults is found with a dose of ≥800 IU/d, after a duration of at least 6 to 12 months, with lower baseline 25(OH)D levels, and in the oldest elderly. Further large prospective dose response trials are needed to confirm these results.

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Chapter 6

Effect of implementation of guidelines on assessment and diagnosis of vertebral fractures in patients older than 50 years with a recent non-vertebral fracture

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Abstract

Summary

We evaluated the impact of a new Dutch guideline on systematic implementation of densitometric Vertebral Fracture Assessment (VFA) in patients with a recent non-vertebral fracture. Systematic implementation resulted in a significant increase of VFA, diagnosis of vertebral fractures (VFs), and percentage of patients eligible for treatment.

Introduction

VFs are underdiagnosed although they are important predictors of fracture risk, independent of age and bone mineral density (BMD). The Dutch guideline on osteoporosis and fracture prevention recommends VFA in all patients aged ≥50 years with a recent non-VF. Our aim was to evaluate the effect of systematic implementation of densitometric VFA in patients with a recent non-VF at the fracture liaison service (FLS).

Methods

VFA was performed on lateral images of the spine using dual-energy X-ray absorptiometry (DXA) and graded according to Genant using Spine Analyzer software.

Results

We evaluated 582 patients before and 484 after implementation (mean age 67 and 66 years; 71 and 74% women, respectively). Performing VFA increased from 4.6 to 97.1% ($p < 0.001$) and the diagnosis of VFs from 2.2 to 26.2% for grade ≥ 1 ($p < 0.001$) and from 0.9 to 14.7% for grade ≥ 2 ($p < 0.001$). Prevalence of VFs increased with age (5.2% in 50–59-year olds to 27.8% in 80+-year olds, $p < 0.001$), but was similar for both genders, non-VF locations, and BMD. Including patients with osteopenia and a VF increased the percentage of patients eligible for treatment by a quarter, from 31.0% in the pre-guideline to 38.4% in the post-guideline cohort.

Conclusions

Systematic guideline implementation resulted in significant increase of VFA, diagnosis of VFs, and percentage of patients eligible for treatment. VFA contributes to documenting the high prevalence of VFs in patients visiting the FLS with a non-VF in both genders, at any age, non-VF location, and BMD.

Introduction

Vertebral fractures (VFs) are the most frequently occurring osteoporotic fractures (1-3). They are underdiagnosed (4, 5) because only one third of patients with VFs present with an acute symptomatic episode (6). Even in the case of acute back pain or height loss, imaging of the spine is not always performed; additionally, when radiographs are available, VFs are also often overlooked (4, 7). The presence, number, and severity of VFs are strong predictors of future fracture risk, independent of age and bone mineral density (BMD) (8, 9). VFs are frequently present in patients with a recent non-VF (>13 to >20%, depending on the grading of deformity) (10, 11) and in patients with osteopenia with or without a recent fracture (12). Therefore, the Dutch guideline on osteoporosis and fracture prevention released in 2011 (www.cbo.nl) recommended systematic evaluation of VFs in patients with a recent non-VF and a BMD T-score of <−1.0 and >−2.5. In those osteopenic patients who have a grade 2 or 3 VF, the guideline recommends the initiation of anti-osteoporotic medication.

The aim of our study was to compare the proportion of patients with a recent non-VF at the fracture liaison service (FLS) that had Vertebral Fracture Assessment (VFA) and the prevalence of VFs, before and after implementation of the guideline, as well as the impact the diagnosis of VF had on the percentage of patients that was diagnosed to have osteoporosis and to be eligible for treatment.

Material and methods

Study population

Patients included in our study were consecutive men and women aged 50 years and older with a recent low-energy non-VF visiting the FLS of VieCuri Medical Center for Northern Limburg (VieCuri) and Maastricht University Medical Center (MUMC). Before guideline implementation, VFA in the FLS at VieCuri was performed only on indication of the clinician; while in MUMC, there was temporarily no FLS because of financial restrictions, but VFA was available and performed on indication of the surgeon who treated the fracture. After guideline implementation, an FLS with densitometric VFA was available in both centres. The study protocol was approved by the local ethical committee of VieCuri (number CEM/11091).

Methods

Both hospitals had the same equipment available for BMD measurement at the lumbar spine and hip and lateral spine imaging, using dual-energy X-ray absorptiometry (DXA) (Hologic QDR 4500, Hologic, Bedford, MA, USA). BMD measurements were classified

according to the lowest value of T-score in the total hip/femoral neck or lumbar spine: osteoporosis as T-score ≤ −2.5, osteopenia as T-score between −2.5 and −1.0, and normal BMD as T-score ≥ −1.0.

After collecting all pre- and post-guideline densitometric lateral spine VFA images, central evaluation by the same experienced researcher was performed using a morphometry software program (Spine Analyzer, Optasia Medical, Manchester, UK) (13). First, the image quality was evaluated and the vertebrae were labelled, starting with the identification of the fourth lumbar vertebra. Subsequently, the evaluable vertebrae were determined. A vertebra was considered evaluable if the posterior and anterior cortices and both endplates were fully and clearly visible. If this was not the case, the vertebra was not evaluated. Images were visually inspected for the presence of a VF. The researcher studied both the vertebral shape and the appearance of the end plate in order to differentiate between VFs and vertebrae with other deformities, e.g., degenerative changes or Scheuermann's disease, only true VFs were counted. When a vertebra was visually suspect for a VF, the point placement of the Spine Analyzer software program was used to measure the anterior, mid-vertebral, and posterior height of the vertebra that had been selected on visual inspection. The point placement was edited occasionally when this was deemed necessary, but we did not keep a record on how often this was done. The vertebral fractures were then graded according to the grading of Genant et al. (14) as grade 0, <20% reduction in expected vertebral body height at the anterior, mid, or posterior location; grade 1, 20–24%; grade 2, 25–39%; or grade 3, ≥40% reduction, respectively.

Non-VFs were classified according to the method of Center (15) into hip fractures, major fractures (multiple rib, humerus, pelvis, distal femur, and proximal tibia), and minor fractures (all remaining fractures except fingers and toes).

Statistical analysis

Data were analyzed using independent samples T-test, chi-square statistics, and odds ratios. Subgroup analyses were performed for BMD (normal versus osteopenia versus osteoporosis) and for fracture type according to Center (minor versus major versus hip fracture). Statistical analyses were performed using SPSS for Mac (version 21.0, IBM SPSS Statistics, USA).

Results

In total, 1066 consecutive patients (768 women, 298 men) were evaluated, 582 (411 women, 171 men) before and 484 (357 women, 127 men) after guideline implementation (Fig. 1). Patients after implementation were somewhat younger and sustained less often

a major or hip fracture, but BMI was similar (Table 1). BMD measurements before implementation were performed in all patients in VieCuri and in 30 (11%) in MUMC (in total 338 out of 582 (58.1%) patients) and in all patients ($p < 0.001$) after implementation. Before and after implementation, the prevalence of osteoporosis, osteopenia, and normal BMD was similar (Table 1). VFA was performed in 4.6% before implementation and in 97.1% of patients after implementation ($p < 0.001$) (Fig. 1). Within the vertebral range Th4 to L4, the percentage of evaluable vertebrae increased from 20% at Th4 to >70% at Th8 and Th9 and to >90% from TH10 to L4 (Fig. 2).

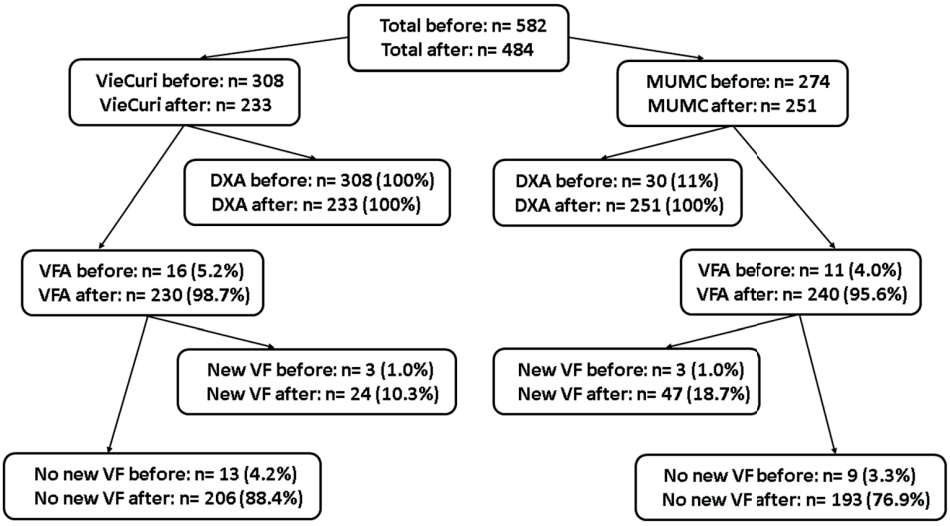

Figure 1. Flowchart with the number and percentage of patients per centre with a dual-energy X-ray absorptiometry (DXA), a vertebral fracture assessment (VFA) and at least 1 newly diagnosed grade 2 or 3 vertebral fracture (VF) before and after the introduction of systematic VFA. VieCuri = VieCuri Medical Center; MUMC= Maastricht University Medical Center.

The diagnosis of a VF increased from 2.2 to 26.2% for grade VF ≥1 ($p < 0.001$) and from 0.9 to 14.7% for grade ≥ 2 VF ($p < 0.001$) (Table 2). The prevalence of VFs grade ≥ 2 increased with age (Table 2) but was similar for both sexes, non-VF locations, and BMD (Table 2). After implementation, in patients with osteopenia, 13.6% had at least one grade ≥ 2 VF (Table 2).

The odds ratio for the presence of a grade ≥ 2 VF was nearly twofold higher ($p = 0.043$) in patients with hip or major fracture compared to that in patients with a minor fracture (Table 2).

Table 1. Baseline characteristics of the study population before and after the implementation of vertebral fracture Assessment according to the Dutch guideline

	Before VFA implementation (n=582)	After VFA implementation (n=484)	p-value
Gender and age:			
Women, n (%)	411 (70.6)	357 (73.8)	
Men, n (%)	171 (29.4)	127 (26.2)	
Age, mean (SD)	67.0(10.6)	65.9 (9.0)	*< 0.001*
Fracture location:			*0.002*
Minor n (%)	386 (66.3)	344 (71.1)	
Major n (%)	126 (21.6)	107 (22.1)	
Hip n (%)	70 (12.0)	33 (6.8)	
BMD[a]:			*0.065*
Normal n (%)	71 (21.0)	91 (18.8)	
Osteopenia n (%)	163 (48.2)	235 (48.6)	
Osteoporosis n (%)	104 (30.8)	158 (32.6)	
Weight and height:			
Weight[b] (kg), mean (SD)	74.5 (13.8)	72.5 (13.9)	*0.651*
Height[c] (m), mean (SD)	1.68 (8.9)	1.67 (12.0)	*0.146*
BMI (kg/m), mean (SD)	26.4 (4.4)	26.0 (3.9)	*0.363*

VFA: Vertebral Fracture Assessment

[a] DXA measurement to assess BMD was performed in 338 (58.1%) patients before guideline and in 484 (100%) after.

[b] Weight was known in 256 patients before guideline and in 234 patients after guideline

[c] Height was known in 257 patients before guideline and in 245 patients after guideline

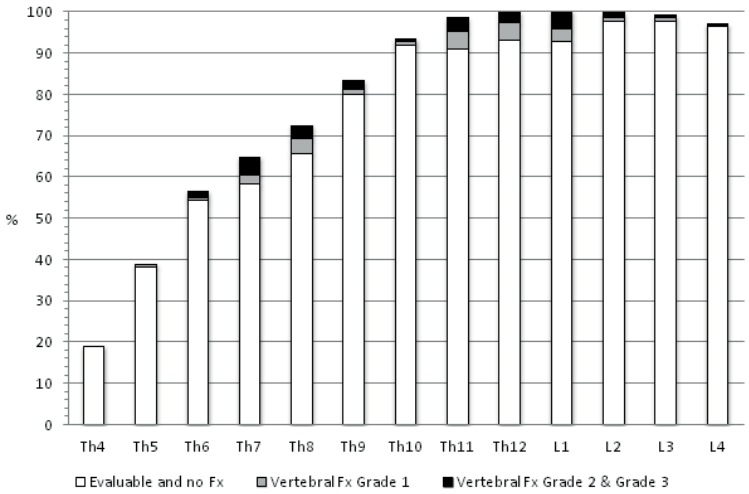

Figure 2. Percentage of evaluable vertebrae on vertebral fracture assessment (VFA) and of grade 1 or grade 2&3 vertebral fractures.

Table 2. Percentage of post-guideline patients with ≥ 1 vertebral fracture grade 1,2,3; ≥ 1 vertebral fracture grade2 or 3; and ≥ 1 vertebral fracture grade 1, 2 or 3

	Grade 1	Grade 2	Grade 3	Grade 2 or 3	Grade 1,2 or 3
Gender	*p=0.56*	*p=0.88*	*p=0.91*	*p=0.74*	*p=0.19*
Women	14.4%	11.4%	3.3%	13.2%	24.1%
Men	20.8%	13.9%	2.8%	16.7%	32.3%
Age	*p=0.12*	*p=0.00*	*p=0.00*	*p=0.00*	*p=0.00*
50-59 years	11.1%	4.4%	0.7%	5.2%	14.8%
60-69 years	14.1%	16.8%	1.6%	16.8%	26.5%
70-79 years	20.3%	12.5%	6.3%	18.0%	34.45
80+ years	19.4%	22.2%	11.1%	27.8%	38.9%
Fracture location	*p=0.44*	*p=0.15*	*p=0.15*	*p=0.07*	*p=0.29*
Minor	14.5%	10.8%	2.3%	12.2%	24.4%
Major	16.8%	17.8%	5.6%	21.5%	30.8%
Hip	18.2%	15.2%	6.1%	18.2%	30.3%
BMD	*p=0.42*	*p=0.63*	*p=0.54*	*p=0.39*	*p=0.44*
Normal	11.0%	11.0%	2.2%	12.1%	20.9%
Osteopenia	15.7%	12.3%	3.0%	13.6%	27.7%
Osteoporosis	17.1%	13.9%	4.4%	17.7%	27.2%

Discussion

After systematic implementation of VFA in FLS patients with a recent non-VF according to the Dutch guideline for osteoporosis, performing VFA increased nearly 20-fold, diagnosis of a VF of grade ≥ 2 increased 15-fold, and one out of six patients was diagnosed with a grade ≥ 2 VF. As a result, the total percentage of patients diagnosed to have osteoporosis and therefore eligible for treatment according to the Dutch guideline increased by one quarter.

The VF prevalence in our study is in accordance with that of two other studies in patients with a non-VF: 20–25% for grade ≥ 1 and 13–17% for grade ≥ 2 (10, 11). The prevalence of VFs in our FLS cohort increased with age; the prevalence of grade ≥ 2 VF increased more than fivefold between the ages of 50 and 80+. A similar increase was found by others (10, 11, 16). Remarkably, the prevalence of VF was similar between genders, non-VF locations, and BMD levels. The similar prevalence of VF seen in women and men in our study contrasts the higher VF prevalence found in women in many studies (17), but other authors also found a similar prevalence in both genders (11, 16, 18) or even a higher prevalence in men (19), which was also seen in a recent Dutch study (20). In contrast to others (10, 11), we found no significant difference in the prevalence of VFs grade ≥ 1 between different non-VF locations but direct comparison to the other studies is difficult since we studied three non-VF groups instead of individual non-VF sites. Our results

underscore the importance of performing VFA even after minor presenting fractures. We found VFs grade ≥ 2 in any BMD category, with a non-significant trend of higher prevalence in patients with osteoporosis (18%) compared to patients with a normal BMD (12%). These results correspond well with those found by other authors (12, 20). In contrast, Gallagher et al. (10) reported VFs grade ≥ 2 in 9% of patients with normal BMD, in 13% with osteopenia, and in 34% with osteoporosis. However, in that study, only lumbar spine BMD was reported, while we used the lowest T-score at the spine, hip, or femoral neck. Howat et al. (11) reported that grades 2 and 3 VFs correlated with spine and hip BMD in women, and in men only grade 3 VFs when compared to patients with a normal BMD. In spite of these differences in prevalence of VFs between studies, the results indicate that VFs are frequently present at any BMD in patients with a recent non-VF.

In the group of patients with a BMD score in the osteopenic range, 13.6% had at least one grade ≥ 2 VF, constituting a diagnosis of osteoporosis and an indication for treatment according to the Dutch guideline (www.cbo.nl). If treatment decisions would have been based on BMD results only, 31.0% of the post-guideline patients would be eligible for treatment because of osteoporosis. With implementation of VFA, this increases by a quarter to 38.4%. Our finding underscores the limitation of using a screening strategy based on BMD measured by DXA, as was also found by other authors (21, 22). We also found VFs in patients with a normal BMD but the Dutch guideline does not recommend performing VFA routinely in these patients; so, in daily practice, these patients would not have been treated (www.cbo.nl).

Our results can be compared with the results of two other Dutch studies. Netelenbos et al. (23) found a 43% increase in the number of patients who qualified for osteoporosis when based on BMD + spine radiograph instead of based on BMD alone, considerably higher than in our study which can probably be explained by the fact that in the study by Netelenbos et al. VFs of all grades were counted as an indication for treatment (instead of only grade ≥ 2 as stated in the Dutch guideline). In our study, of patients with osteopenia, 27.7% had at least one grade 1, 2, or grade 3 VF, so the number of patients from our post-group who would qualify for osteoporosis treatment would be 41% higher than when based on BMD alone, corresponding well with the results from Netelenbos et al. In another study from the Netherlands (20), in the subgroup with osteopenia, 21% had a vertebral fracture, 55% of those were grade 2 or 3, which increased the number of patients eligible for treatment by one fifth from 27 to 32% when the VFA results were considered in the treatment decision, in keeping with our results. In a study from Hull (UK) in women over the age of 65, 20% of osteopenic women had at least one grade 2 or grade 3 vertebral fracture (24). In addition to the 17% of women with osteoporosis, the application of VFA identified another 11% of women with an indication for treatment, a greater increase probably explained by the higher age of the patients (24). Results similar to those of our study were seen in a study from Glasgow (UK) in which overall in 25% of

patients, a previously undiagnosed grade 1, 2, or 3 vertebral deformity was found (10). In osteopenic patients, this was 20%, of which in 13% there was a grade 2 or 3 vertebral fracture. In this study, 28% had a treatment indication based on BMD (osteoporosis) and 9% of patients were likely to have had a change in management based on their vertebral deformity status. In a study conducted in the USA (12), VFs were found in 18% of asymptomatic postmenopausal women. In this study, between 26 and 60% of osteoporotic patients could have potentially been missed if the diagnosis had been based on BMD alone. By contrast, in a study from Glasgow (UK), the authors found that VFA does identify a substantial burden of prevalent vertebral fractures that were not known before (about 20%), but this (in 3%) seldom influenced the need for treatment after a non-vertebral fracture (11). This fact can be explained by the guideline used in this centre, according to which in patients over the age of 65, the BMD threshold is ≤−2 thereby limiting the number of osteopenic patients that would only get medical treatment based on diagnosis of VFs through VFA. In a recent study from Sheffield (25), in 11% of patients undergoing VFA, one or more vertebral fractures were found but this finding changed the management in only 3%. This lower percentage can be explained by two factors: firstly, in this study, the focus was only on previously unidentified VFs diagnosed through VFA scans; and secondly, the methodology used in this study to identify VF (the ABQ method) is known to identify fewer VFs compared with other techniques (26).

The strength of our study is that the same device for DXA/VFA was used in both centres, and that all images were examined by the same experienced investigator using the precise and accurate Spine Analyzer software (www.cbo.nl). Limitations are slight differences in patient characteristics before and after implementation of the guideline, reflecting the real-world response rate of patients invited to the FLS. Only limited vertebrae could be evaluated above the Th7 level. Possibly with today's DXA technology (with improved hardware and software), a higher proportion of vertebrae above the Th7 level could have been evaluated. However, since most osteoporotic VFs occur at the lower spine region, this will not have influenced the results much. Another limitation is the possibility of overdiagnosing VFs, but the VFA evaluation was performed by an experienced researcher, carefully excluding deformities other than VF.

In conclusion, we have found that systematic implementation of the guideline resulted in a significant increase in the diagnosis of VFs. VFA contributes to documenting the high prevalence of VFs in FLS patients with a non-VF in both genders, at any age, non-VF location, and BMD level. The finding of a grade 2 or 3 VF in patients with osteopenia has direct clinical implications, increasing the number of patients in the total cohort eligible for treatment by one quarter.

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Chapter 7

Risk of vertebral and non-vertebral fractures in patients with sarcoidosis: a population-based cohort

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Abstract

Summary

In this retrospective cohort study using the Clinical Practice Research Datalink (CPRD), patients with sarcoidosis have an increased risk of clinical vertebral fractures and when on recent treatment with oral glucocorticoids, also an increased risk of any fractures and osteoporotic fractures.

Introduction

Sarcoidosis is a chronic inflammatory disease, in which fragility fractures have been reported despite normal BMD. The aim of this study was to assess whether patients with sarcoidosis have an increased risk of clinical fractures compared to the general population.

Methods

A retrospective cohort study was conducted using the CPRD. All patients with a CPRD code for sarcoidosis between January 1987 and September 2012 were included. Cox proportional hazards models were used to derive adjusted relative risks (adjRR) of fractures in all sarcoidosis patients compared to matched controls, and within the sarcoidosis group according to use and dose of systemic glucocorticoids.

Results

Five thousand seven hundred twenty-two sarcoidosis patients (mean age 48.0 years, 51% females, mean follow-up 6.7 years) were identified. Compared to 28,704 matched controls, the risk of any fracture was not different in patients with sarcoidosis. However, the risk of clinical vertebral fractures was significantly increased (adjRR 1.77; 95% CI 1.06–2.96) and the risk of non-vertebral fractures was decreased although marginally significant (adjRR 0.87; 95% CI 0.77–0.99). Compared to sarcoidosis patients not taking glucocorticoids, recent use of systemic glucocorticoids was associated with an increased risk of any fracture (adjRR 1.50; 95% CI 1.20–1.89) and of an osteoporotic fracture (adjRR 1.47; 95% CI 1.07–2.02).

Conclusions

Patients with sarcoidosis have an increased risk of clinical vertebral fractures, and when using glucocorticoid therapy, an increased risk of any fractures and osteoporotic fractures. In contrast, the risk of non-vertebral fractures maybe decreased. Further investigation is needed to understand the underlying mechanisms of these contrasting effects on fracture risk.

Introduction

Sarcoidosis is a multi-organ, chronic inflammatory, granulomatous disorder that can affect almost any organ of the body. It may occur at any age, but most frequently in adults younger than 50 years. It is more common in women and certain racial groups, such as African-Americans and northern Europeans (1-4). Around 300–400 new cases of sarcoidosis are diagnosed per year in the UK (5).

Bone mineral density (BMD) is decreased and the risk of clinical and radiological vertebral fractures is increased in chronic inflammatory diseases such as asthma and chronic obstructive pulmonary disease (COPD) (6, 7), rheumatoid arthritis (8-10), ankylosing spondylitis (11, 12), systemic lupus erythematosus (13), and inflammatory bowel disease (14). In addition, treatment with glucocorticoids has been associated with a dose-dependent increase in fracture risk (9, 15-17), at a higher level of BMD than in patients who do not use glucocorticoids.

In patients with sarcoidosis, small cohort studies have demonstrated a high prevalence of fragility fractures (23.5%) (18) and radiographic vertebral fractures (20–30 %) (19), with an increase of incidence (up to 32%) of vertebral fractures during follow-up (20). In contrast, BMD has been found to be normal in most patients with sarcoidosis (19, 21-24) and BMD did not change over time (20, 25). Furthermore, the effect of glucocorticoids on bone might be reversible (26, 27). No studies are available that investigated the prevalence of vertebral and non-vertebral fractures in patients with sarcoidosis compared to a control population and the effect of glucocorticoid therapy on fracture risk in sarcoidosis.

The first objective of this study is to determine whether patients with sarcoidosis have an increased risk of clinical fractures compared to the general population. The second objective is to estimate their fracture risk, stratified by glucocorticoid use.

Methods

Source population

A retrospective cohort study was conducted using the Clinical Practice Research Datalink (CPRD), formerly known as the General Practice Research Database. The CPRD contains computerized medical records of 625 primary care practices in the UK, representing 8% of the British population. The database provides detailed information on demographics, drug prescriptions, clinical events, specialist referrals, and hospital admissions. Previous studies of CPRD data have shown a high level of data validity with respect to the reporting of fractures (>90% of fractures were confirmed) (16). The protocol number is 2010_060.

Study population

All patients with a CPRD read code for sarcoidosis during the study period (from January 1987 through September 2012) were included in the study population. In order to ascertain a more probable diagnosis of sarcoidosis, these patients were stratified into probable and possible cases of sarcoidosis. Probable cases had at least one sarcoidosis CPRD record and any of the following: (1) treatment with methotrexate, azathioprine, leflunomide, chloroquine, hydroxychloroquine, and systemic/inhaled glucocorticoids at any time during follow-up, (2) two or more subsequent diagnoses of sarcoidosis, and/or (3) a specialist diagnosis of sarcoidosis. All other sarcoidosis patients were defined as possible cases. The index date was defined as the first record for sarcoidosis. Each patient was matched by age, sex, calendar time, and practice to up to four patients without a history of sarcoidosis ever during the study period.

Outcomes

All patients had a follow-up from the index date to either the end of data collection, the date of transfer of the patient out of the practice area, the patient's death, or fracture (CPRD read codes), whichever came first.

Earlier studies have demonstrated that there is a high level of data validity with respect to reporting of fractures from CPRD databases and >90% of reported fractures were confirmed (16).

The primary outcome of this study was to determine whether patients with sarcoidosis have an increased risk of clinical fractures compared to the general population. For additional analyses, fracture type was stratified according to the WHO Fracture Risk Assessment Tool into osteoporotic (spine, hip, forearm, or humerus fracture), and non-osteoporotic fractures (all other fractures) and also stratified into vertebral and non-vertebral fractures. The second objective was to estimate their fracture risk, stratified by glucocorticoid use.

Potential confounders

Total follow-up was divided into 30-day intervals. Before the start of each 30-day interval, the presence of general risk factors for fracture was evaluated. At baseline, information was available about age, sex, smoking status, body mass index, alcohol use, a record of falls in the previous 6–12 months, and a history of fracture. Furthermore, we assessed if there was a history of a chronic disease (rheumatoid arthritis, cerebrovascular disease, heart failure, inflammatory bowel disease, asthma/chronic obstructive pulmonary disease, secondary osteoporosis, anaemia, and dementia). Prescriptions for glucocorticoids (systemic and local separately), hypnotic/anxiolytic, antipsychotic, antidepressant, proton pump inhibitor, antidiabetic, or antiepileptic agents, as well as drugs for the treatment of Parkinson's disease, in the 6 months before inclusion, were recorded.

For each sarcoidosis patient, the use of systemic glucocorticoids in the previous 6 months before inclusion was evaluated. Systemic glucocorticoid users were further stratified according to their average and cumulative dose using the World Health Organisation's defined daily dosages (DDD) (28). Exposure was expressed as oral prednisone equivalents. For the cumulative exposure, all prescriptions of the most recent treatment period (allowing a maximum non-use gap of 6 months between two prescriptions) were considered. For the average daily dose, the cumulative exposure of the most recent treatment period was divided by the number of days between start and end of the treatment period. When data on the prescribed quantity were missing, the median expected quantity was used.

Statistical analysis

Cox proportional hazards models were used to derive adjusted relative risks (adjRRs) for fracture (any, osteoporotic, and non-osteoporotic) in sarcoidosis patients compared with matched control subjects (SAS 9.2, PHREG procedure). Potential confounders were entered into the final model if they independently changed the beta coefficient by at least 5%. This main analysis was repeated for possible and probable cases of sarcoidosis. For all other analyses, the full cohort of sarcoidosis patients (probable and possible cases) was used. Within sarcoidosis patients, the individuals were stratified according to their cumulative and average daily dose of systemic glucocorticoid exposure. Furthermore, absolute incidence rates for fractures in sarcoidosis patients and matched controls were calculated.

Timing of fracture occurrence following first sarcoidosis record was examined by including time interaction terms into the model for the following time intervals: < 6 months, 6–12 months, 1–2 years, 2–5 years, 5–10 years, and >10 years. Using smoothing spline regression, the time trend for risk of fracture for these given time intervals was visualized.

Results

We identified 5,722 sarcoidosis patients along with 28,704 age- and sex-matched controls (mean age 48.0 years, 51% females), with a mean follow-up of 6.7 years per patient. Baseline characteristics of patients with sarcoidosis and age and sex-matched controls are shown in Table 1. There were substantially fewer smokers among the sarcoidosis patients than in the matched controls (current smokers 13.8 vs. 25.4%). Furthermore, patients with sarcoidosis were more likely to have used medical drugs in the previous 6 months, in particular systemic/local glucocorticoids, antidiabetics, antidepressants, benzodiazepines, and calcium/vitamin D supplements. Bisphosphonate use was higher among sarcoidosis patients (4.3%) compared to matched controls (1.0%), whereas no differences were observed for use of HRT and other anti-osteoporotic drugs.

Table 1. Baseline characteristics of sarcoidosis patients and matched controls

	Sarcoidosis patients		Matched controls	
Characteristic	N = 5,722	(%)	N = 28,704	(%)
Follow-up (years, mean, SD)	6.7 (5.2)		6.7 (5.2)	
Females	2,918	(51.0)	14,637	(51.0)
Age (years, mean, SD)	48.0 (13.4)		48.0 (13.4)	
18-39 years	1,691	(29.6)	8,479	(29.5)
40-59 years	2,847	(49.8)	14,284	(49.8)
60-79 years	1,115	(19.5)	5,598	(19.5)
80+ years	69	(1.2)	343	(1.2)
BMI (kg/m^2, mean, SD)	27.9 (5.9)		26.8 (5.4)	
< 20.0 kg/m^2	232	(4.1)	1,301	(4.5)
20-24.9 kg/m^2	1,468	(25.7)	8,745	(30.5)
25.0-29.9 kg/m^2	1,943	(34.0)	8,614	(30.0)
30.0+ kg/m^2	1,505	(26.3)	5,538	(19.3)
Unknown	574	(10.0)	4,506	(15.7)
Smoking status				
Never	3,763	(65.8)	15,215	(53.0)
Current	792	(13.8)	7,304	(25.4)
Ex	1,041	(18.2)	4,537	(15.8)
Unknown	126	(2.2)	1,648	(5.7)
Alcohol use				
No	1,104	(19.3)	4,210	(14.7)
Yes	3,973	(69.4)	19,972	(69.6)
Unknown	645	(11.3)	4,522	(15.8)
Falls (6-12 months before)	230	(4.0)	1,050	(3.7)
Fracture ever before	1,079	(18.9)	5,096	(17.8)
History of disease				
Rheumatoid arthritis	79	(1.4)	238	(0.8)
Cerebrovascular disease	111	(1.9)	452	(1.6)
Inflammatory bowel disease	87	(1.5)	237	(0.8)
COPD	157	(2.7)	381	(1.3)
Asthma	923	(16.1)	3,008	(10.4)
Hypertension	900	(15.7)	3,784	(13.2)
Dementia	21	(0.4)	70	(0.2)
Heart failure	98	(1.7)	199	(0.7)
Drug use within six months				
Systemic glucocorticoids	953	(16.7)	492	(1.7)
Topical glucocorticoids	618	(10.8)	1,782	(6.2)
Antidiabetics	263	(4.6)	810	(2.8)
Anticonvulsants	166	(2.9)	467	(1.6)
Loop diuretics	294	(5.1)	568	(2.0)
Proton pump inhibitors	825	(14.4)	1,869	(6.5)
Antipsychotics	59	(1.0)	298	(1.0)
Antidepressants	658	(11.5)	2,418	(8.4)
Anxiolytics / hypnotics	360	(6.3)	1,166	(4.1)
Calcium / vitamin D	251	(4.4)	412	(1.4)

BMI = body mass index, SD = standard deviation.

In the sarcoidosis cohort, 406 patients had at least one fracture; 203 osteoporotic fractures occurred (37 clinical vertebral fractures, 22 hip fractures, 144 other osteoporotic fractures, i.e., forearm or humerus fractures) and 263 non-osteoporotic fractures (Table 2). There was no difference between patients with sarcoidosis and matched controls in the risk of any fracture (adjRR 0.90; 95% CI 0.80–1.02), an osteoporotic fracture (adjRR 1.02, 95% CI 0.85–1.23) or non-osteoporotic fracture (adjRR 0.89, 95% CI 0.76–1.03). Further adjustments for anti-osteoporotic drugs did not alter the relative risk estimates (e.g., for any fracture: HR 0.91 (95% CI 0.81–1.03)). The risk of clinical vertebral fractures was significantly increased in patients with sarcoidosis (adjRR 1.77; 95% CI 1.06–2.96), and the risk for non-vertebral fractures was decreased (adjRR 0.87; 95% CI 0.77–0.99).

Table 2. Risk of fracture in sarcoidosis patients compared with matched controls, stratified by age, sex, and type of fracture.

		Fracture		
	Person years	Events	Age-sex adj RR (95% CI)	Adj RR (95% CI) (a)
No sarcoidosis	183,514	1,815	reference	Reference
Sarcoidosis				
Any fracture	36,760	406	1.14 (1.02-1.27)	0.90 (0.80-1.02)
By age (years)				
18-39	7,384	48	0.67 (0.49-0.91)	0.60 (0.42-0.85)
40-59	19,763	171	1.17 (0.99-1.39)	0.95 (0.78-1.15)
60-79	9,012	166	1.41 (1.18-1.68)	1.07 (0.87-1.31)
80+	601	21	1.07 (0.64-1.78)	0.97 (0.56-1.67)
By sex				
Males	17,529	143	0.98 (0.81-1.18)	0.79 (0.64-0.97)
Females	19,231	263	1.24 (1.08-1.43)	0.97 (0.83-1.13)
Osteoporotic fracture	37,670	203	1.37 (1.17-1.60)	1.02 (0.85-1.23)
Hip fracture	38,397	22	0.93 (0.59-1.48)	0.61 (0.35-1.04)
Vertebral fracture	38,363	37	3.10 (2.04-4.70)	1.77 (1.06-2.96)
Non-osteoporotic fracture	37,256	263	1.07 (0.93-1.23)	0.89 (0.76-1.03)
Non-vertebral fracture	36,852	377	1.08 (0.96-1.21)	0.87 (0.77-0.99)

Adj = adjusted, CI = confidence interval, RR = relative risk.
(a) Adjusted for smoking status, a history of heart failure, asthma / COPD, and use of systemic glucocorticoids, calcium / vitamin D supplements, loop diuretics, benzodiazepines, antidepressants, proton pump inhibitors, and anticonvulsants in the previous 6 months.

The adjRR was not modified by the sarcoidosis case definition (possible sarcoidosis: adjRR 0.92; 95% CI 0.76–1.13; probable sarcoidosis: adjRR 0.89; 95% CI 0.76–1.04 for any fracture) and there was no statistical interaction with age, sex, or type of fracture. When plotted against time since diagnosis, the risk of any fracture was temporarily decreased during the first years after diagnosis, but was not different during longer follow-up (Fig. 1).

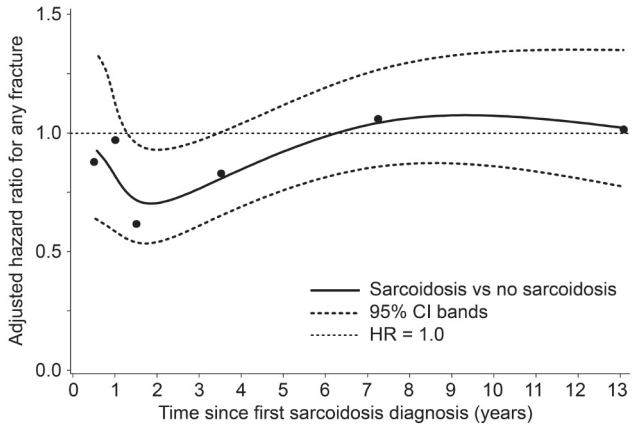

Figure 1. Spline regression plot of time since first sarcoidosis record and risk of any fracture in sarcoidosis patients versus matched controls. Adjusted for confounders as shown in Table 2.

Use of systemic glucocorticoids in the previous 6 months increased the risk of any fracture (adjRR 1.50; 95% CI 1.20–1.89) and of an osteoporotic fracture (adjRR 1.47; 95% CI 1.07–2.02) compared to no use of systemic glucocorticoids (Table 3). The risk of any fracture and of an osteoporotic fracture increased already with a daily dose of <5 mg prednisone equivalents per day (adjRR 1.49; 95% CI 1.12–1.97 and adjRR 1.52; 95% CI 1.04–2.23 for any and osteoporotic fracture, respectively) and with the lowest cumulative doses (<1820 mg; adjRR 1.67; 95% CI 1.08–2.59 and adjRR 2.02; 95% CI 1.14–3.59 for any and osteoporotic fracture, respectively). The fracture risk did not increase significantly with higher dose or higher cumulative dose.

Discussion

In this large population-based study, patients with sarcoidosis had an increased risk of clinical vertebral fractures compared to matched controls and, when on recent therapy with systemic glucocorticoids, an increased risk of any fractures and osteoporotic fractures. In contrast, the risk of non-vertebral fractures was decreased, although marginally significant. To our knowledge, this study is the first population-based study that assessed vertebral and non-vertebral fracture risk in patients with sarcoidosis compared to matched control subjects.

The risk of clinical vertebral fractures was increased, which is in line with findings in other inflammatory diseases such as rheumatoid arthritis (9, 29, 30), ankylosing spondylitis (11, 12), SLE (13, 31), COPD (6, 7) and inflammatory bowel disease (14). Possible explanations for the increased vertebral fracture risk can be found in other studies regarding patients with sarcoidosis, such as the finding of a decreased trabecular BMD within the vertebrae (26), a decreased BMD in the spine in postmenopausal women (22), and an increased

Table 3. Risk of any and osteoporotic fractures within sarcoidosis patients, stratified by use of drugs.

	Any fracture		Osteoporotic fracture	
	Events	Adj RR (95% CI) (a)	Events	Adj RR (95% CI) (a)
By use of systemic glucocorticoids in the previous 6 months (reference = no use) (b)				
No	263	1.00	126	1.00
Yes	143	1.50 (1.20-1.89)	77	1.47 (1.07-2.02)
By average daily dose of systemic glucocorticoid exposure in the previous year, expressed as prednisone equivalents				
≤5 mg (c)	66	1.49 (1.12-1.97)	37	1.52 (1.04-2.23)
5.1-10 mg	45	1.36 (0.97-1.90)	21	1.13 (0.69-1.84)
>10 mg	32	1.88 (1.26-2.79)	19	2.09 (1.24-3.53)
By cumulative dose of systemic glucocorticoid exposure, expressed as prednisone equivalents (d)				
<1820 mg (c)	22	1.67 (1.08-2.59)	13	2.02 (1.14-3.59)
1820-7300 mg	41	1.37 (0.97-1.93)	22	1.36 (0.85-2.17)
>7300 mg	80	1.53 (1.16-2.03)	42	1.39 (0.94-2.04)
By use of antidepressants in the previous 6 months (reference = no use) (b)				
No	318	1.00	157	1.00
Yes	88	1.25 (0.97-1.61)	46	1.08 (0.76-1.55)
By use of anxiolytics / hypnotics in the previous 6 months (reference = no use) (b)				
No	364	1.00	176	1.00
Yes	42	1.16 (0.83-1.63)	27	1.37 (0.89-2.12)

Abbreviations: Adj = adjusted, CI = confidence interval; RR = relative risk.
(a) Adjusted for confounders shown in footnote Table 2.
(b) Reference = no use in the previous 6 months.
(c) Excluding no use of systemic glucocorticoids in the previous 6 months.
(d) Cumulative amount of all previous systemic glucocorticoid prescriptions.

bone resorption (19). In spite of the increased risk of clinical vertebral fractures in patients with sarcoidosis, the total number of vertebral fractures was low. This is in contrast with other studies in patients with sarcoidosis where vertebral fractures were assessed by systemic radiographic evaluation (19, 20), suggesting that most radiographic vertebral fractures are not accompanied by typical signs and symptoms of an acute vertebral fracture. This is also the case for vertebral fractures in postmenopausal osteoporosis (32, 33).

The decreased adjusted risk of non-vertebral fractures in our study is an unexpected finding and only marginally statistically significant. It is in contrast with the increased risk of vertebral fractures in this study and with the increased risk of non-vertebral fractures in inflammatory rheumatic diseases such as rheumatoid arthritis (9, 34, 35), ankylosing spondylitis (36), and JIA (36). Another study did find a high fracture incidence in patients with sarcoidosis (18). However, in the latter study there was no control population, and the study population consisted of patients at a pulmonary outpatient clinic where 62.0% of patients were treated with glucocorticoids (vs. 16.7% in our study). In most studies in patients with sarcoidosis, BMD was normal in all patients (18, 19, 21, 23, 24) even in those

treated with glucocorticoids (18, 19), with the exception of one study that showed a decreased BMD in postmenopausal but not in premenopausal women (22). Why BMD in the spine and hip is normal in most patients with sarcoidosis, is unclear and it does not explain the slightly decreased risk of non-vertebral fractures in patients with sarcoidosis compared to matched controls.

The increased risk of any and of osteoporotic fractures in patients with recent use of systemic glucocorticoids is in line with findings of increased fracture risk in glucocorticoid users in other inflammatory diseases (15–17). However, we did not find a further increase in fracture risk with higher daily or cumulative doses of glucocorticoids. Treatment of inflammatory diseases for example rheumatoid arthritis results in lower disease activity and adequate disease control which contributes to bone protection, even when glucocorticoids are used (37). The time relation between onset of sarcoidosis and initial but not persisting decrease of risk of any fracture indicates that disease or treatment related factors early in the disease could play a protective role on non-vertebral fracture risk.

In population-based cohort studies, a relation between CRP and fracture risk has been reported even after adjustment for confounding factors (38-40), however this relation could be U-shaped (41) or only present when CRP was >3 mg/l (42, 43). In patients with sarcoidosis, however, no correlation was found between bone turnover markers or CRP and BMD or fractures (18). In our study, we did not have additional information on markers for inflammation (IL2R, ACE) or disease activity.

Other factors, such as low dietary calcium intake, low creatinine clearance, and higher 25(OH)D and 1,25(OH) are associated to an increased fracture risk and bone resorption in sarcoidosis (18, 44), but no data were available on these parameters in our study. Besides BMD and bone-related risk factors, other factors could influence fracture risk in patients with sarcoidosis. Patients with sarcoidosis have an increased risk of sarcopenia, which could increase the risk of falls and bone loss (45). We did not have information on diagnostic tests for sarcopenia, such as muscle strength and mass. Body mass index (BMI) in patients with sarcoidosis was not different compared to controls. Sarcoidosis can also be localised in bone, as has been demonstrated by a study with PET scans which show extensive bone marrow involvement in sarcoidosis (46). Sarcoid granulomas are surrounded by osteoclasts, but a local focus of osseous sarcoidosis resulting in a fracture is rare (47). Pulmonary Wnt signalling is altered in patients with sarcoidosis (48); however, whether Wnt signalling in bone is also altered in patients with sarcoidosis is unknown.

The fact that the risk of clinical vertebral fractures was increased, whereas the risk of all fractures was not different compared to matched controls, suggests that sarcoidosis probably has a negative impact on the trabecular bone without affecting the cortical bone. The finding of a decreased risk of non-vertebral fractures in this study was only marginally significant and in combination with data from literature the question is whether non-vertebral fracture risk is actually decreased in patients with sarcoidosis.

Limitations of our study were the lack of information on markers for inflammation (IL2R, ACE), disease activity, and BMD, so we could not adjust for these possible confounders. In addition, no information was available on muscle strength or mass and fall risk. The sarcoidosis case definition was described, but we were not able to confirm the diagnosis based on direct data from rheumatologists, pulmonologists, or other physicians.

In conclusion, patients with sarcoidosis have an increased risk of clinical vertebral fractures, and when on recent treatment with oral glucocorticoids, also an increased risk of any fractures and osteoporotic fractures. The decreased risk of non-vertebral fractures was an intriguing and unexpected finding, however with marginal statistical significance, and further studies should be performed to understand more about the factors that could protect against bone loss and non-vertebral fracture risk in sarcoidosis.

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Chapter 8

Summary

Contributors to secondary osteoporosis and metabolic bone diseases in patients presenting with a clinical fracture. (chapter 2)

In this prospectively planned cross-sectional chart review study, all patients 50 years or older with a recent clinical fracture who presented at the Fracture Liaison Service (FLS) of VieCuri MC, Venlo, the Netherlands, were included. Baseline fractures were classified according to Center into hip, major, minor and finger/toe fractures.

Between January 2007 and September 2008, 626 consecutive patients presented at the FLS, 15.0% had a normal BMD, 45.7% had osteopenia and 39.3% had osteoporosis.

We found a total number of 207 known contributors in 144 patients (23.0%). Furthermore, 200 new contributors to secondary osteoporosis were found in 166 patients (26.5%). We found new contributors in 44 patients who already had a known contributor at the moment of the fracture. In total, 42.5% of patients 50 years or older with a recent clinical fracture and presenting at the FLS, had at least one (new and/or known) contributor to secondary osteoporosis.

Although the prevalence of newly detected disorders was statistically significantly higher in patients with osteoporosis (32.9%), these were also detected in 26.5% of patients with osteopenia and in 9.6% of patients with a normal BMD ($p < 0.001$ for skeletal status).

Another important finding was, that new contributors were found in both men (27.8%) and women (26.1%) (no statistical difference between sexes), at all ages with an increasing prevalence with increasing age decade (13.6% of patients aged 50-59 years to 37.6% in patients > 80 years, $p<0.001$) and after all fractures with an increasing prevalence in more serious fractures (respectively 34.0%; 30.0%; 24.6% and 5.3% in patients with respectively hip; major; minor and finger/toe fracture, $p<0.05$).

524 patients completed the food questionnaire, only 9.4% had a dietary calcium intake of ≥ 1200 mg/day. There was no significant difference for calcium intake less than 1200 mg/d between age decades, fracture type, sex, and skeletal status. Furthermore, 58.2% of patients had a low calcium intake (defined as <1200mg/day) combined with a low serum 25(OH)D (defined as serum 25(OH)D <50 nmol/l).

As could be expected, serum 25(OH)D <50 nmol/l was highly prevalent in this population (63.9% of all patients), however only 7.8% had a secondary hyperparathyroidism. The percentage of patients with serum 25(OH)D <50 nmol/l was significantly higher in higher age decades and lower skeletal status (both $p < 0.001$), in men ($p < 0.01$), and in more serious fracture type ($p <0.05$).

In conclusion, of 626 consecutive patients 50 years or older presenting at the FLS after a recent clinical fracture, 23.0% had at least one known and 26.5% had at least one newly detected contributor to secondary osteoporosis. In total, 42.5% of patients had at least

one (new and/or known) contributor and more than 90% of patients had an inadequate vitamin D status and/or calcium intake.

Newly detected contributors to secondary osteoporosis were not only found in case of osteoporosis, but also in patients with osteopenia and to a lesser extent in patients with a normal BMD.

Secondary osteoporosis and metabolic bone disease in patients 50 years and older with osteoporosis or with a recent clinical fracture: a clinical perspective. (chapter 3)

In this narrative review, we summarized the literature on newly diagnosed contributors to secondary osteoporosis and metabolic bone disorders in patients 50 years or older, in two scenarios: 1) patients referred for DXA and diagnosed with osteoporosis and 2) patients with a recent clinical fracture. Our goal was to provide practical guidance to clinicians who take care of these patients in osteoporosis clinics and in the FLS.

Focussing on the reported prevalence of known secondary osteoporosis, we found a high variability between studies (3-55%), depending on the population and the disorders that were considered as contributors to secondary osteoporosis; glucocorticoid use and inflammatory rheumatic disease were included as secondary osteoporosis in most studies, but there was a large variation in other disorders and medications considered.

The included studies reported a prevalence of newly detected contributors to secondary osteoporosis of 5-48% in patients with osteoporosis, and of 10-51% in patients with a recent clinical fracture. This variability depended on the included population and the included disorders that were considered. Furthermore, most studies also reported a low serum 25(OH)D as secondary osteoporosis, with different cut-off values and different seasonal effects. A few studies reported more than one disorder contributing to secondary osteoporosis in the same patient in 5-29% of patients.

In conclusion, we recommend performing the following tests in all patients with osteoporosis or a recent clinical fracture: calcium, phosphate, creatinine, albumin, erythrocyte sedimentation rate in all patients, 24h urine calcium in men and serum testosterone in men less than 70 years. On indication, additional tests can be performed.

Suboptimal effect of different vitamin D supplementations and doses adapted to baseline serum 25(OH)D on achieved 25(OH)D levels in patients with a recent fracture: a prospective observational study. (chapter 4)

This observational study was designed to examine the effects of vitamin D supplementation on serum 25(OH)D levels in clinical practice in Caucasian patients 50 years or older who presented with a recent clinical vertebral or non-vertebral fracture and were evaluated at the FLS of the VieCuri MC, Venlo, the Netherlands.

In total 1481 patients were evaluated. Of them, 30.6% were diagnosed with osteoporosis, 64.7% with osteopenia, and 4.8% had a normal BMD.

707 patients (47.7%) had a baseline serum 25(OH)D <50 nmol/l and vitamin D supplementation was initiated, dependent on baseline serum 25(OH)D level; doses used were 400IU/day, 800 IU/day, 1700IU/day and 3500IU/day. Serum 25(OH)D ≥50 nmol/l was achieved in 57-76% of patients after 4.2 months and in 73-79% after 11 months. The mean achieved serum 25(OH)D level was similar for all dose groups. The increase in serum 25(OH)D level was dependent on baseline serum 25(OH)D and not on supplementation dose, age, gender, BMI or season. 21-27% of patients did not reach a serum 25(OH)D level >50 nmol/l after 11 months.

In conclusion, baseline serum 25(OH)D levels, but not supplementation dose, determined the response to vitamin D supplementation. The increase in serum 25(OH)D levels was higher in patients with lower baseline levels. In 21–27% of patients, serum 25(OH)D levels did not reach ≥50 nmol/l after 11 months, at any dose.

Serum 25(OH)D response to vitamin D supplementation: a meta-regression analysis. (chapter 5)

In this meta-regression analysis, we included 33 RCTs up to November 2011. In the selected 33 RCTs 43 treatment arms were included; 3659 participants treated with vitamin D supplementation and 3491 placebo-controlled participants. With a mean baseline serum 25(OH)D level of 50.4 nmol/l, the pooled mean difference was 37nmol/l with significant heterogeneity between studies. Dose, trial duration, baseline serum 25(OH)D level and age independently influenced the achieved serum 25(OH)D level. Similar results were achieved with a mean baseline serum 25(OH)D level <50 nmol/l.

In conclusion, this meta regression indicates that a higher increase in serum levels of 25(OH)D in adults was found with a dose of 800 IU/d, after at least 6 to 12 months, and even when baseline 25(OH)D was low and in adults older than 80 years.

Effect of implementation of guidelines on assessment and diagnosis of vertebral fractures in patients older than 50 years with a recent non-vertebral fracture. (chapter 6)

In this prospective cohort study, all patients 50 years or older with a recent clinical non-vertebral fracture who presented at the FLS of VieCuri MC and Maastricht UMC+, the Netherlands, were included, and performance of vertebral fracture assessment (VFA) and diagnosis of vertebral fractures was compared before and after implementation of guidelines.

In total 1066 consecutive patients were included, 582 before and 484 after implementation of the guidelines. Performance of VFA increased from 4.6% to 97.1% before vs. after implementation of the guidelines. The diagnosis of vertebral fractures grade ≥ 1 increased from 2.2% to 26.2%, and diagnosis of vertebral fractures grade ≥ 2 from 0.9% to 14.7%. The prevalence of vertebral fractures was higher with increasing age decade (5.2% in 50-59 year old vs. 27.8% in 80+ old patients, $p < 0.001$), but was similar for gender, baseline non-vertebral fracture location and BMD.

As patients with osteopenia and a vertebral fracture were eligible for osteoporosis treatment, there was an increase from 31.0% to 38.4% in patients who were eligible for treatment before vs. after guideline implementation.

In conclusion, the prevalence of vertebral fractures was high in the FLS patients presenting with a non-vertebral fracture in both genders, at any age, baseline fracture location, and BMD. Systematic implementation of guidelines resulted in an increase of VFAs performed, and increase in patients diagnosed with a vertebral fracture and thus eligible for treatment.

Risk of vertebral and non-vertebral fractures in patients with sarcoidosis: a population-based cohort. (chapter 7)

In this retrospective cohort study using the CPRD database, 5,722 patients with sarcoidosis were identified and compared to 28,704 age and sex-matched controls.

The risk of any fracture (adjusted relative risk, adjRR 0.90; 95% CI 0.80-1.02), major osteoporotic fracture (adjRR 1.02; 95% CI 0.85-1.23) or non-osteoporotic fracture (adjRR 0.89; 95% CI 0.77-1.03) was not different in patients with sarcoidosis compared to the matched controls. The risk of clinical vertebral fractures was significantly increased (adjRR 1.77; 95% CI 1.06-2.96). The risk of non-vertebral fractures was decreased (adjRR 0.87; 95% CI 0.77-0.99). The adjRR was not modified by the sarcoidosis case definition.

Compared to patients with sarcoidosis who did not take glucocorticoids, recent (i.e. within the previous 6 months) use of systemic glucocorticoids was associated with an increased risk of any fracture (adj RR1.50; 95% CI 1.20-1.89) and of osteoporotic fracture (adjRR 1.47; 95% CI 1.07-2.02).

In conclusion, patients with sarcoidosis had an increased risk of clinical vertebral fractures compared to controls, and patients with sarcoidosis who use glucocorticoids had an increased risk of any and osteoporotic fracture compared to patients with sarcoidosis without glucocorticoid use. In contrast, the risk of non-vertebral fractures was decreased in patients with sarcoidosis vs. controls.

Chapter 9

General discussion and future perspectives

In this chapter, the main findings of this thesis and future perspectives for clinical practice and research will be discussed.

Firstly, our main findings on contributors to secondary osteoporosis and other metabolic bone disorders in patients presenting at a fracture liaison service (FLS) after a recent clinical fracture and the results of our literature review will be discussed. Secondly, we will reflect on the effect of vitamin D supplementation on achieved serum 25(OH)D in patients at the FLS, followed by the results of our literature review with meta-analysis on changes in serum 25(OH)D. Thirdly, we will evaluate the impact of systematic evaluation of vertebral fractures on clinical practice in FLS patients with a recent non-vertebral fracture. Finally, we will discuss the risk of clinical vertebral and non-vertebral fractures in patients with sarcoidosis.

Furthermore, we will provide some future perspectives.

Contributors to secondary osteoporosis and other metabolic bone disorders

At the time that the study in chapter 2 was conducted, Dutch and several international guidelines recommended to perform laboratory testing only in patients diagnosed with osteoporosis in order to assess the presence of so-called secondary osteoporosis (1, 2).

Given the high subsequent fracture risk in patients with a recent fracture (3-6) and the finding that less than 50% of all patients with a recent fracture are diagnosed with osteoporosis, defined as a T-score ≤-2.5 (7, 8), we questioned whether it was justified to evaluate only FLS patients for "secondary osteoporosis" if they had a T-score of -2.5 or lower. We hypothesized that disorders contributing to fracture risk may also be present in patients with a recent fracture if they had a T-score > -2.5.

Therefore, we systematically performed laboratory testing in 626 consecutive patients attending the FLS of VieCuri MC, Venlo, The Netherlands, during a period of 20 months to evaluate the presence of chronic kidney disease (CKD), hyperthyroidism, primary or secondary hyperparathyroidism, monoclonal gammopathy of unknown significance (MGUS) or multiple myeloma and hypogonadism in men.

Based on this single set of laboratory tests, newly diagnosed disorders were found in 26.5% of all patients with a recent clinical fracture. The prevalence of disorders was 9.6%, 26.6% and 32.9% in patients with respectively normal bone mineral density (BMD), osteopenia and osteoporosis. The prevalence of new disorders differed according to fracture type and was respectively 34.0% after hip fracture, 30.0% after a major and 24.6% after minor fracture and was lowest in patients with a finger or toe fracture (5.3%). Newly diagnosed disorders were found both in men and women. There was a higher

prevalence of newly diagnosed disorders with increasing age decades; from 13.6% of patients aged 50-59 years to 37.6% in patients > 80 years.

Furthermore, we evaluated the prevalence of vitamin D deficiency, defined as a serum 25(OH)D <50 nmol/l (9) and a normal parathyroid hormone (PTH), which was found in 63.9% of patients. We considered a serum 25(OH)D <50 nmol/l only as a disorder if it was found in combination with increased PTH, and thus if considered as indicative for secondary hyperparathyroidism, which was found in 7.8% of all patients.

A limitation of our study was, that we performed 24h urine excretion of calcium only in men, but we did not systematically evaluate 24h urine analysis in all patients for diagnosis of malabsorption, especially celiac disease. Because low serum 25(OH)D, secondary hyperparathyroidism, and/or low absolute urinary calcium excretion may be seen in patients with celiac disease, this could have influenced our results.

Our study was the first to systematically evaluate the prevalence of disorders that contribute to bone loss and fracture risk in all consecutive patients at the FLS regardless of BMD, age, gender and baseline fracture location. While most studies reported the presence of underlying disorders in patients diagnosed with osteoporosis (10-22), two studies had already reported on the presence of underlying disorders in patients after a recent fracture, regardless of BMD (23, 24). These studies, however, included only women with respectively a hip fracture and a vertebral fracture. *Edwards et al.* included women 50 years or older with a hip fracture, and found that 82% had at least one disorder, compared to 48% of women with low bone mass or osteoporosis but no prior hip fracture (23). In contrast to our study, *Edwards et al.* included vitamin D insufficiency, defined as serum 25(OH)D <75 nmol/l, as a bone related disorder, which was found in 61% of patients with a hip fracture and 44% of controls (23). If we would have included serum 25(OD)D <75nmol/l as a disorder, we would have diagnosed 89.9% of patients as having a bone related disorder. *Caplan et al.* included women with a vertebral crush fracture and found that 30% had at least one bone related disorder, not including vitamin D deficiency, and more than 50% when women with early menopause were also included (24). We considered premature menopause as a known bone related disorder as it could be retrieved from anamnesis.

A more recent study by *Malgo et al.* at a FLS in a Dutch university hospital confirmed our findings. New metabolic bone disorders were reported in 18% of patients with a normal BMD, in 29% of patients with osteopenia and in 35% of patients with osteoporosis. In line with our study, serum 25(OH)D <50 nmol/l was considered as metabolic bone disorder only in the presence of secondary hyperparathyroidism. In that study patients with fractures of hands, feet or skull were excluded (25), while we included patients with finger and toe fractures, who more frequently had normal BMD and the lowest prevalence of newly detected contributors to bone disorders. This might explain the higher prevalence of newly found disorders in patients with a normal BMD in the study by *Malgo et al.*

compared to our results. The findings in our study as well as the study of *Malgo et al*. emphasize that the approach where the decision to perform laboratory testing in patients at the FLS relies on the DXA result (i.e. only in those patients with osteoporosis) is not the most appropriate approach.

Since newly detected metabolic bone disorders were present in patients at the FLS after a recent clinical fracture in both sexes, at all ages, after any type of fracture (except in men with finger and toe fractures) and at any level of BMD, we propose to change the restrictive term "secondary osteoporosis" into the term contributors to secondary osteoporosis and other metabolic bone disorders (SECOB).

As mentioned before, in the so-called "primary" osteoporosis (post-menopausal or age related) some underlying mechanisms are known, i.e. estrogen deficiency in women, or testosterone deficiency in men after the age of 70 years and immobility in the elderly. It is important to note that the term "secondary osteoporosis" refers to patients who are diagnosed with osteoporosis related to underlying disorders, medication or deficiencies that affect bone metabolism negatively (26), which is considered as a different mechanism than in "primary osteoporosis". This arbitrary classification does however not imply that other patient categories, especially those patients with increased fracture risk without having a low T-score, should not be investigated for underlying disorders that attribute to an increased fracture risk. This is even more important since more than half of the patients with a recent fracture at the FLS do not have osteoporosis. According to the Dutch guideline (1), patients with a recent fracture at the FLS who do not have osteoporosis and/or a vertebral fracture are not eligible for treatment with anti-osteoporosis medication. Nevertheless, their subsequent fracture risk is high. It would be a missed opportunity not to evaluate FLS patients with osteopenia and to a lesser extent those with a normal BMD for disorders that contribute to bone loss and fracture risk and that can be treated in order to decrease bone loss and fracture risk. The clinical implication of our finding is that all patients at the FLS with a clinical vertebral or non-vertebral fracture should be evaluated for the presence of previously unknown contributors to secondary osteoporosis and other metabolic bone disorders.

Based on the findings in chapter 2, in **chapter 3** we additionally reviewed the literature for evidence whether the various disorders were associated with bone loss and / or increased fracture risk and if the treatment of the disorder would improve BMD and decrease fracture risk.

We found a large variation in the reported prevalence of secondary osteoporosis and other metabolic bone disorders ranging from 5% to 51%, both in patients referred for dual X-ray absorptiometry (DXA) in osteoporosis outpatient clinics and in patients with a recent clinical fracture at the FLS. The variation depended on the set of laboratory tests that was used for evaluation, the population that was included in the studies, and whether and at which serum level vitamin D deficiency was considered as a disorder.

We found only a limited number of disorders associated with bone loss or fracture risk, for which there is evidence that treatment of the disorder improves BMD or decreases fracture risk: primary and secondary hyperparathyroidism, idiopathic hypercalciuria, hyperthyroidism, hypercortisolism, male hypogonadism and multiple myeloma. Other disorders are associated with bone loss and/or increased fracture risk but evidence that treatment of the disorder improves bone loss or decreases fracture risk is lacking: familial hypocalciuric hypercalcemia (FHH), MGUS, mineral bone disorder associated with CKD, malabsorption, diabetes mellitus.

The main limitation of our narrative review was the high variability in assessed disorders possibly contributing to secondary osteoporosis and metabolic bone disorders, and thus the high variability in reported prevalence of secondary osteoporosis.

The laboratory tests applied to diagnose underlying disorders in patients at high fracture risk should be limited to disorders for which three conditions are fulfilled: 1) the disorder is associated with bone loss and fracture risk, 2) treatment of the disorder may improve BMD and/or decrease fracture risk, and 3) the disorder has a substantial prevalence, as has been shown for primary or secondary hyperparathyroidism, hyperthyroidism and hypercalciuria. The prevalence of CKD is substantial in the FLS population and although there are no data on the effect of treatment of CKD on BMD and fractures, it is important to rule out CKD in the FLS population as bisphosphonates are contra-indicated in patients with a eGFR <30ml/min (27). Although hypercortisolism and multiple myeloma are associated with bone loss and fractures and its treatment improves BMD and fracture risk, the prevalence is low in patients with a recent clinical fracture. For male hypogonadism a positive treatment effect on BMD has been reported, but there are no data with regard to fracture risk. No treatment is available for MGUS and FHH.

Based on these considerations, we recommend including the following laboratory analysis panel in FLS patients independent of the presenting fracture or BMD: serum calcium, creatinine, albumin, erythrocyte sedimentation rate (ESR) and TSH in all patients, and serum testosterone in men <70 years. Based on clinical or biochemical suspicion of hyperparathyroidism, hypercortisolism, multiple myeloma, celiac disease, hypercalciuria or other metabolic bone disorders, additional tests may be indicated.

Vitamin D

In a recent literature review of RCTs, *Bouillon et al.* concluded that serum levels of 25(OH)D >50 nmol/l are sufficient to normalize calcium and bone homeostasis as measured by surrogate endpoints such as $1,25(OH)_2D$, PTH, calcium absorption and bone mass (9).

Considering the high prevalence of vitamin D deficiency both in the general population as in our FLS cohort (chapter 2) and since there was little known about the effect of higher vitamin D supplementation doses at lower baseline serum 25(OH)D levels on the increase and achieved levels of serum 25(OH)D, we performed the study described in chapter 4.

We found that supplementation with higher doses of vitamin D in patients with lower baseline 25(OH)D levels increased serum 25(OH)D to a level >50 nmol/l in at least 57% of patients after 4 months and 73% after 11 months. The increase in serum 25(OH)D was significantly greater with higher vitamin D supplementation doses. However, using a standard dose of 800IU of vitamin D per day resulted in a similar number of patients who reached a serum 25(OH)D ≥50 nmol/l after 11 months than higher supplementation doses. Based on a multivariate analysis, this dose-effect response was mainly explained by the baseline serum 25(OH)D and not by the (higher) supplementation dose itself.

Remarkably, 27% of patients did not reach a serum 25(OH)D ≥50 nmol/l after 11 months. Possible explanations could be low compliance (28, 29) , malabsorption such as in celiac disease (30), or genetic variability in vitamin D receptor polymorphisms or vitamin D binding protein (31, 32).

The use of a standard vitamin D supplementation dose of 800 IU/day, as advocated in many guidelines on osteoporosis and fracture prevention (1, 33, 34), resulted a similar percentage of patients reaching a serum 25(OH)D level >50 nmol/l compared to the use of higher supplementation doses, at any baseline serum 25(OH)D. This result confirms that baseline serum 25(OH)D, and not supplementation dose, is the most important predictor of response to vitamin D supplementation. Therefore, if the aim is to achieve a serum 25(OH)D >50 nmol/l, as in our study, higher vitamin D supplementation doses than 800 IU/day are not needed in most patients (34-36).

The limitations of our study were, that it was an observational, non-randomized study, that we did not assess compliance; we did not have data available on the baseline dietary vitamin D intake, intake from over the counter supplements, or change in intake during the study; and different formulas for vitamin D supplementation were used.

We subsequently performed a meta-regression analysis in chapter 5 to review factors that influence the serum 25(OH)D response when patients are given vitamin D supplementation. We found a dose-dependent increase in pooled mean difference (PMD) in serum 25(OH)D, which was curvilinear with flattening from a dose of 800 IU/day, with only a slight increase with higher doses. In addition, we found a higher increase in serum 25(OH)D with lower baseline serum 25(OH)D and a plateau was achieved after a duration of at least 6 months. This suggests that a measurement of 25(OH)D after 6 months reflects the maximum attained serum 25(OH)D level.

Limitations of our meta-regression analysis were, that we only searched for published articles, that we did not dispose of individual patient data, we could not adjust for BMI,

seasonal effect, sun exposure, ethnical background or dietary intake of vitamin D and calcium because not all studies reported these data, the use of different vitamin D assay types may have influenced the validity of the study outcomes, and finally we did not report on the effect of sex because most studies included participants from only one sex and the other studies did not report results separately by sex.

Based on the findings in chapters 2, 4 and 5, we conclude that serum 25(OH)D <50 nmol/l is highly prevalent in patients at the FLS, regardless of age, fracture location or BMD. We classified a decreased serum 25(OH)D level in combination with an increased PTH level as secondary hyperparathyroidism with a prevalence of 7.8% in FLS patients. Note that the prevalence of serum 25(OH)D <50 nmol/l was 63.9%.

Because of the substantial prevalence of vitamin D deficiency with secondary hyperparathyroidism and high prevalence of a serum 25(OH)D <50 nmol/l in FLS patients we propose a pragmatic approach to supplement vitamin D in all patients with a recent clinical fracture, without the need for evaluation of serum 25(OH)D level.

We would advocate a dose of 800IU of vitamin D per day in all patients after a recent clinical fracture at the FLS and if control measurement of serum 25(OH)D level is indicated (see below), to wait for at least 6 months.

When it is considered necessary to rule out secondary hyperparathyroidism or osteomalacia, for instance when treatment with anti-resorptive medication is indicated, evaluation of serum 25(OH)D and if necessary PTH measurements should be performed. In most of the patients with an indication for anti-osteoporosis treatment, supplementation with 800IU of vitamin D per day will be sufficient. There could however be cases in whom it would be necessary to reach a faster increase in serum 25(OH)D, for example in patients with a very low baseline serum 25(OH)D level and secondary hyperparathyroidism who have an indication for anti-osteoporosis treatment. In those cases, supplementation with higher doses could be considered.

In conclusion, contributors to secondary osteoporosis and other metabolic bone disorders can be found in all patients 50 years or older presenting at the FLS after a recent clinical fracture regardless of BMD, and not only in patients with osteoporosis. Furthermore, contributors to secondary osteoporosis and other metabolic bone disorders are present in both men and women, at all ages, and after all fracture types although the prevalence is increasing with age and more severe fracture type.

From a semantic point of view, we therefore considered that the terminology “secondary osteoporosis” is incomplete, and therefore introduced the terminology “contributors to secondary osteoporosis and other metabolic bone disorders”. However, this goes further than a semantic discussion. We hypothesize, that a fracture may imply vulnerability of the bone, which might not always be reflected by BMD as measured by DXA. Therefore,

contributors to metabolic bone disorders are associated with the fracture itself, and not only with low BMD/osteoporosis.

The clinical implication being that all patients of 50 years or older with a recent clinical vertebral or non-vertebral fracture should be evaluated for the presence of newly diagnosed metabolic bone disorders, regardless of BMD, age, gender and fracture location.

In addition, because of the substantial prevalence of vitamin D deficiency with secondary hyperparathyroidism and high prevalence of a serum 25(OH)D <50 nmol/l in FLS patients we propose to start vitamin D supplementation 800IU per day in all FLS patients and to consider measurement of serum 25(OH)D when anti-osteoporosis treatment is indicated or in case of specific indications such as suspicion of secondary hyperparathyroidism or osteomalacia.

Vertebral fractures

There are many reasons to consider systematic standard evaluation of prevalent vertebral fractures in FLS patients with a recent non-vertebral fracture. First, although radiographic vertebral fractures are the most frequent fractures (37, 38), two thirds of them do not present with an acute symptomatic episode (39-41). This could explain why a clinical vertebral fracture is rarely the presenting fracture in patients attending the FLS (42), in spite of a high prevalence of radiographic vertebral fractures. The presence of a vertebral fracture is a sensitive marker of decreased bone quality. The presence, number and severity of vertebral fractures are strong predictors of short-term subsequent vertebral and non-vertebral fracture risk, independent of age and BMD (43, 44). Furthermore, it has been shown that the short term risk of subsequent radiographic vertebral fractures is high after an incident radiographic vertebral fracture in postmenopausal women (up to 20% within one year) (45) and in current or former heavy cigarette smokers with and without COPD (up to >50% after 3 years) (46).

Additionally, the diagnosis of a prevalent vertebral fracture can have therapeutic consequences. In 2011, the Dutch guideline recommended systematic evaluation of vertebral fractures in patients with a recent non-vertebral fracture and osteopenia as measured by DXA, and to start anti-osteoporosis treatment in patients with any grade 2 or 3 clinical or prevalent vertebral fracture (1). By implementing vertebral fracture assessment (VFA) by DXA in all consecutive patients presenting at the FLS of VieCuri MC and Maastricht UMC+ in **chapter 6**, imaging of the spine increased from 5% to 96% and the detection of any previously unknown prevalent vertebral fracture increased from 2% to 26%, and from 1% to 15% for a vertebral fracture grade ≥2. While the prevalence of vertebral fractures was higher with increasing age, there was no difference between men

and women, or between the locations of the baseline non-vertebral fracture. Furthermore, vertebral fractures grade ≥2 were detected at any BMD, with a trend towards a higher prevalence in patients with osteoporosis (18%) compared to patients with a normal BMD (12%). The diagnosis of vertebral fractures in patients with a non-vertebral fracture at the FLS resulted in adaptations of therapy. In our study indication for treatment according to the Dutch guideline (1) increased by 25% from 31% to 38% due to diagnosis of vertebral fractures grade 2 in patients with osteopenia.

Limitations in our study were differences in patient characteristics before and after implementation of the guideline, reflecting the real-world response rate of patients invited to the FLS. Only limited vertebrae could be evaluated above the Th7 level, possibly with today's software this could be improved. However, since most osteoporotic vertebral fractures occur at the lower spine region, this should not have influenced the results much. Another limitation is the possibility of over-diagnosing of vertebral fractures, sensitivity of VFA by DXA is 60-80% (47), and the VFA evaluation in our study was performed by an experienced researcher, carefully excluding other deformities.

The findings of our study are in line with those reported by others at the FLS, in which it was reported that DXA combined with vertebral morphometry leaded to an increase in patients eligible for anti-osteoporosis treatment compared to DXA alone, leading to treatment decisions that better reflect the subsequent fracture risk (48-51). Not only at the FLS, but also in patients referred for DXA (51) and in women with clinical risk factors for osteoporosis but a T-score > -2.5 as measured by DXA (52), imaging of the spine by DXA or lateral radiographs leaded to diagnosis of (asymptomatic) vertebral fractures.

Diagnosing vertebral fractures is also helpful for decisions about switching anti-osteoporosis treatment from anti-resorptives to bone forming agents such as teriparatide according to the Dutch guideline (1). Furthermore, teriparatide has been shown to reduce vertebral fractures and clinical fractures significantly more than risedronate in postmenopausal women with ≥2 moderate or ≥1 severe vertebral fracture and a T-score <-1.5 (53). The results were similar in pre-specified subgroups, which can influence therapeutic decisions at the FLS: after a recent vertebral fracture, after a non-vertebral fracture and even after the recent use of bisphosphonates (54). In our FLS cohort, approximately 4.5% of patients had at least 2 moderate or 1 severe vertebral fracture and osteoporosis or osteopenia. In those patients, it could be considered to start or switch treatment with or to teriparatide instead of anti-resorptive treatment.

A high prevalence of radiographic vertebral fractures has been documented in patients with inflammatory diseases that can be considered as contributors to secondary osteoporosis and metabolic bone disorders such as rheumatoid arthritis (RA) (55, 56), axial spondyloarthritis (57, 58), systemic lupus erythematosus (SLE) (59, 60), inflammatory bowel disease, chronic obstructive pulmonary disease (COPD) (47, 61) or medications (e.g. glucocorticoids (62)) that increase the risk of fractures. Patients with

RA/SLE, COPD and glucocorticoid users represented respectively 5.2%, 10.4% and 8.5% of our FLS population. This could imply that not only at the FLS but also in the screening for osteoporosis in patients with an inflammatory disease, VFA will be of added value.

In conclusion, the implementation of systematic VFA at the FLS resulted in the identification of patients that otherwise would not have been diagnosed with vertebral fractures and therefore would not have been treated adequately according to the current insights.

Fracture risk in patients with sarcoidosis

In chapter 7 we conducted a large retrospective population-based cohort study, comparing > 5,000 patients with sarcoidosis of whom >1,000 had a history of fractures, with > 28,000 matched controls. We showed that patients with sarcoidosis had an increased risk of clinical vertebral fractures but no increased risk of non-vertebral fractures, and that patients with sarcoidosis treated with glucocorticoids had and increased risk of any and major osteoporotic fracture compared to those who did not use glucocorticoids.

Limitations of our study were the lack of information on markers for inflammation, disease activity, and BMD, so we could not adjust for these possible confounders. No information was available on muscle strength or mass and fall risk.

It was previously reported that patients with sarcoidosis are at risk for radiographic vertebral fractures (63, 64) despite a normal BMD (63, 65), even when BMD did not change over time (64). As also reported by *Ungprasert et al.*, we found an increased risk but a low absolute incidence of vertebral fractures (66). This is in contrast with *Heijckman et al.* who found a prevalence of radiographic vertebral fractures in 20% at baseline, and in 32% of sarcoidosis patients after 4 years of follow-up (63, 64). However, in this study without control group, radiographic vertebral fractures were assessed. Vertebral fractures in the general population and in postmenopausal women can be asymptomatic (39-41). The discrepancy between our findings on the low total number of clinical vertebral fractures and the high prevalence of radiographic vertebral fractures reported by *Heijckman et al.*(63, 64) may suggest that in patients with sarcoidosis most vertebral fractures are asymptomatic as well. Systematic screening for vertebral fractures should therefore be advocated in patients with sarcoidosis even in those without symptoms of vertebral fracture, in order to assess their fracture risk which may influence treatment decisions in order to prevent new fractures.

With regard to other fracture types, we found no increased risk of any fractures, major osteoporotic fractures or non-osteoporotic fractures and a slightly lower risk of non-vertebral fractures. *Saidenberg et al.* found a high incidence of any fracture in patients

with sarcoidosis, in a study without control population. Their study population consisted of patients at a pulmonary outpatient clinic, and 62.0% of them were treated with glucocorticoids (67), whereas only 16.7% of the patients in our general practitioner population study was treated with glucocorticoids. *Ungprasert et al.* showed an increased cumulative incidence of fragility fractures in patients with incident sarcoidosis compared to matched controls without sarcoidosis (5.6% vs. 2.4% in 10 years respectively) (66). In that study, the rate of forearm fractures was higher in patients with sarcoidosis, which was not the case for proximal femur, proximal humerus and vertebral fractures. In addition, *Ungprasert et al.* only adjusted for mortality and glucocorticoid use and not for smoking, heart failure, asthma/COPD, and the use of calcium/vitamin D supplements, and other medications potentially contributing to mineral bone disorders as we did in our study. The question if the increased fracture risk is caused by sarcoidosis itself therefore remains open. Furthermore, they identified both patients with sarcoidosis and fractures from individual medical records, while we used the CPRD database. Previous studies in CPRD however showed that the data validity with respect to identification of fractures was high (68) and thus the risk of underreport of fractures and thus to an underestimation of fracture risk is low.

We found, that in patients with sarcoidosis who had a recent treatment with glucocorticoids, the adjusted risk of any osteoporotic fracture and major osteoporotic fracture was increased compared to patients with sarcoidosis who did not use glucocorticoids. This finding is in line with *Oshagbemi et al.* who reported an increased risk for major osteoporotic fractures in patients with sarcoidosis who currently used glucocorticoids compared to those who did not use glucocorticoids (adjOR for hip fractures 3.80 and adjOR 6.05 for vertebral fractures) (69).

In conclusion, patients with sarcoidosis had an increased risk of clinical vertebral fractures, with a relatively low absolute risk, while earlier studies showed a high prevalence of radiographic vertebral fractures, indicating that most vertebral fractures in patients with sarcoidosis might also be asymptomatic. Current use of glucocorticoids led to an increased risk of any fractures and major osteoporotic fractures, which was confirmed by other studies. It remains however unclear whether the risk of non-vertebral fractures is increased in all patients with sarcoidosis.

General limitation

This thesis describes the prevalence of secondary osteoporosis, the effect of vitamin D supplementation and the prevalence of vertebral fractures before and after the implementation of the Dutch guideline at the FLS of VieCuri MC, Venlo, the Netherlands in chapters 2, 4 and 6. The prevalence of vertebral fractures before and after the implementation of the Dutch guideline was also investigated at the FLS of Maastricht UMC+, Maastricht, the Netherlands.

It is important to consider the fact, that only patients who were able and willing to visit the FLS were included in these three studies. Patients who did not show at our FLSs more frequently were men, had a more serious fracture and were older compared to the patients who did attend the FLS (chapter 2), confirmed in a later cohort (70). This implicates, that the prevalence of contributors to secondary osteoporosis and metabolic bone disorders and the prevalence of morphometric vertebral fractures might even be underestimated in our studies.

Conclusions

In conclusion, contributors to secondary osteoporosis and other metabolic bone disorders, vitamin D deficiency and prevalent vertebral fractures are present in a substantial proportion of patients with a recent clinical fracture at the FLS, regardless of BMD, gender or fracture location. Based on the findings in this thesis, we propose that all patients at the FLS should be assessed by DXA including imaging of the spine using VFA and by a standard laboratory analysis panel (serum calcium, creatinine, albumin, ESR, TSH) in all patients and serum testosterone in men <70 years.

Future perspectives

In this thesis, we focused on the prevalence of secondary osteoporosis and other metabolic bone disorders in patients 50 years or older presenting at the hospital because of a fracture and on the prevalence of vertebral fractures in these patients.

Clearly, the phenotype of the patient 50 years or older presenting with a clinical fracture is complex. In view of the high prevalence of secondary osteoporosis and other metabolic bone disorders, more attention will be needed in such patients before a first clinical fracture has occurred. There is indeed still a significant evaluation and treatment gap for fracture prevention in many diseases that are known to be associated with fractures and osteoporosis. Examples of those diseases are chronic kidney diseases (27, 71), glucocorticoid use (62, 72), diabetes mellitus type 1 and 2 (73-75), monoclonal

gammopathy of undetermined significance (76-79), male hypogonadism (80), sarcoidosis (66, 67, 69), rheumatoid arthritis (55, 56), axial spondyloarthritis (57, 58), systemic lupus erythematosus (59, 60), inflammatory bowel disease, chronic obstructive pulmonary disease (47, 61). Our results support the view that such patients need fracture risk assessment and should have VFA when a DXA is performed.

Patients with a recent fracture have a high imminent risk for subsequent fractures, i.e. the risk of subsequent fracture is much higher at short term than at long term (3, 5, 45, 81). In addition, major fractures are associated with an increased risk of mortality at short term (4, 6). This indicates that after a recent fracture, immediate measures are needed to prevent subsequent fractures. Studies will be needed on the effect of an early approach at the FLS in patients with secondary osteoporosis and other metabolic bone disorders with disease-, bone- and fall-directed treatments.

Furthermore, studies will be needed to evaluate the association of secondary osteoporosis and other metabolic bone disorders and subsequent fracture risk and mortality. Analyses of the cost-effectiveness of secondary fracture prevention in secondary osteoporosis and other metabolic bone disorders will be needed that include also the imminent risk subsequent fracture and mortality in their calculations.

The high prevalence of vertebral fractures in patients 50 years or older at the FLS and the recently published lower risk of new vertebral and clinical fractures in patients receiving the bone forming agent teriparatide compared to the oral bisphosphonate risedronate in women with moderate or severe vertebral fractures provides an opportunity for selection of those patients for treatment with bone forming agents at the FLS (53, 54). Future research should focus on the effect of a systematic diagnostic work-up for the presence of vertebral fractures in the setting of a FLS, to investigate if this real-life scenario indeed leads to starting or switching to a bone forming agent instead of anti-resorptive treatment, and if so, if this strategy would be cost-effective compared to a strategy where FLS patients with (prevalent) vertebral fractures are first being treated with oral anti-resorptive drugs.

A recent fracture reflects vulnerability of the bone which is not fully reflected by low BMD as measured by DXA. Further studies will be needed to examine bone quality of FLS patients in daily practice by additional methods. These include the assessment of bone micro-architectural properties by high resolution peripheral quantitative computer tomography (HRpQCT) and trabecular bone score (TBS) by DXA, and calculated bone strength using HRpQCT images of the distal radius and tibia and CT images of the hip or vertebrae.

In view of the complex phenotype of the patient with a recent fracture, applying machine learning, big data and artificial intelligence could be of interest to further specify the patient phenotype and risk profile by integrating the clinical, laboratory and imaging modalities.

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Nederlandse samenvatting

Fracturen (botbreuken) zijn een veel voorkomend probleem, en vormen een belasting voor zowel de patiënt zelf als de maatschappij. Een fractuur gaat gepaard met een verhoogd risico op nieuwe fracturen: 24% van de vrouwen en 20% van de mannen met een eerste fractuur krijgen binnen 5 jaar opnieuw een fractuur. De kans op nieuwe fracturen is met name verhoogd tijdens het eerste jaar na de eerste fractuur. Ook de kans op voortijdig overlijden is verhoogd na een fractuur, en na een volgende fractuur is de 10-jaars mortaliteit (sterftekans) 50% voor vrouwen en 75% voor mannen. Ook hier is de timing van belang, het risico op overlijden is het hoogste gedurende het eerste jaar na de fractuur.

De post-fractuur zorg is georganiseerd op de polikliniek in zogenaamde fracture liaison services (FLS). Voor de FLS worden alle patiënten 50 jaar of ouder met een fractuur uitgenodigd. Er vindt anamnese en lichamelijk onderzoek plaats, en dual-energy X-ray absorptiometry (DEXA) onderzoek inclusief beeldvorming van de wervelkolom en aanvullend (laboratorium)onderzoek worden verricht. Indien er sprake is van osteoporose of een wervelfractuur, zal er in overeenstemming met de Nederlandse CBO-richtlijn, een behandeling gestart worden.

Een voorspellende factor voor het optreden van fracturen is de botmineraaldichtheid (BMD), die gemeten wordt met de DEXA. Op basis van het aantal standaarddeviaties waarmee de gemeten BMD afwijkt van de referentiepopulatie (een groep jong volwassenen), wordt een indeling gemaakt in osteoporose (T-score ≤ -2.5), osteopenie (T-score tussen -2.5 en -1.0), en een normale BMD (T-score ≥ -1.0). Met elke standaarddeviatie waarmee de BMD afneemt, verdubbelt het fractuurrisico.

Osteoporose wordt van oudsher ingedeeld in primaire en secundaire osteoporose. Men spreekt van primaire osteoporose in geval van postmenopauzale osteoporose of osteoporose op latere leeftijd. De onderliggende oorzaak is oestrogeen deficiëntie bij vrouwen en een fysiologisch lager testosteron bij mannen. In geval van secundaire osteoporose is er een andere onderliggende oorzaak van osteoporose, zoals een chronische inflammatoire aandoening, een endocriene aandoening, malabsorptie, of gebruik van een geneesmiddel dat osteoporose veroorzaakt. Deze aandoeningen gaan gepaard met een verhoogd risico op fracturen, hoewel de BMD normaal kan zijn.

Opvallend is, dat slechts bij minder 50% van de patiënten 50 jaar en ouder met een recente fractuur osteoporose wordt gevonden. Er lijken dus nog andere risicofactoren te zijn voor fracturen dan BMD alleen. Ten tijde van dit proefschrift adviseerde de Nederlandse richtlijnen om alleen aanvullend laboratoriumonderzoek in te zetten naar aandoeningen die secundaire osteoporose kunnen veroorzaken bij patiënten met een T-score ≤ -2.5. Onze hypothese luidde, dat deze aandoeningen aanwezig kunnen zijn bij alle patiënten 50 jaar of ouder met een recente fractuur.

Vitamine D insufficiëntie, gedefinieerd als een serum 25(OH)D concentratie <50 nmol/l komt frequent voor in de algemene populatie. Er was echter geen literatuur over hoe vaak vitamine D insufficiëntie bij patiënten 50 jaar of ouder met een recente fractuur voorkomt. Ook was er weinig literatuur over het effect van de dosis van het vitamine D supplement op de behaalde serum 25(OH)D concentratie in deze patiëntengroep.

Wervelfracturen zijn de meest voorkomende osteoporotische fracturen. Ze kunnen asymptomatisch zijn, er is daarom sprake van onderdiagnostiek. Wervelfracturen komen frequent voor bij patiënten met osteoporose, maar ook bij patiënten met een recente niet-wervelfractuur en osteopenie of een normale BMD. De aanwezigheid van, het aantal en de ernst van wervelfracturen is naast BMD een onafhankelijke voorspellende factor voor het optreden van nieuwe fracturen. Volgens de Nederlandse CBO-richtlijnen is er een behandelindicatie voor alle patiënten met een klinische wervelfractuur, en voor patiënten met een asymptomatische, prevalente wervelfractuur en een T-score <-1.0.

Onze hypothese luidde, dat implementatie van deze richtlijnen zou leiden tot meer gediagnosticeerde wervelfracturen, en dus klinische implicaties zou hebben voor de behandeling.

Sarcoïdose is een voorbeeld van een aandoening die bekend staat als secundaire osteoporose. Er was reeds aangetoond, dat patiënten met sarcoïdose een hoog risico hebben op prevalente wervelfracturen, ondanks een normale BMD. Literatuur naar het risico op andere fracturen bij patiënten met sarcoïdose in vergelijking met een gezonde controle populatie ontbrak echter.

Het doel van dit proefschrift was, om inzicht te verkrijgen in de klinische consequenties van systematische laboratoriumonderzoeken en beeldvorming van de wervelkolom bij patiënten 50 jaar of ouder met een recente fractuur, die de FLS bezoeken.

Secundaire osteoporose

In **hoofdstuk 2** hebben we onderzocht, hoe vaak bekende aandoeningen die kunnen leiden tot secundaire osteoporose aanwezig waren bij patiënten 50 jaar of ouder met een recente fractuur, die zich presenteerden op de FLS van VieCuri MC, Venlo. Ook werd onderzocht bij hoeveel patiënten een nieuwe aandoening gediagnosticeerd kon worden met een standaard pakket aan laboratoriumonderzoeken.

Bij 23.0% van de patiënten op de FLS werd een bekende aandoening gevonden die kan bijdragen tot secundaire osteoporose, en bij 26.5% van de patiënten werd een nieuwe aandoening gediagnosticeerd met het standaard pakket aan laboratoriumonderzoeken. Hoewel er meer aandoeningen werden gediagnosticeerd bij patiënten met osteoporose (in 32.9%), werden deze aandoeningen ook gevonden bij respectievelijk 26.5% en 9.6% van de patiënten met osteopenie of een normale BMD. Deze aandoeningen werden

bovendien gevonden bij zowel mannen (27.8%) als vrouwen (26.1%), in alle leeftijdscategorieën (13.6% van de patiënten tussen 50-59 jaar, tot 27.6% van de patiënten ouder dan 80 jaar), en na alle fracturen (34.0%, 30.0%, 24.6% en 5.3% van de patiënten met respectievelijk een heupfractuur, majeure fractuur, mineure fractuur of vinger-/teenfractuur).

In **hoofdstuk 3** hebben we de bestaande literatuur samengevat naar onderliggende aandoeningen bij patiënten met osteoporose en bij patiënten met een recente fractuur. We vonden een hoge variabiliteit van gevonden aandoeningen, afhankelijk van de onderzochte populatie, de geïncludeerde aandoeningen en of vitamine D insufficiëntie beschouwd werd als aandoening die gepaard gaat met secundaire osteoporose.

Aangezien onderliggende aandoeningen gevonden werden bij *alle* patiënten 50 jaar of ouder met een recente fractuur die zich presenteerden op de FLS, d.w.z. zowel bij mannen als vrouwen, in alle leeftijdscategorieën, na alle fractuurtypes (met uitzondering van mannen met vinger-/teenfracturen), en ongeacht de BMD, stellen we voor om de term “secundaire osteoporose” te vervangen door de term “aandoeningen die bijdragen aan osteoporose en andere metabole botaandoeningen”. Dit gaat verder dan een semantische discussie. Het impliceert, dat ook bij patiënten die een recente fractuur maar geen osteoporose hebben, nagekeken dient te worden of er sprake is van een onderliggende aandoening. Een fractuur is immers een uiting van de kwetsbaarheid van het bot, hetgeen niet altijd wordt weerspiegeld door de gemeten BMD. Het zou een gemiste kans zijn, om bij deze patiënten geen aanvullend onderzoek te doen naar een onderliggende aandoening.

Het standaard pakket laboratoriumonderzoeken naar onderliggende aandoeningen zou ons inziens aandoeningen moeten bevatten die: 1) zijn geassocieerd met osteoporose en/of fracturen 2) waarvan de behandeling leidt tot verbetering van de BMD en/of verlaging van het fractuurrisico 3) een substantiële prevalentie hebben in de algemene populatie.

Ons voorstel is, om bij alle patiënten 50 jaar of ouder met een recente fractuur het volgende pakket aan laboratoriumonderzoek in te zetten: serum calcium, creatinine, albumine, bezinking, TSH bij alle patiënten en testosteron bij mannen jonger dan 70 jaar. Op basis van de kliniek kan aanvullend onderzoek naar andere onderliggende aandoeningen overwogen worden.

Vitamine D

In **hoofdstuk 2** is de prevalentie van vitamine D insufficiëntie onderzocht bij patiënten 50 jaar of ouder met een recente fractuur, die zich presenteerden op de FLS van VieCuri MC, Venlo. Zoals verwacht, had 63.9% van alle patiënten een serum 25(OH)vitamine D

concentratie <50 nmol/l. Slechts 7.8% van alle patiënten met een fractuur had een secundaire hyperparathyreoïdie.

In **hoofdstuk 4** hebben we het effect bestudeerd van vitamine D suppletie op de behaalde serum 25(OH)vitamine D concentratie bij patiënten op de FLS van VieCuri MC, Venlo, met een lage vitamine D spiegel. 47.7% van alle patiënten had een serum 25(OH)vitamine D concentratie <50 nmol/l. Er werd gestart met vitamine D suppletie 400IE/dag, 800IE/dag, 1700IE/dag of 3500IE/dag. Na ongeveer 4 maanden werd een serum 25(OH)vitamine D concentratie >50 nmol/l behaald bij 57-76% van de patiënten, en na 11 maanden bij 73-79% van de patiënten. De stijging van de serum 25(OH)vitamine D concentratie was afhankelijk van de uitgangswaarde van de serum 25(OH)vitamine D concentratie, en niet afhankelijk van de dosis, leeftijd, geslacht, BMI of seizoen.

In **hoofdstuk 5** hebben we een metaregressie analyse uitgevoerd van gerandomiseerde studies (RCTs) naar het effect van factoren gerelateerd aan het supplement (vitamine D dosis en duur van de suppletie) en aan de patiënt (leeftijd en baseline serum 25(OH)vitamine D concentratie) op de behaalde serum 25(OH)vitamine D concentratie. De gemiddelde uitgangswaarde van de serum 25(OH)vitamine D concentratie was 50.4 nmol/l, de pooled mean difference in serum 25(OH)vitamine D concentratie was 37 nmol/l. We vonden nu wel een effect van dosis, behandelduur en leeftijd naast baseline serum 25(OH)vitamine D concentratie op de behaalde serum 25(OH)vitamine D concentratie.

Concluderend komt vitamine D insufficiëntie frequent voor bij de patiënten 50 jaar of ouder met een recente fractuur die zich presenteren op de FLS. We beschouwen een lage serum 25(OH)vitamine D concentratie alleen als aandoening geassocieerd met secundaire osteoporose, indien er tevens sprake is van een secundaire hyperparathyreoïdie. We stellen voor, om bij alle patiënten met een recente fractuur te starten met een vitamine D supplement van 800IE. Alleen als er verdenking bestaat op een ernstige vitamine D deficiëntie, zou er aanvullend een serum 25(OH)vitamine D concentratie en eventueel PTH bepaald hoeven worden.

Wervelfracturen

In **hoofdstuk 6** hebben we onderzocht, hoe vaak wervelfracturen voorkomen bij patiënten 50 jaar of ouder die zich presenteerden met een recente niet-wervelfractuur op de FLS van VieCuri MC, Venlo en MUMC+, Maastricht, voor en na invoering van de Nederlandse richtlijn. Verder hebben we onderzocht, wat de klinische consequentie hiervan was op de behandeling.

We vonden, dat er diagnostiek naar wervelfracturen werd verricht bij 4.6% van de patiënten voor implementatie, en bij 97.1% na implementatie van de richtlijn. De

prevalentie van wervelfracturen steeg van 2.2% naar 26.2%, en de prevalentie van klinisch relevante wervelfracturen steeg van 0.9% naar 14.7%. Patiënten met osteopenie en een prevalente wervelfractuur komen in aanmerking voor osteoporosebehandeling, er was een stijging van 31.0% naar 38.4% van alle patiënten die een behandelindicatie hebben.

Het diagnosticeren van wervelfracturen is van belang voor het starten van osteoporosebehandeling: er is volgens de huidige Nederlandse richtlijn een indicatie voor een anti-resorptivum bij patiënten met osteopenie en een niet-klinische wervelfractuur. Verder adviseert deze richtlijn om bij patiënten met een niet-wervelfractuur en twee wervelfracturen die al behandeld worden met een anti-resorptivum de behandeling te switchen naar een botanabool middel. Een recent onderzoek laat zien, dat patiënten met twee graad 2 wervelfracturen of één graad 3 wervelfractuur en een T-score <-1.5 die behandeld worden met een botanabool middel minder risico hadden op nieuwe wervelfracturen dan als ze behandeld worden met een anti-resorptivum. Het diagnosticeren van wervelfracturen heeft dus klinische implicaties, ook indien het asymptomatische, prevalente wervelfracturen betreft.

Sarcoïdose

In **hoofdstuk 7** hebben we in een Engelse huisartsen database onderzocht, of het fractuurrisico bij patiënten met sarcoïdose hoger is vergeleken met controle patiënten uit de algemene populatie. Ook hebben we gekeken naar de invloed van gebruik van glucocorticoïden op het fractuurrisico.

Het risico op een fractuur, een majeure osteoporotische fractuur of niet-osteoporotische fractuur was niet verschillend tussen patiënten met sarcoïdose en de gezonde controles. Het aantal klinische wervelfracturen was wel hoger bij patiënten met sarcoïdose. Het risico op niet-wervelfracturen daarentegen was verlaagd bij patiënten met sarcoïdose.

Patiënten met sarcoïdose die glucocorticoïden gebruikten hadden een hoger risico op fracturen dan patiënten met sarcoïdose die geen glucocorticoïden gebruikten.

Conclusie

Aandoeningen die bijdragen aan osteoporose en andere metabole botaandoeningen, vitamine D insufficiëntie en prevalente wervelfracturen zijn aanwezig bij een substantieel deel van de patiënten 50 jaar of ouder met een recente fractuur die zich op de FLS presenteren.

Gebaseerd op de bevindingen in dit proefschrift, adviseren we om bij alle patiënten 50 jaar of ouder met een recente fractuur op de FLS naast de DEXA ook beeldvorming van de

wervelkolom te verrichten om wervelfracturen te diagnosticeren, en om een standaard panel aan laboratoriumonderzoek in te zetten: serum calcium, creatinine, albumine, bezinking, TSH en bij mannen <70 jaar ook een testosteron. Op indicatie kan het laboratoriumonderzoek uitgebreid worden. Verder adviseren wij om bij alle patiënten 50 jaar of ouder met een fractuur te starten met vitamine D suppletie middels 800IE/dag, en alleen op indicatie de serum 25(OH)vitamine D concentratie en eventueel PTH te bepalen.

Valorisation

Worldwide, the incidence of fractures is high and is expected to increase. In the Netherlands, the incidence of fractures in patients of 50 years or older was 119,000 between 2009-2011, and is estimated to increase by 40% in 2030. Fractures cause direct costs for society. €200 million was spent on treatment of osteoporosis-related fractures in 2010, which was estimated to increase with 50% by 2030. More importantly, pharmacotherapeutic prevention of fractures could lead to a reduction of costs in 2030. Besides the costs of acute fracture treatment, fractures lead to morbidity, an increased subsequent fracture risk and an increased mortality risk.

Patients with a recent fracture have a doubled risk for (subsequent) fractures as compared to subjects without a fracture. However, this increased fracture risk is not constant over time, and is higher at short than at long-term. This is referred to as imminent fracture risk. As most subsequent fractures occur within short term, early evaluation of this fracture risk, followed by immediate fracture prevention is indicated. The Fracture Liaison Service (FLS) is considered by Dutch and international guidelines, to be the best organisational approach for secondary fracture prevention. Since the implementation of the Dutch guideline of 2011, more than 80% of hospitals in the Netherlands have an FLS, which is substantially higher than in other countries.

Many risk factors for low bone mineral density (BMD) and fracture risk have been documented. However, the frequency in patients who actually present with a recent fracture was not known.

The work presented in this thesis shows, that one in four patients 50 years or older with a recent fracture at the FLS had a previously unknown contributor to secondary osteoporosis and metabolic bone disorders, two thirds of patients had vitamin D insufficiency, most had insufficient daily calcium intake and one in four had a prevalent vertebral fracture in addition to the non-vertebral fracture they presented with at the FLS.

Previously unknown disorders, vitamin D deficiency and prevalent vertebral fractures were not only present in patients with osteoporosis, but at any level of BMD, in both sexes, at any age and any location of the presenting fracture.

In order to fully document their phenotype, systematic evaluation of secondary osteoporosis and metabolic bone disorders and vertebral fracture assessment (VFA) should be considered at the FLS as a standard evaluation of post-fracture care in all patients of 50 years or older with a recent fracture.

Contributors to secondary osteoporosis and metabolic bone disorders

Adequate diagnosis and treatment of underlying disorders that increase bone loss and fracture risk may attribute to a lower subsequent fracture risk in addition to treatment with anti-osteoporosis medication. It also provides an opportunity to reduce subsequent

fracture risk in patients who don't have an indication for treatment with anti-osteoporosis medication. Since known and previously unknown contributors to secondary osteoporosis and metabolic bone disorders are highly prevalent in FLS patients with or without osteoporosis, as shown in this thesis and by others, optimal organisation of FLS care should include laboratory assessment in all patients, regardless of BMD outcome.

These findings may have implication for future guidelines on secondary fracture prevention care, since the current Dutch guidelines advocates laboratory testing in FLS patients only when they have osteoporosis (CBO guideline) or on indication and only in patients with osteoporosis (general practitioners' guideline). It also may have consequences for implementation in (hospital) care systems since standard laboratory testing increases the direct costs of FLS care.

Vitamin D supplementation

Vitamin D insufficiency is endemic worldwide. In this thesis, two thirds of patients at the FLS had vitamin D insufficiency, and 8% had also secondary hyperparathyroidism. This raises the question whether serum levels of 25(OH)D should be measured in all patients with a recent fracture. The assessment of serum 25(OH)D levels is costly. We showed that a dose of 800IU/day was sufficient to achieve a serum 25(OH)D ≥ 50 nmol/l within one year in 80% of patients, regardless of baseline serum 25(OH)D level. The costs of vitamin D supplementation are limited, our data therefore suggest to start supplementation with 800IU of vitamin D per day in all patients with a recent fracture, and only to assess serum 25(OH)D levels in patients in whom severe vitamin D deficiency is suspected.

An important reason for vitamin D supplementation is to provide sufficient calcium absorption. The finding of a suboptimal daily calcium intake in more than 90% of patients indicates that all patients with a recent fracture should also be advised on optimal calcium intake preferably by diet or if needed by calcium supplements.

We advocate the implementation of a standardised approach at the FLS, with an individualised advise on calcium intake and standard supplementation of 800IU vitamin D per day, without serum 25(OH)D measurement.

Diagnosing vertebral fractures at the FLS

Vertebral fractures are the most frequent prevalent and incident fractures, but most vertebral fractures do not present with the acute signs and symptoms of a recent fracture, and therefore are often overlooked. Although most vertebral fractures are

asymptomatic, patients may complain of chronic back pain or have hyperkyphosis or loss of height.

When systematically implementing vertebral fracture assessment using dual X-ray absorptiometry (DXA) in all FLS patients, we found that one in four of patients with a recent non-vertebral fracture also had a prevalent vertebral fracture. This indicates that their non-vertebral fracture was not the first fracture. Patients with a prevalent vertebral fracture in addition to a recent non-vertebral fracture have an even higher imminent fracture risk. Therefore, applying vertebral fracture assessment helped to identify those patients with the highest fracture risk, even at short term.

The diagnosis of prevalent vertebral fractures also has impact on therapeutic decisions. It increases the number of patients eligible for starting treatment and, therefore, adds to the reduction of subsequent fracture risk in FLS patients. It may also be relevant for switching anti-osteoporosis treatment or for the therapy of first choice. As an example, it has been shown that bone-forming agents are superior in fracture prevention as compared to anti-resorptive treatment in patients with vertebral fractures in addition to low BMD.

From a societal perspective, these findings have widespread consequences. The FLS has been documented to be the most effective organisational approach for secondary fracture prevention immediately following a fracture. Considering a yearly incidence of 120.000 fractures in the Netherlands, per hospital a mean of 1.200 patients with a recent fracture present at the emergency department. However, only half of them subsequently attend the FLS. Our findings are restricted to those patients, and cannot be generalised to all patients with a recent fracture. The reasons for this evaluation gap are still unclear. In how far non-attending patients are more or less healthy than those visiting the FLS is unknown.

From a patient perspective, our results support the value of an FLS as an effective way to evaluate the phenotype of the patient, to have better insights in their fracture risk, and to make appropriate decisions on treatment options to decrease the subsequent fracture risk and mortality at short term.

Planning

In the Netherlands, many FLSes are already running, with variation in organisation and diagnostic work-up.

Future planning and realisation about the organisation of the FLS should include improvement of the participation gap, as only 40-60% of patients with a recent fracture are attending the FLS; the evaluation gap; and adherence to treatment.

In this context, further questions in future planning and realisation include: Who does what in the follow-up of patients at short and long term? What is the role of fall prevention immediately after a recent fracture, in preventing the high imminent fracture risk?

Lastly future planning and realisation should also include cost-effectiveness studies with real world data. To answer such questions, more attention will be needed to evaluate the impact of FLS-care on quality of life, subsequent morbidity, falls, fracture risk and mortality.

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Curriculum vitae

Sandrine Bours is geboren op 5 mei 1980, en opgegroeid in Beek. Na het behalen van haar gymasiumdiploma op de Sint Michielsschool te Geleen, ging zij in 1998 geneeskunde studeren aan de Katholieke Universiteit Leuven. Ze behaalde haar artsendiploma in 2005 cum laude.

In 2005 begon ze aan de opleiding interne geneeskunde, in het VieCuri MC (opleider: dr. T. Luik) en vanaf 2009 in het MUMC+ (opleider: prof. dr. C. Stehouwer). Ze besteedde de laatste 2 jaar aan de subspecialisatie endocrinologie (opleider: prof. dr. N. Schaper) en rondde in 2011 de opleiding tot internist-endocrinoloog af. Na het afronden van de opleiding interne geneeskunde, begon ze aan de opleiding tot reumatoloog, eerst in MUMC+ (opleider: dr. D. Vosse) en vanaf 2013 in Zuyderland Heerlen (opleider dr. R. Peeters). In oktober 2014 voltooide zij deze tweede specialisatie.

Tijdens de opleiding tot internist begon zij aan haar promotie-onderzoek, onder begeleiding van prof. dr. P. Geusens, prof. dr. J. van den Bergh en dr. T. van Geel. De resultaten zoals beschreven in dit proefschrift werden gepresenteerd op verschillende nationale en internationale congressen, en zij ontving een ASBMR travel grant, een ASBMR young investigator award en een ECTS new investigator award.

Sinds november 2014 is ze werkzaam als staflid Reumatologie in MUMC+, waarbij ze de reumatologie en interne geneeskunde combineert.