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Contributors to Secondary Osteoporosis and Metabolic Bone Diseases in Patients Presenting with a Clinical Fracture

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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 nonvertebral 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 T_4, 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-hydroxyvitamin D less than 50 nmol/liter (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. **(*J Clin Endocrinol Metab* 96: 1360–1367, 2011)**

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 os-

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Abbreviations: BMD, Bone mineral density; CI, confidence interval; CKD, chronic kidney disease; DXA, dual x-ray absorptiometry; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; fT4, free tetraiodothyronine; iPTH, intact plasma PTH; MGUS, monoclonal gammopathy of unknown significance; 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio; SECOB, secondary osteoporosis and metabolic bone disease.

teoporosis 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 nonvertebral 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 nonvertebral 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 multitrauma, 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 antiosteoporosis 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 antiresorptive 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, anemia) (19).

Statistics

SPSS software (version 16.0; SPSS Inc., Chicago, IL) was used for the statistical analyses. Descriptive statistics, χ^2, and ANOVA were used for comparing the responders with the nonresponders 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 nonvertebral 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.

The distribution of the different types of fractures in the patients who responded and were eligible for this study and nonresponders are as following: the nonresponders 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%; $P = 0.034$).

TABLE 1. Characteristics of patients presenting with a clinical vertebral or nonvertebral 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/d)	763 ± 301	860 ± 290
25(OH)D (nmol/liter)	50.7 ± 26.2	40.1 ± 22.8

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). 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.

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

TABLE 2. Prevalence of known contributors to SECOB at presentation with a clinical fracture

Known contributor	Number of patients (percent of total)	Number of Women (percent of all women)	Number of Men (percent 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 erythematosis	32 (5.2%)	25 (5.2%)	2 (1.4%)
History of COPD	65 (10.4%)	49 (10.2%)	16 (11.1%)
History of CKD	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)[a]	144 (23.0%)	115 (23.9%)	29 (20.1%)

COPD, Chronic obstructive pulmonary disease; –, not applicable.

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

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 3. Newly diagnosed contributors to SECOB in men and women with a clinical fracture

	Prevalence of newly diagnosed contributors to SECOB					
	Men (n = 144)		Women (n = 482)		Total (n = 626)	
Disorders	n	%	n	%	n	%
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)						
1°[a]	1	0.7	16	3.3	17	2.7
2° due to vitamin D deficiency	11	7.6	38	7.9	49	7.8
2° due to CKD	2	1.4	4	0.8	6	1.0
2° due to vitamin D deficiency and CKD	0	0	9	0.8	9	1.4
Hyperthyroidism[b]	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[c]	40	27.8	126	26.1	166	26.5

[a] Of the 17 patients with primary hyperparathyroidism (2.7%), 12 (1.9%) had elevated, and five (0.8%) inappropriately normal iPTH levels.

[b] Of the 39 patients with hyperthyroidism (6.2%), 30 (4.8%) were diagnosed with overt and nine (1.4%) with subclinical hyperthyroidism.

[c] Because there were 31 subjects (six 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 (1° = primary HPT, 2° = secondary HPT).

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 labeled as having SECOB, the number of patients with a newly diagnosed contributor to SECOB would have been 440 (70.3%). With a cutoff 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%.

TABLE 4. Prevalence of newly diagnosed contributors to 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.

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.

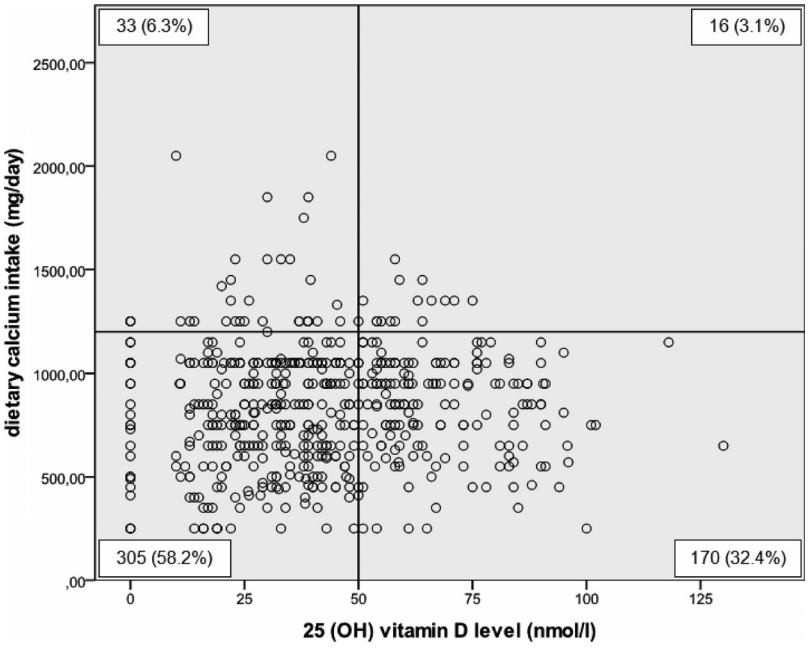

FIG. 1. Serum 25(OH)D levels (x-axis) and the daily calcium intake (y-axis) in 524 patients older than 50 yr at the time they present with a clinical vertebral or nonvertebral fracture. Number and percentages of the patients are given for the four quadrants.

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 age 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 nonvertebral 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 labeled to have one or more contributors to SECOB.

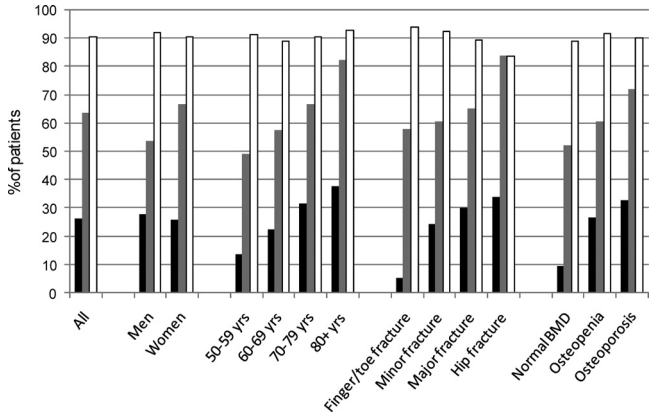

FIG. 2. Percentages of patients with newly diagnosed contributors to secondary osteoporosis and metabolic bone disease (*black columns*), serum 25(OH)D level less than 50 nmol/liter (*gray columns*), and dietary calcium intake less than 1200 mg/d (*white columns*) according to sex, age, fracture location, and 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.

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 age 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 progres-

sion 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 m^2 (stage 4 CKD) were not eligible to receive bisphosphonate therapy (<35 ml/min per 1.73 m^2 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 m^2) (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 m^2, 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 m^2 (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 nonvertebral 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 age 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 antiosteoporosis medication in patients with a recent fracture.

Acknowledgments

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