The Value of Laboratory Tests in Diagnosing Secondary Osteoporosis at a Fracture and Osteoporosis Outpatient Clinic

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Abstract

Background: As more and more patients meeting the criteria for osteoporosis are referred to a fracture and osteoporosis outpatient clinic (FO clinic), the laboratory costs to screen for secondary osteoporosis also increases. This study was conducted to determine the value of screening on underlying diseases at an FO clinic by obtaining a standard set of laboratory tests. **Methods:** We included all 541 patients ≥50 years with a fracture referred to our FO clinic, during the period January 2005 to January 2007. The bone mineral density (BMD) was measured by dual energy x-ray absorptiometry and expressed as a T score. A standard set of laboratory tests was obtained to screen on underlying diseases. **Results:** Laboratory results were as often abnormal in patients with a normal BMD compared to patients with a low BMD. Underlying diseases were infrequently diagnosed. However, the prevalence of secondary osteoporosis in men was quite high, up to 18.2%. The costs to diagnose 1 patient with an underlying disease did vary between €92 and €972 depending on the group of patients described. **Conclusion:** Screening all patients, referred to an FO clinic, for underlying diseases by obtaining a standard set of laboratory tests is probably not useful since laboratory tests are as often abnormal in patients with a normal BMD compared to patients with a low BMD. Moreover, the prevalence of secondary osteoporosis is low, while laboratory costs are substantial.

Keywords

dual energy x-ray absorptiometry, fracture and osteoporosis outpatient clinic, osteoporosis, secondary osteoporosis, trauma surgery

Introduction

Osteoporosis is a common health problem resulting in an increased risk of a fragility fracture.[1] The lifetime risk of an osteoporotic fracture at the age of 50 is up to 53.2% in women and 22.4% in men.[2] The relative risk of an osteoporotic fracture can be reduced up to 50% when osteoporosis is treated.[3] Therefore, case finding osteoporosis in patients at *high risk* of osteoporosis is useful as secondary prevention.[4-6] The Dutch Institute for Health Care Improvement (CBO) stated in its most recent guideline on osteoporosis that patients aged 50 years and older who are admitted to the hospital with a fracture do have an increased risk to have osteoporosis.[7] Case finding osteoporosis is indicated in this group of patients.[7] Case finding osteoporosis can thus be seen as part of the fracture management in the elderly patients, and (orthopedic) surgeons play an important role in initiating this case finding.

The most effective way in case finding osteoporosis is through a fracture and osteoporosis outpatient clinic (FO clinic). At an FO clinic, bone mineral density (BMD) should be measured, risk factors for a fracture should be identified, and laboratory tests to screen for secondary osteoporosis should be obtained.[7,8] It has been suggested to use specialized trained nurses at an FO clinic to coordinate the input of (orthopedic) surgeons and internists.[7] There is no conclusive evidence about which laboratory tests should be used at an FO clinic to screen on secondary osteoporosis.[7,9] Secondary osteoporosis is more often seen in men.[10] Previous studies described a wide range (10%-80%) in the prevalence of secondary osteoporosis in

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patients who met the criteria for case finding osteoporosis and were referred to an FO clinic.[6,9-11]

As more and more patients meeting the criteria for case finding osteoporosis are referred to an FO clinic, the laboratory costs to screen on underlying diseases also increases. This can be justified when the prevalence of underlying diseases is high, and these diseases can be diagnosed because of abnormal laboratory tests. The aim of this study was to establish the value of laboratory testing in identifying underlying diseases in patients with a low BMD. We considered laboratory testing useful when the prevalence of underlying diseases was at least 15%, although this percentage is arbitrary.

Materials and Methods

Study Design

This is a retrospective data collection study conducted in a non-academic teaching hospital.

Patient Selection

All 541 patients ≥50 years admitted to our hospital, with a fracture and referred to the FO clinic from January 2005 to January 2007, were considered eligible for further evaluation. Of these 541 patients, 42 (8%) patients were excluded from further analysis because they refused BMD measurement. Thus, the final study population comprised 499 patients, 108 men and 391 women. The general patient characteristics of our study population are described in Table 1. The standard protocol at our FO clinic is to measure BMD and obtain laboratory tests in every patient admitted to the FO clinic. This allows us to complete the diagnostic workup in all patients admitted to the FO clinic within 4 hours, which is in our opinion patient friendly. However, this approach will also result in the fact that laboratory tests are sometimes obtained in patients who appear to have a normal BMD.

Measurement of BMD

Bone mineral density measurement was performed by dual energy x-ray absorptiometry (DXA; Delft Instruments, Lunar, Delft, the Netherlands and Hologic Discovery A, Hologic, Bedford, Massachusetts). The BMD was measured at the left hip and lumbar spine and expressed as a T score which is the standard deviation (SD) in bone mass compared to the peak bone mass of young adults.[12] As osteoporosis is a systemic disease, the lowest of these 2 T scores was used for further analysis.

Definition of Osteoporosis and Secondary Osteoporosis

The definition of osteoporosis as proposed by the World Health Organization was used.[13] Osteoporosis was therefore defined as a T score ≤ −2.5SD, osteopenia as a T score ≤ −1 and >−2.5SD, and a normal BMD as a T score > −1SD.

Secondary osteoporosis was defined as osteoporosis not caused by menopause or aging. Which laboratory tests should

Table 1. General Patient Characteristics of the 499 Patients ≥50 Years of Age Meeting the Criteria for Case Finding Osteoporosis and Referred to the Fracture and Osteoporosis Outpatient Clinic.[a]

Men:women	108:391
Age, years	66 (50-90)
Length, cm	180 (145-194)
Weight, kg	76 (45-128)
Body mass index, kg/m^2	26.9 (16.7-46.5)

[a] Results expressed as mean (range).

Table 2. Secondary Causes of Osteoporosis and Laboratory Tests Carried Out at the Fracture Prevention Clinic to Screen for This (Number of Patients in Which Test Was Obtained).

Diabetes mellitus type 1
Glucose (490)
Thyreotoxicosis
Thyroid-stimulating hormone (485), free T4 (471)
Hyperparathyroidism
Phosphorus (479), calcium (485)
Inflammatory bowel disease
Calcium, hemoglobin (494)
Chronic renal disease
Creatinine (246)
Bone marrow and malignant disorders
Hemoglobin, hematocrit (486), mean corpuscular volume (430)
Liver diseases
γ glutamyl transferase (487), alkaline phosphatase (486)

be obtained in screening for secondary osteoporosis remains controversial, but some recommendations have been made.[9,10,14,15] Table 2 shows the laboratory tests used at our FO clinic and the underlying diseases that were screened for with these laboratory tests.[9,14,16-19] Vitamin D was not routinely measured at our FO clinic, because it is supplemented to all patients with a low BMD as previous studies showed that most of these patients have vitamin D insufficiency or deficiency.[6,10] Patients with a low BMD and laboratory results outside the reference range were discussed with an internist. If an underlying disease was suspected, the patients were further screened on this. Patients were not further screened when the abnormal laboratory results could be explained by the medical history of the patient or an underlying disease was not suspected by the internist, because the laboratory results were only slightly outside the reference range.

It appeared that the reason why the internist did not suspect an underlying disease was not properly documented in all patients with abnormal laboratory results. These patients were therefore classified as unjustly not referred to the internist to be screened on underlying diseases. Therefore, the prevalence of underlying diseases is expressed as a range in this study. In calculating the lowest value of this range, the numerator contained only patients in which an underlying disease was diagnosed after further screening on this because of abnormal laboratory tests, while the highest value in this range contained all patients in the numerator in which an underlying disease was diagnosed

Table 3. Underlying Diseases Diagnosed Because of Abnormal Laboratory Results.

Bone Mineral Density	Underlying disease	Underlying Disease Can Cause Low BMD	Male	Female	Total	Abnormal Laboratory Result
Osteopenia	↓Vitamin D	Yes		1	1	AP 202
	↓Vitamin D + hypophosphatemia	Yes	1		1	Phosphate 0.68
	Alcohol abuse	Yes	1	1	2	Pat 1: AP 293, GGT 278
						Pat 2: GGT 140
	Hypothyroidism	No		1	1	TSH 4.61
	Hypothyroidism + renal impairment	Yes		1	1	TSH 16 + creatinine 138
	↓Vitamin B12	No		1	1	AP 157, GGT 50
	Hyperthyroidism	Yes		2	2	Pat 1: TSH 0.01
						Pat 2: TSH 0.01, fT4 36
	Type 2 diabetes mellitus	No		1	1	Glucose 16.5
	Medication induced ↑GGT and AP, no liver cirrhosis	No		1	1	AP 212, GGT 318
	Liver cirrhosis by autoimmune hepatitis	Yes		1	1	AP 206, GGT 183
Osteoporosis	Benign paraproteinemia	Yes	1		1	Phosphate 0.81
	Hyperparathyroidism	Yes	1		1	MCV 104
	Immobility	Yes	1		1	Calcium 2.17
	Hyperthyroidism	Yes		1	1	TSH 0.1
	Anemia due to iron deficiency	No		1	1	Hb 5.6, Ht 0.28, MCV 77

Abbreviations: AP, alkaline phosphatase; GGT, γ glutamyl transferase; TSH, thyroid-stimulating hormone; fT4, free thyroid hormone; MCV, mean corpuscular volume; Hb, hemoglobin; Ht, Hematocrit; BMD, bone mineral density; pat, patient.

plus patients who were unjustly not further screened on this. The true prevalence of the underlying diseases will therefore be in between both the values.

Calculation of Laboratory Costs

A true cost-effectiveness analysis is behind the scope of this article and not possible with the presented data because of the retrospective design of this study, but some remarks about the costs could be made. The cost for the set of laboratory tests used at our FO clinic is €25 per patient. The total laboratory costs were calculated for the group of patients with a low BMD (osteopenia and osteoporosis), the group of patients with osteoporosis, and the group of male patients with osteoporosis. This latter group is used because secondary osteoporosis is more often diagnosed in male patients with osteoporosis. In order to compare the laboratory costs in the different group of patients, we also calculated the costs that had to be made to diagnose 1 patient with an underlying disease.

Statistical Analysis

Statistical analysis was performed by using SPSS software program (version 15.1 for Windows XP; SPSS, Chicago, Illinois). Descriptive evaluation was carried out using number and percentages for categorical values and mean and range for normally distributed values.

Results

Of the 499 patients meeting the criteria for case finding osteoporosis and referred to the FO clinic, 149 (30%) patients had a normal BMD, 246 (49%) patients had a BMD in the osteopenic range, and 104 (21%) patients had osteoporosis. Abnormal laboratory results were observed in 238 (48%) of the 499 patients and as often found in patients with a normal BMD compared to patients with osteopenia or patients with osteoporosis, 44%, 50%, and 46% respectively.

Abnormal laboratory tests were found in 172 of the 350 patients with a low BMD. A total of 104 of the 172 patients were not further screened on underlying diseases, as the laboratory tests were only slightly out of the reference range or could be explained by the patient's medical history. Of the remaining 68 patients, 37 were screened on an underlying disease. In 31 patients, the reason why the internist did not suspect an underlying disease was not properly recorded in the patient's medical file, and these patients were classified as unjustly and not further screened on an underlying disease. An underlying disease was diagnosed in 17 of the 37 patients who were further screened on this. Of these diseases, 3 could have been diagnosed by a thorough anamnesis (alcohol abuse [2×] and immobility [1×]) and 5 diseases could not be related to an increased risk of low BMD (hypothyroidism [1×], low vitamin B12 without malabsorption [1×], type 2 diabetes [1×], medication induced ↑γ glutamyl transferase and alkaline phosphatase without liver cirrhosis [1×], and anemia due to peptic ulcer disease [1×])[4,9,15]. Therefore, obtaining laboratory tests in all patients at the FO clinic resulted in the diagnosis of 9 underlying diseases that could be related to a low BMD (Table 3). The prevalence of underlying diseases is therefore 2.6%. However, if all 31 patients who were unjustly not referred to the internist would have been diagnosed with an underlying disease, this prevalence will increase till 11.4% (Table 4). It appeared that the prevalence was highest

Table 4. Number of Patients in Which the Low BMD Could Have Been Caused by an Underlying Disease and the Laboratory Costs to Identify 1 Patient With an Underlying Disease.[a]

	Osteopenia		Osteoporosis	
Total number of patients	246		104	
	♂: 53, ♀: 193		♂: 22, ♀: 82	
Group A	6	♂: 1 (1.9)	3	♂: 2 (9.1)
		♀: 5 (2.6)		♀: 1 (1.2)
Group B	32	♂: 5 (9.4)	8	♂: 4 (18.2)
		♀: 27 (14.0)		♀: 4 (4.9)
Laboratory costs group A	8750/9 = 972[b]		2600/3 = 867[c]	
Laboratory costs group B	8750/40 = 219[b]		2600/8 = 325[c]	

Abbreviation: BMD, bone mineral density.

[a] Number of patients (percentage). Costs expressed in Euro's. Group A: patients in which an underlying disease was diagnosed because of abnormal laboratory results. Group B: patients from group A plus unjustly not referred patients.

[b] Costs to diagnose 1 patient with an underlying diseases when laboratory tests were obtained in all patients with a low BMD.

[c] Costs to diagnose 1 patient with an underlying diseases when laboratory tests were obtained only in patients with osteoporosis.

in male patients with osteoporosis (9.1%-18.2%; Table 4). In all other patient categories, the prevalence was under 15% (Table 4).

The total laboratory costs would have been €8750, when these tests were obtained in all patients with a low BMD, €2600 when obtained in patients with osteoporosis, and €550 when obtained in male patients with osteoporosis. This means a 16-fold increase in laboratory costs depending on which group is tested. The laboratory costs made to identify 1 patient with an underlying disease were comparable between the group of patients with a low BMD and patients with osteoporosis, but these costs would have been lower when only male patients with osteoporosis were tested, respectively, €219 till €972 (all patients with a low BMD) compared to €325 till €867 (patients with osteoporosis) and €92 till €225 (male patients with osteoporosis).

Discussion

The value of laboratory testing in patients meeting the criteria for case finding osteoporosis is questionable, and perhaps laboratory tests should no longer be obtained in *every* patient referred to an FO clinic.

In the first place, and most important, this is because abnormal laboratory tests were as often diagnosed in patients with a normal BMD compared to patients with osteopenia or osteoporosis. This is also confirmed by a previous study.[20] Moreover, neither this study nor previous studies showed a positive correlation between laboratory tests and secondary osteoporosis, with the exception of low thyroid-stimulating hormone (TSH).[20,21] Furthermore, the prevalence of underlying diseases in patients referred to an FO clinic is relatively low.[6,11] The prevalence of secondary osteoporosis *in men* appeared to be higher, which is in accordance with a previous study.[10] The reason that secondary osteoporosis is more often found in men is that secondary osteoporosis is defined as bone loss above that which would be expected for age and natural menopause.[10] As we considered laboratory testing useful when the prevalence of underlying

diseases was at least 15%, laboratory testing might be useful in male patients with osteoporosis but not in other patients.

Another reason why laboratory tests should perhaps be obtained in only a specific group of patients is the laboratory costs. This study described 499 elderly patients with a fracture meeting the criteria for case finding osteoporosis. From the data of this study, it was calculated that the laboratory costs for identifying 1 patient with an underlying disease were as high as €972. These laboratory costs can decrease to less than €225 when only male patients with osteoporosis are tested. In this study, we screened 499 patients which is only 0.625% of all patients with an osteoporotic fracture in the Netherlands per year.[4] Thus, extrapolating our data to all osteoporotic fractures in the Netherlands per year, the laboratory costs will increase 160-fold. As costs are an important issue in general health care, it might be true that only male patients with osteoporosis should be tested on secondary osteoporosis, although a prospective randomized controlled study is necessary to proof this approach to be cost effective.

There are limitations of this study. Although most causes of secondary osteoporosis are covered by the set of laboratory tests used at our FO clinic, the test for albumin is missing. Theoretically, the incidence of malabsorption and chronic diseases might therefore be underreported, but calcium can be used as a rough measurement of malabsorption and hemoglobin for chronic diseases. For this reason, we think the results of this study will not be influenced significantly by not measuring albumin. As with most laboratory tests, the literature remains inconclusive whether or not albumin should be measured.[4,9,10,14] In one study, serum protein electrophoresis (SPEP) is even advocated instead of albumin measurement, but costs for SPEP are substantial, €20.73 compared to €1.76 for albumin.[9] For this reason, the value of SPEP is in our opinion questionable. Another limitation of this *retrospective* study is that some patients were unjustly not referred for further screening on underlying diseases, which undoubtly influenced the prevalence of secondary osteoporosis. By presenting the prevalence of underlying diseases as a range, we think we overcame this problem.

Acknowledgments

Declaration of Conflicting Interests

Funding

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