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Utility of testing for monoclonal bands in serum of patients with suspected osteoporosis: retrospective, cross sectional study

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Abstract

Objective To determine whether measuring monoclonal bands (M component) in serum should be part of the investigation of patients referred to osteoporosis clinics.

Design Retrospective, cross sectional, observational study.

Setting Referral centre for osteoporosis in a university hospital, Denmark.

Participants 799 people (685 women) aged 19 to 94 years newly referred with suspected osteoporosis.

Main outcome measures Proportion of patients fulfilling the Nordic Myeloma Study Group definition for target condition and proportion of patients with other important haematological conditions.

Results 4.9% (18 of 366) of patients with osteoporosis and 2.2% (9 of 408) of patients without osteoporosis had M components in serum ($\chi^2 = 3.66$, $P = 0.04$). Multiple myeloma was diagnosed in three patients with osteoporosis (absolute risk 0.8%, 95% confidence interval 0.11% to 1.7%). The relative risk of multiple myeloma in patients presenting with osteoporosis was 75 (10 to 160). As a diagnostic test for multiple myeloma in patients with osteoporosis, M component in serum had a specificity of 95.0% and a positive predictive value of 17.6%. 122 blood electrophoreses were carried out for each case of multiple myeloma diagnosed. All patients with multiple myeloma had a history of fragility fractures. If lymphoma was included as a target condition, the specificity increased to 95.3% and the positive predictive value increased to 23.5%. Monoclonal gammopathy of undetermined significance was diagnosed in 13

(3.6%) participants with osteoporosis and in eight (2.0%) participants with normal bone mineral density or osteopenia.

Conclusions Patients presenting with osteoporosis should be tested for M component in serum, as 1 in 20 patients with newly diagnosed osteoporosis had multiple myeloma or monoclonal gammopathy of undetermined significance.

Introduction

Compared with osteoporosis, multiple myeloma is a rare disease, yet vertebral fractures and pain are common to both. Multiple myeloma would be expected to be seen more often in osteoporosis clinics than in most other areas of medicine dealing with the care of elderly people. Moreover, monoclonal gammopathy of undetermined significance is a common disorder, with a similar age distribution to that of osteoporosis.

National guidelines in Denmark do not advocate the routine measurement of monoclonal bands (M component) in the serum or urine of patients presenting with osteoporosis. We determined the prevalence of multiple myeloma and monoclonal gammopathy of undetermined significance in unselected patients newly referred with osteoporosis to assess whether measurement of M component should form part of the investigation of patients with suspected osteoporosis.

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Participants and methods

From March 1999 to March 2001, 1372 patients were referred to our clinic with suspected osteoporosis or osteopenia. We retrospectively evaluated all first referrals from primary care (n=799) consecutively by a diagnostic schedule, which included measurement of serum M component and dual energy x ray absorptiometry. The study population consisted of 114 men and 685 women.

Serum M component was measured using cellulose acetate electrophoresis. Urine tests were not carried out. Participants with M component underwent follow-up investigations. Multiple myeloma was diagnosed according to the Nordic Myeloma Study Group definition.¹ People were considered to have monoclonal gammopathy of undetermined significance if malignant monoclonal gammopathies were excluded.

We calculated confidence intervals using the normal approximation to the binary distribution, and we compared proportions using χ^2 tests.

Results

Osteoporosis was diagnosed in 45% (n=308) of the women and 55% (n=63) of the men. Serum M component was evaluated in 366 participants with osteoporosis detected by densitometry and 408 participants with normal bone mineral density or osteopenia. Overall, 30 participants (3.8%) had a positive index test result. However, three patients had known haematological disorders. M component was present in 4.9% (n=18) of patients with osteoporosis and 2.2% (n=9) of patients without osteoporosis ($\chi^2=3.66$, P=0.04; table). Although erythrocyte sedimentation rate was not routinely assessed, six of eight patients with M component had an erythrocyte sedimentation rate of 20 or lower.

Multiple myeloma was diagnosed in three patients with osteoporosis (absolute risk 0.8%, 95% confidence interval 0.11% to 1.7%; see bmj.com) but in no participants without osteoporosis.

We diagnosed monoclonal gammopathy of undetermined significance in 13 (3.6%; see bmj.com) of the participants with osteoporosis and eight (2.0%) of the participants with normal bone mineral density or osteopenia. In patients with osteoporosis, we found no difference in bone mineral density or age between those with multiple myeloma or monoclonal gammopathy of undetermined significance and those with no M component. The three patients with multiple myeloma had a history of fragility fractures, compared with 28% (95% confidence interval 5% to 70%) in patients with osteoporosis with coexisting monoclonal gammopathy of undetermined significance and 36% (30% to 43%) in patients with osteoporosis but no M component.

Compared with the background population, the relative risk of multiple myeloma in patients presenting with osteoporosis was 75 (95% confidence interval 10 to 160). As a diagnostic test for multiple myeloma in patients with osteoporosis, M component in serum had a specificity of 95.0% and a positive predictive value of 17.6%. In practical terms, 122 blood electrophoreses were carried out for each case

Prevalence of serum monoclonal bands (M component) in patients by age and bone mineral density status

Age	No of patients	Prevalence of serum M component		
		No (%) of patients (n=799)	No (%) with normal bone mineral density or osteopenia (n=408)	No (%) with osteoporosis (n=366)
<70	594	16 (2.7)	7 (2.0)	9 (3.9)
70-79	169	8 (4.7)	1 (2.1)	7 (6.2)
≥80	36	3 (8.3)	1 (11.1)	2 (8.3)
Total	799	27 (3.4)	9 (2.2)*	18† (4.9)‡

*95% confidence interval 0.8% to 3.6%.

†95% confidence interval 2.7% to 7.1%.

‡P<0.05 (χ^2 test) compared with patients with normal bone mineral density.

of multiple myeloma diagnosed. If lymphoma was included as a target condition, the specificity increased to 95.3% and the positive predictive value increased to 23.5%.

Discussion

Multiple myeloma and monoclonal gammopathy of undetermined significance are more common in patients referred to an osteoporosis clinic than expected in the background population. Patients newly diagnosed with osteoporosis at our clinic have an absolute risk of 0.8% for underlying multiple myeloma and a 3.6% risk of coexistent monoclonal gammopathy of undetermined significance. Most of these patients have a normal haemoglobin concentration and many have normal erythrocyte sedimentation rates and would be missed by the currently recommended blood tests for osteoporosis. We have introduced routine measurement of M component in serum in patients presenting to our clinic.

Our conservative estimates suggest that an osteoporosis clinic caring for 5000 new patients a year may fail to identify 20 cases of multiple myeloma yearly, even with a young patient base. In addition, 75 to 185 cases of monoclonal gammopathy of undetermined significance may be missed. Despite this, few guidelines and recommendations include routine screening for multiple myeloma or monoclonal gammopathy of undetermined significance in patients with osteoporosis, beyond measuring the erythrocyte sedimentation rate. In accordance with the low frequency in the general population,² we did not observe any cases of multiple myeloma among the 408 people with normal bone mineral density or osteopenia.

Monoclonal gammopathy of undetermined significance and even multiple myeloma do not require specific treatment in all elderly patients. When multiple myeloma occurs in younger patients, aggressive treatment prolongs survival.³ Regardless of age, patients with multiple myeloma benefit from early diagnosis. Some elderly patients with multiple myeloma have major comorbidity, which reduces their ability to tolerate some forms of chemotherapy,⁴⁻⁶ but specialist attention is warranted even in this group.⁷ Similarly, although the general prognosis of monoclonal gammopathy of undetermined significance is good, affected patients must also be followed because of the possibility of malignant transformation and complications.⁸ Although an M component was more

What is already known on this topic

Multiple myeloma is an important differential diagnosis in patients with suspected osteoporosis as it affects patients of the same age and often causes bone fragility

Monoclonal gammopathy of undetermined significance is a benign disorder, but patients should be monitored for progression to malignancy

What this study adds

One in 20 patients presenting with osteoporosis have an M component in serum

Multiple myeloma is 75 times more common in patients with osteoporosis

Measurement of M component in serum may be particularly important in patients with fragility fractures

common in patients with osteoporosis compared with people with normal bone mineral density or osteopenia, stratifying for bone mineral density within the group with osteoporosis did not provide additional information. The three patients with multiple myeloma, however, all had evidence of established osteoporosis, suggesting that measurement of M component may be informative in this group.

Referral patterns vary between osteoporosis clinics, depending on guidelines and the availability of bone densitometry. In our clinic, 46% of referred patients fulfilled the World Health Organization definition of osteoporosis. This agrees closely with the 41% to 53%^{9 10} reported by clinics in the United Kingdom and United States.¹¹ The most important limitation of our study was that we could not calculate the false negative rate. To do this we would have had to rule out non-secretory myeloma and light chain disease by carrying out skeletal x rays and marrow biopsies in all patients with osteoporosis referred to our clinic. It is possible, however, to estimate the number of false negative tests by extrapolating from Mayo clinic data on the distribution of multiple myeloma subtypes at diagnosis.

The number of patients with multiple myeloma in our study is a conservative estimate, because we did not assess urine Bence-Jones protein. Light chain disease, however, is less common and the expense would be greater. Thus, about 600 urine analyses would be needed to diagnose a single case of light chain multiple myeloma in patients with osteoporosis if 20%¹² of cases of secretory multiple myeloma are of the light chain variant.

We know from other studies that normal bone mineral density does not rule out multiple myeloma,^{13 14} but owing to the low prevalence of the disease in referred patients without osteoporosis, we cannot make a strong case for vigilance for M component in the absence of osteoporosis.

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Corrections and clarifications

Short cuts: What's new in the other general journals

We lost a decade somehow when, in the 12 March issue, we cited the reference to the last item ("Review supports more optimistic view of phase I trials in adults with cancer") in this section (*BMJ* 2005;330:561-2). The article about risks and benefits of phase 1 oncology trials was of course published this year, not in 1995. The correct reference is therefore *New England Journal of Medicine* 2005;352:895-904.

Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial

In the paper by Maja Stulemeijer and colleagues the drop-out rate from treatment in the group allocated to immediate cognitive behaviour therapy was given as 19% (*BMJ* 2005;330:14-7, 1 Jan). This should have been 17% (6/35). Also, in the footnote to table 4 (full version only) the cut-off score on the fatigue was given as ≥ 35.7 . As the paper indicates that patients were considered to be improved if the score was < 35.7 , reflecting less fatigue, the cut off in the footnote would be better presented as < 35.7 to match the presentation in the text.