Chapter 8

General discussion

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The studies described in this thesis touch on the diagnosis of osteoporosis in subjects at risk and the clinical implications. The most important findings of the studies performed are:

1. A substantial number of patients with an inflammatory condition as sarcoidosis and inflammatory bowel disease had vertebral deformities suggestive of fracture;
2. Measurement of bone mineral density (BMD) appeared not of value to discriminate between patients with and without vertebral deformities;
3. Bone turnover appeared increased in patients with an inflammatory disease.

These findings indicate that patients with an inflammatory condition have an increased fracture risk due to increased bone remodelling and consequently a decreased bone strength independently of bone mass and BMD.

In contrast, we found no increase of vertebral deformities in patients with differentiated thyroid carcinoma during treatment with a suppressive dose of levothyroxin. In these patients, BMD was also not different from sex- and age-matched controls. These findings are in line with the publication of Reverter and co-workers who also found that the proportion of women with DTC with normal BMD, osteopenia, and osteoporosis is similar to that in healthy control women matched for body mass index and menopausal status.[1] These observations imply that the effects of levothyroxine on bone metabolism and bone strength are minimal and not comparable to the effects of inflammation on bone.

The questions that arise from these studies are how to define osteoporosis and how to involve vertebral fracture assessment (VFA) and bone turnover markers in this definition. In addition, to what extent other imaging techniques may contribute to a redefinition of osteoporosis and better recognition of patients at risk for fracture.

In 1994, an expert panel convened by the World Health Organization (WHO) formulated an operational definition for osteoporosis for postmenopausal women on the basis of BMD with dual energy X-ray absorptiometry (DXA).[2] However, as the majority of fractures occur in persons without osteoporosis,[3,4] it is clear that bone density is not the only determinant for fracture. It is nowadays well recognized that relying on BMD alone as a predictor of fracture risk is of limited value, and that, in addition to fall and bone related risk factors, there is need to include other aspects of bone strength in the definition of osteoporosis as well. In support of this view, a later consensus conference has defined osteoporosis as 'a skeletal disorder characterized by compromised bone strength leading to an increased risk of fracture'.[5] Although BMD determined with DXA is strongly related to bone strength, it is only reflecting

part of its components.[6] There is therefore a need for other imaging tools or markers to determine bone quality and hence to identify patients who are at risk for fragility fractures in a better way than can be done on the basis of DXA alone.

One of the additional tools to recognize decreased bone strength appears to be VFA, as is illustrated by the studies summarized in this thesis. We found a high prevalence of vertebral deformities suggestive of fracture in the patients with inflammatory conditions irrespective of BMD. This indicates that these diseases have an effect on bone strength rather than bone mass and hence is illustrative for the relevance of VFA in addition to DXA to identify patients with reduced bone strength.

As no data on non-clinical deformities in healthy young and premenopausal individuals are available yet, it is questionable whether the prevalence of vertebral deformities in inflammatory conditions we found is indeed high. The best comparison with healthy subjects is offered by the EVOS study, in which in a very large cross-sectional population based study, European subjects aged 50 to 79 years were investigated. The prevalence of vertebral deformities on X-rays in this study was 12% (range 6-21%) in males and females.[7] In addition, the Rotterdam study, in which 3469 men and women aged 55 years and older were studied, revealed a prevalence of vertebral deformity suggestive of fracture in 6.9% of men and 7.5% of women.[8] As the subjects described in our studies are younger and have hence a lower risk to fracture, the prevalence of vertebral deformities we found (21-25%) is probably indeed high. Furthermore, our unique prospective data in patients with sarcoidosis showed that the prevalence of vertebral deformities appeared increased from 20 to 32% after four years of follow-up, and in 26% of subjects one or more new or progressive vertebral deformities were diagnosed. This again supports the relevance of VFA to identify patients with an increased fracture risk and also the view that patients with a vertebral fracture have an increased risk for another vertebral fracture within a couple of years, irrespective of changes in BMD.[9]

Unfortunately, one of the limitations of VFA is lack of a gold standard for vertebral fracture. This is the reason that we prefer the description 'vertebral deformity suggestive of fracture' rather than vertebral fracture as a natural interpretation of a vertebral deformity. Because of the absence of a gold standard, it is still not clear which method is the most appropriate to establish vertebral deformities and on the basis of that to determine the occurrence of vertebral fractures. For the determination of vertebral deformities a variety of morphometric approaches can be used. These different approaches can result in slightly different outcomes.[10-13] Compared with subjective qualitative assessment, quantitative morphometry is a more reproducible method for assessing vertebral deformities and therefore these approaches are often used in conjunction. We followed the method of Genant,[11] which is based on a

reduction of the ratios of anterior, middle or posterior heights and all measurements were performed twice to improve accuracy. This is the simplest and most practical method[14] and an association with future fracture risk is documented.[9,10,15] The above mentioned EVOS study, however, applied the methodologies described by McCloskey and Eastell and co-workers in which measurements are corrected for normal variations in vertebral shape.[13] Vertebrae in the mid-thoracic spine and thoraco-lumbar junction are slightly more wedged than in other regions of the spine[12,16] and, as a result, with the method of Genant normal variations may be misinterpreted as mild vertebral deformities.[17,18] This may have contributed to overestimation of vertebral deformities in our series, although we feel only to a limited extent. In one of our series (IBD patients), we also used the method of Eastell and this resulted in vertebral deformities in 20% of patients (data not shown), compared to 25% found with the method of Genant. This is indeed lower, but still indicates a substantial prevalence in this young population.

We used X-ray absorptiometry (MXA) instead of standard radiographs (MRX) for morphometric determination of vertebral deformities. Several studies have documented that morphometric MXA is comparable to MRX (morphometric radiography) for this approach.[19-22] Vertebral morphometry after MXA has several advantages over conventional radiographs. The radiation dose is much lower (<80μSv) and assessment of BMD and vertebral deformities can be combined. Although MXA is thus an established technology to detect vertebral deformities and to identify patients likely to benefit from pharmacological therapy who otherwise might not be treated,[23] this technology has some limitations as well. These include limited ability to provide a differential diagnosis for the detected deformities, lower sensitivity for milder deformities and inability to evaluate the uppermost thoracic levels. However, its negative predictive value is high.[24] Other disorders that may cause changes in vertebral shape involve congenital abnormalities and conditions as severe osteoarthritis[25] and Scheuermann's disease. These conditions usually present in a characteristic way and are relatively rare. We consider this disadvantage therefore not that relevant.

One of the other alternatives to DXA to analyse bone mass and bone strength is quantitative ultrasound (QUS). QUS of the heel is shown to predict fractures comparable to DXA and independent of spine and femur BMD. As QUS is simple and easy to perform, some consider it a valuable tool to identify postmenopausal women with an increased fracture risk.[26-28] The results of QUS are, however, rather variable, in particular in other populations than postmenopausal women. In our hands, QUS measurements in patients with an inflammatory disease were not associated with prevalent vertebral deformities and therefore likely not of value to recognize patients at risk for fracture. Similar observations have been made by other investigators.[29,30]

Hence, the value of QUS in the diagnostic work up of subjects at risk for osteoporotic fractures is still questionable.

One more alternative to DXA is offered by three dimensional quantification of trabecular structure with high-resolution peripheral quantitative computed tomography (hr-pQCT) or micro-magnetic resonance imaging (µMRI). Although MRI is widely available, the measurement of bone microarchitecture requires special equipment and software. The method is still in development and therefore not applicable in daily practice yet.

With hr-pQCT significant age-related changes in density, trabecular structure, and cortical thickness can be detected.[31] In the OFELY cohort, a study on postmenopausal women, it is found that alterations of cortical and trabecular structure are associated with fragility fractures and that this association is partially independent of BMD assessed by DXA.[32] Thus, hr-pQCT measurements appear useful for gaining an insight into structural mechanisms underlying various causes of skeletal fragility. At present, however, the majority of studies with hr-QCT are done in vitro on bone biopsies, or in vivo on the distal radius.[32] The majority of hr-CT apparatus is still not adequate to study other sites in vivo, in particular the spine. As soon as these technical difficulties are overcome and apparatus become available to study the microarchitecture of vertebrae in detail, it can be expected that hr-QCT will replace DXA to study bone mass and bone strength resulting in better prediction of subjects with an increased fracture risk.

In our studies we have clearly shown that both in patients with inflammatory bowel disease and in patients with sarcoidosis, increased bone turnover is associated with an increased fracture risk, even in patients with a normal BMD, which implies an effect of bone remodelling in these conditions on bone strength rather than bone mass.[33] Long-term prospective studies have shown that markers of bone resorption in particular are beneficial in fracture prediction.[34,35] In a study in elderly women the BMD-corrected risk of hip fracture increased by 1.4 (95% CI: 1.1-1.7) for each SD increase in urinary free deoxypiridinoline (D-Pyr) and by 1.3 (1.0-1.6) for urinary type 1 C-telopeptide (CTX). Garnero et al.[36] found that a combination of high CTX and low BMD had an odds ratio of 4.8 for hip fracture in elderly women after a follow-up of on average 22 months. The same combination in women aged 65 years showed a relative risk of 4.2 for all fractures.[37] These investigators demonstrated in another study, although without data of DXA, that the combination of history of fractures and urinary CTX may predict hip fracture risk in elderly women comparable to hip BMD determinations.[38] Ross and co-workers found an association between spine and non-spine fractures and high serum bone alkaline phosphatase, with an odds ratio of 1.5-1.9 per 1 SD change, which persisted after adjustment for BMD.[39] These studies indicate that indices of skeletal turnover give information on fracture risk independently of BMD and

might therefore complement and improve fracture risk assessment by BMD. These studies are, however, all performed in postmenopausal women only. Prospective studies with fracture endpoints in men and in patients at risk for secondary osteoporosis, like the patient groups we have studied, are lacking. Beside this, the question arises whether measuring bone turnover may be helpful in estimating fracture risk in patients with T-scores above -2.5, and whether medical intervention in subjects with osteopenia but elevated bone markers may lead to a reduction in fractures. A recent study demonstrated that with measurement of bone turnover markers a subset of post-menopausal women can indeed be identified in which therapy with bisphosphonates is cost-effective.[40] Further studies are however needed to substantiate this finding.

Are patients with inflammatory conditions in whom vertebral deformities have been demonstrated, candidates for preventive treatment with - for instance - antiresorptive medications like bisphosphonates? According to current guidelines, patients with prevalent vertebral fractures or a BMD T-score less than -2.5 should receive treatment. Many guidelines are available on the prevention and treatment of patients that are expected to be, or already are, on long-term (>3 months) glucocorticoid treatment. Treatment with oral glucocorticoids has been associated with increase in the risk of fractures, particularly fractures of the hip and vertebrae and this may be partially independent of BMD.[41] This effect is dose dependent and occurs rapidly after the start of treatment.[42] However, intermittent use of high-dose oral glucocorticoids (daily dose ≥15 mg and cumulative exposure ≤1 gm) may result in only a small increased risk of osteoporotic fractures. Conversely, patients who receive several courses of high-dose oral GCs (daily dose ≥15 mg and cumulative exposure ≥1 gm) have a substantially increased risk of fractures.[43]

In the Dutch guidelines, bone measurement is not considered necessary in high risk patients, e.g. those who will take >60 mg/day of hydrocortisone or another equipotent glucocorticoid for more than three months. In such patients preventive treatment is indicated, irrespective of BMD values. The same is recommended for postmenopausal women and older men (>70 years) who will take intermediate doses (30-60 mg hydrocortisone). In all other patients on glucocorticoids a DXA measurement is recommended and if it is found to be low (a T-score of <-2.5), treatment should be started.[44-46] In patients not on glucocorticoids, a BMD measurement is recommended for a) those with a clinical fracture above 50 years, b) patients older than 60 years and at least three clinical risk factors and c) patients >70 years with two risk factors.[44] Specific guidelines for patients with IBD or sarcoidosis do not exist. As both we and others found a high prevalence of vertebral deformities in IBD patients, whereas no discrimination between patients with and without a vertebral deformity could be made with DXA, we feel that in this type of patients morphometric assessment of vertebral deformities better reflects reduced bone

strength than DXA measurements. As we found in patients with sarcoidosis not only a relevant prevalence of vertebral deformities during the initial cross-sectional study, but also a substantial increase of incident deformities after four years of follow-up, one may even wonder whether in this type of patients preventive treatment should be instituted, irrespective of the results of BMD or VFA-studies.

If preventive treatment in subjects at risk is considered, the next question is, which class of medication is to be preferred and for how long the therapy should be continued. At present, the drug of choice for prevention of osteoporotic fractures is a bisphosphonate. If this drug is not tolerated, strontium ranelate can be considered. Both types of drugs have been proven to be effective in the reduction of the risk of vertebral fractures (40-50%) and non-vertebral fractures (20-40%).[47-49] If there is progress of fractures during treatment, recombinant human parathyroid hormone (rhPTH) 1-34 fragment of the whole rhPTH 1-84 can be considered. Unlike bisphosphonates, that act mainly by reduction of bone resorption, and strontium ranelate, that at least in animal models acts by both reduction of bone resorption and stimulation of bone formation, daily injections of rhPTH primarily stimulate bone formation, more than bone resorption.[50] Phase III trials with rhPTH (1-34) in postmenopausal women demonstrated a 65% reduction in risk of new vertebral fractures and a 53% reduction of non-vertebral fractures,[51] while for rhPTH (1-84) only a reduction of vertebral fractures could be demonstrated.[52] So, rhPTH appears to be at least as effective as bisphosphonates and strontium ranelate in the prevention of fractures, which may be relevant if treatment is considered in patients with a substantial fracture risk, as in patients with an inflammatory disease. However, because of still existing safety concerns, the high cost and the fact that treatment periods are at this moment limited to 18-24 months, the benefit in terms of bone mineral density seems to wane after discontinuation unless followed by an antiresorptive agent, we feel that also in patients with an inflammatory disease parathyroid hormone is a second line drug and that bisphosphonates or strontium ranelate are the first drugs of choice.

As for the period that treatment should be continued in patients with an inflammatory disease, no data are available. So far, available data of oral bisphosphonate treatment in postmenopausal women for up to 10 years, show sustained, but not progressive, suppression of bone remodelling and provide no evidence of an adverse effect of bisphosphonates on bone metabolism. In addition, the favourable effect of bisphosphonates on skeletal integrity seems to be sustained.[53] At present, the usual policy is to reconsider continuation of treatment after five years. It is our policy to continue treatment if after five years treatment the T-score with DXA is still <-2.5 and/or a vertebral fracture is evident or new risks appear. In low risk patients (T-score >-2.5, no new fracture) we are used to give a drug holiday. This may be different in patients

with an inflammatory disease as long as activity of the disease is still notable. Follow-up studies are, however, needed to clarify this point.

Recommendations for further studies

Although our studies point to a high prevalence of vertebral fractures in patients at risk for secondary osteoporosis and hence new fractures, these data would be strengthened by studies that evaluate the presence of vertebral deformities in healthy young populations. Prospective follow-up studies in patients with IBD will have to demonstrate whether a similarly high rate of new deformities as in patients with sarcoidosis can be found. Finally, intervention studies on patients with vertebral deformities, irrespective of BMD-measurements, are needed to determine whether or not recognition and treatment of such patients reduce the incidence and progression of vertebral deformities.

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