Osteoporosis: risk factors and diagnostic approach

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Chapter 7

General discussion

SEX STEROIDS AND OSTEPROSIS

It is well established that sex steroids play an important role in the maintenance of bone health. However, association studies on sex steroids and fractures in older persons are not consistent. In our study, we showed that low endogenous serum levels of bioE2 and bioT were associated with low QUS measurements, low total hip BMD, high levels of bone turnover markers, and high risk of osteoporotic fractures in both men and women.
Furthermore, we found an inverse association between bioE2 and bone loss in the femoral neck in women, but the relationship with bone loss in the total hip was not significant. In men, we observed a positive relationship between bioT and BMD, which is also consistent with other studies (1-4).
A trend in the direction of a negative relation between the serum levels of bioE2 and fractures was observed, when men and women were analysed separately. This trend was borderline significant as the incidence of fractures in this healthy population was low. When we performed this analysis in men and women together after sex-specific dichotomization of respondents according to the levels of bioE2, a significant increased risk of osteoporotic fracture was found in men and women with lower (under the median) levels of serum bioE2. This association stayed significant after adjustments for confounding variables. The results of other studies on the association between sex hormones and fractures are not consistent (5,6).
In men in our study, low bioT was associated with an increased fracture risk in univariate analysis, but after adjustment for age, this association was no longer significant. This might be explained by small sample size, as the performed power analysis revealed that in order to obtain statistical significant results on bioT and osteoporotic fractures in men with adjustments for confounders, the sample size had to be 2 – 2.5 times larger than it was in our study. It also shows that the relationship between testosterone and fractures in men is less strong than that between estrogen and fractures in men. Our study showed consistent results on all bone health parameters that we examined, and therefore provides a complete picture of the associations between sex steroids and bone health in elderly, supporting the importance of endogenous sex steroids for bone health in older persons.

Clinical implications
The aim of hormone therapy for osteoporosis is to prevent fractures. Our data shows that even a small decrease in serum bioE2 (from the highest to lowest

quartile in our study) is associated with a higher risk of osteoporotic fracture. It would be interesting to investigate which dose of estrogens is sufficient to shift the endogenous serum level of bioE2 from the lowest to the highest quartile in a given population (Q1: 2.9 – 13.9 pmol/l; Q4: 24.2-73.0 pmol/l in our study) and whether such an intervention could prevent fractures. In a recent study on low-dose hormone replacement therapy and bone protection in postmenopausal women, it was found that low dose hormone replacement therapy (0.5 mg of 17β-estradiol and 0.25 mg of norethisterone acetate) is effective in improving menopausal symptoms and can prevent the bone loss related to the estrogen deprivation (7). Even ultra-low doses of E2 such as 0.25 mg, seem to be effective in the prevention of bone loss (8). However, a recent randomized, placebo-controlled, dose-finding study demonstrated that in women with climacteric symptoms, the dose of 0.25 mg E2 is ineffective in the treatment of vasomotor symptoms (9). Therefore, an ultra low dose may be insufficient for adequate symptom relief, while hormone therapy in early postmenopausal women is primarily indicated for treatment of vasomotor symptoms. In addition, side effects of very low doses of estrogen are uncertain. In men, the use of T or Selective Estrogen Receptor Modulators (SERM's) and Selective Androgen Receptor Modulators (SARM's) still needs to be justified.

VITAMIN D AND OSTEOPOROSIS

Poor vitamin D status is common in elderly and is associated with bone loss and fractures. Our global study on serum vitamin D [25(OH)D] status according to season in postmenopausal women with osteoporosis allows us to compare serum 25(OH)D and PTH levels in postmenopausal women with osteoporosis throughout the world. A central laboratory facility was used to perform the measurements in 7441 women who were enrolled in one double blind, randomized, controlled clinical trial, thereby eliminating the variation in assay methods between the laboratories in different countries.

We found considerable differences in vitamin D status in different countries depending on season and latitude, with high prevalence of serum 25(OH)D <25, and 25-50 nmol/L in many countries. The results are consistent with the previous global study with similar design, in which the highest prevalence of vitamin D deficiency (25(OH)D <25 nmol/L) was observed in countries of Central and Southern Europe. Worldwide, serum 25(OH)D was negatively correlated with latitude, a finding which is to be expected. For Europe, however, this correlation was paradoxically positive, as was also seen in other studies (10-12). In our study,

gross domestic product (GDP) as a marker of affluence is positively correlated with 25(OH)D in Europe, also after correction for latitude. Therefore, it would be interesting to assess the relationship between income level per person, the diet, fortification policy, the use of supplements and holidays in sunny destinations, and to investigate the share of each factor that influences the relation between latitude and serum 25(OH)D.

In our both studies on vitamin D, the inverse relationship between serum PTH and 25(OH)D, did not show a plateau at serum 25(OH)D up to 100 nmol/L. Above that level, a plateau might appear in the global study; but as serum 25(OH)D was below 100 nmol/L in 95% of the subjects, and the CI's above 100 nmol/L are wide, conclusions can not be drawn for serum 25(OH)D levels above 100 nmol/L. This is consistent with other studies (13-15). A small increase of serum PTH when serum 25(OH)D fell from 100 to 50 nmol/L was interpreted as a physiological compensatory mechanism to increase renal 1-α hydroxylation and serum $1,25(OH)_2D$ in order to maintain a stable serum calcium level.

The required serum 25(OH)D has usually been established by assessing the threshold of serum 25(OH)D below which serum PTH starts to rise. It has been suggested that the simultaneous measurement of serum PTH may aid to interpret the circulating level of serum 25(OH)D because of the inverse relationship between serum 25(OH)D and PTH. The tendency of establishing the required serum 25(OH)D by assessing the threshold below which serum PTH starts to rise could lead to the use of the upper limit of serum 25(OH)D level in different data sets as a threshold, therefore establishing the required serum 25(OH)D level at 100-120 nmol/L. Furthermore, the increases of serum PTH associated with vitamin D deficiency usually are within the normal reference range, and serum PTH only exceeds the upper reference limit in a small percentage. In addition, serum PTH has a short half life and depends on calcium intake, so different data sets could lead to different conclusions according to fasting or non-fasting condition or dairy intake (16).

This threshold might vary between 30 nmol/L in the Amsterdam vitamin D study (17), 37.5 nmol/L in a study in American hospital inpatients (18), 50 nmol/L in an American study on vitamin D supplementation (19), 75 nmol/L in the French SUVIMAX study (20) or 80nmol/L in an American rural female population (21). In a study that did provocative testing which is often used in endocrinology to ultimately determine the homeostatic level for a particular hormone, 50 nmol/L was considered the minimum 25(OH)D value for vitamin D sufficiency in the age group of 49-83 years (19). A significant positive association between 25(OH)D levels and BMD was observed in the NHANES III study, where a threshold of about

80-90nmol/L was found, representing the serum 25(OH)D level above which BMD did not increase significantly (22). A recent review suggests that a desirable serum 25(OH)D concentration for optimal health begins at 75 nmol/L, with the optimal concentration being 90-100 nmol/L (23).
Our study yields a lower threshold (50-60 nmol/L) which may be partly due to differences between assays for serum 25(OH)D (24). Different thresholds of serum 25(OH)D for serum PTH, bone turnover, BMD, and neuromuscular function may also be explained by different thresholds at the organ level. This could be caused by the extra-renal hydroxylation of 25(OH)D to the active metabolite 1,25-$(OH)_2$D in different organs, as it is known that 1,25-$(OH)_2$D is capable of acting via autocrine and paracrine mechanisms (25).

Clinical implications
In both studies, mean values of BMD at all measured sites (lumbar spine, total hip, femoral neck and femoral trochanter) were higher in groups with higher serum 25(OH)D level (Tables 3.2 and 4.2). These absolute differences in mean BMD between the different vitamin D groups might be small, but at the population level these differences could mean a substantial reduction in fracture risk. Hip fractures were found to be strongly related to reduced bone mineral density in all regions of the proximal femur, with a risk ratio of 2.5- 2.7 for hip fracture (95% CI 1.9-3.6) with each SD decrease of BMD at any site of the proximal femur, after adjustment for age (26). So a decrease in BMD of the femoral neck from 0.729 to 0.700 g/cm^2 (0.25 of SD) in our data may increase the RR for hip fracture by more than 50%.
The fact that in our LASA study, all BMD parameters and total body BMC increased up to the serum 25(OH)D level of at least 50-60 nmol/L, while physical performance increased up to 25(OH)D levels of 60 nmol/L, indicates that the optimal serum 25(OH)D should be at least 50–60 nmol/L.
As was shown in a meta-analysis on vitamin D and fracture prevention, a dose of 700-800 IU per day appears to reduce the risk of hip and any non-vertebral fractures in older persons (27). Indeed, with a daily supplementation of 800 IU, the mean levels of 25 (OH)D became 75 nmol/L, being >60 nmol/L in 80% of participants with good compliance after 6 months (28). In a study on supplementation of vitamin D in institutionalized elderly with a very good compliance, 90% of participants achieved a serum 25(OH)D > 50 nmol/L after 4 months of a daily supplementation with 600 IU of vitamin D (29). In a global study, vitamin D supplementation had more effect on serum 25(OH)D and serum PTH when baseline serum 25(OH)D was lower (10).

Therefore, the supplementation dose should be 600-800 IU per day when sunshine exposure is insufficient, and a decision about it should be made on an individual basis with respect to baseline serum 25(OH)D level, lifestyle and diet. For our older population it means that at least 64% should receive vitamin D supplements as they had a serum 25(OH)D level lower than 60 nmol/L. A recent advice from Dutch Health Counsil (Gezondheidsraad 2008) advises 10 microgram of vitamin D daily to healthy white women > 50 years and healthy white men >70 years; and 20 microgram of vitamin D daily to persons with osteoporosis or institutionalized eldery (http://www.gezondheidsraad.nl/nl/adviezen/naar-een-toereikende-inname-van-vitamine-d).

CASE-FINDING IN OSTEOPOROSIS

1. Successful implementation of case-finding as a basis for fracture and osteoporosis (FO) outpatient clinic

In this study, we implemented the case-finding approach for osteoporosis in patients with a recent fracture, which is recommended by the Second Dutch Osteoporosis Guidelines (30). We combined the clinical risk score assessment with BMD measurement and later also with the assessment of prevalent vertebral fractures by Vertebral Fracture Assessment (VFA) to optimize the diagnostic process. Although the acceptance of this approach by the patients was less than 50% (39% of approached patients underwent full assessment), it is comparable to 30% achieved in a study with a similar design (31), in which a similar approach was proven to be very effective. The strength of our study is mainly in its realistic approach and usefulness in daily practice. In contrast to other studies, we did not just exclude non-responders, but tried to analyze the available information to understand the reasons for non-participating. So, in the first study, we only asked the patients once by letter whether they wanted to participate and to be tested for osteoporosis. In the amended protocol, we tried to decrease non-response by sending reminding letters to the patients when they did not respond within 6 weeks. This action increased the percentage of refusers (i.e. those who did not participate but provided a reason for non-participation), and increased the percentage of complete responders. The percentage of responders may grow in the future when awareness of osteoporotic fractures increases in the general population.

Clinical implications

Case-finding may further improve with establishing a fracture and osteoporosis outpatient clinic with a specialized nurse, whose main task is to explain the risk of osteoporosis and to offer BMD and VFA-measurements to the patients of 50 years and older with a fracture. At the VU University Medical Center, a fracture and osteoporosis (FO) outpatient clinic was started based on experience of our study, with the use of the fracture risk factors, and both BMD measurement and VFA. In order to improve the acceptance by patients, all of them receive an appointment with a specialized nurse who is supervised by a physician.

2. Risk factors

From all patients with a recent fracture, 22% of men and 30% of women had osteoporosis according to WHO criteria (T-score ≤ -2.5). The remaining fractures occurred in patients with a normal or osteopenic BMD. Indeed, repeat fractures contribute substantially to overall fracture burden (32). From the assessed clinical risk factors, well-established risk factors such as one or more previous fractures after the age of 50 years, low body weight, and osteoporotic type of fracture were common risk factors in patients of both sexes with osteoporosis, in accordance to other studies (33-35). A diagnosed vertebral fracture appeared to be the most common risk factor in women, with a prevalence reaching 47% in the osteoporosis group.

In our study, if VFA would not have been performed, 8 men (34.8%) and 15 women (11.9%) with vertebral fractures would not have been diagnosed and treated, due to normal or osteopenic BMD. Our data show that although the prevalence of vertebral fractures is highest in women with osteoporosis (who already have been diagnosed by BMD measurement alone), VFA still has important additive value for staging of osteoporosis. In clinical practice, the treatment decision is made based on BMD measurement of lumbar spine or hip, or by the presence of a vertebral fracture. Therefore, for men in our study, in whom prevalent vertebral fractures were more often observed in patients with normal BMD or osteopenia, the additive value of VFA was high.

In the Second Dutch Osteoporosis Guidelines, treatment is recommended independently of BMD values if a patient has a vertebral fracture (30). So, in attempt to predict 10-years fracture risk, it is vital to introduce this risk factor into the model. Although the possibility of elegant diagnosis of a vertebral fracture using VFA in a single session with BMD measurement is not everywhere available, plain radiographs of the thoraco-lumbar spine, which are still the gold standard

for diagnosis, are everywhere available. On the other side, the advantage of VFA is the perpendicular path of the X-rays during the scanning procedure, while a vertebral radiograph is centered on one vertebra only. Therefore, the assessment of fracture risk can not be complete without vertebral assessment, especially when risk factors are present and osteopenia is diagnosed with BMD measurement.

Clinical implications
We believe that in case-finding, where all evaluated persons already are at higher fracture risk compared to the general population, the fracture risk assessment should include vertebral assessment. The best tool for the case-finding of osteoporosis will be a combination of clinical risk factors, BMD, and vertebral fracture assessment.

3. Treatment advice

Following the diagnosis, letters with treatment recommendations for the GP's were sent (Table 7.1). We advised an antiresorptive treatment in all patients with a T-score ≤-2.5 SD. This was in accordance to the study from the UK showing that in women at the threshold of osteoporosis with a T-score of -2.5 SD, it was cost-effective to intervene if there was a history of a prior fracture, irrespective of age (36). In patients with a T-score being normal or representing osteopenia, we have chosen an intervention threshold (IT) at a 10-years hip, wrist or vertebral fracture risk of 10%. In the UK, the 10-year probability of a major osteoporotic fracture at which intervention becomes cost-effective is approximately 7.5%, which is comparable to the Netherlands, according to the population risk of a hip fracture (37). We advised antiresorptive treatment or referral to a specialist in all patients with a vertebral fracture, irrespective of BMD.

Clinical implications
We believe that the approach with the use of the results of BMD and vertebral assessment on the one side, and clinical risk factors with absolute 10-years fracture risk on the other side, can easily be used in general practice.

Table 1. Recommendations in different BMD diagnosis groups for men and women with a recent fracture.

	Men			*Women*		
Recommendation	Normal	Osteopenia	Osteoporosis	Normal	Osteopenia	Osteoporosis
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Lifestyle advice	35 (94.6)	38 (66.7)	0 (0)*	92 (94.8)	124 (60.5)	0 (0)*
Antiresorptive treatment	0 (0)	8 (14.0)	8 (29.6)	3 (3.1)	62 (30.2)	104 (79.4)
Specialist	2 (5.4)	8 (14.0)	17 (63.0)	1 (1.0)	6 (2.9)	18 (13.7)
Continue treatment	0 (0)	3 (5.3)	2 (7.4)	0 (0)	13 (6.3)	9 (6.9)
Stop treatment	0 (0)	0 (0)	0 (0)	1 (1.0)	0 (0)	0 (0)
Total	37 (100)	57 (100)	27 (100)	97 (100)	205 (100)	131 (100)

* Patients with osteoporosis received lifestyle advice in addition to other (usually antiresorptive) treatment.

4. Adherence, persistence, concordance

Patient adherence to advice and persistence in taking medication are crucial for a successful treatment, as well as concordance of general practitioners (GPs) with a treatment advice.

The term “adherence” is now preferred over the earlier term “compliance” because it recognizes patient choice as opposed to passive obedience to the physician (38,39). Adherence to a medication regimen is defined as the extent to which the patient’s behaviour matches agreed recommendations from the prescriber. An even better term is “concordance”, which implies a negotiated agreement between the patient and the physician or other healthcare professional and therefore implies patient involvement in the treatment process. In our study, we used a term concordance to describe the acceptance of our advice by GPs. We used terms “persistence” (or continuation rate), to describe the percentage of patients still on treatment at the end of the period of interest (38,40), and “adherence” (or the range of behaviours shown by an individual in

response to medical advice or any health advice) (38), to describe whether patients followed our advice or not.

The current study showed high adherence of patients to advice and their high persistence to therapy at the 1st year of follow-up. Reminders in this period increased both adherence and persistence of patients, as well as the concordance of their GPs.

In our study, 87% (123 from 142) of those who started to use prescribed antiresorptives, were still using them at the 1st year of follow-up, which represents good persistence. The awareness of DXA results and the fact that our patients already had a fracture and were at high risk of suffering a new fracture, may explain their high persistence. We found that the concordance of GPs with our advice is as important for successful treatment after a diagnosis of osteoporosis, as the adherence and persistence of patients. A patient who was advised to visit the GP to initiate antiresorptive treatment, was four steps away from successful treatment. A patient had to visit a GP (adherence to advice 89%), receive a prescription (concordance of GP with advice 72%), start to use it (97%), and continue to use it at the end of the 1st year (persistence 87%). Although each of these percentages are quite high, the result is that from every 100 patients, only 54 (100x0.89 x 0.72 x 0.97 x 0.87=54) will end up using antiresorptives at the end of the 1st year of follow-up, which is a quite disappointing result. So, all factors which influence each of this steps, need to be addressed in order to improve the overall percentage of patients who are treated as a result of case-finding.

Furthermore, we found that the predicted 10-years fracture risk for hip, wrist or vertebral fracture was similar to the incidence of any new fracture already in 3 years of follow-up. The incidence of new fractures in those who were at high 10-yrears risk for hip, wrist or vertebral fracture at baseline, was already higher in the 1st year of follow-up, and stayed higher after 3 years of follow-up. Those who reported a hip fracture, had high 10-year risk of hip fracture at baseline, while those who did not report a hip fracture were at low 10-year risk for hip fracture at baseline (14.0±9.0% and 6.1±6.1%, respectively, $p<0.01$). Therefore we can conclude that the use of estimated absolute fracture risk at baseline (Chapter 5) appears to be a valuable tool for fracture risk prediction.

Clinical implications

Every effort should be made to continuously stimulate the patients who attended FO clinics, explaining the importance of good adherence and persistence. Patients showed high adherence to advice and high persistence to therapy at the 1st year

of follow-up. Reminders in this period increased both adherence and persistence of patients, as the concordance of their GPs. We believe that the first year of follow-up is most important in the monitoring of patients and should be a part of the service provided by a FO clinics.
Furthermore, the use of estimated absolute fracture risk at the baseline is a valuable tool for fracture risk prediction.

RECOMMENDATIONS FOR FURTHER RESEARCH

In the field of osteoporosis, fractures and their prevention, many research questions remain. In this thesis, we focused mainly on the diagnostic process, involving the clinical fracture risk factors, measurement of BMD and assessment of vertebral fractures, as well as the serum measurements of hormones influencing bone metabolism, and bone markers. We also investigated the implementation program for the diagnosis and treatment of osteoporosis, including the assessment of patient adherence and persistence, as well as acceptance of such a program by their GPs.

The challenges still remain not only to develop better diagnostic tools and better treatment options, but also to apply the current knowledge in the community in order to increase the adherence and persistence of patients to therapy. Therefore, further research should focus on the following topics:

1. Developing new tools to identify patients at risk for fractures. New imaging techniques could provide information on bone architecture and therefore predict the risk of fracture more accurately than conventional BMD measurement.
2. To elucidate the role of bone markers in prediction of fractures and in the decision making about the treatment options.
3. To search for new possibilities in improving adherence and persistence of patients who start with antiresorptive treatment.
4. To develop better tools for diagnosis and follow-up of patients, for example by means of online programs.
5. Studies on the optimal dosing regimen for vitamin D to reach the optimal serum level of minimum 50 nmol/l or higher.
6. Studies on the ultra-low dosis of estrogens to investigate which dose of estrogen is sufficient to shift the serum level of bioavailable estradiol from the lowest to the highest quartile in a given population and whether such an intervention could prevent fractures.

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