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## **Osteoporosis: risk factors and diagnostic approach**

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## Summary

This thesis focuses on the diagnostic approach to osteoporosis, risk factors for osteoporosis, and recommendations for case-finding and follow-up. An integrated algorithm for case-finding is proposed, based on the Dutch Osteoporosis Guidelines (Appendix).

**Chapter 1** is an introduction to the work presented in this thesis. The definition of osteoporosis and pathogenesis of osteoporosis and related fractures are briefly described. The relationship between some endogenous parameters such as serum sex steroids and serum 25 hydroxyvitamin D (25(OH)D) and different parameters of bone health are described in Chapters 2-4.

In **Chapter 2**, we examined whether serum estradiol and testosterone are associated with quantitative ultrasound (QUS), bone mineral density (BMD), bone turnover markers and fracture incidence. The study was performed within the framework of the Longitudinal Aging Study Amsterdam, an ongoing cohort study including 623 men and 634 women, 65-88 years.

In this study, men in the lowest quartile (Q1) of bioavailable estradiol (bioE2) had higher levels of bone turnover and lower BMD and QUS than men in the highest quartile (Q4). This applied also to Q1 of bioavailable testosterone (bioT). Women in Q1 of bioE2 had higher levels of bone turnover and lower BMD and QUS than women in Q4. In men and women, levels of bioE2 under the median were associated with an increased risk of osteoporotic fractures after adjustment for confounding. We concluded that low levels of bioE2 and bioT were associated with high bone turnover, low QUS and BMD and high risk of osteoporotic fractures both in men and women.

**Chapter 3** describes the worldwide vitamin D status in postmenopausal women with osteoporosis according to latitude and economic status, in relation to parathyroid function, bone turnover markers and bone mineral density (BMD). The study was performed in 7441 postmenopausal women from 29 countries, participating in a clinical trial on bazedoxifene (SERM), with BMD T-score at the femoral neck or lumbar spine  $\leq -2.5$ , or 1 to 5 mild or moderate vertebral fractures. In these women, the mean serum 25(OH)D level was  $61.2 \pm 22.4$  nmol/L. The study showed a high prevalence of low 25(OH)D in post-menopausal women with osteoporosis. With increasing 25(OH)D categories of  $<25$ , 25-50, 50-75 and  $>75$  nmol/L, mean PTH, OC and CTX decreased, while BMD of all sites increased. A negative correlation between serum 25(OH)D and latitude was observed. Along with latitude, affluence seems to be an important factor determining serum 25(OH)D status, especially in Europe where affluence is strongly correlated with latitude. A threshold in the positive relationship between 25(OH)D and different BMD parameters was visible at a serum 25(OH)D level of 50 nmol/L.

In **Chapter 4**, we describe a study on the estimation of the thresholds of serum 25(OH)D with regard to serum PTH, bone turnover markers, bone mineral density, bone ultrasound parameters and physical performance in a population-based study, the Longitudinal Aging Study Amsterdam. We found that low serum 25(OH)D concentrations are common in the elderly. Mean serum PTH decreased gradually from 5.1 pmol/L when serum 25(OH)D < 25 nmol/L to 3.1 pmol/L when serum 25(OH)D >75 nmol/L, without reaching a plateau. All bone mineral density values were higher in the higher serum 25(OH)D groups, although only significantly for total hip, trochanter and total body BMC. A serum 25(OH)D threshold of about 40 nmol/L was observed for OC and DPD/Cr, 50 nmol/L for BMD and 60 nmol/L for physical performance. We concluded that bone health and physical performance in older persons are likely to improve when serum 25(OH)D is raised over 50-60 nmol/L.

A practical study on the implementation of case-finding for osteoporosis including follow-up is described in Chapters 5 and 6. **Chapter 5** describes the results of the successful implementation of a case-finding strategy in patients with a recent fracture, recommended by the Dutch Guidelines for Osteoporosis. It investigates the additive value of Vertebral Fracture Assessment (VFA). 1435 patients of 50 years and older with a recent fracture were invited to participate. They received a questionnaire on risk factors for fractures and subsequently underwent a BMD measurement. A sub-sample of 372 patients was additionally invited for VFA. A treatment advice was based on absolute 10-years fracture risk and BMD results. Assessment was completed by 554 patients. From those, 22.3% of men (n=27) and 30.3% of women (n=131) were diagnosed with osteoporosis (T-score $\leq$ -2.5). The most common fracture risk factors were low body weight, previous fracture, and use of a walking aid in both sexes. Prevalent vertebral fractures were diagnosed by VFA in 40 from 149 patients (27%). Of those, 23 had a T-score >-2.5 and would not be diagnosed properly without VFA. We concluded that the case-finding approach was successfully implemented, and that VFA proved to be an important tool in diagnosing prevalent vertebral fractures and a major step in case-finding, leading to an important increase of diagnosis of vertebral fracture.

The evaluation of the acceptance of abovementioned strategy both by the patients and their general practitioners is discussed in **Chapter 6**, which provides information on adherence and persistence of patients, and concordance of GPs with our advice. Patients who participated in a case-finding program for osteoporosis, received a recommendation letter with a treatment advice, based on absolute 10-years fracture risk and BMD results. One, two and three years later, they received follow-up questionnaires to collect information on their

adherence and persistence, concordance of GPs to advice, and new fractures. Follow-up was completed by 504 (91%) patients at the 1<sup>st</sup> year, 458 (83%) at the 2<sup>nd</sup> year, and 355 (64%) at the 3<sup>rd</sup> year. In total, 229 of 504 patients received a treatment advice. At the 1<sup>st</sup> year, adherence of patients to new treatment advice was 89% (203 of 229), concordance of their GPs with our advice was 72% (146 of 203), persistence of those who started medication following our advice, was 87% (123 from 142). Overall, this resulted in 58% of patients on antiresorptive treatment due to our advice at the end of the 1<sup>st</sup> year of follow-up, from 229 patients who were advised antiresorptive treatment. Due to reminders, this percentage increased to 69% at the 2<sup>nd</sup> year, and remained 67% at the 3<sup>rd</sup> year of follow-up. Overall, 51 patients (10%) reported 61 fractures: 20 (4%), 22 (4.8%), and 19 (5.4%) in the 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> years of follow-up, respectively. The incidence of new fractures in patients who were at high 10-years risk for hip, wrist or vertebral fracture at baseline, was already higher in the 1<sup>st</sup> year of follow-up than in patients at low risk (8.2% vs. 2.4 %,  $p=0.003$ ), and remained higher after 3 years of follow-up (14.9% vs. 8.4%,  $p=0.031$ ). Patients with a new hip fracture had high 10-year risk of hip fracture at baseline, while patients who did not suffer a new hip fracture were at low risk at baseline ( $14.0\pm 9.0\%$  and  $6.1\pm 6.1\%$ , respectively,  $p<0.01$ ). We concluded that the first year of follow-up is important in the monitoring of patients and should be a part of the service provided by a fracture and osteoporosis (FO) clinics. Interventions in this period increase both adherence and persistence of patients, as well as the concordance of their GPs.

At the VU University Medical Center, a (FO) clinic was started based on the experiences with the latter two studies, with the use of the fracture risk factors, and both BMD measurement and VFA (Algorithm, Appendix). A special database combines the information on clinical risk factors and the results of additional investigations, helps to generate a standardized advice letter to a general practitioner, and contains valuable information for future research. In order to improve the acceptance by patients, all of them receive an appointment with a specialized nurse practitioner who is supervised by a physician. The investigation of the additive value of these improvements and their influence on patient's adherence and persistence will be the subject of further studies. We can recommend the use of the Algorithm (Appendix) in the clinical practice. In order to increase the acceptance by the diagnostic program by the patients and their physicians, 1<sup>st</sup> year follow-up after a treatment advice should be performed by a FO nurse practitioner.