Chapter 8

Discussion and future perspectives
Osteoporosis is a common disease with a major mortality and morbidity. Fractures and their complications are the relevant clinical sequelae of osteoporosis. In the Netherlands 850,000 people suffer from osteoporosis and this number will increase till an estimated 1.2 million in 2025[6,7]. Per year 85,000 osteoporosis related fractures occur with an estimated cost to treat these fractures of 378 million euro, which is 0.5% of the total medical costs per year in the Netherlands[8,6]. Eighty-five percent of these costs are related to hip fractures, which is especially important as the number of hip fracture patients will increase significantly from 15,000 in 2002 till an estimated 24,000 in 2020[9,10]. In addition, several studies have shown that osteoporotic fractures are independent risk factors for future fractures: vertebral fractures are associated with a 5-fold increased risk of a new vertebral fracture and a 2-fold increased risk of hip fractures and non-vertebral fractures are associated with a 2-fold increased risk of a subsequent fragility fracture[11,12,3]. The risk of a subsequent fracture can be reduced by 50% because adequate treatment for osteoporosis in the elderly is available[13-15].

In general practice osteoporosis is diagnosed by making a DXA-scan (Dual Energy X-ray Absorptiometry). A general screening program for osteoporosis (primary prevention) cannot be recommended because DXA has a low (about 50%) sensitivity for diagnosing osteoporosis, which implies that BMD (bone mineral density) measurement can only be advocated in populations with a high fracture risk (case-finding)[9]. Diagnosing and treatment of osteoporosis should therefore primarily focus on reducing subsequent fracture risk (secondary prevention). Such secondary prevention programs for osteoporosis have also been shown to reduce mortality[16-19]. Fracture patients over 50 years of age are at high risk for osteoporosis and should be screened for this[3]. In the Netherlands, since 2003, this screening is arranged through the Fracture Liaison Services (FLS). This resulted in an improvement of patients being screened for osteoporosis from 5 to 51%[20]. Although this is a good result, it also means that almost half the fracture patients do not attend the FLS, which is not acceptable. In a recent study among 2,207 fragility fracture patients, the most important reasons for not attending the FLS were: not interested (38%), not capable (11.5%), or death (5.2%)[20]. This suggests that further improvement of screening for osteoporosis through an FLS is probably limited. In this thesis we describe options to further increase the number of patients being screened for osteoporosis and we suggest on how to arrange an FLS.

Conventional radiographs in diagnosing osteoporosis

In the screening program for osteoporosis, performing a BMD by DXA-scanning is still the golden standard. New insights however show that a vertebral fracture in the elderly is also a reason to initiate anti-osteoporotic therapy, independent on BMD[3,21]. For a good understanding of the basics of the diagnostic osteoporosis philosophy it is important to realize that osteoporosis is defined as a low BMD and/or a diminished bone quality (bone quality can be defined as the sum total of characteristics of the bone that influences the bone’s resistance to fracture). Spinal radiographs can represent a test for bone quality, whereas DXA represents bone mineral density[22,23]. So one of the possible options, apart from performing a BMD measurement, is looking for vertebral fractures in elderly patients. Both modalities do have their own advantages and disadvantages. The most important advantage of BMD measurement is that follow-up measurements are possible to evaluate the effect of medication. The disadvantage is that it takes several weeks time
to perform the first (DXA) BMD measurement in the FLS-setting resulting in a considerable initial time loss. A great advantage of spinal radiographs is that it can be obtained very easily in the primary clinical phase and will identify more than 40% of all patients in which treatment can already be initiated. This latter can be important as most subsequent fragility fractures occur in the first year suggesting that anti-osteoporotic therapy should be initiated as soon as possible[24,25].

In chapter 2 of this thesis we established the prevalence of vertebral fractures in patients screened at our FLS to determine whether or not spinal radiographs can be used as a first step in screening on osteoporosis.

Vertebral fractures are the most common fractures in the elderly and their incidence is rising with age[26]. The prevalence of vertebral fractures in patients over the age of 50 after a low energy fracture, other than a vertebral fracture, is 5-31% in women and 8-32% in men[27]. In women this prevalence is highest after hip fracture (31%) and hand- or foot fracture (29%), in men after hip fracture (32%) and shoulder fracture (24%) (table 1)[27]. At 70 years of age the prevalence of vertebral fractures in the above described patient category is 30% in women and 25% in men, increasing to 50% in a geriatric population (frail, elderly people with multiple co-morbidity)[27-29].

<table>
<thead>
<tr>
<th>Females (n = 455)</th>
<th>Males (n = 122)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence of vertebral fractures (%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>n</td>
</tr>
<tr>
<td>Radius or ulna</td>
<td>176</td>
</tr>
<tr>
<td>Hip</td>
<td>59</td>
</tr>
<tr>
<td>Humerus</td>
<td>55</td>
</tr>
<tr>
<td>Ankle</td>
<td>62</td>
</tr>
<tr>
<td>Hand or foot</td>
<td>65</td>
</tr>
<tr>
<td>Other sites</td>
<td>38</td>
</tr>
</tbody>
</table>

Table 1. Numbers, sites and age of non vertebral fracture presentations in women and men. The prevalence of vertebral fractures identified by VFA are shown[27].

In our FLS-study population we found a prevalence of vertebral fractures of 42%. Interestingly, only 36% of the patients with a vertebral fracture did have an osteoporotic BMD. So assessment of the spinal column seems to be a very important diagnostic procedure as in order not to withheld patients adequate anti-osteoporosis treatment[21,30,31,22]. As mentioned before, both vertebral fractures and an osteoporotic BMD are considered a reason to initiate anti-osteoporotic medication. Our study showed that spinal radiographs already identified 77% of all patients who would benefit from anti-osteoporotic medication. It also meant that 23% of the patients with an indication for anti-osteoporotic medication did not have a vertebral fracture and could only be identified by BMD measurement. Therefore, we suggest that the combination of BMD measurement and
assessment of the spinal column is probably the best way in screening for osteoporosis at an FLS. In this regard it is interesting to realize that nowadays software is available for most DXA machines to provide images from the thoracic and lumbar vertebrae. This offers the possibility of BMD measurement combined with morphometry or vertebral fracture assessment (VFA) (VFA allows manual or automatic placement of markers at the anterior, middle, and posterior height of the vertebra to calculate ratios[32]). VFA has the advantage of a lower dose of ionizing irradiation and greater patient convenience compared to conventional spinal radiographs[33-36]. VFA has been compared with spinal radiographs in terms of sensitivity and specificity in previous studies. In the Dutch guidelines on “osteoporosis and fracture prevention” a vertebral deformity measured by VFA below 25% is considered as no fracture, when the deformity is in between 25-40% spinal radiographs should be obtained and above 40% deformity on VFA a vertebra can be considered fractured[3]. The sensitivity of VFA in diagnosing vertebral deformities over 25% is in between 63-93% with a specificity of 93-99%. It makes the VFA suitable as a first step in screening the vertebral column for fractures[37,3].

Apart from vertebral fractures, it is known that distal radial fractures in elderly patients are associated with osteoporosis. As osteoporosis in this patient category is related to malunion, early instability and late carpal malalignment early information about the osteoporotic status of a patient could thus be helpful in the decision making process in choosing for an operative approach versus conservative treatment in order to prevent the above mentioned complications. But as we all know: direct BMD measurement with DXA is not feasible in the early clinical setting. Therefore we wondered if it might be possible to relate the existence of osteoporosis to fracture type and degree of comminution of the fracture. So in chapter 3 we studied the relationship between BMD and the AO-classification of the distal radial fracture. We hypothesized that, with an increasing loss of BMD the same force applied to the distal radius would result in a more severe (type C) fracture pattern. This idea was based on an in vitro study by Lill who found a good correlation (r=−0.70) between BMD and the Melone classification for distal radius fractures[38]. However, we did not find a correlation between BMD and the AO classification. It must be said that in the study by Lill the correlation between the other classification systems (AO, Cooney, Fernandez and Frykman) and BMD was also very weak (r≤−0.25). In this we should realize that the Melone classification is only applicable to intra-articular fractures and therefore less useful as a general classification system for distal radial fractures[39]. Supportive for our negative results was a clinical study describing the non-existence of a correlation between different fracture classification systems (including AO) and BMD[40].

In an attempt to explain the non-existence of a relation between BMD and (AO)-classification systems we suggested the following items to be of importance:

First, there is a known variability in classification of groups and subgroups with the use of the AO-classification (inter and intra observer variability)[41,42].

Second, the amount of energy transmitted during the fall to the distal radius differs in each patient. It relates for example to the angle of the wrist and forearm during the fall and patient’s neuromuscular capabilities of correction during the fall[43].
Third, by evaluation of the contribution of the cortical and trabecular compartments of distal radius it is shown that it is the cortical shell which contributes substantially to bone strength[44]. The cortex is thicker in the metaphyseal area compared to the epiphyseal area. DXA cannot distinguish between cortical and trabecular bone[45]. A decrease in BMD in the metaphyseal area of the distal radius will probably result in more decrease in cortical bone and therefore will effect bone strength more. A more severe osteoporotic fracture might thus be a metaphyseal fracture instead of an intra-articular fracture.

Nonetheless, in patients with a distal radial fracture it is clear that we need an early and adequate test to diagnose osteoporosis. This is illustrated by the fact that we found in these patients an overall prevalence of subsequent fragility fractures of 5.3% (median time interval 138 days (IQR: 52-529)); in osteoporotic patients significantly higher compared to patients with osteopenia or a normal BMD, 14%, 1.8% and 2.4% respectively. These are important results as the median time interval after which patients are screened at the FLS was 83 days and the maximum effect in risk reduction of anti-osteoporotic medication will take at least 90 days[46]. So an early and adequate test can reduce the time period after which anti-osteoporotic therapy is started by almost three months and thus be effective in the prevention of subsequent fractures. In fact this statement applies to every patient category in which an osteoporosis related fracture is diagnosed.

**Part 2: Calscan compared to DXA**

As previously described DXA is considered the golden standard in measuring BMD. It has some disadvantages as discussed earlier like the impossibility to perform DXA early after the accident in the clinical setting. Alternative ways, such as measurement of BMD at the calcaneus with the DXL Calscan (Demetech Sweden), would be an attractive alternative. Advantages of the Calscan are that it is a portable device, and easy to use. Moreover, measurements take less time, effective radiation dose is low (<0.2µSv), and even immobile patients or patients with problems in positioning the hip can be scanned. This latter is of upmost importance as patients who probably favour most from screening for osteoporosis are the frail elderly patients, in which fracture risk is increased because of the higher fall risk and diminished bone strength[47,48]. This patient group is often less mobile, which makes it impossible for them to attend an FLS, which can be the reason that they abandon from screening for osteoporosis[20]. In these patients the Calscan might be used to measure BMD at the same time they attend the emergency department, during admission to the hospital, or when their regular checks at the outpatient clinic are planned.

The Calscan measures BMD at the calcaneus. The Calcaneus consists of more than 90% of trabecular bone, which has a high turnover rate, making it ideal for measuring osteoporotic changes[49]. The Calscan uses two X-ray energies in combination with laser to determine the different absorptions of bone mineral, lean soft tissues and adipose tissues[50]. The Calscan has no known physical side effects and can be easily managed. A disadvantage of the Calscan is that Calscan T-scores cannot be used according to WHO standards for diagnosing osteoporosis, because there are no studies showing a reduce in fracture risk when patients are treated for osteoporosis based on the Calscan T-score. Therefore, the United Kingdom National Osteoporosis Society (NOS) stated that the Cals-
can T-score should be interpreted using an upper and lower threshold\[51\]. These thresholds should be defined in a way that patients with osteoporosis of the hip or spine are identified with 90% sensitivity and 90% specificity \[52\]. The upper threshold for the Calscan is therefore the Calscan T-score under which 90% of patients with osteoporosis are classified by the Calscan as having osteoporosis (sensitivity). All patients with a Calscan T-score above the upper threshold are considered not to suffer from osteoporosis. The lower threshold for the Calscan is the Calscan T-score above which 90% of the patients without osteoporosis were classified by the Calscan as not having osteoporosis (specificity). All patients with a Calscan T-score under or equal to the lower threshold were considered to suffer from osteoporosis. Patients in between both thresholds cannot be classified by the Calscan (figure 1).

We calculated the thresholds in two clinically relevant, though different study populations: a first group, including all patients over 50 years admitted to the hospital with a low energy fracture (group 1) and a group, including only hip fracture patients over 65 years also admitted to the hospital (group 2). Chapter 4 of this thesis describes the calculation of the thresholds for the Calscan T-scores in relation to DXA in group 1. The mean age of this study population was 66 years. The mean BMD measured by DXA was -1.63 SD (−4.9...
to 2.1) and the mean BMD measured by Calscan -1.91SD (-5.3 to 1.4). The correlation between DXA and Calscan was r=0.47. With an upper threshold on the Calscan T-score of -1.45SD, 91.1% of the osteoporotic patients were classified correctly by the Calscan. Using a lower threshold on the Calscan T-score of -2.95SD, 90.5% of non-osteoporotic patients were correctly classified by the Calscan. When both thresholds were used 28.5% of the patients did not have to be assessed by DXA because of the low probability of osteoporosis and 18.6% did not need DXA evaluation because of the high probability of osteoporosis. Therefore, 47% of the patients could be reliably classified on the basis of the Calscan T-score and did not need further DXA evaluation.

In the second group (**chapter 5**) all patients ≥65 years who were admitted to the hospital with a hip fracture were evaluated in the same way. The mean age of this study population was 78 years. The mean BMD measured by DXA was -1.91 SD (-5.2 to 1.1) and the mean BMD measured by Calscan -2.45SD (-5.5 to 1.3). The correlation between DXA and Calscan was r=0.61. With an upper threshold on the Calscan T-score of -1.85SD, 91.4% of the osteoporotic patients were classified correctly by the Calscan. Using a lower threshold on the Calscan T-score of -3.55SD, 89% of non-osteoporotic patients were correctly classified by the Calscan. When both thresholds were used 30% of the patients did not have to be assessed by DXA because of the low probability of osteoporosis and 23% did not need DXA evaluation because of the high probability of osteoporosis. Therefore, 53% of the patients could be reliably classified on the basis of the Calscan T-score and did not need further DXA evaluation.

Based on these two studies we showed that by using thresholds for the Calscan T-score it is possible to classify almost half the patients as either osteoporotic or non-osteoporotic, with a sensitivity and specificity of 90%. The Calscan is therefore a valid measurement instrument which can be used in the screening for osteoporosis. An interesting result from our studies is that the height of the thresholds for the Calscan T-score became lower with advancing subject age. This is conform a mathematical model and also comparable to previous clinical studies in Caucasian patients, table 2[53,54,52].

<table>
<thead>
<tr>
<th>Mathematical Model, age 60</th>
<th>Mathematical Model, age 70</th>
<th>Mathematical Model, age 80</th>
<th>Thorpe, mean age 63</th>
<th>Blake, age in between 55-70</th>
<th>Albertsson, age in between 72-98</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper threshold</td>
<td>-1.15SD</td>
<td>-1.55SD</td>
<td>-2.15SD</td>
<td>-1.45SD</td>
<td>-1.45SD</td>
</tr>
<tr>
<td>Lower threshold</td>
<td>-2.35SD</td>
<td>-2.85SD</td>
<td>-3.45SD</td>
<td>-2.75SD</td>
<td>-2.75SD</td>
</tr>
</tbody>
</table>

*Table 2. Thresholds for the Calscan T-score calculated in different studies[53,54,52]*
We considered the range between the upper and lower threshold to be remarkably wide. An explanation for this might be the relatively low correlation between the Calscan and DXA (r=0.47 to 0.61, this thesis). This low correlation might be caused by the different percentages of trabecular bone at the calcaneus, hip or spine which are 90%, 40% and 66%, respectively. As trabecular bone is metabolically active in contrast to cortical bone, it is reasonable to expect that this leads to different measurements of BMD. A second reason for the low correlation might be the more accurate technique of measuring BMD by the Calscan. The Calscan adds a laser beam to conventional DXA technology which makes it possible to measure bone mineral content without the influence of adipose tissue both inside and outside the measured bone[50]. The absorption of X-rays in adipose tissue, bone mineral and lean soft tissue is different, which gives rise to accuracy errors up to 20% in measurements of BMD with DXA[55,50]. Thus, based on the probably more accurate measurement of BMD by the Calscan and because the Calscan is an user-friendly apparatus for both patient and doctor, it is favourable to use the Calscan over DXA in the measurement of BMD in clinical patients. In case osteoporosis is detected by the Calscan, anti-osteoporosis medication can be initiated immediately. Because almost half the patients cannot be classified on the basis of the Calscan the following observation described in chapter 5 is of extra importance: only 44% of hip fracture patients were screened for osteoporosis at the FLS. This is an interesting observation seen in the light of the fact that the American National Osteoporosis Society considers a hip fracture as a proof for osteoporosis without a previous BMD measurement[56]. Supportive for the American strategy is the fact that hip fractures are associated with at least a 2-fold increase in mortality and a 2.5-fold increased risk of a subsequent fracture[57,58]. Moreover, a previous study described a 35% reduction in subsequent fractures in patients who were treated for osteoporosis because of their hip fracture, and without a previous BMD measurement[16]. So in the clinical setting early treatment for osteoporosis might be started based on Calscan measurements and in those patients with a hip fracture.

Based on these assumptions we describe in chapter 6 of this thesis several ways in which the percentage of patients being screened for osteoporosis can increase. We also describe the reasons why patients did not attend our FLS and which patients did not attend our FLS. The first way of increasing the number of patients being screened for osteoporosis is an active approach to all patients who did not show up for their appointment to the FLS. For the purpose of this study all “no-shows” were contacted by phone, resulting in an increase of attendance to our FLS from 44 to 64%. Another way of improving the percentage of patients being screened for osteoporosis is a better selection of patients who need this screening. A hip fracture can be considered a proof for osteoporosis without the need for measurement of BMD with DXA[59,16]. This is an important conclusion because hip fractures are the most frequent occurring fractures in elderly patients and in chapter 5 and 6 we show that 47-56% of hip fracture patients did not attend the FLS. When only non-hip fracture patients do have to be referred to the FLS, the percentage of patients being screened for osteoporosis at our FLS would have been 72%. Another way of improving the percentage of patients being screened for osteoporosis is incorporating the Calscan in this screening. By doing that, 83% of all patients could be classified as either osteoporotic or non-osteoporotic. Combining all measures the percentage of patients being screened for osteoporosis can increase to an impressive 91% (table 3).
We already showed that the Calscan is a valid measurement instrument in screening for osteoporosis (this thesis). However, the Positive Predictive Value (PPV) of the Calscan in diagnosing osteoporosis has yet not been calculated but is important because anti-osteoporotic treatment has adverse effects. The PPV is calculated by comparing the number of patients classified osteoporotic by the Calscan correctly (DXA T-score ≤-2.5SD) versus the total number of patients classified osteoporotic by the Calscan. In chapter 6 we showed that the PPV was 68% when the whole group of fracture patients was analyzed, improving to 75% when only non-hip fracture patients were analyzed. Although a PPV in between 68 and 75% is low, we think it is acceptable as side effects of anti-osteoporotic medication are relatively mild and treating osteoporosis as soon as possible is important to prevent subsequent fragility fractures[29,25].

The main reasons why patients did not show up for their appointment to our FLS, were: not interested 68%, succumbed 24%, no appointment 3%, or living outside the region 5%. It appeared that patients admitted to the hospital from a nursery home or discharged to a nursery home, patients with cognitive impairment or a delirium, and elderly patients significantly less often attended the FLS. In other words the geriatric patient, who probably favors most from screening for osteoporosis, did not attend the FLS. It is therefore important to improve the percentage of patients being screened for osteoporosis, which also will result in an increase of geriatric patients who are screened for this. Other ways than DXA in this screening should be considered.

**Part 3: Secondary osteoporosis**

Adequate screening for osteoporosis depends not only on a reliable measurement tool, but also on identifying risk factors for subsequent fragility fractures. Certain diseases, drugs, or deficiencies can decrease BMD or bone quality, resulting in an increased fracture risk. This is called secondary osteoporosis. Laboratory tests can be obtained in patients to

<table>
<thead>
<tr>
<th>Fracture Liaison Service</th>
<th>Active approach to “no-shows”</th>
<th>Improving selection for screening through FLS</th>
<th>Incorporating the Calscan in screening for osteoporosis</th>
<th>Diagnosing osteoporosis by either: hip fracture, Calscan, or DXA</th>
</tr>
</thead>
<tbody>
<tr>
<td>44%</td>
<td>64%</td>
<td>72%</td>
<td>83%</td>
<td>91%</td>
</tr>
</tbody>
</table>

**Table 3: Percentage of patients being screened for osteoporosis**

1 This is the percentage of patients being screened for osteoporosis by DXA through an FLS[3]
2 This the percentage when all patients who did not show up for their appointment at the FLS, were contacted by phone
3 This is the percentage when only non-hip fracture patients over 50 years do have to be referred to the FLS, hip fracture patients are considered osteoporotic without a previous BMD measurement, conform the American Osteoporosis Guideline
4 This is the percentage when the Calscan is incorporated in the screening for osteoporosis in all fracture patients >50 years of age
5 This is the percentage when all hip fracture patients are considered to be osteoporotic, and non-hip fracture patients are classified either by Calscan or DXA
screen for secondary osteoporosis. However, there is no conclusive evidence about which panel of laboratory tests should be used[3,60]. As more and more patients are being screened through FLSs, it is important to address the need for screening for secondary osteoporosis in this specific patient group as well as which laboratory tests should be used for this screening and the financial aspects of this screening. In chapter 7 we describe our study about the value of laboratory tests in screening for secondary osteoporosis at the FLS. Secondary osteoporosis in this study was defined as an underlying disease which could be related to a low BMD (osteopenia and osteoporosis). We considered laboratory testing useful when the prevalence of underlying diseases was at least 15%. This was only true for osteoporotic male patients in which the prevalence of secondary osteoporosis was up to 18.2%. Laboratory tests appeared to be as often abnormal in patients without osteoporosis compared to patients with a low BMD. The costs to diagnose 1 patient with an underlying disease were significant (up to €972). If only male patients with osteoporosis were screened for underlying diseases these costs could be reduced till €225. We therefore concluded that screening all patients at an FLS for secondary osteoporosis by a standard set of laboratory tests is probably not useful, but male osteoporotic patients might benefit from this screening. However, our study had some limitations. The most important limitation was that the set of laboratory tests was not complete in all patients, and vitamin D was not routinely measured. Moreover, we only described patients with a low BMD.

Recently, some new insights in the definition and importance of screening for secondary osteoporosis were published. It was emphasized that secondary osteoporosis not only points to contributors decreasing BMD, but also bone quality, or both, resulting in an increased fracture risk (Table 4)[61]. The term SECOb (secondary osteoporosis and other metabolic bone diseases) was introduced, and is more adequate than secondary osteoporosis, as SECOb can be found in patients with a recent clinical fracture, regardless of BMD[61].
Secondary osteoporosis and metabolic bone disease

Regardless of osteoporosis, as SECOB can be found in patients with a recent clinical fracture, other metabolic bone diseases) was introduced, and is more adequate than secondary osteoporosis. The term SECOB (secondary osteoporosis and metabolic bone disease) was introduced, and is more adequate than secondary osteoporosis and may benefit from this screening. However, this chapter focuses on SECOB and their contribution to bone loss or fracture risk or both.

Table 4. Overview of SECOBs that contribute to bone loss or fracture risk or both.

<table>
<thead>
<tr>
<th>Endocrine diseases</th>
<th>Hematologic and oncologic diseases</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acromegaly</td>
<td>Hemophilia</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Multiple myeloma</td>
<td>Antidepressants</td>
</tr>
<tr>
<td>GH deficiency</td>
<td>MGUS</td>
<td>Antiepileptics</td>
</tr>
<tr>
<td>Hypercortisolism</td>
<td>Lymphoma/leukemia</td>
<td>Aromatase inhibitors</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Systemic mastocytosis</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Thalassemia</td>
<td>Cyclosporin</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Disseminated carcinoma</td>
<td>Glitazones</td>
</tr>
<tr>
<td>Male hypogonadism</td>
<td>Chemotherapy</td>
<td>Gonadotropin-releasing hormone agonists</td>
</tr>
<tr>
<td>Premature menopause</td>
<td></td>
<td>Heparin</td>
</tr>
<tr>
<td>Central adiposity</td>
<td>Connective tissue diseases</td>
<td>Loop diuretics</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Marfan’s syndrome</td>
<td>Proton-pump progesterone acetate</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Osteogenesis imperfecta</td>
<td>Thiazolidinediones</td>
</tr>
<tr>
<td>Chronic biliary tract obstruction</td>
<td>Pseudoxanthoma elasticum</td>
<td>Thyroxine (excessive)</td>
</tr>
<tr>
<td>Gastrectomy/gastric bypass</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Miscellaneous conditions and diseases</td>
<td>Other</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>AIDS/HIV</td>
<td>Anorexia nervosa</td>
</tr>
<tr>
<td>Malabsorption (other than celiac disease)</td>
<td>Amyloidosis</td>
<td>Osteomalacia</td>
</tr>
<tr>
<td>Rheumatic diseases</td>
<td>Chronic metabolic acidosis</td>
<td></td>
</tr>
<tr>
<td>Spondyloarthritides, including ankylosing spondylitis and psoriatic arthritis</td>
<td>Congestive heart failure</td>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Depression</td>
<td>Smoking</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>End-stage renal disease</td>
<td>Immobilization</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>Muscular dystrophy</td>
<td>Low calcium intake</td>
</tr>
<tr>
<td></td>
<td>Sarcoïdosis</td>
<td>Low protein intake</td>
</tr>
<tr>
<td></td>
<td>Weight loss</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Overview of SECOBs that contribute to bone loss or fracture risk or both. Vitamin D Deficiency was only considered to be a SECOB when it resulted in secondary hyperparathyroidism and therefore not included in the presented list above.

The prevalence of contributors to SECOB described in the literature is with 26-51% higher than the prevalence we calculated in our study. Moreover, the importance of diagnosing and managing these contributors in fracture patients over 50 years is emphasized in literature, to maximize subsequent fracture prevention. The reason that we found a lower prevalence might be caused by the previously mentioned limitations of our study, the difference in definition of secondary osteoporosis and SECOB, and the different set of laboratory tests used to screen for contributors to SECOB.

In the discussion which contributors to SECOB should be considered at an FLS it is important to realize which contributors are: treatable (e.g. hyperthyroidism, male hypogonadism, and primary hyperparathyroidism), results in a contra-indication for specific anti-osteoporosis therapy (e.g. bisphosphonates in renal insufficiency or in patients with Calcium malabsorption), or demands follow up (e.g. monoclonal gammapathy of undetermined significance) [61,62,60]. On the other hand not all contributors to SECOB can be treated and not all treatment of contributors to SECOB result in a decrease of subsequent fracture risk [61]. Table 5 shows the suggested laboratory tests by Bours and the Dutch guideline on osteoporosis (CBO).
Table 5. Laboratory tests advised by Bours to screen for newly diagnosed SECOB and by CBO to screen for secondary osteoporosis

<table>
<thead>
<tr>
<th>Bours[61]</th>
<th>CBO[3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>Calcium</td>
</tr>
<tr>
<td>Phosphorus</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>Creatinine</td>
</tr>
<tr>
<td>Albumin</td>
<td>Albumin</td>
</tr>
<tr>
<td>ESR¹ rate (ESR)</td>
<td>ESR²</td>
</tr>
<tr>
<td>24h urine Calcium in men</td>
<td>TSH²</td>
</tr>
<tr>
<td>Serum testosterone in men &lt; 70 years</td>
<td>Serum testosterone in men &lt; 70 years</td>
</tr>
<tr>
<td>Under debate: 25(OH)vitamin D</td>
<td>25(OH)vitamin D</td>
</tr>
</tbody>
</table>

¹ ESR: Erythrocyte sedimentation rate
² TSH: Thyroid stimulating hormone

Bours did not include TSH to the laboratory panel, although thyreotoxosis is a treatable disorder with a clear impact on BMD and fractures. TSH should therefore be included in the screening for SECOB. The routine evaluation of erythrocyte sedimentation (ESR) rate is questionable as there is no evidence that ESR contributed to the finding of new contributors to SECOB[63]. The value of measuring vitamin D at an FLS is also under debate. Hegeman and Dumitrescu confirmed the high prevalence of vitamin D deficiency in Dutch patients screened at an FLS, respectively 64% and 73%[64,14]. The Dutch CBO Consensus on osteoporosis states that vitamin D should always be prescribed to patients living in nursery homes or discharged to nursery homes[65]. All these arguments suggest that vitamin D should be prescribed to all fracture patients over 50 years of age*. A reason why vitamin D should perhaps be measured is that in patients with secondary hyperparathyroidism, the administration of bisphosphonates without a previous correction of vitamin D levels can result in a dangerous decrease of the level of serum Calcium. In this specific group of patients a booster of vitamin D is advocated to correct the vitamin D level as soon as possible and before bisphosphonates are initiated.

In conclusion, we showed in our study that screening all patients at an FLS with a standard set of laboratory tests is not useful. This is in contrast to recent literature, which advocates this screening because of the high prevalence of contributors to SECOB. However, the true advantage of screening for contributors to SECOB has to be determined, because there is no evidence that this will reduce the number of subsequent fractures. Moreover, a true cost effectiveness analysis is lacking and probably worthwhile. Important data from our study is that laboratory costs to diagnose a contributor to SECOB can be enormous. These are the reasons that I think that the routine use of laboratory tests at an FLS should be reconsidered.

* The benefits of vitamin D supplementation in older people are well recognized, which is the reason that previous studies suggest to supplement 800IU vitamin D per day to all patients, especially osteoporotic patients[1-5]. When Vitamin D is routinely supplemented to patients, one should keep in mind that the total intake of vitamin D has to be below 2000IU (50ug) per day, which is considered the safe upper threshold[3]. On the other hand, toxic effects of vitamin D are not described in dosages below 4000IU per day[3].
**Part 4: Epilogue**

Screening for osteoporosis has improved quite a lot over the last few years. However, almost half the patients who should be screened for osteoporosis do still not attend the FLS. It appears to be especially the older geriatric (hip fracture) patient who is not attending the FLS, whereas this patient group probably favors most from osteoporosis screening[20,66]. In this thesis we highlighted some other options than BMD measurement with DXA to diagnose osteoporosis which can improve the number of patients being screened for osteoporosis and we suggested on how the FLS could be arranged.

First of all, as vertebral fractures can be seen as a proof for osteoporosis we suggest that this diagnosis can be easily made in case a lateral chest X-ray is available. When a lateral chest X-ray is not available spinal radiographs can be obtained. The diagnosis of a hip fracture might also be used as a proof for osteoporosis, conform the American guideline on osteoporosis[67]. In the United Kingdom, the National Osteoporosis Guideline Group also recommends osteoporotic treatment in women with a prior fragility fracture, particularly of the hip, wrist and spine, without BMD measurement[68]. By using a hip fracture as a proof for osteoporosis the percentage of patients being screened for osteoporosis will definitely further improve. Another option to improve the percentage of patients being screened for osteoporosis, is the incorporation of the Calscan in this screening. Because measurement of BMD with the Calscan is not the golden standard we still advice to refer all patients to an FLS, but those patients who are not capable or willing to attend the FLS will at least receive the best possible diagnostic work up (figure 2). In figure 3 we show a possible treatment algorithm which can be used in screening for osteoporosis in fracture patients over 50 years of age.

When all these options are incorporated in the screening for osteoporosis the percentage of patients being screened will further improve, which probably results in a decreased fracture risk in these patients.
Figure 2. Flowchart describing the diagnostic process of screening for osteoporosis as can be used in patients over 50 years admitted to the emergency department.

* Patients treated for osteoporosis because they suffer from a vertebral- or hip fracture should also be referred to the FLS. Although treatment for osteoporosis is indicated in this group of patients BMD measurement with DXA at the beginning of treatment can be compared to BMD measurement with DXA after 5 years of treatment to decide whether or not treatment should be continued.
Figure 2. Flowchart describing the diagnostic process of screening for osteoporosis as can be used in patients over 50 years admitted to the emergency department.

* Patients treated for osteoporosis because they suffer from a vertebral- or hip fracture should also be referred to the FLS. Although treatment for osteoporosis is indicated in this group of patients, BMD measurement with DXA at the beginning of treatment can be compared to BMD measurement with DXA after 5 years of treatment to decide whether or not treatment should be continued.

**Figure 3.** Treatment protocol of patients screened at the FLS.

The two important questions which should be addressed in the near future are:

1. How can we better assess bone strength using non-invasive technologies and thus further refine or identify patients at high risk for a fragility fracture?

   As we know the goal of an FLS is to prevent subsequent fractures. The pathogenesis of osteoporosis related fractures is shown in figure 4.

**Figure 4.** Pathogenesis of osteoporosis related risk factors (original from Cooper, modified in the NOF guideline 2014) [59,69]
Chapter 8

This figure clearly shows that osteoporosis is not equivalent to low BMD measured by DXA. This awareness is crucial in further improvement of osteoporosis care. Too many clinicians still use BMD measurement as the only criterion of proofing osteoporosis, which results in under diagnosing osteoporosis.

As is shown in the introduction of this thesis, fracture risk is multicausal, which resulted in different fracture risk algorithms. These fracture risk algorithms include bone- and/or fall related risk factors to calculate the probability of a subsequent fracture. One of these fracture risk algorithms is FRAX®, which is introduced by the WHO to calculate the probability of a fracture with or without BMD measurement. I expect FRAX® to be used in the near future to diagnose osteoporosis, independent on BMD. However, at the moment, evidence is lacking to use FRAX® in choosing specific osteoporosis medication to reduce fracture risk. Further studies will be needed to provide greater insight into the potential correlation between osteoporosis treatment efficacy and FRAX® based 10-year probabilities[70]. At the moment FRAX® is incorporated in the Dutch, British and American guidelines on osteoporosis but only advised to use in patients with an osteopenic BMD[56,67,3]. In patients with osteopenia and a 10-year hip fracture probability ≥3% or a 10-year major osteoporosis-related fracture probability ≥20% based on FRAX®, treatment for osteoporosis is advocated[56,67].

2 Geriatric Fracture Care, what does it mean?

Special care for the elderly fracture patient is developing quickly in the Netherlands. An important initiative was the initiation of care for assessing osteoporosis, resulting in the first Dutch FLS in 2003. Because of its success, nowadays almost every hospital has an FLS. In 2008 fracture care in elderly patients was further improved by the foundation of the Geriatric Fracture Center (GFC) in Almelo, the Netherlands. Till then, fracture treatment in geriatric patients was characterized by low treatment urgency at the emergency department, consultation with several specialists in case of co morbidity, and consultation with a geriatrician only in cases of severe postoperative confusion. There were no standard clinical pathways, nor was there a multidisciplinary treatment plan with a proactive approach to prevent or limit complications. Patients were admitted to various surgical wards to spread the care burden between the nursing staff. This is in contrast to the process at the GFC which is based on the treatment principles of a clinic in Rochester, New York, with a “lean-business-model” in mind[71,72]. This approach examines every step of the intervention, eliminating those that are not per se useful, and standardizing best practices where appropriate[73]. The key concept is one co-managed model with trauma surgeons and geriatricians working together[73]. Care is described as patient-centered protocol-driven standardized care[73]. All patients follow the same care pathway with allowances for individual patient needs[73]. A care pathway is a multidisciplinary management tool for a specific group of patients based on evidence-based practice, in which the different interventions involved in the patient care are defined, optimized, and sequenced; outcomes are tied to specific interventions[74,75]. Implementing the concepts of the GFC results in an increased quality of care and decreased morbidity, mortality, and medical costs[76,77]. Non-published data from Almelo confirmed these good results. A total of 920 patients were admitted to the GFC in a 5 year period. The in house mortality decreased from 9 to 4%, with a 1 year mortality of 21.7%. This latter was a 33% decrease,
as based on the Charlson Comorbidity Index the expected 1 year mortality would have been 32.4%. The percentage of readmission within 30 days was 1.6%, which was 12% in a historic cohort of hip fracture patients treated in Almelo before the GFC was implemented.

By organizing care through care pathways and reviewing these care pathways, a continuously improvement is possible based on the most recent insights. Moreover, lacunas in knowledge becomes evident resulting in scientific research to overcome these lacunas. With this thesis I hope I contributed to a better understanding of osteoporosis and osteoporosis care in fracture patients and an improvement of geriatric fracture care.
References

8. RIVM Kosten van Ziekten database (2013)


66. De Klerk G (non published data): Osteoporosis screening among elderly patients with fractures: is there room for improvement?


