Chapter 1

General introduction and outline of the thesis
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**General Introduction**
Vertebral fractures are investigated in population-based studies of community dwelling elderly and in several patient groups, such as postmenopausal women and patients with rheumatic arthritis. Still vertebral fractures are often missed in clinical practice [1,2]. Since vertebral fractures are not yet explored and studied in geriatric patients, under diagnosis of vertebral fractures in geriatric patients is very likely. The first step to counteract this was to start up a study on the prevalence and clinical aspects of vertebral fractures in geriatric patients.

**Osteoporosis and vertebral fractures**
Osteoporosis is a chronic progressive metabolic bone disease, characterized by low bone mass and micro-architectural deterioration, which leads to enhanced bone fragility and an increased fracture risk [3]. In Caucasian populations, about 50% of the women and 20% of the men will have a fragility fracture in their remaining lifetime [3]. Osteoporosis is usually diagnosed by measuring bone mineral density (BMD) of the femoral neck of the hip or lumbar spine using a dual X-ray absorptiometry machine (DXA). The diagnosis of osteoporosis is confirmed when the BMD is below or equal to -2.5 standard deviations of the BMD of a young adult reference population, translated as a T-score [4].
To understand the main risk factors for osteoporosis, we have to understand bone remodelling, which starts at young age. There is a constant remodelling by bone resorption and bone formation, and during the last decade there has been much more understanding of the complex system influencing the bone remodelling. In youth bone is build up due to more bone formation than bone resorption. Peak bone mass is reached around the age of thirty, and varies due to genetic background, calcium intake and exercise [5]. Getting older, bone mass starts to decline in both women and men [5]. During and after menopause women tend to decline more rapidly for around 5 years when oestrogen protection diminishes [6,7]. In men bone mass declines as well, but less rapidly [8]. Therefore, after the age of forty, bone remodelling shows an imbalance with more bone resorption than bone formation. Therefore, the most important risk factor for osteoporosis and vertebral fractures is high age [3].
Another important risk factor is immobility, because bone is likely to build up when osteocysts are stimulated by body-weighted-activity, such as walking [9]. Underweight is a risk factor for vertebral fractures as well [3]. In addition, underlying diseases can provoke the onset of osteoporosis, especially diseases with malabsorption of calcium such as inflammatory bowel disease, or the incapacity to activate vitamin D in severe kidney failure, or diseases with a low rate of inflammatory response such as inflammatory rheumatic diseases (rheumatoid arthritis, ankylosing spondylitis, SLE) and COPD) [10]. Moreover, the use of glucocorticoids (in patients with inflammatory diseases) undermines bone health and is a major risk factor for osteoporosis [10].
Due to the age related decline in bone mass, bones get more fragile, and are more likely to fracture. The most prevalent type of fracture associated with osteoporosis is the
vertebral fracture [11]. In contrast to peripheral fractures, fractures in the vertebrae may occur even without an evident trauma. Although it has been suggested that 2 out of 3 vertebral fractures are asymptomatic, (e.g. they do not come to medical attention) [12], it has also been documented that vertebral fractures may lead to an increased morbidity: longstanding back pain, decreased mobility due to hyperkyphosis of the thoracic spine, breathing difficulties and loss of quality of life [13]. Moreover they are associated with increased mortality [14,15]. In addition, several studies have shown that vertebral fractures are important independent predictors of future fractures: prevalent vertebral fractures are associated with a 5-fold increased risk of a new vertebral fracture and a 2-fold increased risk of hip fractures [16-18]. Treatment for osteoporosis is available and has shown to be effective for elderly [19-21]. The main goal for treatment is secondary prevention by decreasing the risk for a new vertebral and non-vertebral fracture.

To select patients who might benefit from treatment, vertebral fractures should be diagnosed reliably. Vertebral fractures can be diagnosed on lateral X-rays of the spine with the semi quantitative method of Genant [22]. This method is widely used in scientific research [23,24]. However, as mentioned above, vertebral deformities often remain undiagnosed and therefore untreated. Underdiagnosis could be due to the fact that two-third of the vertebral fractures are ‘asymptomatic’. Another reason is that the diagnosis is missed on x-rays [1]. In addition, under treatment can be caused by doctors who do not fully understand the clinical relevance of vertebral fractures and their implications for future fracture risk [2].

Geriatric patients
Geriatric patients are elderly patients who can be distinguished from other patients due to their vulnerability and multi morbidity (more than one chronic illness). Geriatric patients show the maximum result of aging, when ageing can be seen as the result of a lifelong accumulation of molecular and cellular damage [25]. When this damage has almost used up the organ- and body reserves, functional decline occurs. The crucial threshold of age-related cumulative decline is the point on which ‘frailty’ becomes evident [26]. Frailty can be defined as “a geriatric syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, causing vulnerability to adverse health outcomes including falls and fractures, disabilities, hospitalization, institutionalization and mortality” [27].

It is estimated that one third of the people aged 85 and over are frail [28], which means that frailty does not becomes evident in all elderly. In fact, it can be undetected, and only comes to clinical attention when illness occurs. Loss of muscle mass (sarcopenia) and reduction in bone mineral density appear to be major drivers of frailty [28,29]. Although there is not much evidence on prevention or treatment of frailty, exercise and vitamin D can gain strength, increase mobility and therefore slow down or even restore functional decline [26].
General introduction and outline of the thesis

There are many tools to assess frailty in patients, but the most widely used frailty assessment are the criteria of Fried [28]. When 3 or more of the next 5 items are present, a patient is defined as frail: unintentional weight loss, slow gait, exhaustion, low energy and sarcopenia, measured with a hand-held dynamometer.

Aim of the thesis
Prevalence and incidence of vertebral fractures among geriatric patients are unknown, and the clinical burden of these fractures is not yet explored. The goal of our research that led to this thesis was to determine prevalence of vertebral fractures in geriatric outpatients and investigate the risk factors and clinical consequences.

Outline of the thesis
In chapter 2 the methodology of diagnosing vertebral fractures on a lateral X-ray of the chest is discussed. The result of the detection of vertebral fractures on the chest X-ray was matched with the diagnosis of vertebral fractures on a lateral X-ray of the thoracic spine. Chapter 3 consists of 2 articles on the prevalence of vertebral fractures among geriatric patients in total, and in geriatric males. Risk factors were explored. We especially searched for risk factors specific for the geriatric population such as co morbidity, cognitive decline and immobility.

To explore the consequences of prevalent vertebral fractures in this patient group we report in chapter 4 on incident vertebral fractures and associated mortality after a follow up of 3 years. It is well known that vertebral fractures in population-based studies are associated with mortality. We conducted our study to determine whether this association still exist in a patient group with high prevalence co morbidity, immobility and cognitive decline.

Chapter 5 describes our research on the relationships between vertebral fractures and the influence on postural control, gait pattern and falls. We started with a literature search, because there was no consensus in literature about measuring postural control in osteoporotic patients. Moreover, almost no studies on this subject are reported in elderly. The second article show results of a cohort of mobile geriatric patients who had a prospective fall calendar. It was postulated that vertebral fractures could contribute to an increased kyphosis, which in extreme forms can lead to a flexed posture and would contribute to more fall incidents.

Chapter 6 is an article on the statistical concept of the ‘time to benefit’ in preventive medication. We have performed a literature review on the methods in randomised clinical trials on osteoporosis treatment to express an early effect of treatment. We especially searched for methods that report on the exact moment in time when medication becomes effective. We used statistical process control to determine the time to benefit of alendronate based on data from the pivotal ‘Fracture Intervention Trial’ (FIT-trial) in which more than six thousand postmenopausal women were treated with alendronate or
Chapter 1

placebo. The article reveals the results of statistical process control that we conducted on the database of the FIT-trial.
In chapter 7 the summary and general discussion on the thesis is presented, focused on the clinical relevance and future studies for geriatric patients.
General introduction and outline of the thesis

References
