

# The phenotype and outcome of patients with a recent fracture at the Fracture Liaison Service

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## SUMMARY

Fractures constitute a major health care problem worldwide, and are expected to increase due to aging of the population. Fractures are associated with increased morbidity and mortality, have an impact on patients' quality of life, and result in major health care costs. They indicate an increased risk of subsequent fractures, which in highest immediately after the fracture. This means there is a window of opportunity for immediate recognition of this imminent subsequent fracture risk and start interventions to reduce the risk. Despite the well-known importance of secondary fracture prevention and various effective treatments being available, such as anti-resorptive drugs (i.e., bisphosphonates, denosumab, raloxifene) and osteoanabolic drugs (i.e., teriparatide and romosozumab), only a minority of patients receive appropriate evaluation and treatment. To close this treatment gap, Fracture Liaison Services (FLS) have been designed and implemented in post fracture care, since the first initiative reported in 1999, to facilitate case finding of patients aged 50 years and older with a recent fracture to provide routine assessment, and treatment in high-risk patients.

To further improve secondary fracture prevention, knowledge about risk factors in and outcomes of FLS patients is important. Potential risk factors are numerous and diverse and include both bone- and fall-related factors.

The overall aim of this thesis was to examine the bone- and fall-related phenotype of patients with a recent clinical fracture attending the FLS. Additionally, we aimed to examine the incidence of falls and subsequent fractures prospectively in a FLS population, and to study the impact of FLS care on subsequent fracture and mortality risk by comparing these outcomes before and after the implementation of a FLS.

For all chapters in this thesis, except Chapter 2, we used data from the FLS in the VieCuri Medical Center (Venlo, The Netherlands). This FLS was initiated at the end of 2007 at the outpatient clinic of the department of Internal medicine in close collaboration with the department of Trauma surgery and Orthopedic surgery. Procedures at the FLS were as follows. A trained nurse systematically selected all patients aged 50-90 years who visited the emergency department because of a clinical fracture using diagnostic codes. Patients with a radiologically confirmed fracture were invited at the FLS. Those who responded positively, visited the FLS approximately 3 to 4 months after the fracture event. Patients received a detailed questionnaire for the evaluation of clinical risk factors for falls and fractures, including medical history and medication use. Further, bone mineral density (BMD) was assessed by Dual Energy X-Ray Absorptiometry (DXA) at the lumbar spine, total hip, and femoral neck, and a blood sample was collected to detect contributors to secondary osteoporosis and metabolic bone disease (SECOB). In addition, from 2011 onwards, vertebral fracture assessment was performed using the DXA device. Based on the BMD and VFA results, calcium intake and serum 25(OH)D levels, treatment was initiated with anti-osteoporosis medication and calcium and vitamin D supplements according to the Dutch osteoporosis and fracture prevention guideline of 2011. Regular FLS care data were used in Chapter 3-5 and 7.

Additionally, we conducted a prospective observational cohort study in 500 consecutive patients who visited the FLS, and who were willing and able to participate (called the FX MoVie study). Excluded were non-Caucasian patients, patients with a fracture due to high energy trauma (i.e., another trauma than a fall from standing height or less (e.g., a fall from higher height than standing height and motor vehicle accident)), bone metastasis, failure of prosthesis or osteomyelitis, and patients with cognitive impairment (i.e., patients who were not *compos mentis* and could not understand the patient information). The primary objective of this study is to assess bone structure parameters and bone strength by HR-pQCT and physical activity in relation to falls, fractures and mortality in patients with a recent clinical fracture. Data from the FX MoVie study were used in Chapter 6 and 8.

## PART I – PHENOTYPE OF PATIENTS AT THE FRACTURE LIAISON SERVICE

In the first part of this thesis, we focused on several characteristics of the phenotype of patients at the FLS. In Chapter 2, we performed a literature survey to describe components of the bone- and fall-related phenotype of patients attending the FLS that had been reported in 33 FLS papers. The reported patient selection varied widely in terms of patient identification, selection for invitation and the proportion of patients that attended the FLS. Consequently, the reported phenotypic characteristics varied widely among the publications in terms of mean age (64-80 years), proportion of men (13-30%), and fracture location (2-51% hip, <1-41% vertebral, and 9-95% non-hip/non-vertebral fractures). Furthermore, the studies varied in performance of fracture risk evaluation. This high variability in patient selection and risk evaluation resulted in a highly variable phenotype. When reported, there was a high variability in the proportion of patients with osteoporosis (12-54%), prevalent vertebral fractures (20-57%), newly diagnosed contributors to secondary osteoporosis and metabolic bone disorders (3-70%) and fall-related risk factors (60-84%). We concluded that systematic studies on the presence and combinations of these risks are needed, to specify the bone- and fall-related phenotypes of patients attending the FLS.

In Chapter 3, we systematically evaluated the prevalence of comorbidities and medication use associated with increase bone- or fall-related fracture risk in patients attending our FLS clinic. In total, 66% of FLS patients had at least one bone- or fall-related risk factor, with at least one bone-related risk factor in 53%, and at least one fall-related risk factor in 46%. At least one bone-related risk factor and/or at least one fall-related risk factor was associated with age, BMI and major fractures, but not with gender and BMD. Nevertheless, comorbidities and medication associated with an increased bone- or fall-related risk were found across all subgroups (age, gender, fracture type, BMD and BMI). This indicates that systematic evaluation of these factors is important for a more profound assessment of subsequent fracture risk in FLS care.

In Chapter 4, we specifically evaluated the prevalence of celiac disease (CD) in FLS patients. CD was already diagnosed in 2 patients (0.19%), of whom 1 still had positive serology. Three other patients (0.29%) had positive serology for CD (one with gastro-intestinal complaints). In 2 of them, CD was confirmed by duodenal histology, resulting in a newly diagnosed biopsy-proven CD prevalence of 0.19%. The other patient refused further evaluation.

The total prevalence of CD at our FLS was 0.38% and within the range of reported prevalence in the Western-European population (0.33-1.5%). Based on these results, we concluded that standard screening for CD is not recommended in FLS care.

In Chapter 5, we specifically focused on the prevalence of cardiovascular risk factors in patients at the FLS. Based on medical history, 29.9% had at least one cardiovascular risk factor. Cardiovascular disease (CVD), venous thromboembolic events (VTE), hypertension (HT), and diabetes mellitus (DM2) were found in 13.7%, 1.7%, 14.9%, and 7.1%, respectively. CVD were more frequently present in men, whereas the prevalence of VTE, HT, and DM2 were similar in men and women. The prevalence of all cardiovascular risk factors increased with increasing age, with a prevalence up to 50% of men 70 years and older, and women 80 years and older. Myocardial infarction was found in 2.9% (2.0% in women, and 5.2% in men) and a stroke in 3.2% of patients (2.7% in women, and 4.7% in men). These results indicate that careful evaluation of medical history with respect to these risk factors should be performed in FLS patients before starting treatment with medications that are associated with an increased risk of cardiovascular events, such as Raloxifene, the recently new available osteo-anabolic drug romosozumab, and nonsteroidal anti-inflammatory drugs for fracture pain management (NSAIDs).

Many patients with a non-vertebral fracture (NVF) at the FLS also have a prevalent vertebral fracture (VF). The prevalence of prevalent VFs has been reported to be similar among BMD subgroups. No studies were available that evaluated whether the presence of a prevalent VF is associated with impaired bone micro-architecture in patients with a recent NVF.

In Chapter 6, we therefore evaluated the association between prevalent vertebral fractures (VF) and bone quality in terms of micro-architecture and calculated bone strength at the distal radius and distal tibia as measured with HR-pQCT in postmenopausal women with a recent non-vertebral fracture (NVF) at the FLS. Compared to postmenopausal women with a recent NVF without a prevalent VF, those with a recent NVF and at least one prevalent VF had lower total and trabecular volumetric BMD (vBMD) and trabecular number, and higher trabecular separation at the radius and tibia, and lower cortical thickness and calculated ultimate failure load and compressive bone strength at the tibia. Further, more severe prevalent VFs were associated with even lower total and trabecular vBMD and lower ultimate failure load and compressive stiffness at the radius and tibia, and lower trabecular number and higher trabecular separation at the radius. These results indicate that the presence and severity of prevalent VFs reflect generalized bone deterioration in postmenopausal women with a recent NVF, independent of femoral neck aBMD.

## PART II – OUTCOME OF PATIENTS AT THE FRACTURE LIAISON SERVICE

The second part of this thesis focused on outcomes of patients with a recent fracture at the FLS. Patients with a recent fracture have an increased risk of subsequent fractures and mortality. Subsequent fracture risk changes over time and is the highest immediately after a fracture. In Chapter 7, we evaluated whether FLS care was associated with reduced subsequent fracture and mortality risk over 3 years of follow-up by using data before FLS introduction (pre-FLS) and after FLS introduction (post-FLS). We found that the adjusted mortality risk in patients with a major/hip fracture as index fracture was 16% lower in the post-FLS group as compared to the pre-FLS group. Further, the subsequent major/hip fracture risk after a major/ hip index fracture was 33% lower in the first 360 days after index fracture post-FLS compared to pre-FLS, taking the competing risk of death into account. In patients presenting with a non-major/non-hip fracture, there was no difference in mortality or subsequent fracture risk between post- and pre-FLS. Based on these results, we concluded that FLS care was associated with a lower mortality risk in the first 3 years and a lower subsequent major/hip fracture risk in the first year in patients with a major/hip index fracture but not in patients with a non-major/non-hip fracture. The early impact on subsequent fractures may suggest that more focus on long-term adherence to treatment could further improve outcomes.

Finally, Chapter 8 described the 3-year incidence of incident falls and subsequent fractures, and their association in patients at the FLS. During the 3-year follow-up, 959 falls had been ascertained in 296 patients (60.7%) (i.e., fallers), and 60 subsequent fractures were ascertained in 53 patients (10.9%). Of all subsequent fractures, 78.3% were fall-related, of which 53.2% were sustained at the first fall incident at a median of 34 weeks. An incident fall was associated with an approximately 9-fold increase in the risk of subsequent fractures. These data indicate that subsequent fractures among patients on adequate treatment prescribed in a FLS setting are common and an incident fall is a strong predictor of subsequent fracture risk. Immediate attention for fall risk could be beneficial in an FLS model of care.

In conclusion, this thesis showed that the phenotype of FLS patients is heterogenic and that risk factors for osteoporosis, fractures and falls are common in a FLS population. Systematic evaluation of comorbidities and medication associated with an increased bone- and fall-related fracture risk, including cardiovascular risk is necessary for a profound fracture risk evaluation and adequate treatment recommendation. On the other hand, the prevalence of CD is low and comparable to that in the general population, hence systematic screening of CD is not recommended. Further, the presence and severity of prevalent vertebral fractures can be used as a marker for generalized bone deterioration, independent of BMD.

Implementation of the FLS has an important positive impact on subsequent fractures and mortality in patients aged 50-90 years with a recent fracture. However, despite treatment according to the current Dutch osteoporosis and fracture prevention guideline at the FLS, subsequent fractures are still common and an incident fall is a strong predictor for subsequent fractures, suggesting that immediate attention to fall risk could be beneficial in FLS care.