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

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ADDENDUM

IMPACT PARAGRAPH

SOCIAL AND SCIENTIFIC IMPACT

In this thesis we focused on the phenotype and the outcomes of patients aged 50+ years with a recent fracture attending the Fracture Liaison Service (FLS) for fracture risk evaluation and secondary fracture prevention. In the first part (**Chapter 2-6**), we focused on the phenotype of FLS patients and in the second part (**Chapter 7 and 8**), we focused on outcomes of patients with fracture at the FLS.

In **Chapter 2**, a literature survey was performed to describe components of the bone- and fall-related phenotype of patients attending the FLS and we found that there was a high variability in terms of patient identification (case finding), selection, and FLS attendance among the different studies. This resulted in a high variability in patient characteristics, such as mean age, proportion of men and fracture locations. Based on this survey it can be concluded that there is not a uniform phenotype of FLS patients in literature. This has the implication that many concepts, findings and reported outcomes of FLS patients cannot be compared and this limits the implementation of FLS care. It is therefore needed that the FLS care pathway has to be described in a clear manner, including at least a minimum set of key performance indicators and that we need a more standardized approach for reporting outcomes of FLS care.

We have translated the findings of **Chapter 2** in **Chapter 3**, where we systematically evaluated patients' medical history and medication overview to identify comorbidities and medications associated with an increased bone- or fall-related fracture risk in FLS patients. We found a high prevalence of patients with bone-related risk factors (53.2%), fall-related risk factors (45.6%) and a combination of both was present in 65.6% of patients. In line with the findings of chapter 2, these findings indicate that a systematic evaluation of medical history and medication use is important for a more profound assessment of subsequent fracture risk in FLS patients.

These findings have important implications for health care professionals in FLS care, but also for health care professionals in general since they should be aware of the impact the diseases they treat and the medication they prescribe have on fall and fracture risk. These findings also indicate that FLS care should not only be focused on performing a DXA, which is the case in many FLS facilities, but should also pay attention to specific fall and bone related risk factors, which was further addressed in detail in **Chapter 4 to 6**.

Based on previous work, where we have showed that ± 25% of FLS patients has an underlying disorder that attributes to fracture risk and that can be detected by laboratory evaluation, we specifically focused on the prevalence of celiac disease (CD) in **Chapter 4**. We found that the prevalence of CD was low and within the range of the general West-European population. Therefore, based on this study, standard

screening for CD as a part of the standard laboratory evaluation of FLS patients is not recommended. Nevertheless, it is still indicated to analyze the presence of CD in FLS patients with laboratory results, comorbidities or symptoms suggestive of CD. This finding is also important for efficient use of health care resources which are constantly increasing both in terms of health care costs as well as the number of patients in need of FLS care.

In **Chapter 5**, we specifically focused on the prevalence of cardiovascular risk factors in FLS patients and found that 30% of patients had a medical history of cardiovascular disease, venous thromboembolic event, hypertension and/or diabetes mellitus type 2. The prevalence of cardiovascular risk factors increased with age, was higher in men than in women but independent of BMD and fracture type. These findings indicate that, in line with the findings of chapter 2 and 3, FLS patients often have several fall and bone related comorbidities and that a substantial proportion of patients (also) has cardiovascular risk factors. In addition, the presence of cardiovascular disease has implications for osteoporosis medication such as the selective estrogen receptor modulator raloxifene, the recently approved osteo-anabolic drug romosozumab and non-steroidal anti-inflammatory drugs frequently used for pain management.

The association between prevalent vertebral fractures and decreased bone micro-architecture and strength of the distal radius and distal tibia assessed with high resolution peripheral computed tomography (HR-pQCT) in postmenopausal women with a recent non-vertebral fracture at the FLS as presented in **Chapter 6**, is relevant to patients and health care professionals as well as health care policy makers and health insurance providers. These findings underline the importance of detecting subclinical, prevalent, vertebral fractures in patients that present with a non-vertebral fracture since it is known that the risk of subsequent fracturs is substantially higher in patients with a prevalent vertebral fracture compared to not having a prevalent vertebral fracture, independent of BMD, and emphasize the importance of performing systematic vertebral fracture assessment, which is now also implemented in the recently updated new Dutch guideline on osteoporosis and fracture prevention . In addition, the presence of a vertebral fracture has impact on the choice of treatment, since the Dutch guideline recommends treatment with osteoanabolic medication as first line therapy in high-risk patients with a low BMD in combination with one or more moderate or severe vertebral fractures. Furthermore, information on baseline vertebral fracture status allows reliable identification of incident vertebral fractures during treatment, which may change treatment. Besides on lateral DXA images, prevalent vertebral fractures can be identified with other imaging modalities such as chest X-ray, thoracal and abdominal CT and magnetic resonance imaging (MRI).

Thus, improvement in patient care can also be achieved by increasing awareness for the presence of vertebral fractures as opportunistic finding among radiologists and other health care professionals. The use of software tools can help identify and classify prevalent vertebral fractures accurately and efficiently. Also, the application of artificial intelligence to detect vertebral fractures is emerging.

In **Chapter 7 and 8**, we focused on outcomes of patients with a recent fracture. In **Chapter 7**, we evaluated the impact of FLS care on subsequent fracture and mortality and concluded that the implementation of the FLS resulted in a lower mortality risk and a lower subsequent major or hip fracture risk in patients presenting with a recent major or hip fracture at the emergency department. Good quality studies reporting the impact of FLS care on subsequent fractures and mortality are urgently needed to demonstrate value to patients, health and social care systems and ultimately justify sustainable support by health insurers and health care policy makers. Currently, secondary fracture prevention management is assigned low priority by primary care physicians, specialists, health administrators, policy makers, and the general public. Fractures are still perceived as a problem related to aging or the result of an unfortunate trauma and consequently, secondary fracture risk evaluation and prevention is considered unnecessary. Even though health initiatives, such as the international Capture the fracture program and the Dutch 'verbetersignalement osteoporose, Zorginstituut Nederland', were started to improve awareness and quality of care, the proportion of fracture patients receiving adequate diagnostic evaluation for fracture risk and treatment or fracture prevention is still low and may be even declining. There is an urgent need for recognition of the impact of fractures on quality of live, subsequent fractures and mortality by the general public, health care professionals and policy makers. More research on the impact of FLS care on subsequent fractures and mortality, as well as quality of life and health care and social costs may help further improvement of FLS care implementation.

The prospective evaluation of incident falls in relation to subsequent fractures in patients who visited the FLS due to a recent fracture as presented in **Chapter 8**, provides novel information regarding the imminent fall risk that may contribute to the well-known imminent subsequent fracture risk in patients with a recent fracture. The finding that 10% of FLS patients sustained a subsequent fracture within three years after an index fracture, despite adequate evaluation and treatment directly after their index fracture, and that 90% of all subsequent fractures were fall-related, suggests that immediate attention to fall risk could be beneficial in FLS care. Despite conflicting results that have been published about the effect of fall prevention strategies on subsequent fractures, we hypothesize that fall interventions could be effective in

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patients at highest risk, namely those with a recent fracture at risk of falling. Future research should focus on how to identify patients at highest risk of falling and to evaluate multifactorial fall prevention interventions in these patients.

The findings in this thesis have been widely distributed to and recognized by the scientific society. The work of all chapters has been presented at international and national conferences and published in peer reviewed international journals, including the highest ranked journals in the field of bone research. The work presented in **Chapter 3** was awarded with an allied health professional award by the European Calcified Tissue Society in 2015.