

Metabolic Bone Disorders in patients attending the Fracture Liaison Service

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Valorisation

Worldwide, the incidence of fractures is high and is expected to increase. In the Netherlands, the incidence of fractures in patients of 50 years or older was 119,000 between 2009-2011, and is estimated to increase by 40% in 2030. Fractures cause direct costs for society. €200 million was spent on treatment of osteoporosis-related fractures in 2010, which was estimated to increase with 50% by 2030. More importantly, pharmacotherapeutic prevention of fractures could lead to a reduction of costs in 2030. Besides the costs of acute fracture treatment, fractures lead to morbidity, an increased subsequent fracture risk and an increased mortality risk.

Patients with a recent fracture have a doubled risk for (subsequent) fractures as compared to subjects without a fracture. However, this increased fracture risk is not constant over time, and is higher at short than at long-term. This is referred to as imminent fracture risk. As most subsequent fractures occur within short term, early evaluation of this fracture risk, followed by immediate fracture prevention is indicated. The Fracture Liaison Service (FLS) is considered by Dutch and international guidelines, to be the best organisational approach for secondary fracture prevention. Since the implementation of the Dutch guideline of 2011, more than 80% of hospitals in the Netherlands have an FLS, which is substantially higher than in other countries.

Many risk factors for low bone mineral density (BMD) and fracture risk have been documented. However, the frequency in patients who actually present with a recent fracture was not known.

The work presented in this thesis shows, that one in four patients 50 years or older with a recent fracture at the FLS had a previously unknown contributor to secondary osteoporosis and metabolic bone disorders, two thirds of patients had vitamin D insufficiency, most had insufficient daily calcium intake and one in four had a prevalent vertebral fracture in addition to the non-vertebral fracture they presented with at the FLS.

Previously unknown disorders, vitamin D deficiency and prevalent vertebral fractures were not only present in patients with osteoporosis, but at any level of BMD, in both sexes, at any age and any location of the presenting fracture.

In order to fully document their phenotype, systematic evaluation of secondary osteoporosis and metabolic bone disorders and vertebral fracture assessment (VFA) should be considered at the FLS as a standard evaluation of post-fracture care in all patients of 50 years or older with a recent fracture.

Contributors to secondary osteoporosis and metabolic bone disorders

Adequate diagnosis and treatment of underlying disorders that increase bone loss and fracture risk may attribute to a lower subsequent fracture risk in addition to treatment with anti-osteoporosis medication. It also provides an opportunity to reduce subsequent

fracture risk in patients who don't have an indication for treatment with anti-osteoporosis medication. Since known and previously unknown contributors to secondary osteoporosis and metabolic bone disorders are highly prevalent in FLS patients with or without osteoporosis, as shown in this thesis and by others, optimal organisation of FLS care should include laboratory assessment in all patients, regardless of BMD outcome.

These findings may have implication for future guidelines on secondary fracture prevention care, since the current Dutch guidelines advocates laboratory testing in FLS patients only when they have osteoporosis (CBO guideline) or on indication and only in patients with osteoporosis (general practitioners' guideline). It also may have consequences for implementation in (hospital) care systems since standard laboratory testing increases the direct costs of FLS care.

Vitamin D supplementation

Vitamin D insufficiency is endemic worldwide. In this thesis, two thirds of patients at the FLS had vitamin D insufficiency, and 8% had also secondary hyperparathyroidism. This raises the question whether serum levels of 25(OH)D should be measured in all patients with a recent fracture. The assessment of serum 25(OH)D levels is costly. We showed that a dose of 800IU/day was sufficient to achieve a serum 25(OH)D \geq 50 nmol/l within one year in 80% of patients, regardless of baseline serum 25(OH)D level. The costs of vitamin D supplementation are limited, our data therefore suggest to start supplementation with 800IU of vitamin D per day in all patients with a recent fracture, and only to assess serum 25(OH)D levels in patients in whom severe vitamin D deficiency is suspected.

An important reason for vitamin D supplementation is to provide sufficient calcium absorption. The finding of a suboptimal daily calcium intake in more than 90% of patients indicates that all patients with a recent fracture should also be advised on optimal calcium intake preferably by diet or if needed by calcium supplements.

We advocate the implementation of a standardised approach at the FLS, with an individualised advise on calcium intake and standard supplementation of 800IU vitamin D per day, without serum 25(OH)D measurement.

Diagnosing vertebral fractures at the FLS

Vertebral fractures are the most frequent prevalent and incident fractures, but most vertebral fractures do not present with the acute signs and symptoms of a recent fracture, and therefore are often overlooked. Although most vertebral fractures are

asymptomatic, patients may complain of chronic back pain or have hyperkyphosis or loss of height.

When systematically implementing vertebral fracture assessment using dual X-ray absorptiometry (DXA) in all FLS patients, we found that one in four of patients with a recent non-vertebral fracture also had a prevalent vertebral fracture. This indicates that their non-vertebral fracture was not the first fracture. Patients with a prevalent vertebral fracture in addition to a recent non-vertebral fracture have an even higher imminent fracture risk. Therefore, applying vertebral fracture assessment helped to identify those patients with the highest fracture risk, even at short term.

The diagnosis of prevalent vertebral fractures also has impact on therapeutic decisions. It increases the number of patients eligible for starting treatment and, therefore, adds to the reduction of subsequent fracture risk in FLS patients. It may also be relevant for switching anti-osteoporosis treatment or for the therapy of first choice. As an example, it has been shown that bone-forming agents are superior in fracture prevention as compared to anti-resorptive treatment in patients with vertebral fractures in addition to low BMD.

From a societal perspective, these findings have widespread consequences. The FLS has been documented to be the most effective organisational approach for secondary fracture prevention immediately following a fracture. Considering a yearly incidence of 120.000 fractures in the Netherlands, per hospital a mean of 1.200 patients with a recent fracture present at the emergency department. However, only half of them subsequently attend the FLS. Our findings are restricted to those patients, and cannot be generalised to all patients with a recent fracture. The reasons for this evaluation gap are still unclear. In how far non-attending patients are more or less healthy than those visiting the FLS is unknown.

From a patient perspective, our results support the value of an FLS as an effective way to evaluate the phenotype of the patient, to have better insights in their fracture risk, and to make appropriate decisions on treatment options to decrease the subsequent fracture risk and mortality at short term.

Planning

In the Netherlands, many FLSes are already running, with variation in organisation and diagnostic work-up.

Future planning and realisation about the organisation of the FLS should include improvement of the participation gap, as only 40-60% of patients with a recent fracture are attending the FLS; the evaluation gap; and adherence to treatment.

In this context, further questions in future planning and realisation include: Who does what in the follow-up of patients at short and long term? What is the role of fall prevention immediately after a recent fracture, in preventing the high imminent fracture risk?

Lastly future planning and realisation should also include cost-effectiveness studies with real world data. To answer such questions, more attention will be needed to evaluate the impact of FLS-care on quality of life, subsequent morbidity, falls, fracture risk and mortality.