The influence of vitamin D and osteoporosis on fracture healing

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General introduction and outline of this thesis

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GENERAL INTRODUCTION

Bone is a fundamental part of the musculoskeletal system. Sufficient strength is needed to bear loads and transmit muscles forces.[1] There are three types of cells present in bone that are involved in the growth and healing of bone; osteoblasts (differentiated bone-forming cells), osteocytes (differentiated osteoblasts fully surrounded by osteoid or bone matrix, which maintains the bone matrix) and osteoclasts (bone resorption).The major structural component (90%) of bone matrix is collagen. This matrix together with other components becomes mineralized to form bone. During mineralisation hydroxyapatite crystals are formed. These consist of calcium and phosphate, which can be released into the blood after bone resorption by osteoclasts. Due to the storage of calcium and phosphate, bone also plays a role in homeostatic regulation of blood calcium level (Figure 1).[2] The homeostasis of calcium is regulated by parathyroid hormone (PTH), vitamin D and calcitonin. PTH secreted by the parathyroid gland, stimulates bone resorption by osteoclasts resulting in the release of calcium. It also reduces excretion of calcium by the kidneys and stimulates calcium absorption by the small intestine. Vitamin D also results in an increased calcium concentration. Calcitonin, produced by the thyroid gland, and PTH have reciprocal effects in the regulation of calcium homeostasis.

Vitamin D has been discovered during the search for a treatment of rickets, an emerging disease during the 19th century. Around 1900 it was accepted that rickets was associated with abnormally low mineralisation of bones, but it took till 1922 to prove that it was caused by a deficiency of vitamin D.[3,4] Vitamin D can be synthesized in the skin through sunlight exposure. Ultraviolet B radiation penetrates the skin and converts 7-dehydrocholesterol to vitamin D3 (cholecalciferol). Vitamin D is also obtained from food products containing vitamin D3 or vitamin D2 (ergocalciferol). Both forms are converted to 25-hydroxyvitamin D [25(OH)D] (calcidiol) in the liver, and hydroxylated by 25-hydroxyvitamin-D-1α-hydroxylase in the kidneys to its most active form: 1,25-dihydroxyvitamin D [1,25(OH)2D3] (calcitriol) (Figure 1.).[5]

Vitamin D acts in its classical endocrine function to increase calcium concentration in the blood via vitamin D receptors (VDRs) in the intestine, kidney, parathyroid glands and bone. In the duodenum and small intestine activated VDRs lead to increased epithelial absorption of calcium.[6,7] In the kidney vitamin D stimulates the re-absorption of calcium in the distal tubules.[8] In the parathyroid glands vitamin D gives a negative feedback on the PTH production. In bone vitamin D results in the expression of the receptor activator of nuclear factor-κB ligand (RANKL). RANK, the receptor for RANKL on preosteoclasts, binds RANKL, which induces preosteoclasts to become mature osteoclasts. Mature osteoclasts remove calcium and phosphorus from the bone, maintaining calcium and phosphorus levels in the blood.[5]

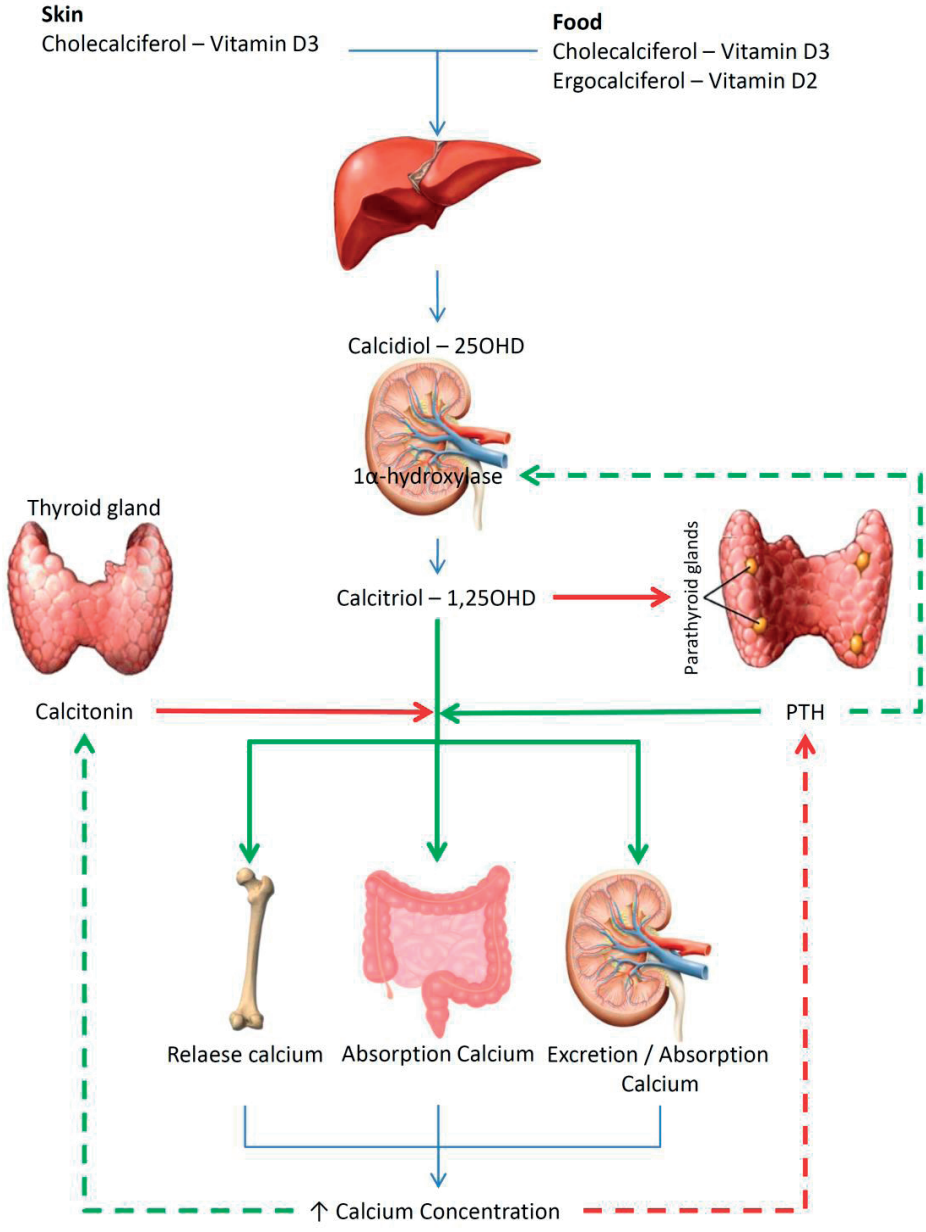

Figure 1. Calcium homeostasis

Another condition leading to bone fragility is Osteoporosis. Osteoporosis is a skeletal disorder that is characterised by low bone mass and micro-architectural deterioration of bone structure, resulting in bone fragility and an increased fracture risk.[9] It is caused by an imbalance between bone resorption and bone formation, in favour of bone resorption. The definition of osteoporosis is based on the T-score for bone mineral density[9], measured at the femoral neck by dual energy X-ray absorptiometry (DXA). T-score for osteoporosis is defined as a value for BMD ≤ -2.5 below the young female adult mean[9]. Typical osteoporotic fractures are located in the spine, hip, distal forearm and proximal humerus.[9] At the age of 50, the remaining lifetime probability for any of these fractures is 22.4% for men and 46.4% for women. These fractures, except for forearm fractures, are associated with increased mortality. Bisphosphonates are the initial treatment option and treatment should be reviewed after 3-5 years. The initiation of pharmacological treatment is based on the FRAX, an algorithm that calculates the 10-year probability of a major fracture (hip, spine, humerus or wrist).

A fracture is a common injury to the bone after a trauma, which is a result from of different loads in both magnitude and direction than the loads normally experienced.[1] Fracture healing is the subsequent difficult biological process resulting in restoration of the bone and two basic types of bone healing are described.[10]

1. Natural or secondary fracture healing

This is a process that can be divided into four overlapping stages: the inflammation stage, the soft callus formation stage, the hard callus formation stage and the bone remodeling stage. Each stage is characterized by specific cellular and molecular processes.[11] The inflammatory stage starts immediately after fracture when a fracture haematoma appears and forms a fibrin clot. In the weeks after the fracture chondrocytes produce a cartilaginous matrix until all the granulation tissue is replaced by cartilage. Where cartilage production is deficient, fibroblasts fill the area with fibrous tissue, forming a semi rigid fibrous cartilaginous matrix called soft callus. Hard callus formation is the result of mineralized bone matrix / calcified callus by osteoblasts. During the remodeling stage hard callus is transformed into the original cortical and/or trabecular bone configuration. This process is started with resorption by osteoclasts followed by the formation of lamellar bone.

2. Direct or primary bone healing

This is the result of surgical anatomical fracture reduction, with compression of both de fracture ends with almost complete stability[1]. This healing process relies on direct bone remodeling, whereby osteoclasts cuts cones across the fracture and osteoblasts form new bone.[1]

The diamond concept of fracture healing was introduced by Giannoudis *et al.*[10] in 2007. Mechanical stability was added to the above described complex of interaction of osteogenic cells, osteoconductive scaffolds and growth factors, that should result in fracture healing. These three biological elements with mechanical stability are needed for proper fracture healing and the absence could result in delayed fracture healing or non-union. Delayed union is defined as a fracture which takes longer than usual to heal unite. A non-union is a fracture which fails to achieve union by 9 months since the injury, and for which there has been no signs of healing for 3 months. Some, have recommended that for long bones non-union should be considered after a period of 6 months if no evidence of radiological fracture healing is present.[12] The incidence of fracture non-union is estimated to be up to 10%.[13-15] Delayed and non-union are accompanied by additional burden for the patients and increased costs (€18.000 – €20.000)[16], as a result of increased duration of treatment with additional visits, radiological examinations and possible additional surgery. Several risk factors of impaired fracture healing have been identified in the literature.[12,17,18] Vitamin D deficiency and osteoporosis have been suggested as risk factors.

Since the high prevalence of vitamin D deficiency in adults[19,20] and osteoporosis[9] in Europe, the question rises about their actual role in fracture healing. Since both conditions interfere negatively with the homeostasis of bone, it could be expected that these impair fracture healing resulting in delayed and or non-union. Aim of this thesis is to investigate the effect of vitamin D status and osteoporosis on fracture healing.

OUTLINE OF THIS THESIS

This thesis is divided in two parts. The first parts focus on the effect of vitamin D on fracture healing and in the second part the effect of osteoporosis on fracture healing is discussed.

An extensive review of literature about the effect of vitamin D on fracture healing is presented in **Chapter 2.** Since fracture healing is a result of rather complex consecutive biological events, this second chapter focuses at first on the cellular effects of vitamin D during fracture healing. Subsequently the available evidence regarding its clinical involvement in the process of fracture healing is reviewed. **Chapters 3 and 4** present the results of two cross sectional studies performed in fracture patients. The main scientific research question for both studies was to determine the prevalence of vitamin D deficiency in adults (**Chapter 3**) and children (**Chapter 4**). In both studies risk factors for vitamin D deficiency were investigated and compared to known risk factors. In children additionally the occurrence of complications during the fracture healing was examined and plotted against vitamin D status. **Chapter 5** describes a retrospective study regarding the effect of vitamin D deficiency on fracture healing in adult fracture patients. The main question of interest in this study was the effect of vitamin D status on fracture healing.

In the **Chapters 6, 7, and 8** of this thesis, bone quality in relation to fracture healing are evaluated, with a specific focus on osteoporosis. **Chapter 6** provides a review of the evidence regarding the effect of osteoporosis on fracture healing. A retrospective study on the effect of osteoporosis on fracture healing is presented in **Chapter 7. Chapter 8** comprises a more fundamental study on osteoporosis. In this study the levels of sclerostin are determined in fracture patients with osteoporosis. Since sclerostin causes increased bone resorption and decreased bone formation, it could by hypothesized that it might be involved in the in the development of osteoporosis.

In the appendix of this thesis, two case reports are presented in **Chapters 9 and 10** which illustrate the role of vitamin D plays in bone metabolism and fracture healing. The first case report is about a patient with multiple pathological fractures due a severe vitamin D deficiency induced autonomous hyperparathyroidism. The second case report describes a successful treatment of a non-union in a patient with a femur fracture and vitamin D deficiency. The illustrations act as the bridge towards the general discussion and future perspectives.

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