Pathophysiology and Pathomorphology of Osteoporosis

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Abstract
Osteoporosis is a disease that leads to fragility fractures due to the loss of bone mass and bone microstructure. This review presents an update on the fundamental pathophysiological and pathomorphological mechanisms of bone loss. Pathomorphological characteristics such as perforations and microcallus formations are explained. The physiological relevance of the remodeling process and its control by local paracrine, systemic endocrine, and central neural signaling pathways are discussed. Hormones, such as estrogen, follicle stimulating hormone, and leptin, transcription factors, such as Runx2 and osterix, and the Wnt signaling pathway are discussed in terms of their roles in bone cell differentiation and function. On the basis of current knowledge, osteoporosis can be diagnosed and treated and fractures can be prevented. However, it is likely that new and even more effective diagnostic and therapeutic strategies will emerge as our understanding of the remodeling process that controls osteoblast and osteoclast function increases.

Key Words
- Microcallus
- Osteoblast
- Osteoclast
- Osteoporosis
- Remodeling

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Introduction
Osteoporosis is characterized as a disease with a loss of bone mass and bone stability associated with an increased fracture risk. Due to the resulting osteoporosis-related fractures, this disease is not only a massive clinical problem but also a major public health-economic challenge.

Osteoporotic fractures are a commonly encountered problem in orthopedic and trauma surgery. Due to the demographic changes that are occurring in developed countries, osteoporotic fractures are expected to double within the next 25 years [1]. The increased life expectancy in the Western world has resulted in osteoporosis becoming one of the ten most frequent diseases. In fact, osteoporosis currently affects more than 45 million patients worldwide, with a fracture frequency that far exceeds the combined incidence of breast cancer, stroke, and cardiac infarction [2].

Osteoporosis presents a number of challenges to trauma and orthopedic surgeons. Because of the fragility of osteoporotic bone, the surgeon using standard fracture fixation devices often encounters unforeseen problems, such as difficulties in engaging standard fracture fixation devices. The ability to support joint arthroplasty or rigid spinal instrumentation is diminished in osteoporotic bone [3]. In addition to providing surgical treatment, orthopedic surgeons must begin to take an increasingly active role in diagnosing and treating the underlying metabolic disorder with the aim of also providing the appropriate fracture treatment.

Osteoporosis is not a new disease; rather, it has been documented in the scientific literature for nearly 200 years. In the early nineteenth century, the English surgeon Sir Astley Cooper [4] described that the sleaziness and softening of the bone acquired at advanced ages clearly favors the appearance of fractures. In the 1940s, the American endocrinologist Sir Fuller Albright [5] described postmenopausal osteoporosis as the result of a disturbed bone formation due to estrogen deficiency. Based on these studies, two different
types of osteoporosis were differentiated: type 1, defined as a menopausal estrogen deficiency osteoporosis, and type 2, defined as a calcium deficiency senile osteoporosis [6]. This conception of the pathophysiology of osteoporosis was replaced by the current concept of a multicausal process in which different pathogenetic mechanisms interact to cause a loss of bone mass and bone microarchitecture [7, 8].

The factors directly affecting bone microarchitecture in combination with an increased tendency to fall are the main reasons for the high incidence of fractures caused by low energetic traumas in osteoporosis patients.

Pathophysiological Principles and Remodeling
A skeletal loss of function can occur for different reasons:

- a disorder in the skeletal development, resulting in an insufficient formation of bone mass and stability,
- increased bone resorption, resulting in a bone mass loss syndrome and destruction of the trabecular microarchitecture, or
- decreased bone formation after a period of higher resorption in the remodeling process.

In addition, the appearance of osteoporosis-related fractures, forearm and hip fractures in particular, is influenced by the frequency and type of falls that occur. To understand how increased bone resorption and inadequate bone formation can result in a skeletal failure, it is necessary to first understand the process of bone remodeling (Figure 1).

Figure 1. Bone remodeling. Presentation of the different levels that control the concerted action between osteoclasts and osteoblasts. This regulation includes a systemic hypothalamic relay as well as local fine tuning. Bone remodeling is the physiological process used by vertebrates to maintain a constant bone mass between the end of puberty and gonadal failure. Note that the most abundant bone cell, namely the osteocyte, is still not integrated into the remodeling concept because we still lack in vivo evidence on the function of this cell type (SNS: sympathetic nervous system).

Bone remodeling is the physiological process by which bone mass is maintained constant in vertebrates between the end of puberty and gonadal failure [9]. This is a very unusual process, as bone is the only organ that contains a cell type, the osteoclast, whose only function is to destroy or resorb the organ hosting it [10–12]. Indeed, every day and simultaneously at multiple locations, bone tissue is resorbed by osteoclasts. This lost bone is then replaced by new bone tissue laid down by osteoblasts, the bone-forming cells. This process not only maintains bone mass but also defines the regenerative capacity of the skeleton and allows constant renewal of the matrix and continuous functional adaptation at the organ and tissue level. Bone remodeling occurs simultaneously in multiple locations in the skeleton, with bone formation and bone resorption occurring in close proximity in the so-called BMUs – "bone multicellular units" or "bone metabolic units". Both this process and the well-documented role of osteoblast-lineage cells of favoring osteoclast differentiation in vitro have long been seen as proof that bone remodeling is primarily an autocrine/paracrine process [13]. A large body of experimental evidence has demonstrated that such regulation does exist [14]; for example, many cytokines present in the extracellular matrix or synthesized by bone cells have been shown to be involved in bone remodeling.

Because the resorption and reversed phase are relatively short processes in bone remodeling in comparison to the phase of osteoblastic formation with a re-filling of the bone defects, it is understandable why increased bone remodeling often leads to a bone loss syndrome. While a larger number of unfilled bone defects causes another impairment of the bone, increased bone remodeling does not necessarily lead to bone loss, as demonstrated by the growth spurt in puberty. It has become clear that an inadequate osteoblastic function during bone remodeling has an essential role in the pathogenesis of bone loss syndromes.

Morphological Characteristics
All structural changes in bone microarchitecture, and the accompanying changes in bone mass, are the result of the cellular activity of osteoclasts and/or osteoblasts. In addition to the regulated bone remodeling process, at least two specific features have to be considered on a microstructural level as being relevant to the development of an osteoporosis: the so-called perforations and microcallus formation. Perforations are continuity interruptions of trabeculae due to osteoclast activity. Within the context of skeletal ageing, perforations are