Neuroendocrine regulation of human bone metabolism
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Chapter 1

Introduction
INTRODUCTION

The skeleton is perhaps the most multifunctional part of our body. First of all, it provides an internal framework and enables locomotion; without a skeleton we would be lying flat on the floor. Secondly, it provides a hard outer shell, protecting the vulnerable internal organs from damage. Thirdly, it hosts the delicate bone marrow, providing a supportive environment for hematopoiesis. Finally, the skeleton serves many metabolic and endocrine functions, from the storage and release of calcium and phosphate to the production of hormones. To maintain its functional integrity and to serve these important functions, the skeleton undergoes constant remodeling, effectively renewing all of its tissue every seven years. This energy-consuming process of bone remodeling is influenced and regulated by mechanical forces, hormones, metabolic factors, and, more recently discovered, the sympathetic nervous system.

Bone and bone marrow

To provide strength, bones are made up of an outer layer of thick, cortical bone. In order to provide lightweight flexibility at the same time, the inside of bones consists of a meshwork of trabecular bone. The bone marrow lies interspersed within this trabecular network.

Bone is composed of cells and extracellular matrix. The three major bone cells are the osteoblast, originating from the mesenchymal stem cell, the osteoclast, originating from the hematopoietic stem cell, and the osteocyte, a descendant of the osteoblast. The osteocyte lies embedded within the bone matrix and senses mechanical forces and damage to the bone. In response, it secretes factors activating bone resorption by the osteoclast, effectively removing the damage. This is followed by bone formation by the osteoblast, synthesizing new bone to fill the cavity created by the osteoclast. These coupled processes of bone resorption and bone formation are known as 'bone remodeling'. The bone matrix consists of inorganic matrix, mainly hydroxyapatite, a mineral complex of calcium and phosphate crystals, deposited into the organic matrix, mainly consisting of type I collagen. During bone resorption and formation, degradation and synthesis products of collagen are released into the circulation. These products can be measured and used as markers of bone resorption and formation, collectively termed ‘bone turnover markers’. Bones start to develop during fetal life and continue to grow after birth. During these years, bone formation dominates bone resorption. Around the age of 30, peak bone mass is attained. Bone formation and resorption are now balanced to maintain bone mass. With aging, bone resorption gradually increases and bone formation decreases, leading to a loss of bone mass, increasing the risk of fractures (1-4).
Bone marrow exists in two variants, red or hematopoietic marrow and yellow or fatty marrow. Hematopoietic marrow is made up of hematopoietic stem cells and its descendants, cells of the erythrocyte, thrombocyte and leukocyte lineage, and provides all the blood cells. Fatty marrow consists of adipocytes originating from the mesenchymal stem cell. At birth, the bone marrow consists entirely of red or hematopoietic marrow and during aging the hematopoietic marrow is gradually converted into yellow or fatty marrow. This conversion proceeds from the peripheral to the central skeleton and by the age of 25, the conversion is almost complete in the femora whereas in the vertebrae only 40% of the bone marrow is fatty marrow. Historically, fatty marrow was considered passive filling of the bones but over the last years, evidence is accumulating that the bone marrow fat actively influences hematopoiesis and bone metabolism by providing energy and secreting mediators and fatty acids. However, the precise characteristics, kinetics and function of the bone marrow adipocytes remain to be elucidated (5-7).

**Sympathetic innervation of bone and bone marrow**

The autonomic nervous system controls homeostatic organ function and is divided into the sympathetic and parasympathetic nervous system. The sympathetic nervous system connects the brain to the visceral organs and is known for its ‘fight or flight’ response. Noradrenaline, the neurotransmitter of the sympathetic nervous system, activates the adrenergic receptors on the target tissues. Subtypes of the adrenergic receptors, alpha (1 and 2) and beta (1 to 3), have variable affinities for noradrenaline and differential tissue distributions (8).

Bones and bone marrow are innervated by sympathetic nerve fibers (9;10) and both bone cells as well as bone marrow cells express adrenergic receptors (11-13). Therefore sympathetic control of bone metabolism and hematopoiesis is likely. Indeed, a series of experiments in mice have shown that disruption of sympathetic signaling, ultimately by genetic deletion of the beta-2 adrenergic receptor on the osteoblast, decreases bone resorption leading to an increase in bone mass (14-17). In addition, pharmacological inhibition (beta-blockers) and stimulation (beta-agonists) of sympathetic signaling, respectively, increases and decreases bone mass (18;19). Hematopoietic stem cells in the bone marrow are in close contact with osteoblasts and migration of hematopoietic stem cells from the bone marrow into the blood depends at least partly on sympathetic signaling (13;20).

In humans, the sympathetic control of bone metabolism remains uncertain. Retrospective observational studies investigating the association between beta-blocker treatment and fracture risk reported inconclusive results, although a meta-analysis showed some fracture reduction in patients using beta-blockers (21). However, the only prospective intervention study showed no effect of a beta-adrenergic antagonist
on bone metabolism in postmenopausal women (22). The sympathetic control of bone marrow migration and hematopoiesis in humans is still unknown, although there are reports that sympathetic nerve damage is involved in failure of hematopoietic bone marrow repopulation following chemotherapy (23). In addition, high catecholamine concentrations following trauma suppress erythropoiesis (24) and sympathetic nerves may be able to regulate hematopoietic stem cells in myeloproliferative diseases (25).

**Hormonal control and activity of bone and bone marrow**

Estrogen has long been recognized as a key hormone controlling bone metabolism (26). The decline in estrogen production during menopause induces bone loss, ultimately leading to postmenopausal osteoporosis. This postmenopausal decrease in bone is accompanied by an increase in bone marrow fat (27), which was traditionally considered passive filling of the vacant bone marrow cavity. Recent studies have challenged this view. Firstly, bone marrow adipocytes and osteoblasts both originate from the mesenchymal stem cell and estrogen has been shown in vitro to induce the differentiation of the mesenchymal stem cell towards the osteoblast at the expense of the adipocyte (28;29). Secondly, bone marrow adipocytes were shown in vitro to release fatty acids and secrete adipokines (30;31), which could both negatively impact bone metabolism. However, the active role of bone marrow adipocytes and their interaction with bone cells are areas of active investigation at this moment.

Insulin is another important hormone involved in bone metabolism. Bone remodeling consumes energy and one of the major sources of energy comes from glucose metabolism, hormonally controlled by insulin (32). Insulin also exerts a direct anabolic effect on bone. Insulin deficiency and overproduction, as in diabetes type 1 and 2, are associated with decreased and increased bone mass, respectively, both resulting in increased fracture risk (33). Recent studies have shown that the endocrine relationship between insulin and bone might not be unidirectional, since bone influences the production of insulin by the secretion of osteocalcin, a bone matrix protein. In mice, the ablation of osteocalcin decreased insulin concentrations whereas the infusion of recombinant osteocalcin stimulated insulin production by the pancreas (34;35). In humans, the role of osteocalcin in insulin and glucose metabolism is less clear and remains to be experimentally confirmed.

**AIM AND OUTLINE OF THE THESIS**

The first part of this thesis investigates the role of the sympathetic nervous system in human bone metabolism and hematopoiesis. We used three different approaches: a clinical approach, a genetic approach, and a pharmacological approach. In *chapter*
we studied bone turnover in pheochromocytoma patients as a model of sympathetic overstimulation. In chapter 3 we determined the association between polymorphisms in the beta-2 adrenergic receptor and fracture risk in two large, Dutch cohorts and we determined the association between these polymorphisms and bone mineral density in a large international consortium. In chapter 4 we conducted a randomized controlled trial to investigate the effects of a beta-adrenergic agonist and an antagonist on bone turnover in healthy, postmenopausal women. And in chapter 5 we studied the effect of administration of a beta-adrenergic agonist and antagonist on circulating CD34+ hematopoietic stem cells in healthy, postmenopausal women.

The second part of this thesis focuses on the hormonal control and activity of bone and bone marrow. In chapter 6 we described the variation in bone marrow fat during the menstrual cycle and investigated the changes in bone marrow fat during two weeks of estradiol treatment in postmenopausal women. Finally, in chapter 7 we reviewed the evidence concerning the interaction between bone metabolism and glucose metabolism in humans putting it into clinical perspective.
REFERENCES


Introduction


