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Review Article

Homeostatic Adjustments in Obesity: Narrative Review

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Abstract

Numerous regulatory mechanisms are activated by the human body to restore altered metabolic conditions to normal, i.e. to re-establish disrupted homeostasis. This occurs when there is a deficiency of a crucial metabolic factor such as Vitamin D (Vit D) or in the presence of a more complex pathophysiological condition, such as obesity. The organism adopts compensatory measures to correct these metabolic disturbances, which may in turn induce temporary functional imbalances in other organs, with outcomes that are not always fully understood. Obesity induces an imbalance not only due to elevated leptin levels but also by promoting the adipogenic differentiation of mesenchymal stem cells and enhancing parathyroid hormone (PTH) secretion. This leads to increased osteoclastic activity, secondary hyperparathyroidism, enhanced bone resorption and interference with renal function. Consequently, in the broader context of homeostatic regulation, much remains unknown regarding the intricate mechanisms by which the body maintains physiological equilibrium and how these are affected by disease states or pharmacological therapies.

Keywords: *Homeostasis; Deficiencies; Obesity; Hypovitaminosis; Metabolic Complications*

Introduction

In the presence of a metabolic imbalance, the human body activates compensatory processes aimed at restoring the previous physiological condition, thereby re-establishing homeostatic balance. In doing so, the organism corrects both intentional and unintentional human errors. This intrinsic protective and reparative capacity appears to be an innate force within the body tasked with maintaining health. A Hippocratic aphorism states: *"All parts of the body that have a function, if used in moderation and exercised in the tasks they are meant for, become healthier, more developed, and age more slowly; but if they are left unused and become inactive, they become prone to illness, poor development, and premature aging..."*. To this, we might add: even if those body parts are mistreated, as is often the case, the body reacts and attempts to correct the damage.

Homeostasis of vitamin D

To better understand one of the most clinically frequent conditions such as Vitamin D deficiency, or more precisely, a deficiency of its active form $1\alpha,25(OH)_2D$ it is useful to outline the body's compensatory efforts to restore optimal levels. Inadequate Vit D intake leads to impaired Calcium (Ca) absorption, triggering increased parathyroid hormone (PTH) secretion. This, in turn, activates enzymes responsible for the conversion of 25(OH)D into its active form $1\alpha,25(OH)_2D$, thereby enhancing both intestinal calcium absorption and renal tubular calcium reabsorption. The overall goal is to restore serum calcium levels, which are critical for numerous physiological processes [1]. However, while these metabolic adaptations are beneficial, they can also transiently affect the function of other organs, sometimes with poorly understood consequences [2]. In fact, alterations at the vascular and renal levels are quite common due to activation of the renin-angiotensin-aldosterone system (RAAS). Pancreatic effects are also noted, resulting from both direct cellular actions (e.g. increased leptin levels) and indirect mechanisms (e.g. hyperglycemia-induced responses). Elevated PTH levels exert a lipolytic effect, increasing free fatty acid flux from adipose tissue and promoting ectopic lipid deposition factors implicated in insulin resistance. Bone effects, on the other hand, appear to be more balanced [3].

Obesity and homeostatic factors

Homeostatic imbalance can also result from specific physical conditions, such as obesity (BMI > 30). Excessive adipose tissue, particularly visceral fat, promotes low-grade systemic inflammation through the release of pro-inflammatory cytokines (e.g. TNF-α and IL-6) and the polarization of macrophages toward the M1 phenotype. Elevated leptin levels further disrupt the leptin/adiponectin balance, impair pancreatic β-cell function, and promote insulin resistance, thereby predisposing individuals to type 2 diabetes mellitus (T2DM) [4,5].

The metabolic imbalance associated with obesity extends beyond leptin dysregulation. It also includes increased secretion of parathyroid hormone (PTH), which stimulates osteoclastic bone resorption and reactive oxygen species (ROS) production. Concurrently, obesity favors the adipogenic differentiation of mesenchymal stem cells (MSCs). Furthermore, obesity activates the renin-angiotensin-aldosterone system (RAAS), contributing to adverse cardiovascular effects via increased levels of aldosterone, angiotensin II (Ang II), and advanced glycation end-products (AGEs) [6].

Bone metabolism in the context of obesity is particularly complex. Due to resistance at hypothalamic leptin receptors (LepR), the central anti-osteogenic effects of leptin are diminished, while its peripheral osteoblast-stimulating effects, enhanced by mechanical loading, are amplified [7]. In non-obese individuals with high leptin levels, the situation differs: leptin stimulates peripheral bone formation but inhibits central osteogenesis by suppressing serotonin production, activating the sympathetic nervous system (SNS). The increased noradrenaline release leads to interference with β2-adrenergic receptors on osteoblasts. These central effects result in suppressed bone formation. Other contributing mechanisms include Wnt signaling inhibition and impaired maturation of osteoprogenitor cells. Although PTH suppresses osteocyte-derived sclerostin and thereby supports osteoblast function, this effect is offset by increased expression of matrix Gla protein (MGP), which inhibits bone morphogenetic proteins (BMPs) and limits osteoblast differentiation [8] (Figure 1).

Obesity also increases the release of 5-HT from duodenal chromaffin cells. This serotonin directly activates 5-HT1B receptors on osteoblasts, inhibiting their proliferation and function. This adverse effect on osteoblastic function is compounded by the central inhibition of 5-HT synthesis and SNS activation mediated by leptin [9]. These mechanisms are particularly evident when leptin levels are elevated but not sufficient to induce hypothalamic receptor resistance.

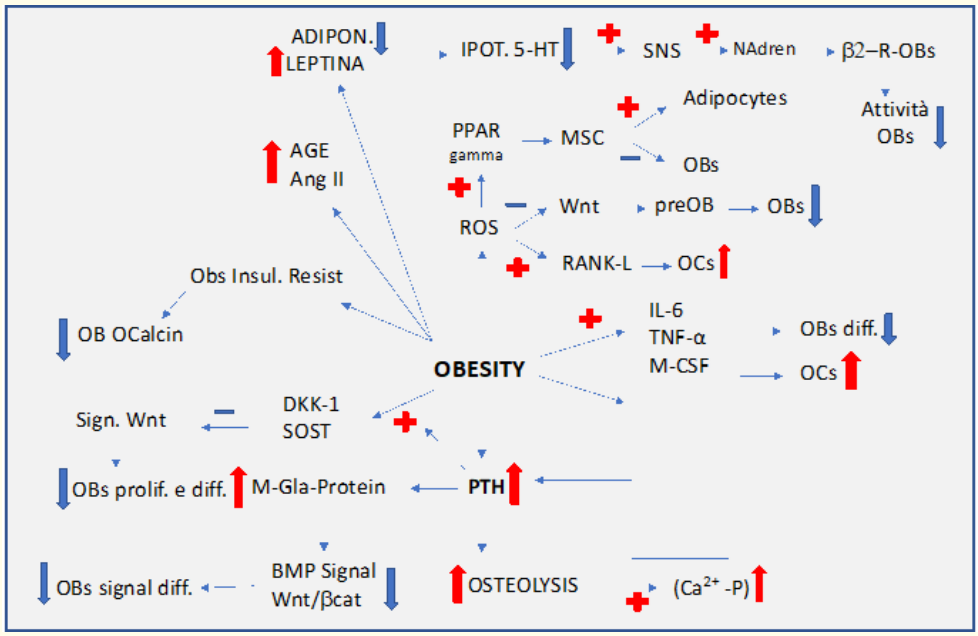

Figure 1: *Obesity-induced imbalance with elevated leptin and PTH secretion, and their impact on bone.(Legend: ROS: Reactive Oxygen Species; AGE: Advanced Glycation End-products; SNS: Sympathetic Nervous System; M-Gla: Matrix Gla Protein; OCs: Osteoclasts; OBs: Osteoblasts; PPARγ: Peroxisome Proliferator-Activated Receptor gamma; BMPs: bone morphogenetic proteins; MSC: Mesenchymal Stem Cell.*

It is crucial to highlight that excessive PTH levels-whether due to poor intestinal calcium absorption or high adiposity-can lead to secondary hyperparathyroidism. This condition enhances bone resorption, resulting in increased release of calcium and phosphate, which in turn triggers a compensatory rise in fibroblast growth factor 23 (FGF-23). FGF-23 inhibits renal 1α-hydroxylase, reducing conversion of 25(OH)D to $1,25(OH)_2D$, thereby impairing calcium and phosphate absorption. Additionally, FGF-23 may deteriorate renal function, leading to phosphate retention, further FGF-23 production, and a self-perpetuating cycle. Despite these disruptions, compensatory mechanisms attempt to restore calcium balance by increasing renal tubular calcium reabsorption and upregulating 1α-hydroxylase activity to normalize calcium absorption and suppress PTH secretion.

Although homeostatic responses are often conserved across individuals, even minor variations in metabolic parameters can significantly alter intercellular signaling. For example, individuals with high BMI but moderate leptin levels (not typical of overt obesity) often lack hypothalamic leptin resistance. In such cases, central serotonin synthesis is still suppressed, reducing osteoblast differentiation. However, this is counterbalanced by leptin's peripheral anabolic effects on osteoblasts. These individuals also benefit from increased skeletal mechanical loading and a mild rise in PTH, which suppresses sclerostin expression and enhances osteoblast activity and osteoprotegerin secretion [10].

Increased osteocyte stimulation and osteoblast activity lead to elevated levels of osteocalcin and FGF-23. Undercarboxylated osteocalcin acts as an endocrine hormone promoting insulin secretion and shifting adipocyte differentiation toward adiponectin expression-effects that counterbalance leptin signaling [11,12]. Meanwhile, FGF-23, through its regulatory roles in phosphate and vitamin D metabolism, contributes to further PTH elevation. However, if the underlying cause such as high BMI persists, these adaptive mechanisms may fail to re-establish full metabolic homeostasis.

Energy homeostasis is clearly governed by a sophisticated neuroendocrine network, predominantly within the central nervous system (CNS). Insulin and leptin function as key messengers of energy status, exerting catabolic effects via hypothalamic pathways that regulate appetite, energy expenditure, and glucose metabolism.

While insulin is critical for long-term glycemic control, glucose homeostasis also depends heavily on leptin. Under physiological conditions, insulin promotes lipogenesis in adipose tissue and stimulates leptin secretion. In turn, leptin inhibits insulin production by the pancreas and modulates the activity of pro-opiomelanocortin (POMC) and agouti-related protein (AgRP) neurons in the hypothalamus, thereby influencing energy intake and expenditure. The regulation of glycemia is thus highly intricate, given leptin's multi-organ effects, including on the brain, muscle, pancreas, adrenal glands, liver, and adipose tissue.

Discussion and Conclusion

Among the many factors affecting human health, obesity plays a leading role, not only due to its growing prevalence but also because of its association with decreased life expectancy and the onset of numerous comorbid conditions. As previously described, adipose tissue dysfunction contributes to insulin resistance, type 2 diabetes mellitus, hepatic steatosis, hypertension, atherosclerosis, neurodegenerative disorders, and even some malignancies.

Surprisingly, not all individuals with obesity develop metabolic diseases. The integrity and function of adipose tissue may be more critical than its quantity. A combination of genetic, environmental, and behavioral factors can lead to adipose tissue dysfunction, which manifests as increased secretion of pro-inflammatory adipokines and cytokines that attract inflammatory cells, particularly in visceral fat.

From a pathophysiological perspective, adipose tissue quality is more important than quantity, although visceral fat remains the main determinant of adipose function. Adipose tissue hosts two types of macrophages: pro-inflammatory M1 macrophages and phenotype M2. M1 phenotype prevails in obese individuals and produces TNF-α and IL-6, which promote inflammation and insulin resistance while M2 macrophages secrete anti-inflammatory cytokines. Hypertrophic and dysfunctional adipocytes favor the polarization of macrophages toward the M1 phenotype, contributing to low-grade chronic inflammation. This inflammation can extend to CNS metabolic regulation and the cardiovascular system, promoting atherosclerotic plaque development.

Despite significant progress in biomedical and pharmaceutical research, we are still far from fully decoding the complex regulatory mechanisms that maintain physiological balance. Moreover, the presence of comorbid conditions and pharmacological interactions adds further complexity. As Hippocrates aptly stated: "Vita brevis, ars longa, occasio volucris, experimentum periculosum, judicium difficile" (*Life is short, art is long, opportunity fleeting, experiment dangerous, judgment difficult*) [13-17].

Author Contributions

All authors contributed equally to the article.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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