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Osteocalcin: A new phenomenon for type 2 diabetes and obesity

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ABSTRACT

Objectives: The molecular biology revolution has emerged with the determination that bone tissue is an endocrine organ that regulates many physiological processes, and osteocalcin (OCN), an osteoblast-derived protein that provides endocrine control, is a hormone that regulates glucose and energy homeostasis. By controlling gene expression in β-cells and adipocytes, OCN improves glucose intolerance, obesity, and insulin expression. In addition, OCN stimulates the secretion of adiponectin, a molecule that increases fatty acid oxidation and insulin secretion and sensitivity in adipose tissue and reduces adipose tissue accumulation. Recent research suggests that serum OCN increases the expression of peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) and uncoupling protein-1 (UCP1) genes, which play a role in thermogenesis in brown adipose tissue, it also affects insulin sensitivity by increasing adiponectin expression in white adipose tissue. OCN the target gene of insulin, and resting energy expenditure and mitochondrial biogenesis. With all these effects, OCN is a protein that has recently been found to be associated with diabetes and obesity components.

Conclusions: This review aims to present an overview of understanding the interaction of OCN produced by osteoblasts with insulin, glucose metabolism, adipose tissue, skeletal and muscle tissue, and appetite metabolism in understanding the endocrine functions of bone. In addition, it was conducted to examine the role of OCN in energy metabolism and to evaluate the relationship of energy metabolism pathways affected by OCN with non-communicable chronic diseases such as type 2 diabetes mellitus and obesity.

Keywords: osteocalcin, type 2 diabetes mellitus, obesity

INTRODUCTION

Bone tissue consists of osteoblasts, osteocytes, and osteoclast cells. For many years, it was thought to be just a build organ [1]. The molecular biology revolution that we have lived through for the last half-century has changed our understanding of the biological processes that occur in complex organisms and especially in bone tissue, revealing that bone tissue is an endocrine organ that regulates many physiological processes [2]. Osteocalcin (OCN), also known as bone protein, is secreted by osteoblastic streak cells, which is a 5-kDa non-collagenous protein. OCN hormone is involved in the regulation of bone mineralization and energy metabolism [3]. Once OCN is synthesized, it forms most of the bone matrix, while a small amount of OCN is released into the bloodstream as a hormone after vitamin K-dependent gamma-carboxylation. Therefore, undercarboxylated OCN enters the circulation and acts directly on pancreatic β cells and adipocytes [4]. Type 2 diabetes mellitus (T2DM) is a systemic disease characterized by hyperinsulinemia, IR (IR), and relative insulin deficiency [5]. Bone tissue plays a role in the prevention of diabetic complications by playing a role in the regulation of physiological functions such as insulin sensitivity and energy metabolism, together with OCN [6]. OCN improves glucose tolerance by increasing β-cell proliferation and insulin expression and secretion. In humans, high serum OCN concentrations have been found to be associated with optimal glycemic homeostasis [7].

OCN optimizes insulin expression, obesity formation, and glucose intolerance by regulating gene expression in pancreatic β-cells and adipocytes. Recent research proved that serum OCN plays a key role in the pathogenesis of IR and energy expenditure [8]. Bone mineral density and serum OCN levels are associated with obesity. In the study, a negative correlation was found between body fat percentage and HOMA-IR and OCN levels, regardless of body mass index (BMI). These data provided new evidence for an association between body fat mass, insulin sensitivity, and OCN levels [9]. Another study found lower OCN concentrations in obese women compared with non-obese women. In a recent study, it was shown that 160 female adolescents were divided into three groups according to their OCN levels, an inverse and significant relationship was found between BMI and OCN [10].

In conclusion, OCN is a protein that has recently been found to be associated with T2DM and obesity components. This review examines the role of OCN produced by osteoblasts in energy metabolism by affecting insulin, glucose metabolism, adipose tissue, skeletal and muscle tissue, and appetite metabolism in understanding the endocrine functions of bone. One of the situations in which bone tissue functions as an endocrine organ is the synthesis of OCN. In addition, it was aimed to evaluate the relationship of energy metabolism pathways affected by OCN with non-communicable chronic diseases such as T2DM and obesity.

Endocrine Role of Bone Metabolism

As with other organs and tissues of the body, bone tissue also consists of specialized structures [11]. The inorganic component contains mainly calcium and phosphate ions and acts as a reservoir. The organic component, on the other hand, includes collagenous (proteins type I collagen, type III, type V, and type IX collagens) and non-collagenous proteoglycans, glycoproteins, and sialoproteins (osteopontin, osteonectin), and OCN proteins [12, 13]. The most obvious evidence of the endocrine function of bone tissue is its capacity to secrete OCN, a molecule expressed by the osteoblast-specific gene [6]. Epidemiological studies to analyze the relationship between OCN and metabolic parameters such as glycemia, insulin secretion, cell proliferation, and lipid profile revealed the effect of bone metabolism via OCN on energy, insulin, glucose metabolism, adipose tissue, skeletal and muscle tissue, and appetite metabolism [14-20]. However, OCN has another hormonal role by affecting the release of testosterone. It has been found that it can induce testosterone production in Leydig cells of the testicles by affecting the release of OCN G protein-coupled receptor 6A (GPRC6A) [21]. In addition, maternally secreted OCN crosses the placenta and supports hippocampal development in the fetus. In adults, OCN affects metabolic functions by crossing the blood-brain barrier and regulating the synthesis of various neurotransmitters [22].

Regulation of Osteocalcin Expression and Activity

OCN or bone Gla-protein is synthesized by osteoblasts as a pre-pro molecule. OCN is a Ca++ binding non-collagenous bone matrix protein with 49 amino acids and three amino acid gamma-carboxyglutamic acid residues at positions 17, 21, and 24 in humans and positions 13, 17, and 20 in rats [23]. OCN expression is regulated by various factors, including parathyroid hormone (PTH) 1.25-dihydroxy vitamin D3, estrogens, glucocorticoids, growth factors, and cyclic AMP [24]. Other molecular mechanisms regulating OCN secretion and activity in osteoblasts are forkhead box protein O1 (FOXO1), which controls the energy balance in glucose or metabolism, and activation transcription factor 4 (ATF4), a cyclic AMP-dependent transcription factor [25]. The pathway by which FOXO1 OCN regulates its bioactivity with osteotestular protein tyrosine phosphatase (OST-PTP) is the most important. FOXO1 increases OCN carboxylation of OST-PTP by stimulating the expression of OST-PTP [26]. The binding of more catecholamines to the β2 adrenergic receptor with the increase in the central nervous system activity and the reduction of the insulin signal of runt-related transcription factor 2 affecting the osteoblast inhibits the OCN activity [27]. The bioactivity of OCN reduces the expression of pro-osteoclastogenic RANK ligand (RANKL) and osteoprotegerin (OPG), a member of the tumor necrosis factor receptor (TNF) by affecting insulin signaling in osteoblasts and increases bone resorption by stimulating osteoclastogenesis. In addition, the acidic pH that occurs in the osteoclast resorption environment, besides demineralizing the matrix, also activates the carboxylated OCN attached to hydroxyapatite by decarboxylation [28, 29]. Vitamin K-sensitive carboxylated OCN is “inactive OCN (Gla-OCN)” and binds to calcium and hydroxyapatite crystals in the bone matrix. OCN, which is decarboxylated at an acid pH of 4.5 as a result of bone resorption that does not enter the carboxylation process, is “active OCN (Glu-OCN)” and is released into the bloodstream and acts as a multifunctional hormone [12]. After secretion, OCN is stored in the bone matrix in a decarboxylated (inactive) form with no metabolic effects, and OCN must be activated and carboxylated to exert its beneficial effects on glucose metabolism [30].

The Relationship Between Endocrine Functions and Energy Metabolism of Osteocalcin

The basis of human energy metabolism is based on the adequate supply of glucose to the tissues in need by tightly specialized pathways. In humans, glucose homeostasis is regulated by insulin-sensitive tissues, mostly including glucagon-producing α and insulin-producing β cells and pancreatic islet cells, liver, muscle, and adipose tissue [31]. OCN increases the expression of genes involved in β-oxidation (peroxisome proliferator-activated receptor α and fork-head box protein A2 and electron transport chain (Atp5a1, Atp5b, Mt 2 nd2, Cox, and Cyc1) in adipose tissue. It affects carbohydrate, lipid, and energy metabolism by reducing fat mass and increasing energy expenditure [32]. Since there is no feedback mechanism between insulin and OCN, it is under the control of the leptin hormone released from adipocytes [33].

Fibroblast growth factor-21 (FGF-21) increases adipogenesis by activating peroxisome proliferator-activated receptor γ (PPARγ), while releasing higher levels of adiponectin through adipogenesis [34]. In addition, leptin both inhibits serotonin and increases the expression of cocaine and amphetamine-regulated transcripts that regulate bone resorption by binding to neurons of the arcuate nucleus. With these effects, leptin prevents bone resorption, stimulates osteoblast proliferation and differentiation, and plays a role in inactive OCN synthesis [35]. At the same time, the insulin binds to a specific receptor in osteoblasts and suppresses the transcription factor FOXO1. As a result, the RANK/RANKL complex, which is formed as a result of the reduction of OPG in osteoblasts, performs acidification by stimulating the T cell immune regulator 1, which activates the H+ pump in osteoclasts. When the pH is 4.5 as a result of acidification, Gla-OCN decarboxylation is normally activated at the bone level. Active OCN, which is formed as a result of this activation and released into the circulation, again stimulates the release of insulin from the pancreas, and as a result of all these interactions, a feedback mechanism occurs [12].

Uncarboxylated OCN binds to GPRC6A (seven-transmembrane receptor), which plays a role as an OCN receptor in the pancreas, and the secretion of PTH is regulated. In this way, β-cell proliferation, insulin secretion, and glucose

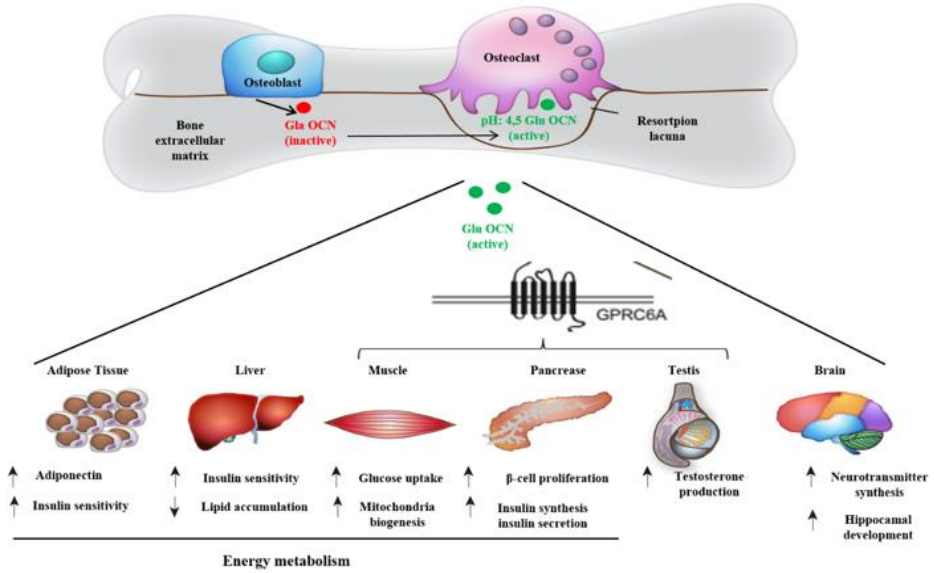

Figure 1. Endocrine functions of osteocalcin [37] (licensed under a creative commons attribution 4.0 international license [CC BY 4.0])

tolerance are provided by inducing CREB, PPARγ, and Ppara phosphorylation, and thus energy metabolism is regulated [36]. OCN supports the adaptation to exercise by affecting the GPRC6A pathway and interleukin 6 (IL-6) expression. In addition, IL-6 stimulates fatty acid production in white adipose tissue (WAT) and glucose production in the liver and sends signals to the bone to increase glu-OCN production [37]. In addition, OCN increases insulin sensitivity by stimulating cyclin D1 expression in β cells [38]. G-protein coupled receptor 6A is also expressed in epithelial cells of the small intestine, a region responsible for the secretion of glucagon-like peptide 1 and stimulates glucose-dependent insulin secretion [39].

While OCN increases the expression of Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC-1α) and uncoupling protein 1 (UCP1) genes that play a role in thermogenesis in brown adipose tissue (BAT), it also increases the expression of adiponectin in WAT and affects insulin sensitivity [40]. Peroxisome proliferator-activated receptor-gamma coactivator-1α is plays a role in metabolism as a master regulator of mitochondrial biogenesis and basal energy expenditure [41, 42]. Recent work has highlighted that PGC-1α can alter the composition and functions of individual mitochondria. Thus, it appears that PGC-1α controls global oxidative metabolism through two types of pathways. First, it reshapes cellular activity through mitochondrial biogenesis. Secondly, it provides remodeling of the organelle by changing the intrinsic pathways of the mitochondria [43]. OCN increases total and basal energy expenditure, and mitochondrial biogenesis in muscle by increasing the expression of PGC-1α, the target gene of insulin, and nuclear respiratory factor-1, which is the target gene of PGC-1α, and medium-chain acyl-CoA dehydrogenase [32]. Uncoupling protein 1 is identified as a specific membrane transporter [44]. Since it is expressed in BAT, it is considered a BAT-specific molecule. Uncoupling protein 1 stops oxidative phosphorylation from ATP synthesis and ensures that energy is released as heat instead of ATP. Thermogenesis is regulated by sympathetic nerves, which are abundant in BAT [45]. Under normal conditions, UCP2 and UCP3 do not contribute significantly to energy expenditure. However, conditions such as nutrition, fasting, a high-fat diet, and thyroid hormone status affect energy expenditure by significantly increasing the expression of UCP2 and UCP3 [46]. With all these pathways, OCN affects energy metabolism by affecting glucose metabolism, adipose tissue, skeletal and muscle tissue, and appetite metabolism. OCN has the potential to be a target in future therapeutic interventions for metabolic diseases such as T2DM and obesity [47]. Endocrine functions of OCN are presented in **Figure 1** [37].

The Potential Role of Osteocalcin in the Glucose Homeostasis via Energy Metabolism in the Treatment of Type 2 Diabetes Mellitus

T2DM is a metabolic disease of our era, which is affected by many etiological factors, characterized by hyperglycemia, caused by the deficiency in the secretion of the hormone insulin or the resistance in the effect of insulin on the cells in metabolism, or both [48]. T2DM, which is common in obese individuals with increasing age, genetics, environmental factors, and lifestyle changes, is associated with hyperinsulinemia, hyperlipidemia, hypertension, and cardiovascular diseases [49]. Bone tissue has recently emerged as a new and important organ in the regulation of glucose metabolism with OCN [50]. OCN plays an important role in β-cell proliferation, regulation of insulin gene expression and secretion, glucose metabolism, and T2DM pathophysiology in both rats and humans [32, 51].

In a study designed on rats with glucose intolerance as a result of OCN deficiency, daily three or 30 ng/g/day therapeutic OCN injections were found to significantly improve glucose tolerance and insulin sensitivity in rats fed a normal diet. In addition, when rats were fed a high-fat diet, daily injections of OCN partially improved insulin sensitivity and glucose tolerance, while increasing basal energy expenditure with increased mitochondria numbers in skeletal muscles and protected from diet-induced obesity [52]. In the study, the defects of GPRC6A especially in the pancreas

resulted in glucose intolerance and decreased insulin secretion [53]. These findings were confirmed by the study of [54], which showed that the OCN acts on GPRC6A and promotes proliferation of pancreatic β-cells during din developmental age and adulthood. In a study on rats with hypoinsulinemia and insulin insensitivity and OCN deficiency, OCN treatment decreased gluconeogenesis and increased basal energy expenditure by decreasing the expression of the PGC-1α pathway and the gene expression of glucose-6-phosphatase and phosphoenolpyruvate kinase 1 in rats [54]. In another study on rats, increased OCN -associated PGC-1α expression in muscle resulted in a 2.4-fold increase in mitochondrial density, resulting in an approximately 60% increase in ATP synthesis [56]. In another study in rats, altered OCN-associated PGC-1α gene expression was associated with mitochondrial biogenesis, angiogenesis, GLUT4 expression, and improved exercise performance [57]. It was determined that OCN was associated with the development of exercise-induced insulin sensitivity, and strength changes during exercise were associated with serum OCN concentrations, positively affecting insulin secretion and insulin sensitivity [58]. In the study examining the relationship between the decrease in serum glucose level and increased non-carboxylated OCN during the aerobic exercise period, it was found that aerobic exercise significantly increased total and non-carboxylated OCN and adiponectin [59]. The relationship between OCN and lower extremity muscle strength was investigated in women over 70 years of age, and as a result, it was found that exercise was associated with an increase in insulin sensitivity and muscle strength by increasing circulating OCN levels [60]. In a study on rats, a decrease in circulating OCN levels was detected in 15-month-old wild type (WT) rats. It was determined that the increase in circulating IL-6 levels observed during exercise in exercised rats also increased the exogenous OCN level. These observations indicate that OCN plays a role as the main regulator of IL-6 expression in muscle, and there is a feedback mechanism between OCN and IL-6 during exercise [61].

In another study on rats lacking the Esp gene, which encodes an OST-PTP receptor-like protein that affects the bioactivity of OCN injection was found to be effective in increasing energy expenditure, lowering triglyceride levels, and preventing diet-induced obesity and T2DM [62]. In addition to its role in carbohydrate metabolism, insulin contributes to nutritional increases in thermogenesis (the thermic effect of food and diet-induced thermogenesis) [63]. In one study, 19 healthy and normal-weight individuals aged 18-26 years who were given 160 IU of intranasal human insulin were compared with the placebo group. As a result, postprandial energy expenditure (diet-induced thermogenesis) increased, and postprandial circulating insulin and C-peptide concentrations decreased. Postprandial plasma glucose concentrations were similar in the two groups. In addition, intranasal insulin provided a temporary decrease in prandial serum free fatty acid levels [64]. It was shown that non-diabetic individuals found that serum OCN is associated with insulin sensitivity and insulin secretion, and weight loss provides significant increases in circulating OCN levels [65]. In addition, serum OCN levels were associated with both insulin sensitivity and fasting triglycerides. In another study, the relationship between serum OCN level and glucose metabolism of thirty-nine postmenopausal women was investigated, and as a result, it was determined that OCN levels were inversely proportional to glucose, insulin, HbA1c, and IR [66]. As a result, OCN is an important parameter that affects fasting insulin level and REE by affecting insulin metabolism.

OCN has a protective effect in T2DM with its effects on energy metabolism by affecting glucose metabolism, adipose tissue, skeletal and muscle tissue and appetite metabolism. On the other hand, gluconeogenesis and the resulting hyperglycemia increase in patients with T2DM who have insulin defects, and accordingly, a physiological process that consumes energy occurs. Due to this increase in energy expenditure, REE is increased in patients with uncontrolled T2DM [67]. In the study, a 3-8% increase in REE was found in diabetic patients with high fasting blood glucose (FBG)>180 mg/dl [68]. In another study, it was found that endogenous insulin secretion and exogenous insulin level have significant and independent effects in reducing REE in patients with T2DM [69]. In a study conducted on rats, it was observed that thermogenesis and energy expenditure increased as a result of insulin injection in the paraventricular hypothalamus [70]. In another study, it was reported that REE decreased with the decrease in fasting insulin level in individuals included in a weight loss program [71]. When relationship between hyperglycemia and IR and total OCN serum concentrations was assesed, serum OCN levels in individuals with T2DM were found to be inversely proportional to chronic hyperglycemia, but no significant relationship was found between IR [16]. Effects of OCN on T2DM are shown in **Table 1**.

The Potential Role of Osteocalcin in the Treatment of Obesity

Adipose tissue takes an active role metabolically by secreting cytokines and adipokines that can affect the activity of other tissues and has endocrine effects [72]. There are adipose tissue types that have different relationships with bone mineral density, namely subcutaneous WAT, visceral WAT, BAT, and bone marrow adipose tissue [73]. Bone marrow is a tissue rich in mesenchymal and hematopoietic stem cells. These different stem cell populations both have wide differentiation potential. Some of the hematopoietic stem cells with mesenchymal properties migrate to other tissues, where they can leave the marrow and transform into adipocytes [74]. In the study, it was determined that osteoblasts and adipocytes shared the same progenitors known as bone marrow mesenchymal stem cells. Bone marrow adipocytes histologically resemble white adipocytes and differentiate from mesenchymal stem cells in the bone marrow [75]. Visceral adipose tissue in the mesentery has more cellular, vascular, and neural innervation structures than subcutaneous tissue. However, contains more inflammatory and immune cells, less preadipocyte differentiation capacity, and an excess of large adipocytes [76]. Bone marrow adipose tissue is associated with bone, bone marrow homeostasis, and systemic energy metabolism. Bone marrow adipose tissue adipocytes are able to secrete adipokines, including adiponectin and leptin, which exert both local and systemic effects on bone and energy metabolism [75]. The amount of bone marrow adipose tissue is associated with decreased bone

Table 1. Effects of osteocalcin on type 2 diabetes mellitus

References	n	Study design	Conclusion
[52]	30 C57Bl/6J mice	16 weeks, intraperitoneal injection of osteocalcin once daily (6 pm) at a concentration of 0.3 ng/µl or 3 ng/µl in mice consuming a normal diet and a high-fat diet	Daily injections of (3 and 30 ng/g) osteocalcin improved glucose tolerance, increased energy expenditure, and prevented obesity in wild-type mice p<0.05
[55]	40 ROSA26-lacZ$^{fl/fl}$ mice	Four weeks, 30 ng/g per day of recombinant intraperitoneal injection of osteocalcin	The results presented in this study proved that the skeleton acted through the osteocalcin to potently regulate all determinants of energy metabolism p<0.05
[56]	16 PGC-1alpha transgenic and 16 wild type mice	16 mice (8 PGC-1alpha transgenic and 8 wild type mice) fed a regular diet, and 16 mice (8 PGC-1alpha transgenic and 8 wild type mice) fed a High-fat diet	Increased osteocalcin-associated PGC-1α expression in muscle resulted in a 2.4-fold increase in mitochondrial density, resulting in an approximately 60% increase in ATP synthesis p<0.05.
[62]	78 pregnant 34 postpartumwomen	Osteocalcin measurement and an oral glucose tolerance test performed in 78 pregnant women (26 women had GDM, and 52 women had normal glucose tolerance during pregnancy; women were matched for age and BMI) and in 34 women postpartum	Osteocalcin injection was found to be effective in increasing energy expenditure and lowering triglyceride levels and preventing diet-induced obesity and diabetes p<0.05.
[65]	37 women & nine men	Aimed to evaluate circulating osteocalcin in association with insulin sensitivity and insulin secretion	Osteocalcin concentration reduced visceral fat mass, associated with insulin sensitivity p<0.05.
[66]	39 postmenopausal women	Three hundred thirty-nine postmenopausal women were recruited for this study. Glucose metabolism related substance and serum osteocalcin were assayed.	Serum osteocalcin levels were inversely correlated with fasting glucose, HbA1c, fasting insulin and HOMA-IR. Serum osteocalcin levels were shown to have a negative correlation with BMI,), but were positively correlated with age p<0.05

density in aging, menopause, anorexia nervosa, and is considered a marker of dangerous bone integrity [77].

In a study conducted with thirty-four obese adolescents aged 15-19 years and body weight >95th percentile, both lean body mass and body fat mass levels were found to be associated with OCN level [78]. In a study conducted on rats, it was determined that exposure to cold increased PGC-1α mRNA expression in key thermogenic tissues such as brown fat and skeletal muscle tissue. As a result, PGC-1α and the UCP1 promoter, PPARγ, and the thyroid hormone receptor play a key role in adaptive thermogenesis by greatly increasing the transcriptional activity. In conclusion, adaptive thermogenesis is an important component of energy homeostasis and a metabolic defense against obesity and is induced by PGC-1α [79]. In another study, it was determined that serum adiponectin administration to rats fed a high-fat diet for four weeks and developing IR and dyslipidemia provided both PPARγ activation and a decrease in IR and dyslipidemia [80]. Also, it was reported that GluOC administered intraperitoneally or even orally can improve high-fat-diet-induced diabetic status [81]. In a study on pregnant individuals, it was found that serum adiponectin levels showed an inverse correlation with HOMA-IR at 32 weeks of pregnancy [82]. In the study on rats, the roles of adiponectin on the hypothalamus were examined and was determined that adiponectin plays a role in regulating energy homeostasis by regulating food intake and energy consumption. In line with the concept that total energy intake may play a key role in adiponectin expression, serum and cerebrospinal fluid adiponectin levels increased in the fasting state and decreased after refeeding [83]. It was found that intravenous administration of adiponectin increased thermogenesis and weight loss in ob/ob rats with leptin deficiency [84]. In another study, the effect of FGF-21 application on the effect of adiponectin signaling was investigated; as a result, it was determined that FGF-21 application was associated with adiponectin signal. This study shows that there is not only communication between tissues, but that these signals interact with each other to regulate energy homeostasis [85]. In another study, it was seen that the adiponectin bioactive molecule has a potential role in mediating the adaptive response adapted to exercise in the human brain [86]. In the study investigating the role of resting metabolic rate (RMR) in the regulation of adiponectin level, 457 overweight, and obese individuals were included in the study. RMR was measured with an indirect calorie meter (deltatrac; datex), and RMR relationship with serum adiponectin levels was examined. As a result, it was found that low RMR was associated with high serum adiponectin. It was emphasized that individuals with low RMR, who are at risk of more obesity-related diseases, can be protected by increasing RMR levels, especially by adiponectin [87].

In a study on rats, it was determined that UCP -/-1 rats could not improve BAT thermogenesis, and they expended extra energy by increasing their metabolic rate (~50%) to maintain their body temperature under chronic thermal stress [88]. Uncoupling protein 1 mediated BAT thermogenesis, which is activated as a result of cold exposure, increases not only the stored lipids but also the oxidation of metabolic substrates such as circulating glucose and triglycerides (mainly in the form of chylomicrons) [89]. Cold sensing transient receptor potential melastatin (TRPM8) regulates UCP1 expression. In a study conducted on rats with both TRPM8 and UPC 12/2 genes inactive, it was determined that diet and cold exposure significantly increased core temperatures and locomotor activity in rats. In conclusion, stimulation of the TRPM8 channel mediates BAT thermogenesis, which may be a promising avenue in the treatment of obesity [90]. In another study, cell death-inducing DNA fragmentation factor-a-like effector A (CIDEA),

Table 2. Effects of osteocalcin on obesity

References	n	Study design	Conclusion
[78]	34 post-puberty obese adolescents of both genders	Investigate the role of inflammatory state on bone turnover markers in obese adolescents undergoing interdisciplinary (clinical approach, physical exercise, physiotherapy intervention, nutritional & psychological counseling) weight loss treatment for one year.	Both lean body mass and body fat mass levels were found to be associated with OCN level $p<0.05$
[80]	52 mice ZDF & SD rats	After an adaptation period of 1 week, SD and ZDF rats were fed an HF diet, and treated with PPARγ agonist or PPARγ agonist for the last 2 weeks.	Serum adiponectin administered reduce improved insulin sensitivity and dyslipidemia provide both (OCN can affect) PPARγ activation and a decrease in insulin resistance and dyslipidemia $p<0.05$
[83]	18 original adipo/ mice (C57BL/6 & 129/Sv mixed background)	The mice were housed under a 12 hr light/dark cycle and given ad libitum access to food. Fasting, when needed, fed a High-fat diet	Osteocalcin can affect this pathway by increasing the expression of adiponectin in WAT.
[88]	12 UCP1-ablated male mice	The control-diet mice had access only to chow (R70, Lactamin), and the high-fat-fed mice had access only to a high-fat diet (research diets D12451)	UCP1 in mediating diet-induced adrenergic thermogenesis, and that UCP1 activity can be determinative for obesity development in mice and possibly in humans. Osteocalcin can affect this pathway by increasing the expression of UCP1.
[95]	51 middle-aged (12-mo-old) $Ldlr^{-/-}$ mice	Mice were fed a chow diet (14% kcal fat; or WHFD (41% kcal fat, 1.5% cholesterol; for 12 weeks, and a subset of animals from each diet group was treated with osteocalcin (4.5 ng/h) for the study duration.	Osteocalcin improves insulin sensitivity and liver function in metabolic syndrome mice $p<0.05$.

defined as an apoptotic gene, was found to be inversely related to CIDEA gene expression, body composition, and basal metabolic rate in BAT, independent of age and gender [91].

In a study conducted on rats, it was determined that exogenous lipocalin-2 (LCN2) infusion decreased appetite and increased β-cell and insulin secretion, glucose metabolism, and energy expenditure [92]. Another study on rats compared normal rats with osteopenia and less trabecular bone volume and number LCN2 -/- rats with WT rats and as a result, LCN2 -/- rats showed hyperphagia, body weight, fat mass, hyperinsulinemia, polyuria, glycosuria, and an increase in fasting hypoglycemia was observed. Impairment of GLUT1 expression in LCN2 -/- rats has been associated with reduced glucose metabolism and basal energy expenditure [93].

By increasing the expression of adiponectin and decreasing the expression of TNF-α in WAT, OCN decreases lipid accumulation and inflammation in the steatotic liver, decreases adipose tissue adiposity, and increases peripheral insulin sensitivity and glucose tolerance [94]. In a study on middle-aged (12 months old) male $Ldlr^{-/-}$ rats fed a western-style high-fat diet and high-cholesterol diet for 12 weeks, the rats were treated with OCN (4.5 ng/hr) during the diet. OCN treatment not only protected against IR induced by a western high-fat and high-cholesterol diet, but also significantly reduced multiple components of NASH, including steatosis, balloon degeneration, and fibrosis [95]. Effects of OCN on Obesity are presented in **Table 2**.

CONCLUSION AND RECOMMENDATIONS

As a result, studies have shown that bone tissue can affect the whole organism with its support and movement functions as well as its physiological effects.. Bone tissue provides these physiological functions by secreting OCN, which is both a bone-specific and metabolically active protein. OCN affects energy metabolism by regulating glucose metabolism, adipose tissue, skeletal and muscle tissue, and appetite metabolism. It reveals that bone tissue is a true endocrine organ with a new perspective in the treatment of T2DM and obesity. With all these effects, OCN, which is on the way to becoming a new phenomenon, sheds light on new therapeutic interventions in the treatment of frequently seen non-communicable chronic diseases such as obesity and T2DM. However, studies to date have been inconclusive, and specifically designed studies in humans are needed to confirm the hypothesis between bone tissue and energy metabolism.

Contribution to the Field

Effects of OCN, which is on the way to becoming a new phenomenon, sheds light on new therapeutic interventions in the treatment of frequently seen non-communicable chronic diseases such as obesity and T2DM. However, studies to date have been inconclusive, and specifically designed studies in humans are needed to confirm the hypothesis between bone tissue and energy metabolism.

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