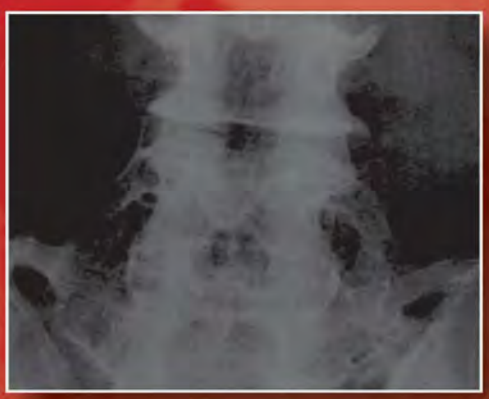
nformation on endocrinology books, visit our website www.jaypeebrothers.com, for detailed information on endocrinology books, visit our website www.jaypeebrothers.com

Diabetes and Musculoskeletal Disorders





Author
Debasis Basu
Author Assistant
Kiran Bahrus

Foreword
Arlan L Rosenbloom

JAYPEE

Contents

Chapter 1.	Introduction	1
Chapter 2.	Pathogenesis: Theory	4
Chapter 3.	The Connecting Link	7
Chapter 4.	Bone as an Endocrine Organ	17
Chapter 5.	The Disease Spectrum	23
Chapter 6.	Antidiabetic Medicines and Bone Safety	75
Chapter 7.	Linking Inflammation in Arthritis and Diabetes	85
	References	95
	Index	123

4

CHAPTER

Bone as an Endocrine Organ

GLUCOSE METABOLISM AND BONE TURNOVER

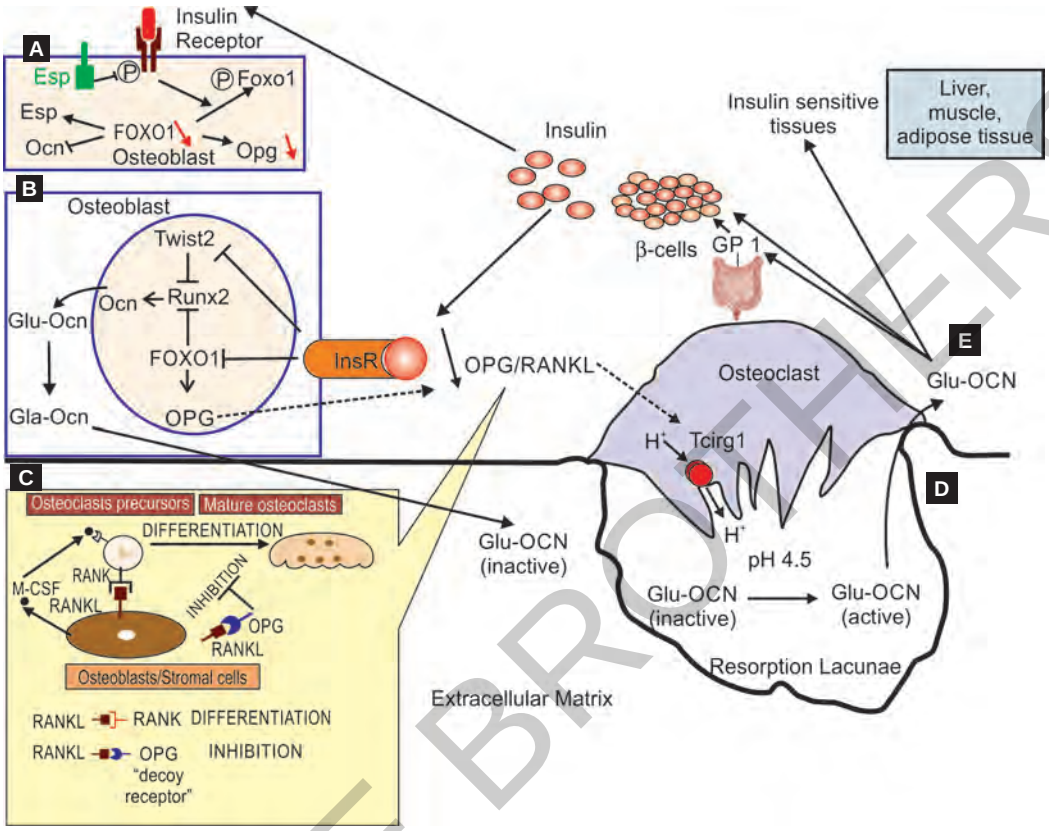
The recognition of bone as a true endocrine organ represents a fertile area for further research and should improve the diagnosis and treatment of metabolic diseases such as osteoporosis and diabetes mellitus.[178]

Karsenty was the first to propose, in 2006, that there was endocrine regulation of energy metabolism in the skeleton.[179] In this chapter, a brief discussion on this mechanism will be elucidated.

Deletion of insulin receptors (IRs) in muscle, the most important site of glucose uptake, does not affect blood glucose levels, insulin concentration, and glucose tolerance, suggesting that other tissues, like bone, could be involved in glucose regulation.[180,181] A major unanswered question is exactly what happens to bone in cases of peripheral insulin resistance? Insulin has been demonstrated to be an osteogenic hormone both *in vitro* and *in vivo*. Osteoblasts (OBs) express abundant IRs and respond to insulin treatment[101,103] by increasing cell proliferation,[104,105] collagen synthesis,[102,106-108] and glucose uptake.[109,110] Are the IRs in pre-OBs and OBs downregulated? It is known that osteocalcin (Ocn) levels are lower in type 2 diabetics.[182,183] Bone remodeling is a highly conserved and regulated process that controls calcium homeostasis within a very tight range and maintains the structural integrity of the skeleton. It is now being hypothesized that the insulin regulatory system mediates communication between metabolic control and bone remodeling.[181,184] There are two principal hormones which control the key aspects of energy homeostasis as well as bone remodeling.

The first of these two hormones is insulin. Indeed, the IR is a substrate of the tyrosine phosphatase activity of an enterococcal surface protein (Esp) and, accordingly, mice lacking IR specifically in OBs are glucose intolerant and hypoinsulinemic (Fig. 1A).[181,184] The human orthologue of Esp (OST-PTP also called osteotesticular protein tyrosine phosphatase) is not active in humans, but recent studies have shown that there are additional tyrosine phosphatases, such as TC-PTP1, that are expressed in OBs. These can regulate Ocn activity and glucose homeostasis by acting on the insulin-signaling pathway in the OB.[185-187] From a mechanistic point of view, it was demonstrated that IR signaling in OBs has a dual and positive action on Ocn biology. On the one hand, IR induces Ocn gene expression in OBs by repressing the negative activity that the nuclear factor Twist2 exerts on Runt-Related Transcription Factor 2,[188] a transcriptional master gene of OB differentiation and a major regulator of Ocn expression (Fig. 1B).[181,189] Osteoprotegerin (OPG) is a soluble glycoprotein which decreases bone resorption by inhibiting the differentiation and activation of osteoclasts.[190] The discovery of the receptor activator of nuclear factor kappa-B ligand (RANKL)/RANK/OPG system and its role in

JAYPEE BROTHERS



Esp, enterococcal surface protein; OPG, osteoprotegerin; RANK, receptor activator of nuclear factor kappa-B; RANKL, RANK ligand; OCN, osteocalcin, CSF, colony stimulating factor; InsR, insulin receptor gene.

Figure 1: A to E, Extracellular matrix.

the regulation of bone resorption exemplifies how both serendipity and a logic-based approach can identify factors that regulate cell function. The RANKL/RANK signaling regulates the formation of multinucleated osteoclasts from their precursors as well as their activation and survival in normal bone remodeling and in a variety of pathologic conditions. Osteoprotegerin protects the skeleton from excessive bone resorption by binding to RANKL and preventing it from binding to its receptor, RANK. Thus, RANKL/OPG ratio is an important determinant of bone mass and skeletal integrity (Fig. 1C)

On the other hand, through the phosphorylation-mediated destabilization of a Forkhead box protein O1 (FOXO1), IR signaling in OBs reduces the ability of FOXO1 to activate the OPG promoter and thereby decreases the secretion of this inhibitor of osteoclast function by these cells. The FOXO1 is downstream of the insulin signaling pathway in OBs[191] acting as a negative regulator of insulin sensitivity in liver, adipocytes, and pancreatic β-cells[192] (Fig. 1A). In response to this stimulation of bone resorption, Ocn is released from the bone matrix and activated via decarboxylation. Thus, in a feed-forward loop, insulin signaling in OBs promotes

JAYPEE BROTHERS

the production of active Ocn by bone cells, which in turn enhances insulin production and release by beta cells (Figs 1B, D, E). How is this feed-forward regulation counterbalanced?

Studies investigating this identified a second hormone, leptin, as a negative regulator of Ocn activity. A large body of work has shown that both arms of bone remodeling, resorption and formation, are negatively controlled by leptin, an adipocyte-specific hormone that appeared during evolution at the same time as a remodeling skeleton.[193]

Leptin is known to initiate intracellular signals within the hypothalamus through its binding to Ob-Rb, the leptin receptor isoform present in hypothalamic nuclei.[194] At least two different central hypothalamic pathways, through which leptin influences bone formation in an antagonistic manner, have been identified (Fig. 2).[195-201]

To exert its functions, leptin binds to receptors expressed on brainstem neurons where it inhibits the synthesis of serotonin, a positive regulator of appetite and an inhibitor of catecholamine production that signals to hypothalamic neurons.[202] It is known that β-blockers, e.g., propranolol resolve reflex sympathetic dystrophy associated symptoms and osteopenia.[203] Outside the context of reflex sympathetic dystrophy, people receiving β-blockers experience 24–32% reductions in the risk of fractures.[204-207]

The first, antiosteogenic, influence of leptin involves upregulation of RANKL, an osteoclast differentiation factor, through sympathetic signaling via β2-adrenergic receptors, the only adrenergic receptor present on OBs.[198,201] Sympathetic signaling on β_2-adrenergic receptors induces phosphorylation of activating transcription factor 4, a cell-specific cAMP response element binding-related transcription factor that is essential for OB differentiation and function.[194] The second, more recently defined, osteogenic influence of leptin involves binding to receptors on the neurons of the arcuate nuclei and inducing an increase in the expression and modulation of a gene called CART (cocaine- and amphetamine-regulated transcript),[198,208,209] a hypothalamic neuropeptide encoded by the *CARTPT* gene whose expression is increased by leptin.[210] Downregulation of RANKL expression by CART is unfavorable to bone resorption and inhibits osteoclast differentiation.[198,199]

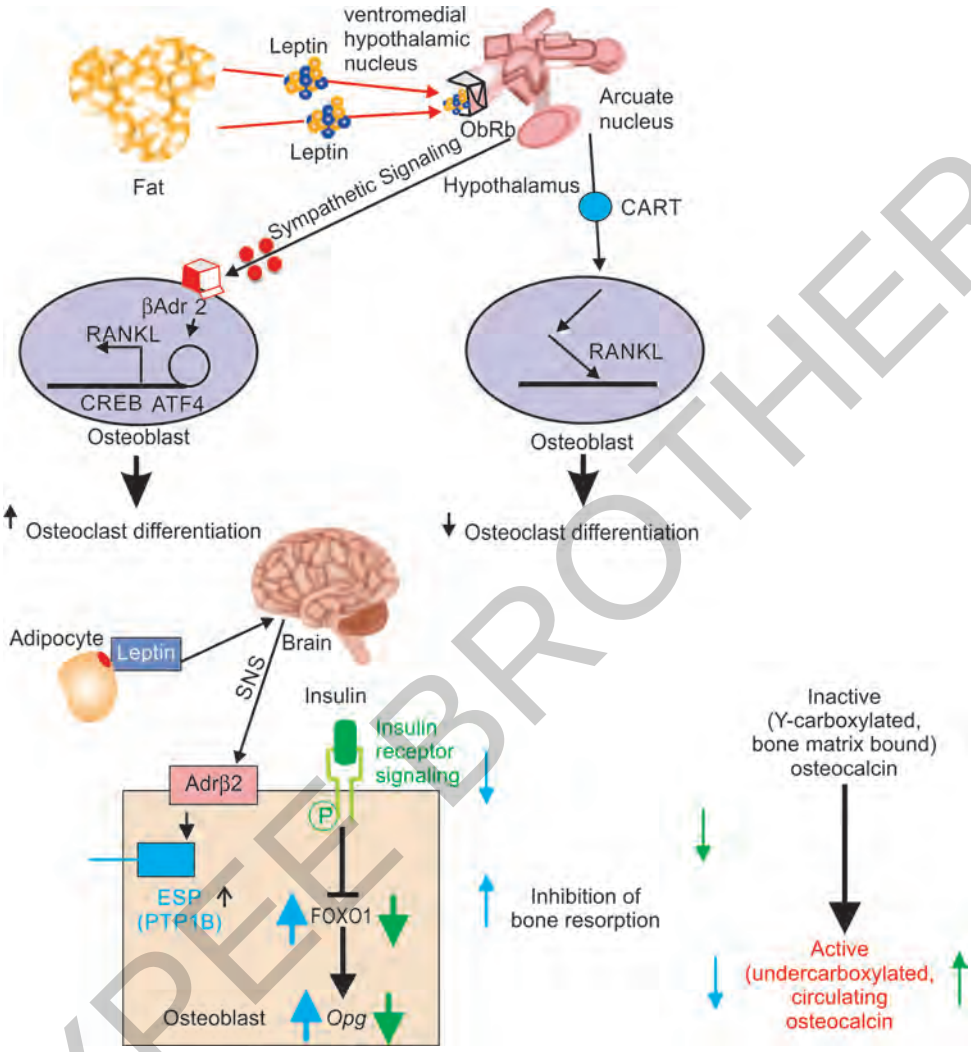
Although this latter regulation should favor Ocn activation, the fact that Adrβ2 signaling also strongly favors Esp expression, and thus enhances OPG secretion via the IR/FOXO1 pathway, offsets this effect.[184,210] Accordingly, Adrβ2-deficient mice have low serum levels of undercarboxylated osteocalcin (ucOC) and are glucose intolerant and insulin resistant.[210]

CART decreases RANKL expression by OBs via a yet unknown mechanism and thus inhibits bone resorption – the second pathway of leptin regulation.

These data established that leptin, through its stimulation of sympathetic output, negatively regulates Ocn activity. Insulin signaling in OBs decreased OPG expression and increased expression of Cathepsin K (*CTSK*) and *Tcirg1*, two genes expressed by osteoclasts and implicated in bone resorption.[184]

Osteoprotegerin acts as a decoy receptor for the OB membrane protein RANKL. A decrease in OPG/RANKL ratio results in an increase in osteoclast formation (Fig. 1E). The decrease in the OPG/RANKL ratio results in an increased expression of *Tcirg1* in osteoclasts. *Tcirg1* encodes for a proton (Hþ) pump subunit and contributes to acidification of the resorption lacunae. The acidic pH of approximately 4.5 generated during bone resorption is a sufficient means to decarboxylate and activate the inactive Ocn molecules (Gla-OCN) stored in the bone extracellular matrix. The undercarboxylated active Ocn (Glu-OCN) promotes insulin sensitivity in peripheral organs and stimulates insulin secretion by the β-cells of the pancreas. Indeed, it is ultimately the activity of the osteoclast that determines the carboxylation status and function of Ocn secreted by the OBs.[184]

JAYPEE BROTHERS

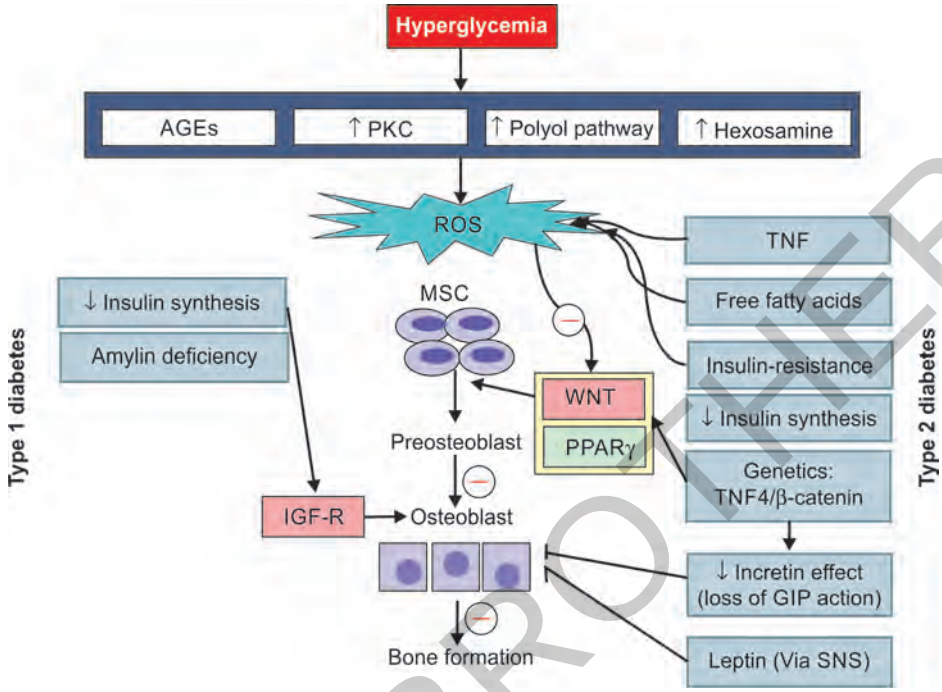


Leptin, via its central serotonin-mediated stimulation of sympathic output, through Adrβ2 signalling strongly favours enterococcal surface protein (or PTP1B, its functional counterpart in humans) expression which inhibits this process though dephosphorylation of the insulin receptor (blue arrows), enhances OPG secretion via the insulin receptor gene/FOXO1 pathway which is inactivated by insulin receptor signalling (green arrows), and finally indirectly inhibits osteocalcin activation.

OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor kappa-B ligand; SNS, sympathetic nervous system; CART, cocaine- and amphetamineregulated transcript; FOXO1, Forkhead box protein O1.

Figure 2: Interactions between fat, brain, pancreas, and bone. Leptin activates the sympathetic tonus, which inhibits insulin secretion and stimulates enterococcal surface protein expression in the OB (via stimulation of the adrenergic β2 receptor). Enterococcal surface protein inhibits Ocn, decreasing insulin expression. Leptin inhibits pancreatic insulin. Insulin, in turn, stimulates leptin expression in the white adipose tissue. Leptin, via its central serotonin-mediated stimulation of sympathic output, through Adrb2 signalling strongly favours enterococcal surface protein (or PTP1B, its functional counterpart in humans) expression which inhibits this process though dephosphorylation of the insulin receptor (blue arrows), enhances OPG secretion via the InsR/FOXO1 pathway which is inactivated by insulin receptor signalling (green arrows), and finally indirectly inhibits osteocalcin activation.
Source: Adapted from Kieffer and Habener.[220]

JAYPEE BROTHERS



AGE, advanced glycation end-products; GIP, gastric inhibitor peptide; IGF-R, insulin-like growth factor receptor; MSC, mesenchymal stem cells; PKC, protein kinase C; ROS, reactive oxygen species; SNS, sympathetic nervous system; TNF, tumor necrosis factor.

Figure 3: Diabetes-bone interaction. Several factors associated with diabetes may impair bone health. These factors may create, either directly or indirectly, a milieu that disrupts osteoblast differentiation and function, describing a low bone turnover phenotype.

It is this undercarboxylated form of Ocn that appears to function as a hormone-stimulating insulin production and secretion by pancreatic β-cells and adiponectin by adipocytes. Insulin sensitivity increases, lipolysis decreases, and energy expenditure increases. The results are consistent with the existence of a bone-pancreas endocrine loop through which insulin signaling in the OBs stimulates Ocn production, which in turn regulates pancreatic insulin secretion to control glucose homeostasis.[181,184,185,210-213]

Elevated levels of both carboxylated and uncarboxylated forms of Ocn were associated with improved glucose tolerance in healthy men given an oral glucose load.[214] In another study conducted in older healthy men, serum Ocn concentrations were inversely associated with blood markers of dysmetabolic phenotype and measures of adiposity.[215] Such studies and others like them[212,216-219] suggest that the endocrine loop comprising insulin, the OB, and Ocn represents a conserved regulatory pathway that participates in the global control of glucose metabolism in all bony vertebrates, including humans (Table 1).

Increased sympathetic output from the hypothalamus arising from leptin action acts on the osteoblastic β2-adrenergic receptors to upregulate OST-PTP expression.[210,224] Insulin signaling within OBs is also inhibited by transcription factors Twist 2 and FOXO1. Current evidence shows that antagonism of insulin action on OBs results in decreased

JAYPEE BROTHERS

Table 1: Studies of undercarboxylated osteocalcin, insulin sensitivity and diabetes control in humans[49,55-57]

Study (year)	*Study (type)*	*Results*
Hwang et al. (2009)	199 men (X)	Higher ucOC level associated with greater insulin sensitivity (highest vs lowest tertile: HOMA-B vs 65%, $p < 0.05$)
Shea et al. (2009)	348 nondiabetic men and women (M = 142, F = 206; X, L)	Lower total and carboxylated osteocalcin levels (not ucOC) associated with IR ($p = 0.006$ and $p = 0.02$, respectively), association attenuated by adjustment for adiponectin. Higher carboxylated osteocalcin level at baseline predicted less change in IR at 3 years, lower % ucOC predicted greater increase in IR.
Kanazawa et al. (2009)	50 men and women with poorly controlled type 2 diabetes (L)	After 1 month of improved glycemic control, TOC level increased (+1.9 µg/L, $p < 0.001$) and the ratio of ucOC/TOC decreased (–0.15, $p < 0.01$)
Kanazawa et al. (2011)	180 men and 109 postmenopausal women with type 2 diabetes (X)	In adjusted analyses, log (ucOC) was inversely correlated with fasting glucose ($\beta = 0.32$, $p < 0.001$) and HbA1c ($\beta = -0.22$, $p = 0.17$) in men. No corresponding associations of ucOC were seen in postmenopausal women

B, β-cell function; F, female; HbA1c, glycosylated hemoglobin; HOMA, homeostasis model assessment; IR, insulin resistance; L, longitudinal study; M, male; ucOC, undercarboxylated osteocalcin; X, cross-sectional.

bone formation and resorption and reduced production of carboxylated as well as ucOC. Consequently, insulin production and adiponectin are decreased. The result is hyperglycemia associated with hypoinsulinism, increased fat accumulation, reduced insulin sensitivity, altered lipid metabolism, and reduced energy expenditure.

JAYPEE BROTHERS

for detailed information on endocrinology books, visit our website www.jaypeebrothers.com, for detailed information on endocrinology books, visit our website www.jaypeeb

Diabetes and Musculoskeletal Disorders

Key Features

- A comprehensive book that describes the case scenarios with various afflictions of the musculoskeletal system in the setting of diabetes mellitus in a concise and clinically-oriented manner
- Musculoskeletal disorders are known to cause pain and functional impairment, and might adversely affect management of diabetes
- An illustrative text which provides deep insight into the pathomechanism of each disease entity
- The book has been divided into seven chapters connecting the entire ambit of both ends of the spectrum of diabetes and diseases of bones and joints
- The book provides streamlined content supplemented by tables, images, and algorithms
- An ideal reference book for all endocrinologists, diabetologists, rheumatologists, internists, and even primary care physicians; a unique one indeed
- Contains up-to-date reviews of modern understanding and current practice recommendations.

Debasis Basu MD (Internal Medicine)
Consultant
Department of Diabetes
Apollo Gleneagles Hospital
Kolkata, West Bengal, India
President, Diabetes Awareness & You
www.day.org.in



Kiran Bahrus MSc (Clinical Research - UK)
Clinical Research Coordinator, ICH
Kolkata, West Bengal, India
Secretary, Diabetes Awareness & You
www.day.org.in



Available at all medical bookstores or buy online at www.jaypeebrothers.com

JAYPEE BROTHERS
Medical Publishers (P) Ltd.
www.jaypeebrothers.com

Join us on facebook.com/JaypeeMedicalPublishers

Shelving Recommendation
DIABETOLOGY

ISBN 978-93-5270-024-0