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Adipokines, Osteokines and Pancreas: Key Players in Type 2 Diabetes Mellitus - A Review

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Abstract

Recent studies showed the role of adipokines, osteokines, and the pancreas plays in the development of diabetes. Numerous studies have conclusively demonstrated the importance of adiponectin, leptin, insulin, and osteocalcin in the regulation and metabolism of glucose. Along with other contributing variables, pro-inflammatory and/or oxidative stress mediators like TNF-alpha and IL-6 are one of several that significantly affect the pathogenesis of type II DM and the development of insulin resistance. For many years, it was believed that there was one pathway connecting the pancreas, adipose tissue, and bone. According to recent research that highlighted the importance of the connections between these organs, insulin resistance in adipose tissues is also thought to have a role in beta cell failure. However, there are still few conclusive studies demonstrating the relationship between adipose tissue, pancreas, bone and T2DM. Further research is required to evaluate the link between these organs and developing type 2 DM patients.

Keywords: *Adipokines, Diabetes mellitus, Inflammatory Markers, Osteocalcin, Osteokines, Pancreas.*

Introduction

Diabetes mellitus is defined by high blood sugar levels due to insufficient insulin production or effectiveness. In India, the rise in diabetes rates is caused by a mix of genetic factors and environmental influences like the increase in obesity due to improved living conditions, migration to urban areas, and lifestyle changes. In India, comprehensive, multi-faceted studies are scarce on the frequency and consequences of diabetes, despite its high occurrence [1]. It was estimated that around 536.6 million people, or 10.5% of individuals aged 20 to 79, had diabetes in 2021. The percentage is expected to increase to 12.2% (783.2 million) by 2045. The frequency is quite comparable between males and females, with the greatest levels detected in individuals between 75 and 79 years old. Urban locations are anticipated to exhibit a greater prevalence rate of 12.1%, in contrast to rural areas with an 8.3% prevalence. Furthermore, by 2045, it is expected that high-income countries will have a higher prevalence rate (11.1%) compared to low-income countries (5.5%) [2]. Since the 1990s, there has been a sharp rise in type 2 diabetes in South Asia, especially India, making it a crucial public health concern. It is projected that in 2025, India will have 69.9 million diabetes cases, with most of them going untreated. It is anticipated that the disease will affect 2.1% of people in urban areas and 1.5% in rural areas [1, 2].

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Adipokines

Adipose tissue produces proteins called adipokines, which are essential to many physiological functions. Adipose tissue is essential for thermoregulate (Figure 1) [3]. Adipocytes generate a range of metabolites, lipids, and bioactive peptides that are generally referred to as adipokines, along with progenitor cells, endothelial cells, immune cells, fibroblasts, and other cells [4, 5]. Many physiological functions, including blood pressure regulation, insulin sensitivity and secretion, appetite and satiety, fat distribution, and inflammation, are influenced by adipokines. Many biological processes, including immunological responses, are impacted by adipokines, such as adipsin, serum amyloid A3, and acylation-stimulating protein. These biological processes are also impacted by inflammatory indicators such as resistin, C-reactive protein, and tumor necrosis factor [3, 5]. Leptin, adiponectin, resistin, and vaspin are important hormones in the metabolism of glucose. Among these, hormones like apelin and nesfatin-1 are implicated in insulin secretion, and leptin and adiponectin are important in improving insulin sensitivity. The pancreas and adipose tissue were thought to be unidirectionally connected in the past, with increased triacylglycerol storage coming from improved glucose uptake into adipocytes because of insulin released by pancreatic islets in response to elevated blood glucose levels. But as recent studies have shown, beta-cell loss and dysfunction can also be attributed to insulin resistance in adipose tissue [6]. Moreover, adipose tissue contains a variety of cell types other than fully developed adipocytes, such as multipotent mesenchymal progenitor cells that can develop into osteogenic, adipogenic, or chondrogenic lineages. Studying the various purposes and potentials of adipose tissue has become more popular because of its flexibility [4].

Osteokines

Osteoblasts, which are specialized mesenchymal cells, play a crucial role in bone formation through the mineralization and deposition of a collagen-rich matrix. New research has emphasized the important function of osteocalcin, which comes from osteoblasts, in controlling glucose metabolism. There are three forms of osteocalcin that circulate in the body, which are uncarboxylated, undercarboxylated, and carboxylated, and are produced by osteoblasts. Studies have indicated that uncarboxylated or undercarboxylated osteocalcin improves insulin sensitivity by directly impacting the pancreas. This type of osteocalcin enhances glucose absorption and boosts insulin release. While there is no evidence of osteocalcin directly binding to insulin-producing cells, research using knockout models has shown that it effectively improves glucose metabolism [7, 8]. Karsenty's group discovered that osteocalcin plays a role in glucose metabolism, as shown by their research findings that mice lacking osteocalcin had higher body fat and glucose metabolism problems. This led to additional research on the roles of osteocalcin in humans [9]. Cross-sectional research has investigated the association between overall and undercarboxylated osteocalcin levels and glucose metabolism. These research findings demonstrate an inverse relationship between osteocalcin levels and different markers of unhealthy glucose metabolism, including hyperlipidemia, body mass index, fasting glucose, fasting insulin, and HOMA-IR (an insulin resistance indicator) [10,11]. Untreated diabetics and pre-diabetics show reduced levels of undercarboxylated osteocalcin, whereas elevated serum levels are associated with higher HOMA-IR and hyperlipidemia. Some research has discovered a strong correlation between serum osteocalcin levels and insulin resistance in postmenopausal women, with a weaker connection found in premenopausal women [12]. There is a lack of research on the impact of insulin on osteocalcin and bone turnover.

Pancreatic Adipokines and Leptins

Pancreatic fat cells (adipocytes) are responsible for producing and secreting hormones like leptin and adiponectin, which play a key role in regulating metabolic balance. Adiponectin, a major adipokine, is recognized for its ability to improve insulin sensitivity and control lipid levels in the body. This hormone achieves its effects by attaching to the AdipoR1 and AdipoR2 receptors, triggering the activation of AMPK and PPAR pathways, along with possibly other undiscovered signaling pathways [13]. Low levels of adiponectin are associated with increased fat storage, and its release is decreased in cases of obesity and insulin resistance. Since its discovery in 1994, leptin's function in glucose metabolism has attracted a lot of interest. By modifying glucagon levels and acting on the central nervous system (CNS), it affects the control of glucose. While leptin's effect on beta-cells can reduce insulin synthesis and release, it also improves insulin extraction in the liver. This procedure is a component of a feedback loop in which insulin sensitivity is increased and adipogenesis is decreased by leptin [14]. Studies show that leptin treatment improves insulin sensitivity in organs like the liver and adipose tissue while also helping people lose weight and reduce their fat mass [15]. People with diabetes have been found to have elevated levels of leptin, which suggests that it plays a role in maintaining glucose homeostasis [16]. Leptin and adiponectin are essential for controlling insulin sensitivity and glucose metabolism. While leptin affects glucose metabolism through direct effects on insulin secretion and glucose production as well as CNS control, adiponectin improves insulin signaling and lowers fat levels. To effectively treat metabolic diseases, it is imperative to comprehend these pathways [13, 14, 17].

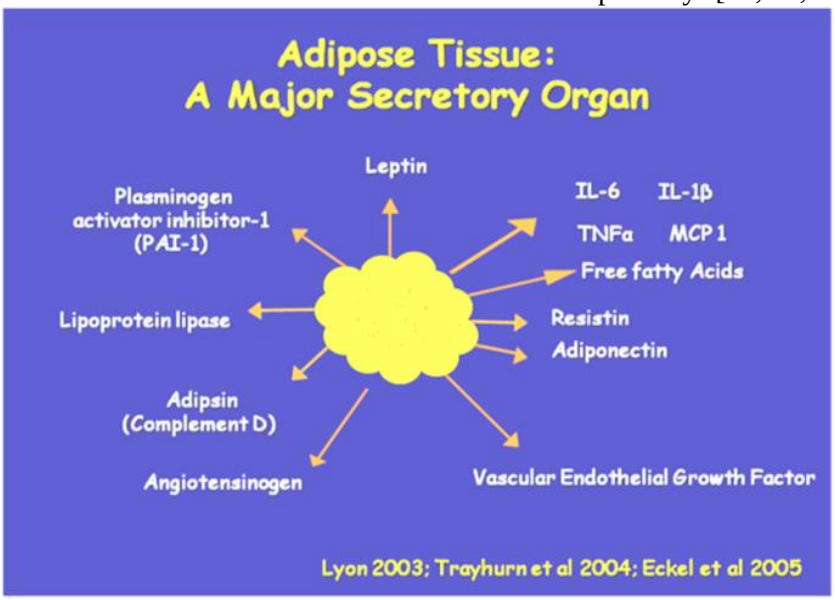

Figure 1: Adipose tissue.

TNF alpha and IL-6

Insulin resistance and the development of type 2 diabetes mellitus are closely linked. Pro-inflammatory and/or oxidative stress mediators are the one among many causative factors that have a significant impact on the pathogenesis of type II DM and the emergence of insulin resistance. Table 1 shows the association of various cytokines with type II diabetes mellitus. TNF-alpha is the main inflammatory marker which causes inflammation in pancreatic islets which are responsible for development of apoptosis. Other most significant pro-inflammatory mediators that cause inflammation are interleukin-6, interleukin-1 beta (IL-1), TNF – alpha, and several other pro-inflammatory cytokines

and chemokines [18, 19]. IL-6, also known as interleukin 6, was first identified as a β cell differentiation factor. IL-6 is thought to cause insulin resistance and contribute to the development of T2D. However, due to its varied activities in various tissues, IL-6's role in the emergence of insulin resistance has been a source of controversy [1].

Table 1: Following are the Results of Study on Various Cytokines in Relationship with Type 2 Diabetes Mellitus

Authors/Year	**Study Design**	**Participants (sample size)**	**Age group/ Sex**	**Biochemical parameters analyzed**	**Results**
Sarkar PD et al. [20]	Cross-sectional	56 men	45-60	Lipid profile, fasting insulin, Total osteocalcin, HOMA-IR	Osteocalcin may potentially protect against the development of type 2 diabetes by enhancing lipid profile.
Liu C et al. [21]	Meta analysis				Lower serum total osteocalcin is seen in type 2 DM patients.
Ferron M et al. [22]	Animal study				Daily-dose (injection) of osteocalcin can enhance glucose control and delay the onset of type 2 diabetes.
Wang Q et al. [23]	Cross sectional	46 men and 20 women	40-60	HOMA-IR, Total osteocalcin	Declining tOC level will worsen glucose metabolism.
Liang Y et al. [24]	cross-sectional	2,353 men	30-50	FPG, HbA1c, Osteocalcin	A risk factor for poor glucose metabolism and ultimately type 2 diabetes was a low serum osteocalcin level.
Chen Y et al. [25]	Cross sectional	1397	30-50	FPG, Lipid profile, ALP, TOC, HOMA-IR	Observed distinct relationship with TOC and glucose homeostasis and -cell function.

Garćia-Marťin A et al. [26]	Cross sectional	54 post-menopausal women	53 - 59	Lipid profile, FPG, FPI, osteocalcin	Potential usefulness of serum osteocalcin as a predictor for increased risk of diabetes in postmenopausal women
Shams HA et al. [27]	Case control study	62(obese T2DM patients),28 healthy	30-50	Lipid profile, HOMA-IR, Total osteocalcin	The serum level of osteocalcin was lower and had a negative correlation with HOMA-IR, HbA1c, and FBG.
Gateva A et al. [28]	Cross sectional	84	40 - 60	Adiponectin, leptin, lipid profile	In patients with normal glycemic control versus those with prediabetes, serum adiponectin is notably higher and has a positive correlation with serum adiponectin. When compared to those who have prediabetes, it is much higher in those with normal glycemic control.
Sheng L et al. [29]	Cross-sectional	382 men and 435 postmenopausal women	Over 50	Osteocalcin levels were associated inversely with age, fasting serum insulin, HOMA-IR, ALT, triglycerides, total cholesterol, LDL-cholesterol, CRP	Serum osteocalcin levels are a distinct risk factor for carotid atherosclerosis.

Discussion

Insulin plays a vital role in regulating glucose metabolism and is necessary to keep blood glucose levels within a narrow physiological range. It works by reducing liver glucose production and helping glucose absorption in tissues like muscle and fat. Insulin resistance, a key feature of type 2 diabetes mellitus (T2DM), hinders these functions, causing increased blood sugar levels and resulting metabolic issues. Adiponectin, a hormone derived from fat tissue, has a central role in regulating glucose metabolism and enhancing insulin sensitivity. In people who have obesity and T2DM, there is

often a decrease in adiponectin levels, leading to worsened glucose control and insulin resistance [17]. Activating AMP-activated protein kinase (AMPK) boosts glucose uptake and fatty acid oxidation, improving energy metabolism. Adiponectin carries out its actions by interacting with its receptors, known as AdipoR1 and AdipoR2, which are responsible for its insulin-sensitizing effects. The importance of adiponectin in regulating metabolic balance is emphasized by its dysfunction in disorders like obesity and T2DM, indicating its crucial role in metabolic disruptions [30].

Studies have demonstrated that osteocalcin, a hormone produced in the bones, can impact how the body processes glucose and responds to insulin. Osteocalcin signaling plays a vital role in metabolic adaptation in muscle and adipose tissue [7]. Osteocalcin enhances glucose uptake and insulin sensitivity through different signalling pathways, such as the PI3K/Akt and ERK1/2 pathways, further connecting bone metabolism with glucose balance [8]. Lower levels of osteocalcin in the blood have been linked to metabolic syndrome and type 2 diabetes. This indicates that osteocalcin, along with adiponectin, is essential in controlling glucose metabolism and emphasizes the intricate relationship between bone and metabolic systems in managing glucose balance. Leptin, a hormone created by fat cells, has a vital function in controlling energy equilibrium and sugar processing. Its main effects are on the hypothalamus, which in turn impacts appetite, energy expenditure, and ultimately glucose balance [31]. Furthermore, leptin also increases glucose absorption in muscle and adipose tissues, playing a crucial role in regulating glucose levels [32].

Osteocalcin, a protein found in the bone matrix and produced by osteoblasts, has been recognized as a key controller of glucose metabolism. Studies have shown that there is an inverse relationship between levels of osteocalcin and markers of glucose metabolism, such as fasting insulin, blood glucose, and HbA1c [10]. Decreased levels of osteocalcin are associated with an increased likelihood of developing T2DM and impaired glucose metabolism [20]. For example, lower levels of osteocalcin have been linked to metabolic syndrome in elderly individuals, affecting the body's ability to regulate glucose and lipid levels [11]. Additionally, research indicates that giving recombinant osteocalcin can enhance glucose tolerance and insulin secretion in animal models, suggesting its potential as a therapy for Type 2 Diabetes Mellitus (T2DM) [22]. These results emphasize the interconnected functions of leptin and osteocalcin in regulating glucose metabolism and their potential as targets for T2DM treatment. The importance of both leptin in regulating energy balance and glucose uptake and osteocalcin in influencing glucose metabolism and insulin sensitivity is underscored in managing diabetes and maintaining metabolic health.

The interaction between osteocalcin and metabolic hormones such as insulin and leptin is complex, highlighting the skeleton's role as an endocrine organ that impacts metabolic regulation. Insulin and leptin can regulate the release of osteocalcin from bone tissue, showing a dynamic connection between bone metabolism and glucose control. Increased insulin and leptin levels activate the release of osteocalcin, which influences glucose metabolism, underscoring the interconnectedness of these bodily systems [7].

Studies have emphasized the possible function of osteocalcin in regulating glucose levels and its benefits in preventing type 2 diabetes mellitus (T2DM) [21]. The negative relationship between osteocalcin levels and glucose metabolism markers indicates its potential as a biomarker for metabolic risk and a potential focus for therapeutic approaches [24]. Still, the precise ways in which osteocalcin impacts glucose metabolism are currently being studied. Research has demonstrated that osteocalcin could enhance glucose metabolism and protect against T2DM, as suggested by results from animal studies [22]. Lower levels of osteocalcin in human populations have been linked to poor

glucose metabolism and a higher likelihood of developing T2DM [26].

It has been documented that osteocalcin levels are negatively correlated with fat mass and plasma glucose in older men [10]. Moreover, research has explored the connection between osteocalcin and insulin resistance, uncovering its possible impact on regulating insulin sensitivity [12]. Clinical studies are crucial to confirm the effectiveness of osteocalcin as a marker for metabolic disorders and to understand how it works. Further research is needed to fully comprehend how osteocalcin can be utilized in managing metabolic diseases such as T2DM and to optimize its potential in clinical treatment strategies. Understanding the relationships among adipose tissue, the pancreas, and bone, as well as the impacts of hormones such as adiponectin, leptin, and osteocalcin on glucose metabolism, is essential for creating successful treatments for Type 2 Diabetes Mellitus (T2DM). Adiponectin and leptin, which are mainly synthesized by fat cells, have important functions in regulating blood sugar levels and how sensitive the body is to insulin. Adiponectin enhances insulin sensitivity and glucose uptake and shows an inverse correlation with obesity [17, 30]. However, it is reduced in obesity, leading to insulin resistance [33]. On the other hand, leptin, which is also produced by fat cells, controls energy levels and sugar processing by triggering AMP-activated protein kinase (AMPK) and phosphatidylinositol-3-OH kinase (PI3K) pathways, improving sensitivity to insulin [31].

Osteocalcin, a hormone sourced from bones, has been recognized as a key controller of glucose metabolism. Studies have shown that osteocalcin injections in mice can enhance glucose metabolism and insulin sensitivity, according to research [22]. Decreased osteocalcin levels in the blood are linked to elevated blood sugar levels and a greater likelihood of developing type 2 diabetes. This hormone affects glucose balance by regulating the activities of fat cells and pancreatic beta cells. For example, osteocalcin's function in bone metabolism also affects glucose control, as seen by its opposite correlation with fat mass and plasma glucose in older people [10]. The complexity in regulating glucose metabolism is highlighted by the interactions among these hormones. For example, the signalling pathways of adiponectin and leptin can impact the production of osteocalcin, which then affects glucose metabolism [13, 15]. This complex web underscores the importance of fully grasping these connections to create specific treatments for T2DM. By explaining the interactions of these hormones in various tissues and their impact on metabolic processes, new approaches to treating and possibly preventing T2DM could be created.

Table 2: Effect of Cytokines and Inflammatory Markers on Metabolism of Glucose

Name of the cytokines	**Metabolic actions of cytokines**	**Circulating levels of cytokines**	**Reference**
Adipokines			
Leptin	Increases insulin sensitivity, accelerates the absorption of glucose, and regulates eating by encouraging the fatty acid oxidation process.	↑ Type 2 Diabetes mellitus	[31]
Adiponectin	Increases insulin sensitivity, has anti-steatosis, anti-inflammatory, anti-fibrotic properties, and promotes healthy ageing.	↓ Type 2 Diabetes mellitus	[32]

Cytokines which are inflammatory marker			
TNF α	Promotes lipolysis, mediates insulin resistance, and is pro-inflammatory	↑ Type 2 Diabetes mellitus	[34,35]
Osteokines			
Osteocalcin	Increases muscle fatty acid absorption and utilization, favors fatty acid uptake and secretion from the pancreas, and encourages cell proliferation. It also encourages insulin expression and secretion.	↓ Type 2 Diabetes mellitus	[22]

In summary, the control of glucose metabolism is intricately coordinated by the interactions of insulin, adiponectin, leptin, and osteocalcin as listed in Table 2. Every hormone plays a distinct role in regulating glucose balance: insulin aids in glucose absorption, adiponectin improves insulin sensitivity, leptin controls energy levels, and osteocalcin impacts glucose metabolism via communication between bone, fat, and pancreas. The complexity of metabolic regulation is highlighted by the interaction between these hormones. Continuing research on these mechanisms is essential for furthering our comprehension of Type 2 Diabetes Mellitus (T2DM). These findings will be necessary for creating specific and efficient treatments, enhancing management techniques, and possibly averting the disease. Calcium carbonate, PRF, and nano-hydroxyapatite, when mineralized, have proven beneficial across diverse clinical disciplines [36-38].

Conclusion

This review highlights the complex web of connections among adipokines, osteokines, and pancreatic hormones in controlling glucose metabolism and the development of Type 2 Diabetes Mellitus (T2DM). The intricate interactions of adiponectin, leptin, and osteocalcin, combined with the influence of inflammatory markers such as TNF-alpha and IL-6, depict a multifaceted network of metabolic regulation that surpasses basic one-dimensional frameworks. The complex connections between these molecules demonstrate how interruptions in their signalling pathways can lead to insulin resistance and compromised glucose regulation. The evidence shows the possibility of focusing on these hormones and cytokines for treatments, providing hopeful opportunities to improve metabolic health. Even though there has been considerable advancement, more research is still necessary to understand the exact ways in which these factors interact and impact the development of T2DM. This understanding is vital for improving treatment plans and discovering new biomarkers for early detection and personalized treatment. By enhancing our knowledge of these relationships, we can enhance management strategies and potentially reduce the increasing worldwide impact of Type 2 Diabetes Mellitus.

Conflict of Interest

None Declared.

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