บทความฟื้นวิชา **Review Article**

ภาวะแทรกซ้อนของกระดูกในผู้ป่วยโรคเบาหวานและความบกพร่องของการเปลี่ยนแปลงไปเป็นเซลล์กระดูกของเซลล์ต้นกำเนิด
Bone related complications in diabetic patients and an impaired osteogenic differentiation of stem cells

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บทคัดย่อ

โรคเบาหวาน (Diabetes Mellitus : DM) เป็นโรคทางเมตาบอลิซึมเรื้อรังที่มีลักษณะอาการ คือ ระดับน้ำตาลในเลือดสูงอย่างต่อเนื่อง ซึ่งนำไปสู่ภาวะแทรกซ้อนที่เกิดขึ้นในหลายระบบของร่างกาย รวมถึงปัญหาทางกระดูกที่มักไม่ถูกวินิจฉัยหรือได้รับการวินิจฉัยล่าช้า เนื่องจากมีการตรวจพบความหนาแน่นแร่กระดูกปกติ แต่มีความเสี่ยงในการเกิดการหักกระดูกสูงขึ้น การศึกษาครั้งนี้มีวัตถุประสงค์ เพื่อรวบรวมและสังเคราะห์ข้อมูลเกี่ยวกับพยาธิสภาพของปัญหากระดูกในผู้ป่วยเบาหวานโดยเฉพาะ การศึกษาพบว่าโรคเบาหวานมีผลกระทบต่อการแตกต่างของเซลล์ต้นกำเนิดในการสร้างกระดูก ซึ่งเป็นกระบวนการที่สำคัญในการฟื้นฟูกระดูก การศึกษานี้ใช้วิธีการทบทวนข้อมูลจากวรรณกรรมโดยเลือกงานวิจัยที่เผยแพร่ระหว่างปี ค.ศ. 2000 ถึง ค.ศ. 2024 จากฐานข้อมูลต่างๆ ได้แก่ PubMed, ScienceDirect, Scopus และ Google Scholar ผลการศึกษาแสดงให้เห็นว่าโรคเบาหวานส่งผลกระทบต่อความสมดุลของกระดูกผ่านกลไกหลายอย่าง เช่น ความเครียดจากปฏิกิริยาออกซิเดชัน การสะสมของสารผลิตภัณฑ์การกลายพันธุ์ของกลูโคซิล และการส่งสัญญาณของไซโตไคน์ที่ก่อให้เกิดการอักเสบ ซึ่งทั้งหมดนี้ส่งผลให้การทำงานของเซลล์สร้างกระดูก Osteoblast เสียหายและลดคุณภาพกระดูก นอกจากนี้เซลล์ต้นกำเนิดจากผู้ป่วยเบาหวาน โดยเฉพาะเซลล์ต้นกำเนิดจากเนื้อเยื่อไขมัน ยังมีความบกพร่องในการสร้างกระดูก ซึ่งเชื่อมโยงกับการหยุดชะงักของเส้นทางโมเลกุลต่างๆ เช่น การแสดงออกของ RAGE ที่มากเกินไป การเพิ่ม O-GlcNAcylation ของ Runx2 ระดับ BMP-4 ต่ำ และการทำงานที่ผิดปกติของสัญญาณ PI3K/AKT/β-catenin ปัจจัยเหล่านี้มีส่วนทำให้กระดูกเปราะและการหักกระดูกเกิดการฟื้นตัวช้า การเข้าใจกลไกเหล่านี้จึงเป็นสิ่งสำคัญสำหรับการพัฒนาการรักษาที่มุ่งเป้า

และการปรับปรุงผลลัพธ์ทางกระดูกในผู้ป่วยเบาหวาน และการศึกษาทางคลินิกเพิ่มเติมจะช่วยในการนำผลการศึกษานี้ไปใช้ในกลยุทธ์การรักษาที่เหมาะสม และเป็นส่วนตัวมากขึ้น

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Abstract

Diabetes mellitus (DM) is a chronic metabolic disorder that causes persistent hyperglycemia and leads to various systemic complications, including bone-related issues, which are often underdiagnosed due to a paradox of normal bone mineral density (BMD) despite an elevated fracture risk. This review synthesizes current evidence on a pathophysiology of bone complications in diabetic patients, particularly focusing on how diabetes impairs the osteogenic differentiation of stem cells, a key process for bone regeneration. A narrative literature review was conducted, analyzing studies published between 2000 and 2024 from sources including PubMed, ScienceDirect, Scopus, and Google Scholar. Findings indicate diabetes disrupts bone homeostasis through mechanisms such as oxidative stress, accumulation of advanced glycation end products (AGEs), and inflammatory cytokine signaling, all of which negatively affect osteoblast function and reduce bone quality. Additionally, stem cells, especially mesenchymal stem cells (MSCs) from diabetic patients, exhibit impaired osteogenic differentiation, a defect linked to molecular disruptions like RAGE overexpression, O-GlcNAcylation of Runx2, low BMP-4 levels, and dysfunction in PI3K/AKT/β-catenin signaling. These factors contribute to bone fragility and delayed fracture healing, underscoring the need for a deeper understanding of these mechanisms to develop targeted regenerative therapies and improve skeletal outcomes for diabetic patients. Further clinical studies are necessary to translate these findings into personalized treatment strategies.

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Keywords: Diabetes, Bone Complications, Stem Cells, Osteogenic Differentiation

Introduction

Stem cells are unique in their capacity for self-renewal and multilineage differentiation, enabling them to maintain tissue homeostasis and facilitate regeneration after injury. Among these, mesenchymal stem cells (MSCs) play a critical role in skeletal repair, given their ability to differentiate into osteoblasts, chondrocytes, and adipocytes. The osteogenic differentiation of MSCs is essential for bone remodeling, fracture healing, and osseointegration. Any dysfunction in their regenerative capacity whether due to intrinsic abnormalities or systemic disease can hinder bone formation and repair, leading to long-term musculoskeletal complications[(1)].

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. It is classified into two major types: type 1 diabetes mellitus (T1DM), caused by autoimmune β-cell destruction, and type 2 diabetes mellitus (T2DM), marked by insulin resistance and relative insulin deficiency[(2)]. While the complications of DM such as cardiovascular disease, nephropathy, neuropathy, and retinopathy are well known, its negative impact on bone health has received less attention despite its clinical significance.

Patients with diabetes have an increased risk of fractures, even when bone mineral density (BMD) appears normal or elevated[3,4]. This paradox suggests that DM compromises bone quality more than bone quantity. Recent studies have shown that diabetes induces oxidative stress, chronic inflammation, and the accumulation of advanced glycation end products (AGEs), all of which impair osteoblast function, disrupt bone matrix architecture, and delay healing[5,6]. These metabolic insults not only affect mature bone cells but also interfere stem cell differentiation into osteogenic lineages.

Specifically, hyperglycemia, AGEs, and dysregulated cytokine signaling are implicated in the impaired osteogenic differentiation of various stem cell types, including bone marrow-derived MSCs, adipose-derived stem cells, and periodontal ligament stem cells[7-9]. These alterations are linked to molecular mechanisms such as RAGE overexpression, excessive O-GlcNAcylation of Runx2, and suppressed BMP-4 expression, all of which compromise the ability of stem cells to support bone regeneration[10-12].

Despite mounting evidence, significant gaps remain in our understanding of how diabetes alters osteogenic signaling across stem cell populations. There is limited insight into how disease duration, glycemic control, and pharmacologic therapies influence stem cell behavior, in vivo. Moreover, the translation of in vitro findings to clinical interventions remains underdeveloped.

This review aims to synthesize current evidence on bone-related complications in diabetes and to elucidate how impaired osteogenic differentiation of stem cells contributes to these outcomes. By identifying key molecular mechanisms and research gaps, this review seeks to inform future strategies for regenerative therapy and fracture risk reduction in diabetic patients.

Methodology

A narrative literature review was conducted using databases, including PubMed, ScienceDirect, Google Scholar, and Scopus. Articles published between 2000 and 2024 were searched using keywords such as “diabetes mellitus,” “bone complications,” “osteogenic differentiation,” “stem cells,” and “fracture risk.” Inclusion criteria focused on peer-reviewed studies involving bone metabolism or stem cell differentiation in diabetic contexts, including both human and experimental studies. Non-English and non-peer-reviewed articles were excluded. Over 30 relevant articles were selected and synthesized into two main themes: bone-related complications in diabetes and impaired osteogenic differentiation. No formal quality appraisal was performed, but preference was given to recent and methodological studies.

Literature Review

Bone related complications in DM patients

DM is associated with significant bone-related complications, notably an increased risk of fractures, which is a serious concern for both T1DM and T2DM diabetes patients. Despite normal or even increased bone mineral density (BMD) in some cases, the fracture risk is underestimated by current diagnostic tools. The pathophysiology of diabetes-related bone disease is multifaceted, involving both metabolic and structural changes in bone tissue. This complexity necessitates a comprehensive understanding of the underlying mechanisms and the development of improved diagnostic and management strategies.

Bone-related complications in DM patients typically include decreased BMD and an increased risk of fractures. Bone fragility is a significant complication. The risk of fractures is higher in T1DM compared to T2DM[4]. T1DM is associated with lower BMD and accelerated postmenopausal bone loss, while T2DM may present normal or high BMD but still has a comparable fracture risk due to altered bone microarchitecture[3,13,14]. In T1DM, lower BMD and a higher prevalence of asymptomatic vertebral fractures are observed[15]. The complications include Charcot joint involvement, which results from neuropathy and altered blood flow, causing local inflammation and joint erosions, ultimately increasing the risk of ulcer formation, especially diabetic foot ulcers[16]. T2DM is linked to increased fragility fracture risk, despite normal bone mineral density and higher body mass index. Factors such as exogenous insulin therapy, vascular complications, and poor glycaemic control contribute to this elevated risk. The underlying mechanisms are complex, involving obesity, hyperinsulinemia, hyperglycemia, and the accumulation of advanced glycation end products, which negatively affect bone-cell function and bone-matrix composition[17]. Post-fracture mortality is also notably worse in T2DM patients.

This is due to an imbalance between bone formation and resorption, driven by hyperglycemia-induced oxidative stress, advanced glycation end products (AGEs), and persistent inflammation[6]. DM negatively provides impact to bone health by disrupting various processes, including bone formation and resorption, collagen formation and cross-linking, and calcium metabolism. Low bone turnover is due to osteoblastic dysfunction resulted in abnormalities in microarchitecture[5]. AGEs and homocysteine negatively impact osteoblasts and osteocytes. Anti-diabetic drugs also influence bone metabolism, contributing to the complexity of these complications. Additionally, hyperglycemia influences the secretion of inflammatory cytokines, skeletal muscle function, and increases bone marrow adiposity[18]. Alterations in the insulin signaling pathway and impaired osteocyte characteristics further compromise bone formation. These factors collectively lead to a heightened fracture risk and delayed fracture recovery in individuals with DM.

DM patients experience of impaired bone healing due to alterations in bone metabolism, characterized by reduced bone formation and increased bone resorption. Chronic hyperglycemia leads to the accumulation of AGEs in bone collagen, compromising its mechanical properties. Additionally, DM complications like peripheral neuropathy and microvascular disease further contribute to osteoporotic fractures[19]. Complications like retinopathy and neuropathy heighten fall risk, further exacerbating fracture likelihood and leading to poorer healing outcomes post-fracture[14].

While the increased fracture risk in diabetes is documented, the precise mechanisms remain incompletely understood, and further research is needed to elucidate these pathways. Additionally, the impact of diabetes medications on bone health requires careful consideration in the management of diabetic patients to mitigate fracture risk, effectively.

Osteogenic Differentiation Impairment

DM adversely affects the osteogenic differentiation of stem cells, which is crucial for bone health and regeneration. Osteogenic differentiation impairment in diabetic patients is a multifaceted issue influenced by various biological and molecular factors. This impairment is linked to factors such as AGEs, high glucose concentrations, and specific gene expressions.

In patients with T2DM, peripheral blood-derived mononuclear cells (PBMCs) exhibit significantly impaired osteogenic differentiation, with a rate of 7.4% compared to 86.7% in age-matched controls ($p < 0.0001$)[11]. This impairment is associated with lower expression levels of osteogenic markers *ALPL*, *COL1A1*, and *BGLAP*, and non visualized mineralization. Fasting plasma glucose (FPG) was identified as an independent risk factor for this defect. Additionally, T2DM patients showed increased sensitivity to the receptor of AGER and higher cellular apoptosis, contributing to the differentiation impairment. Osteogenic differentiation impairment was observed in approximately 60% of PBMCs from T2DM patients treated with metformin monotherapy. Only 40% of these cells expressed osteoblast-specific genes, compared to 90% in age-matched non-diabetic controls[20]. The study identified higher expression of RAGE and apoptotic signals in diabetic patients with impaired differentiation, indicating a significant link between RAGE overexpression and reduced osteogenic potential in early-stage diabetes.

The osteogenic differentiation of mesenchymal stem cells (MSCs) is obviously poorer in DM patients. Nguyen et al.[7] indicates that osteogenic differentiation of human adipose tissue-derived MSCs is impaired under high D-glucose concentrations, specifically at 25, 50, and 100 mM. This impairment is evidenced by decreased expression of osteogenic-specific genes, such as *Runx-2* and *ALP*, as well as reduced mineralization, as shown by Alizarin Red S staining. Diabetes impairs osteogenic differentiation of bone marrow-derived MSCs by down-regulating key transcription factors associated with the osteogenic pathway, such as *Runx2* and *Tgfb3*. In vitro studies demonstrated that BM-MSC from diabetic Zucker rats exhibited significantly reduced osteogenic differentiation compared to lean controls, while no significant differences were observed in adipogenic or endothelial differentiation[21]. This imbalance in gene expression and differentiation capabilities may contribute to the impaired regenerative potential of stem cells in diabetic patients. This impairment is linked to decreased integrin subunit alpha10 (ITGA10) expression, which disrupts the FAK/PI3K/AKT/GSK3β/β-catenin signaling pathway, ultimately affecting the adhesion, migration, and osteogenic differentiation abilities of bone marrow-derived MSCs in T2DM patients[9].

Osteogenic differentiation impairment in DM patients is linked to high glucose environments, which inhibit the differentiation of periodontal ligament stem cells (PDLSCs). This study found that high glucose reduces the expression of osteogenesis-related markers like RUNX2 and promotes the sumoylation of IGF-1R, which binds to SLUG, further inhibiting osteogenic differentiation[8]. Consequently, this mechanism contributes to alveolar bone loss in diabetic patients. Osteogenic differentiation impairment is significantly influenced by low

expression levels of bone morphogenetic protein-4 (BMP-4) in their blood. This deficiency hinders the osteogenic potential of alveolar bone marrow-derived MSCs, leading to reduced proliferation, migration, and differentiation. Consequently, this impairment contributes to the lower success rates of implant osseointegration in T2DM patients compared to nondiabetic individuals[12].

Osteogenic differentiation impairment in diabetic patients is linked to hyperglycemic conditions that induce excessive protein O-GlcNAcylation. High glucose, glucosamine, or N-acetylglucosamine treatments increased O-GlcNAcylation of *Runx2*, a key transcription factor for osteoblast differentiation. Consequently, this led to decreased transcriptional activity of *Runx2* and reduced expression of osteogenic marker genes, ultimately suppressing osteogenic differentiation[10]. Thus, excessive O-GlcNAcylation is a contributing factor to impaired osteogenic differentiation in diabetes. A comparative summary of these molecular mechanisms across different stem cell types is presented in Table 1

Table 1 Summary of mechanisms impairing osteogenic differentiation across stem cell types in diabetes mellitus.

Mechanism	Stem Cell Type	Key Studies	Effects
Advanced Glycation End Products (AGEs) & RAGE overexpression	Peripheral blood-derived mononuclear cells (PBMCs), MSCs	(11, 20)	Reduced osteogenic markers (ALPL, COL1A1), increased apoptosis
High Glucose / Hyperglycemia	MSCs from bone marrow, adipose tissue, PDLSCs	(7, 8)	Suppressed osteogenic gene expression and mineralization
O-GlcNAcylation of Runx2	MSCs (C2C12 model)	(10)	Decreased Runx2 activity, impaired differentiation
Low BMP-4 Expression	Alveolar bone marrow-derived MSCs	(12)	Reduced proliferation, migration, and osteogenesis
FAK/PI3K/AKT/catenin Pathway Disruption	Bone marrow-derived MSCs	(9)	Impaired adhesion, migration, and osteogenic potential
IGF-1R Sumoylation & SLUG Binding	Periodontal ligament stem cells (PDLSCs)	(8)	Inhibited RUNX2 expression and osteogenic capacity

Discussion

The relationship between diabetes mellitus (DM) and impaired bone health is multifactorial, involving a complex interplay between hyperglycemia, oxidative stress, inflammatory cytokines, and advanced glycation end products (AGEs). This review highlights how these systemic effects of DM compromise the osteogenic differentiation potential of mesenchymal stem cells (MSCs), which plays a pivotal role in bone remodeling and repair. Multiple studies consistently report reduced expression of osteogenic markers such as Runx2, ALP, and COL1A1 in MSCs derived from diabetic patients or cultured under high-glucose conditions[7,10,11]. However, while this impairment appears universal across different stem cell sources bone marrow, adipose tissue, periodontal ligament, the extent and mechanism of disruption vary depending on the stem cell type, diabetic model, and disease stage. For example, Phimphilai et al.[20] found that only 40% of peripheral blood-derived mononuclear cells (PBMCs) from T2DM patients expressed osteoblast-specific genes, compared to 90% in controls, underscoring a significant decline in osteogenic potential even in early-stage T2DM.

Interestingly, certain signaling pathways such as RAGE overexpression, O-GlcNAcylation of Runx2, and downregulation of BMP-4 appear to be consistently implicated across studies[10,12,20]. These pathways offer promising targets for therapeutic intervention. For instance, metformin has been shown to partially rescue osteogenic differentiation by modulating BMP-4 expression and reducing apoptosis, suggesting that pharmacologic modulation of these pathways could mitigate skeletal complications in diabetes[12].

Clinically, the findings help explain the paradox of elevated fracture risk in diabetic patients with normal or even high BMD, particularly in T2DM. Bone fragility in diabetes is increasingly understood as a quality rather than density problem linked to poor collagen integrity, disrupted bone architecture, and impaired cellular turnover[4,5]. Moreover, complications such as neuropathy and visual impairment further increase fall risk, while impaired healing exacerbates post-fracture morbidity[14].

Despite these advances, several gaps still-remain. A few studies have longitudinally tracked changes in osteogenic capacity over the course of diabetes progression, nor evaluated how factors such as glycemic control, insulin use, or comorbidities influence stem cell behavior. Furthermore, most evidence is derived from in vitro studies or animal models, highlighting a need for human clinical data to confirm translational relevance.

In summary, impaired osteogenic differentiation in diabetic conditions is a critical contributor to bone fragility and delayed fracture healing. Understanding these mechanisms not only enhances our biological insight but also opens avenues for targeted regenerative therapies and personalized care strategies for diabetic patients at risk of skeletal complications.

Conclusion

It is anticipated that this review will provide researchers with a clearer insight into the roles of stem cells in diabetic complications, thereby facilitating the advancement of stem cell therapies for these conditions. While the primary focus is on the impairment of osteogenic differentiation due to DM, it is important to consider that not all DM patients

experience the same degree of impairment. The factors such as the stage of DM, individual genetic predispositions, and the presence of other comorbidities can influence the extent of osteogenic differentiation impairment. Additionally, therapeutic interventions targeting these molecular pathways may offer potential solutions to mitigate these effects in DM patients.

Challenges and Future Directions

Despite significant progress in understanding the impact of diabetes mellitus (DM) on bone health and stem cell function, several key challenges remain that hinder clinical translation and targeted therapeutic development.

1. Limited human clinical data

Most current evidence arises from in vitro studies and animal models. While these models provide valuable insights into molecular mechanisms, their applicability to human bone biology is limited. There is a pressing need for longitudinal human studies to validate these findings and assess how disease progression, age, and comorbidities influence osteogenic capacity in diabetic patients.

2. Heterogeneity of stem cell responses

The degree of osteogenic impairment varies significantly among different stem cell sources bone marrow, adipose, periodontal ligament, diabetes types (T1DM vs. T2DM), and individual patient characteristics. Future research should focus on comparing stem cell populations under standardized diabetic conditions to identify the most suitable sources for therapeutic use.

3. Lack of integrated biomarker studies

Reliable biomarkers for early detection of bone quality deterioration and stem cell dysfunction in diabetes are lacking. Investigations into circulating factors, such as BMP-4 levels, AGEs, or RAGE expression, could offer non-invasive tools for patient risk stratification and monitoring of bone regeneration potential.

4. Limited exploration of therapeutic modulation

Although some agents such as metformin restores osteogenic function via BMP-4 modulation, there is limited research on other pharmacologic interventions that could target pathways such as O-GlcNAcylation, RAGE, or PI3K/AKT/β-catenin. Preclinical studies should explore combination therapies or biomaterial-based delivery systems for more effective outcomes.

5. Clinical translation and personalized regenerative therapies

A critical gap exists in translating these cellular and molecular findings into practical clinical solutions. Future directions should focus on developing stem cell-based therapies, tissue engineering strategies, and personalized medicine approaches tailored to the metabolic profile and osteogenic potential of individual diabetic patients.

By addressing these challenges, future research can move closer to developing effective interventions that restore bone health and regenerative function in patients with diabetes, ultimately reducing fracture risk and improving quality of life.

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