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Relationship between Diabetes Mellitus and Bone Health – A Review

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Abstract**—***Through a number of biochemical and structural processes, long-term exposure to a diabetic environment causes alterations in bone metabolism and poor bone micro-architecture. These modifications make the bone more prone to fractures and impede osseous healing. In clinical practice, management of diabetes mellitus plays important role for preventing bone health complications. To effectively identify fracture risk in individuals with diabetes mellitus, alternate fracture risk assessment techniques may be required. There is currently no definitive model describing how diabetes mellitus affects bone health, particularly in view of progenitor cells. The best available information on the influence of diabetes mellitus on bone health in vitro and in vivo is summarised in this review, with a focus on future translational research prospects.*

Keywords**—***Diabetes Mellitus, Bone Remodeling, Fracture Healing, Bone Marrow Dysfunction*.

I. INTRODUCTION

Diabetes mellitus has been linked to decreased bone quality and an increased risk of fracture [1]. Two meta-analyses with a total of 7,832,213 participants found an increased incidence of hip fractures in people with diabetes mellitus compared to the general population, with type 1 diabetes mellitus (T1DM) (relative risk (RR) = 5.76 – 6.3) having a higher incidence than type 2 diabetes mellitus (T2DM) (RR = 1.34 – 1.7) [2, 3]. Furthermore, efficient clinical care reduces diabetic fracture risk, since fracture risk is greater in diabetes mellitus with poor glycemic control compared to diabetes mellitus that is well managed [4, 5]. Fracture risk is raised in those with diabetes mellitus, which is exacerbated by poor fracture healing. Changes in bone metabolism and the onset of microvascular illness can increase healing time by 87 % [6]. Furthermore, diabetic individuals are more likely to experience problems such as delayed wound closure [7], infection complications [8], and peri-operative cardiovascular events [9]. Given the increasing prevalence of diabetes mellitus and the significant socioeconomic burden posed by fragility fractures [10], our findings highlight the need for further understanding of the variables that influence bone health and fracture risk in diabetic individuals.

The goal of this review is to summarise the best available current literature in order to gain a better knowledge of the molecular interactions between bone health and diabetes mellitus and to identify future research opportunities in this subject.

1. Bone Mineral Density

Patients with T1DM have a total failure of the pancreatic cells, as well as low levels of insulin like growth factor 1 (IGF1). In addition to osteoblastic activity, low IGF1 levels and a lack of insulin, among other pancreatic anabolic hormones, restrict the final differentiation of mesenchymal stem cells (MSCs) into osteoblasts [11]. As a result, skeletal development is inhibited at a young age, resulting in an insufficient accumulation of peak bone mass [12, 13, 14, 15, 16]. In advanced stages of T2DM, however, multiple variables such as insulinopenia, hyperglycemia, the development of advanced glycation end products (AGEs), chronic inflammation, and microvascular illness combine to significantly impact bone architecture and biomechanical characteristics [17, 18]. As a result, the chance of experiencing a hip fracture rises as T2DM progresses [1]. Whereas T1DM is associated with modest reductions in bone mineral density (BMD) (Hip Z-scores of -0.37 ± 0.16) and an increase in fracture risk, patients living with T2DM have higher BMD (Hip Z-scores of 0.27 ± 0.16) with an increased fracture risk [19, 21, 22]. This inconsistency can be explained in the following way. Individuals with diabetes mellitus have an increased risk of falling as a result of long-term consequences. After accounting for increased falls as well as other variables such as hypoglycemia episodes and the use of anti-diabetic drugs, individuals with T2DM still had a higher risk of fracture in a meta-analysis [23, 24]. As a result, the evidence implies that fracture risk in diabetes mellitus is unrelated to both changes in BMD and an increased risk of

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falling. This can be explained by bone structural abnormalities [24].

The introduction of non-invasive imaging methods has made it easier to investigate bone architecture in people with diabetes mellitus [25, 26]. T2DM is linked to a 10 % increase in trabecular BMD and an increase in intracortical porosity, according to a research utilising high-resolution peripheral quantitative computer tomography (CT) [27]. Patients with diabetes mellitus had greater adiposity and a larger proportion of saturated fat in their bone marrow, according to several recent imaging investigations. These investigations have not yet taken into account obesity-related bone marrow adiposity [28, 29]. Changes in bone structure were recently verified in individuals with T2DM compared to controls utilising in vivo micro-indentation of the tibia to quantify bone micro-architecture. In comparison to healthy controls, these individuals had considerably higher cortical porosity and decreased bone mineral strength [30].

2. Biochemical Impact on Bone Micro-Architecture

The extracellular bone matrix is made up of two different components. Stiffness, which is evaluated by a traditional BMD scan, is provided by the inorganic mineral component, which is mostly hydroxyapatite. The organic component, which is mostly made up of interconnected collagen fibres, offers tensile strength and protects against shear pressures [31, 32]. Cellular activity, bone tissue turnover rate, and collagen cross-link production all influence the material characteristics of bone tissue [32, 33].

Many other parameters linked to hyperglycemia have an indirect effect on bone micro-architecture in diabetes mellitus. For example, glycosuria increases calcium output in urine proportionately [37]. Furthermore, in the population of diabetic individuals, the interaction of hyperglycemia with the parathyroid hormone (PTH) and vitamin D system influences bone turnover [34, 38]. Vitamin D and calcium supplementation may be essential for avoiding T2DM in people with impaired glucose tolerance, according to a meta-analysis published in 2007 [39].

2.1 Insulin Signaling

Insulin, along with other pancreatic hormones, may operate as anabolic agents in bone growth, according to the research [34, 40]. Conditional deletion of the gene encoding the IGF1 receptor in osteoblasts inhibits their proliferation and mineralization, according to one in vitro investigation. However, insulin therapy was able to correct this flaw. Furthermore, in vivo evidence in a mouse model shows that IGF1 is important for MSC final differentiation into osteoblasts [11]. As a result, insulin regulates osteoblastic activity directly by activating its cell surface receptor, while IGF1 modifies the intensity of the insulin-generated signal via interactions with the IGF1 receptor [40]. Absolute insulinopenia, in conjunction with low IGF1 levels, inhibits bone growth in T1DM patients by inhibiting osteoblasts and their progenitor cells in the early stages of the illness [17]. However, in advanced stages of T2DM, this inhibitory impact produced by insulinopenia and low IGF1 levels would be predicted [17]. Because T1DM is most common in children, teenagers, and young adults, absolute insulinopenia correlates to a skeletal development stage. As a result, these findings imply that poorly managed T1DM has an influence on bone accrual and peak bone mass growth [34].

2.2 Hyperglycemia and AGEs

The function and development of osteoblasts are affected by a hyperglycemic environment in both direct and indirect ways [41, 42]. In vitro investigations suggest that hyperglycemia has a direct impact on osteoblast metabolism and maturation by modifying gene expression [41, 42] and by lowering the quality of bone mineral [43]. In addition, hyperglycemia has been shown to increase the expression of pro-inflammatory cytokines in humans, such as tumour necrosis factor alpha , interleukin 1 beta, interleukin 6, interleukin 8 [43, 44], as well as the receptor activator of nuclear factor kappa-B ligand (RANKL) [43], which mediates osteoblast death and osteoclastogenesis [35]. Because inflammatory variables are high in the early phases of T1DM [45], the pro-inflammatory cytokines may have a role in the slowed bone mass accumulation [46]. The data demonstrates that oxidative stress and a hyperglycemic metabolic state, both of which are caused and maintained by diabetes mellitus, cause AGEs (such as pentosidine) to develop more quickly [35, 47, 48, 49]. In both trabecular and cortical bone, AGEs crosslink collagen fibres, resulting in brittleness and a loss of post-yield characteristics (making bones less able to bend before shattering). Physiological enzymatic cross-links between collagen fibres improve the quality and strength of bone [36, 50, 51]. After the start of diabetes mellitus in spontaneously diabetic WBN/Kob rats, a gradual decline in favorable enzymatic cross-links was seen, along with a steady increase in pentosidine. In addition, despite no changes in BMD values, worse bone biomechanics correlated with these changes in collagen cross-linking [52]. As a result, AGEs are hypothesised to impair bone biomechanical performance by changing the physical characteristics of bone collagen, resulting in bone fragility [53]. AGEs damage bone tissue by directly interfering with the growth and function of bone cells, which occurs in tandem with the modification in collagen cross-links [54, 55]. In vitro, AGEs influence osteoblast phenotypic expression, limiting nodule development in osteoblasts in a cell culture [56]. Furthermore, AGEs may reduce bone resorption by decreasing orthoclastic differentiation activity and, as a result, changing the collagen matrix's structural integrity [57]. AGEs have been shown to affect osteoblastic function by upregulating the cell surface receptor for advanced glycation end products (RAGE), which is found on osteoblasts [58, 59]. These receptors have been demonstrated to enhance pro-inflammatory cytokine production, which may fuel a loop of increased bone resorption and chronic inflammation [60]. Furthermore, treating an osteocytic cell line with AGEs promotes sclerostin expression while decreasing RANKL expression, according to a study. As a result, both bone growth and bone resorption are inhibited [61]. These negative effects of AGEs on bone cells increase the onset of bone fragility in diabetics [33]. Galectin-3, a protein found in bone tissue, has been demonstrated to play a significant role in the absorption and elimination of AGEs, acting on AGE-receptors in the opposite way as RAGE does.

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As a result, this might be a preventive factor against AGE buildup in diabetes mellitus [62, 63].

3. Epigenetic Changes

Diabetic complications in T1DM and T2DM continue to worsen after patients achieve good glycemic control, according to large clinical trials [64, 65, 66, 67, 68, 69]. Furthermore, HbA1c only accounts for 25% of the variance in the likelihood of developing problems, suggesting that transitory hyperglycemic episodes result in long-term cellular alterations [66, 70]. Recent studies have begun to shed light on the patho-mechanism of metabolic memory in diabetes mellitus, which leads to the development of end-organ damage, notably in mouse models of cardiovascular disease [64, 71, 72, 73, 74, 75]. MicroRNA (miRNA)-155, for example, was shown to be reduced in streptozotocin-induced diabetic rats and to be adversely linked with NF-κB activity and apoptotic rate [76]. This was supported by a research that found miRNA-155 was downregulated in bone marrow-derived progenitor cells isolated from T2DM patients [77]. Gene expression of p66Shc in peripheral mononuclear cells was linked to new onset problems in individuals with diabetes mellitus that had identical baseline characteristics in a clinical investigation [78]. These latest findings highlight the necessity of treating uncontrolled diabetic mellitus early and aggressively. The discovery of epigenetic therapeutic targets might lead to the development of medications that enhance patients' outcomes when glucose homeostasis is established [65, 79, 80].

4. Bone Turnover

Bone turnover indicators can be used to indirectly quantify the impact of a diabetic environment on bone metabolism. Osteocalcin, in particular, is a bone growth signal generated by osteoblasts [81]. Low levels of osteocalcin were identified in children with T1DM, which were found to be adversely linked with HbA1c levels [82, 83]. Furanocoumarin derivatives restored osteocalcin suppression and diabetes-related reduced trabecular thickness in diabetic mice, as well as drastically decreasing osteoclast-related gene expression such RANKL [84]. When T1DM and T2DM patients are compared to healthy controls, osteocalcin blood levels are lower in T1DM patients and much lower in T2DM patients [82, 85, 86, 87]. Sclerostin is a bone resorption marker [81] and is negatively linked with bone turnover indicators for bone formation in T2DM patients [88, 89, 90]. Changes in sclerostin levels have not been proven in people with T1DM [88]. Bone turnover indicators might be used to predict fracture risk in diabetic individuals in the future [91, 92, 93].

In primary osteoporosis, "signature miRNAs" of bone turnover, such as miR-148a-3p, are used as biomarkers [94, 95, 96]. In 2016, Heilmeyer et al. looked at circulating miRNAs and found that miR-550a-5p, miR-96-5p, miR-382-3p, and miR-181c-5p were all linked to T2DM-induced fragility fractures with good specificity and sensitivity [97]. The effect of miR-550a-5p, miR-382-3p, and miR-188-3p on adipose tissue-derived MSCs was also measured in vitro in this work. MiR-382-3p was discovered to enhance osteogenic differentiation while inhibiting adipogenesis.

5. Fracture Risk

This might be explained by the fact that the level of miR-382-3p in fractured T2DM patients was seven times lower than in T2DM patients without a history of fragility fractures. MiR-550a-5p, on the other hand, was shown to be a potent inhibitor of osteogenesis and was increased 22-fold in the diabetic fracture group compared to non-fracturing T2DM patients [97]. Hyper-expression of miR-148a and miR-21-5p was found in the sera of T1DM patients, which was linked to lower BMD and higher levels of circulating PTH [98]. Studies on the impact of diabetes mellitus on osteoclasts have yielded mixed results. In vitro and animal studies report an unaltered rate of bone resorption [99, 100] whereas some studies have suggested increased osteoclastic activity in diabetes mellitus under certain conditions, such as periodontal disease [101] and osteoporosis [102]. Other studies have even reported inhibited osteoclast function and differentiation in a diabetic environment [103, 104, 105].

Because of the inconsistent findings and overall inattentive impact reported in osteoclasts, it appears more plausible that reduced bone formation in diabetes mellitus is related to restrict osteoblastic and progenitor cell activity rather than a change in bone resorption. However, further study is needed to fully understand the impact of diabetes on osteoclastic activity and differentiation.

6. Fracture Healing

Individuals with diabetes mellitus are predisposed to fragility fractures due to altered biomechanical characteristics of the bone due to degradation in bone micro-architecture [106, 107, 108]. Individuals with T2DM and T1DM have a greater risk of fracture in various bone regions than the general population, with hip fractures in T2DM being the most thoroughly studied [109, 110, 111]. In a meta-analysis, T1DM was shown to be related with a greater risk of hip fractures than T2DM patients [19]. Women with diabetes mellitus had a considerably higher incidence of hip, pelvic, upper leg, foot, and vertebral fractures when fractures are compared by anatomical site [112]. Diabetes mellitus is also a poor predictive factor for post-fracture mortality in hip fracture patients [17, 113, 114]. In traditional Dual-energy X-ray absorptiometry (DEXA) scans, individuals with T2DM had a greater BMD at the femoral neck and lumbar spine, despite the increased fracture risk [115].

According to Schwartz et al. in the Health Aging and Body Composition research, [116] accumulation of AGEs, notably pentosidine, is linked to a higher risk of fracture in older persons with diabetes mellitus. Similarly, in non-diabetic individuals, a high amount of pentosidine excretion in the urine was found to be an independent risk factor for vertebral fractures [117]. T2DM patients had higher cortical bone AGEs, according to one clinical investigation [118]. Another research found that fracturing T1DM patients' trabecular bone had much greater amounts of pentosidine than non-fracturing T1DM patients' trabecular bone, [119] however this does not infer causation. Due to secondary deficiencies in bone micro-architecture, large retrospective investigations have demonstrated that traditional methods for predicting fracture risk, such as BMD and the

Fracture Risk Assessment Tool (FRAX), underestimate the fracture risk for individuals with diabetes mellitus [120, 121]. However, the trabecular bone score, which is related to bone micro-architecture, has been demonstrated to be more accurate in predicting fractures in diabetic patients [122, 123, 124]. A stabilising callus is created during normal fracture healing, in which cartilage is formed, then reabsorbed and replaced by bone tissue. Blood flow to the healing site aids this process [125]. Many researchers have demonstrated that diabetes mellitus is linked to a poor healing response in animal models of fracture healing [126, 127, 128, 129, 130]. The animals in a diabetic mouse model had a higher concentration of TNF-α at the fracture site, which was connected to a faster rate of cartilage resorption [127]. Furthermore, a diabetic cell environment may result in decreased callus size and bone formation, lowering the mechanical strength of the healed fracture site [126, 127, 128]. Cell proliferation and mechanical stiffness were both reduced at the fracture site of poorly managed diabetic rats in one in vivo research. Rats on a strict insulin therapy, on the other hand, maintained physiological fracture repair [131]. A fracture response is indicated by a surge in osteocalcin, alkaline phosphatase (ALP), and IGF1 in healthy human persons during the first few weeks of healing, indicating accelerated bone turnover [132, 133]. Those with diabetes mellitus, on the other hand, had lower bone turnover indicators post-fracture, [134] which might be a sign of a problem with fracture consolidation.

The number and functioning of progenitor cells are linked to fracture healing [135, 136]. According to one study, atrophic non-union fractures are linked to a lower pool of MSCs, which affects the amount of chemokines implicated in fracture healing [137]. In individuals with diabetes mellitus, limited MSC availability may obstruct callus remodelling, resulting in callus material that is biomechanically inferior [130, 138, 139, 140]. Microvascular problems are associated to vascular insufficiencies in the fracture site, and complications such as fracture non-union are linked to vascular insufficiencies in the fracture site [141, 142, 143]. Because MSCs influence vascularization, [144, 145] vascular deficits in diabetic fracture healing may be exacerbated by the lower number and potential of progenitor cells, as well as the chronic inflammatory state. Angiogenic genes (VEGF-A, VEGF-C, angiopoietin 1, and angiopoietin 2) and proteins were shown to be expressed at lower levels in MSCs derived from diabetic patients [146, 147]. In addition to these challenges, diabetic patients have a higher risk of wound infection, local post-operative problems such poor wound healing, and peri-operative cardiovascular issues than non-diabetic patients [6, 8, 9, 148].

7. Effect of Diabetes on Progenitor Cells

Adipocytes and osteoblasts are both produced from the MSC, which is a shared progenitor. The interplay of multiple distinct mechanisms influences MSC differentiation. WNT signalling and the PPAR-gamma (peroxisome proliferator-activated receptor gamma) pathways control a delicate balance between adipogenesis and osteoblastogenesis [149]. The WNT signalling pathway enhances osteogenesis and inhibits adipogenesis when it is activated. PPAR-γ, which is mediated by reactive oxygen species (ROS) [150], on the other hand, promotes MSC development into adipocytes [18]. When muscle-derived MSCs were cultured in high glucose media versus low glucose media, they showed higher expression of adipogenesis markers (PPAR-γ, LPL, adiponectin, GLUT4, and SREBP1c) and lower regulation of chondrogenic and osteogenic markars [151]. Hyperglycemia increases the Notch2 signalling pathway, which was found to be adversely linked with ALP expression levels, according to a recent study using rat bone marrow derived MSCs , osteoblastogenesis was suppressed [152, 153]. Recent animal investigations have found that diabetic animals had greater bone marrow adiposity, [151, 154] implying that bone marrow fat composition may be a cause of diabetes fragility fractures [155, 156]. In humans, one research used proton magnetic resonance spectroscopy to find a considerably greater bone marrow fat content as well as a predominant saturated lipid component in the diabetes mellitus group compared to healthy controls [157]. Another research used M.R.I (magnetic resonance imaging) to show a shift in bone marrow saturated to unsaturated fat content [29]. However, animal models may not always predict human responses [158] and clinical investigations that indicate increased bone marrow adiposity in diabetic patients have not ruled out obesity as a confounding factor. T2DM is linked to insulin resistance pathophysiologically. As a result, cells from diabetes mellitus patients are less prone to collect lipids [159]. Changes in growth hormone levels, increased visceral adiposity, increased circulating lipids, and hypoleptinemia have all been linked to increased bone marrow adiposity [28]. There is presently no proof that diabetes mellitus is directly responsible for increased bone marrow obesity in individuals.

Obesity causes compromised metabolic pathways, which leads to chronic inflammation and insulin resistance, according to recent research. As a result, obese people are more likely to acquire diabetes mellitus. When compared to obese persons without diabetes mellitus, white adipose tissue (WAT) in people with diabetes has been demonstrated to have elevated levels of inflammation [160]. Hypoxia-inducible factor 1-alpha (HIF-1α), as well as other inflammatory genes, is upregulated in adipose tissue due to reduced perfusion of hypertrophic adipocytes [161, 162]. Insulin resistance has been linked to increased levels of inflammatory cytokines, particularly TNF-α [163, 164]. In addition to hyperglycemia, free fatty acids generated by adipocytes create reactive oxygen species (ROS), which exacerbates the impaired osteoblast growth and function maintained in a diabetic environment [165, 166, 167, 168].

In vitro models have shown that chronic inflammation in diabetes mellitus is caused by a hyperglycemic bone marrow milieu mixed with oxidative stress, which slows osteoblast maturation and causes MSC differentiation to shift from osteoblastogenesis to adipogenesis [136, 169, 170]. This causes a vicious loop of metabolic stress, which maintains a chronic inflammatory process that may de-mineralize trabecular bone [171] and results in increased generation of ROS, which has a direct influence on MSCs, osteoclasts, osteoblasts, and osteocytes' development and function [172]. Indeed, the growing recognition of T2DM as a chronic inflammation cycle

has paved the way for the development of anti-inflammatory therapies [173].

In vitro, the expression of transcription factors needed for MSC osteoblastic development was inhibited in a streptozotocin-induced T2DM diabetic mouse model [134]. This was shown in a T2DM mouse model, in which diabetic mice had less viable MSCs that were functionally compromised ex vivo [174]. The viable MSC population is reduced when healthy cultured human MSCs are exposed to hyperglycemia, AGEs, and oxidative stress [54]. Only one study has been conducted so far to compare BM-MSCs isolated from people with T1DM and healthy controls. Despite long-term exposure to a diabetic stem cell environment in a young population, this study found that BM-MSC cell count, cell shape, and growth kinetics remain unaffected [175].

However, no research has yet established the effect of a diabetic environment on human MSCs isolated from T2DM patients [176].

Hematopoietic stem cells (HSCs) are mobilised into the circulation by the sympathetic nervous system, which has been found to be negatively linked with cardiovascular events in clinical investigations [177, 178]. It has been proposed that diabetes mellitus causes bone marrow remodelling and autonomic neuropathy. As a result, the number of CD34+ cells in the blood is affected [179]. These alterations were prevented in p66Shc knockout mice, and they are linked to Sirt1 gene downregulation [180, 181, 182, 183]. An insulin-resistant hyperglycemic environment causes epigenetic alterations in bone marrow via activation of JMJD3, a histone H3K27 demethylase, resulting in enhanced production of inflammatory cytokines in a mouse model. These modifications were also seen in peripheral monocytes, leading to the theory that epigenetic changes in the diabetic bone marrow milieu cause altered macrophage activity and chronic wound inflammation [74]. Inhibition of dipeptidyl peptidase-4 (DPP-4) has been demonstrated to increase circulating HSCs in people, suggesting that DPP-4 dysregulation is a key factor in diabetes-related HSC mobilization [184, 185].

8. Effects of Insulin and Anti-Diabetic Drugs

Reduced differentiation of osteoblasts, [186, 187] growth retardation, and a 60-fold greater expression of a hepatic IGF binding protein were all observed in mice missing an insulin receptor substrate, a mediator of insulin and IGF1 signaling. Furthermore, osteoblasts missing the insulin receptor substrate gene demonstrated an increase of receptor activator of RANKL expression in an ex vivo manner. As a result, osteoclastogenesis in co-culture is stimulated [186]. In contrast, a non-obese T2DM mouse model demonstrated a lower bone turnover rate, which was improved by insulin therapy [189]. The incidence of osteoporosis or osteopenia in adults with T1DM was observed to be considerably greater in patients before insulin therapy. Bone turnover indicators and BMD at all anatomical locations improved considerably after seven years of insulin therapy [190]. Despite the fact that insulin is anabolic to bone and can repair indicators of bone turnover and BMD, comprehensive reviews have found no substantial reduction in the risk of fracture in people with diabetes who are on insulin [191, 192]. In fact, certain epidemiological studies have found an increased fracture risk in insulin-treated patients, which may be related to a higher chance of falling [192].

As indicated by consensus recommendations, metformin is commonly provided to patients as a first-line therapy for T2DM [193]. Metformin has been shown in one population research to have a possibly beneficial effect on fracture risk [191, 194]. However, it is unclear whether this impact is due to metformin directly interacting with progenitor cells to alter bone metabolism or if it is due to blood sugar level optimization. Metformin's effect on MSCs has been studied in vitro, however the results have been mixed. Metformin increased osteoblastic activity while inhibiting adipogenesis in rodent BM-MSCs [195]. Studies utilising supra-pharmacological quantities of metformin in murine-derived preosteoclasts demonstrate a reduction in osteoclastogenesis [196, 197, 198]. Human MSCs treated with metformin showed lower angiogenic capacity and apoptosis upon transplantation in several in vitro experiments [199, 200]. Metformin increased osteoblastic activity in human induced pluripotent MSCs by boosting ALP activity and mineralized nodule formation, which was partly mediated by the LKB1/AMPK pathway [201]. In a clinical investigation, [202, 203] bone turnover indicators were evaluated after metformin therapy and revealed reduced bone resorption (CTX-1) and a substantial reduction in bone creation (P1NP) [203].

Many people require additional anti-diabetic drugs after an initial response to metformin. Glitazones are rarely recommended due to their negative effects on bone health [202, 204]. After a meal, the "incretin effect" (increased insulin stimulation produced by oral glucose delivery) [205] has been shown to be considerably lower in diabetes mellitus compared to healthy patients [206]. The hormone glucagon-like peptide 1 (GLP1), which enhances the 'incretin effect' has been demonstrated to improve bone formation markers [207] and prevent the degeneration of bone micro-architecture in mouse models [208]. Through GLP1 receptors expressed on progenitor cells [209, 210] GLP1 increases the proliferation of human MSCs while inhibiting their differentiation into adipocytes [209].

GLP1 receptor analogues (GLP1RAs) are becoming more popular as it help people to lose weight and don't induce hypoglycemia [211]. Exenatide medication had no effect on blood indicators of calcium homeostasis (ALP, calcium, and phosphate) in one clinical investigation [212]. In addition, a recent meta-analysis demonstrated no link between the usage of GLP1RAs and the risk of fracture in people with T2DM [213]. DPP-4 inhibitors are the second type of anti-diabetic medication, and they work by increasing GLP1 levels. DPP-4 has been shown to have an effect on circulating progenitor cells, which may help to reduce cardiovascular risk by promoting HSC mobilization [185, 214, 215]. Nonetheless, meta-analysis has yet to show that DPP-4 inhibitors have a cardiovascular advantage in patients [216]. To fully explore the disparity between pre-clinical and clinical data, more translational research is needed.

In individuals with T2DM, however, there is compelling evidence that therapy with sodium glucose cotransporter-2 (SGLT-2) inhibitors improves cardiovascular and renal

outcomes [217, 218, 219]. As a result, it has been proposed that greater mobilisation of pro-vascular progenitor cells in bone marrow is responsible for this protective impact [220]. Following six months of therapy with empagliflozin, circulating CD133+ progenitor cells and monocytes with an anti-inflammatory phenotype were dramatically increased, whereas pro-inflammatory granulocyte precursors were significantly reduced [220]. A comparable research looking at the effects of dapafliflozin found an increase in CD34+KDR+ endothelial progenitor cells, which correlated with a reduction in HbA1c, but no change in circulating stem cells. This suggests that circulating progenitor cells may not be directly involved in the cardiovascular benefit [221]. Despite these significant breakthroughs, the mechanism of SGLT-2 inhibitors' cardiovascular and renal benefits remains unclear. Furthermore, the epigenetic influence of these innovative medications on the incidence of diabetes-related bone fractures is unknown [222].

II. Conclusions

According to recent research, the risk of fracture in diabetes mellitus elevated more than can be explained by changes in BMD and confounding variables such the risk of falling [19, 23]. A diabetic environment is assumed to predominantly alter biomechanical aspects of the bone by decreasing its organic composition and bone material strength, rather than influencing the mineral phase [29, 30, 33]. This is caused by alterations in cross-link creation or changes in cellular activity in osteoblasts and bone progenitor cells [41, 42, 50, 223, 224]. Aside from changing osteoblast gene expression and activity, [41, 42] the diabetic environment lowers MSC population and viability greatly [151, 171]. Increased bone marrow fattiness may worsen MSC and osteoblast impairment in obese patients with T2DM by releasing cytokines and free fatty acids from hypoxic adipose tissue, which maintains a vicious circle of chronic inflammation and reduced osteoblastic activity [165, 168]. The combination of these alterations affects bone tensile strength and post-yield characteristics, making diabetic bone tissue more susceptible to micro damage buildup; fragility fractures at most skeletal locations, and poor fracture healing [32, 225]. In individuals with diabetes mellitus, a decreased MSC population and poor differentiation ability may be the common connection between defective bone micro-architecture and a greater incidence of non-union [137, 225]. Furthermore, because MSCs promote vascularisation, [143, 144] a reduction in the population and potential of progenitor cells in the fracture site may result in vascular shortages, which might exacerbate diabetic fracture recovery. Returning to glucose homeostasis did not restore capability in previously diabetic MSCs, which is consistent with findings of hyperglycemic memory in cells exposed to a diabetic environment [64, 65, 66, 67, 68, 69]. As a result, investigations looking into diabetes-induced epigenetic modifications in precursor cells that contribute to diabetic osteopathy would be fascinating.

Because well treated diabetes mellitus has been repeatedly implicated in having a favourable influence on bone health, which reverses bone deficiencies in certain investigations, this review emphasises the need of effective clinical care of patients with diabetes mellitus [130, 189, 190, 208, 226, 227, 228, 229, 230]. It is necessary to keep in mind that patients on a treatment regimen that causes hypoglycemia episodes are more likely to have fractures [231, 232, 233]. Health care providers should focus on bone protection therapies and fall prevention methods in individuals at high risk of fracture in clinical practice [234]. Traditional osteoporosis risk assessment techniques, such as BMD tests and the FRAX score, are ineffective in predicting fracture risk in people with diabetes [120, 121, 235]. As a result, there is still a pressing need to investigate innovative risk assessment approaches, such as assessments of bone turnover and AGE levels that may account for the changed metabolic state of diabetes mellitus [236, 237]. MiRNAs are potential new blood biomarkers that, in the next years, might be utilised to identify people with diabetes who are at high risk of fragility fractures [97, 98]. New anti-inflammatory therapy methods have opened up as a result of recent scientific advances in the knowledge of the molecular pathways implicated in diabetes mellitus [173]. Further study is needed to determine the mechanism of action by which diabetes mellitus impacts the survival and differentiation potential of the progenitor cell population, which will aid future translational research into the prevention of fragility fractures in diabetic patients.

Abbreviations

T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
IGF1	Insulin-like growth factor 1
MSC	Mesenchymal Stem cell
AGE	Advanced glycation end products
BMD	Bone mineral density
PTH	Parathyroid hormone
TNF-α	Tumor necrosis factor alpha
RANKL	Receptor activator of nuclear factor kappa-B ligand
RAGE	Receptor for advanced glycation end products
MiRNA	MicroRNA
DEXA	Dual – energy X- ray absorptiometry
FRAX	Fracture Risk Assesment Tool
ALP	Alkaline phosphate
PPAR-γ	Peroxisome proliferator activated receptor gamma
ROSBM-MSCs	Reactive oxygen species Bone marrow (BM) derived MSC's
WAT	White adipose tissue
HIF-1α HSCDPP-4	Hypoxia – inducible factor 1 – alpha Haematopoietic stem cell Dipeptidyl peptidase – 4
GLP1	Glucagon-like peptide
GLP1RA	GLP1 receptor analogue
SGLT-2	Sodium glucose cotransporter-2

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