THE CONSOLIDATION OF FRACTURES OF THE DISTAL METAEPIPHYSIS OF THE RADIAL BONE IN PATIENTS WITH DIABETES MELLITUS: PROBLEMS AND SOLUTION APPROACHES

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ABSTRACT

The fractures of the distal segment of the radial bone in diabetes mellitus patients is a problem which requires special attention, for the processes of healing in such patients are slower and are often accompanied by a number of complications. This article reviews the basic mechanisms affecting the consolidation of fractures in diabetes patients, including the metabolic disorders, the hyperglycemia, the micro- and macroangiopathy, the polyneuropathy and other systemic abnormalities. An analysis was carried out of the specific features of the anatomy of the distal metaepiphysis of the radial bone, which make it vulnerable to fractures that are difficult to heal. The research provides a detailed analysis of the factors inhibiting the regeneration of the bone tissue, such as the accumulation of glycation end-products, the increased activity of the osteoclasts, the decreased immune protection and the high risk of infectious complications. Also, the methods were highlighted that are used for prevention and treatment, including the control of glucose levels, the correction of vitamin D deficit, the repositioning of the fractured bone fragments and the reliable immobilization. The research emphasizes the necessity of combined approach to the treatment of fractures in diabetes patients, with taking into consideration both the orthopedic and the endocrinological aspects.

Keywords: *diabetes mellitus; fracture of the radial bone; consolidation; hyperglycemia; osteoporosis; microangiopathy; immobilization.*

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INTRODUCTION

According to the data from 2022, published in "The Lancet" journal, the number of adults with diabetes mellitus (DM) worldwide has exceeded 800 mln people, increasing more than four times from 1990 [1]. One of the systemic complications of DM is the metabolic disorder of the bone tissue, which leads to the decrease in its strength, to developing osteoporosis and to the increased risk of fractures in patients both with type 1 and type 2 diabetes [2.3].

In recent years, special attention is paid to investigating the impairments of the regeneration processes in the bone tissue in diabetic patients. It was found that the healing of fractures in such patients is significantly complicated and is accompanied by higher rate of complications [4, 5]. This is due to the following set of factors: hyperglycemia, angiopathies, polyneuropathy, decreased immune protection and dysfunction of the osteoblasts.

The most frequent clinical models for investigating the bone tissue regeneration in cases of DM are the fractures in the zones with anatomically vulnerable structure, in particular — fractures of the distal metaepiphysis of the radial bone, or the so-called "typical fractures" [6]. These fractures are properly illustrating both the general and the specific mechanisms of impaired regeneration in patients with diabetes mellitus.

Thus, the analysis of the specific features of the consolidation of fractures of the radial bone in DM patients may serve as a basis for wider understanding the pathogenesis of impaired bone tissue healing in cases of this disorder [7–9].

Aim of the review — to summarize the modern outlooks on the pathogenesis of impaired bone tissue regeneration in cases of diabetes mellitus, with an accent to the clinically significant example — fractures of the distal metaepiphysis of the radial bone. The main pathophysiological mechanisms were considered, which

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КОНСОЛИДАЦИЯ ПЕРЕЛОМОВ ДИСТАЛЬНОГО МЕТАЭПИФИЗА ЛУЧЕВОЙ КОСТИ У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ: ПРОБЛЕМЫ И ПУТИ РЕШЕНИЯ

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АННОТАЦИЯ

Переломы дистального отдела лучевой кости у пациентов с сахарным диабетом — это проблема, которая требует особого внимания, так как процессы заживления у таких пациентов протекают медленнее и сопровождаются рядом осложнений. В данной статье рассматриваются основные механизмы, влияющие на консолидацию переломов у пациентов с диабетом, включая метаболические нарушения, гипергликемию, микро- и макроангиопатию, полинейропатию и другие системные изменения. Анализируются особенности анатомии дистального метаэпифиза лучевой кости, которые делают его уязвимым к переломам и сложным для заживления. В работе приводится детальный разбор факторов, тормозящих регенерацию костной ткани, таких как накопление конечных продуктов гликирования, повышенная активность остеокластов, снижение иммунной защиты и высокий риск инфекционных осложнений. Освещаются также методы профилактики и лечения, включая контроль уровня глюкозы, коррекцию дефицита витамина D, репозицию костных отломков и надёжную иммобилизацию. Подчёркивается необходимость комплексного подхода к лечению переломов у пациентов с диабетом, учитывающего как ортопедические, так и эндокринологические аспекты.

Ключевые слова: *сахарный диабет; перелом лучевой кости; консолидация; гипергликемия; остеопороз; микроангиопатия; иммобилизация.*

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are complicating the consolidation of fractures, also, the approaches were submitted for the prevention and treatment, taking into account both the general and the local aspects of bone tissue regeneration in DM patients.

Algorithm of searching the publications

This review was based on the publications, submitted during the period from 2018 until 2024 to the PubMed bibliographical system. The key words that were used for selecting the articles are the following: diabetes mellitus type 1 and 2, fractures of the distal metaepiphysis of the radial bone, consolidation, ankylosis, pseudoarthrosis, aseptic necrosis, hyperglycemia, RANK, RANKL.

The selection of articles was carried out taking into consideration the following criteria:

- Estimation of the factors affecting the process of bone regeneration, including the distal metaepiphysis of the radial bone in patients with diabetes mellitus and the ways of preventing the development of complications;
- Information on the specific features of the consolidation of typical fractures of the radius is the main method of conducting the clinical research or the object of the literature review.

As a result of searching with using the key words in the PubMed search engine, a total of 93 publications were found, of which 62 were full-text articles completely matching the selection criteria and were included into the scientific review.

ANATOMIC-BIOMECHANICAL SPECIFIC FEATURES OF THE DISTAL SEGMENT OF THE RADIAL BONE

The distal metaepiphysis of the radial bone has its specific features of the anatomic structure and biomechanics, which affect the rate of developing fractures in this area [10].

The distal segment of the radial bone has a thin cortical layer and relatively large spongy bone part, which decreases its resistance to compression and torsion forces. The radial bone in its distal part has a deviation angle from the axis of the forearm, which makes the bone more vulnerable to fractures upon falling onto the extended arm, for the impact force is distributed inhomogeneously [11].

A number of features of anatomy and blood supply of the distal segment of the radial bone increases the risk of developing complicated fractures in this area, as well as the risk of impaired consolidation, such as ankylosis of the radiocarpal joint, pseudoarthrosis and developing an aseptic necrosis of the radial bone [12].

The distal metaepiphysis of the radial bone has a complex anatomy with the presence of articular surfaces, processes and multiple foramens for the passage of vessels and nerves. Fractures in this area can damage multiple small vessels, altering the blood supply of the bone tissue [13]. The blood supply of the distal segment of the radial bone is relatively limited, some vessels are terminal and have no anastomoses, due to which the collateral vessels cannot always compensate the damage of the main vessels in cases of fracture. This makes the bone very susceptible to the impairment of blood supply and to developing aseptic necrosis [14]. After falling on the extended hand, the forearm muscles are at tension, which can destabilize the bone fragments, impeding their correct consolidation [15]. This increases the risk of bone fragments dislocation and of the complications, such as pseudoarthrosis.

SPECIFIC CLINICAL FEATURES OF THE CONSOLIDATION OF FRACTURES IN CASES OF DM

In patients with diabetes mellitus, the specific features of the consolidation of typical fractures in the radial bone are due to not only the anatomical characteristics of the bone, but also due to the systemic abnormalities, characteristic for this disease. Diabetes mellitus is accompanied by the development of osteoporosis and by the increased fragility of bones [16].

In cases of type 1 diabetes, the basis of the pathogenesis of the bone tissue remodeling includes the decreased activity and impaired differentiation of the osteoblasts. On the other hand, for type 2 diabetes, the characteristic features include hyperinsulinemia, promoting to an increase in the division and in the differentiation of osteoblasts and, as a result, to the increased values of bone mineral density (BMD). High BMD values in type 2 diabetic patients are combined with slower bone tissue metabolism, which results in a decrease in the bone strength.

Diabetes mellitus not only increases the risk of developing fractures, but also affects the processes of bone tissue regeneration, impairing it [17]. This is due to the fact that, in patients with this disease, the processes of bone tissue metabolism are also impaired along with the bone remodeling [18.19].

THE MECHANISMS OF DAMAGING THE BONE TISSUE REGENERATION IN DIABETES MELLITUS

One of the complications of diabetes mellitus, affecting the consolidation of fractures, is the micro- and macroangiopathy, which leads to a decrease of BMD, to the slower formation of the osteotylus, as well as to the increased risk of developing complications [20]. Microangiopathy develops due to long-term hyperglycemia and concomitant metabolic disorders. It plays a significant role in the impairment of the consolidation of fractures in diabetic patients [21]. The mechanisms of developing the microangiopathy include the non-enzymatic glycation of proteins in the basal membrane of the capillaries and other components of microvessels in the settings of increased glucose levels. This leads to the accumulation of glycation end-products, impairing the structure and function of the vascular wall and increasing the thickness of the basal membrane, resulting in an impaired blood supply of the bone tissue [22]. In the settings of hyperglycemia, there occurs an increase in the formation of free radicals, which damage the endothelial cells and contribute to the development of endothelial dysfunctions, the result of which is the impairment of the microcirculation [23].

The mechanisms of developing macroangiopathy also include the dyslipidemia. Diabetic patients often show increased blood levels of cholesterol and triglycerides, which promotes to developing atherosclerosis, and, consequently, results in an impaired blood supply of the bone tissue, as well as an activation of the renin-angiotensin-aldosterone system, regulating the blood pressure along with the water and salt balance. In cases of diabetes, its activity increases, owning also to the development of diabetic nephropathy, which promotes to developing hypertension and aggravates the damaging of the vessels [24].

As mentioned earlier, the distal segment of the radial bone has a number of specific features of its blood supply, capable of resulting in an impaired fracture healing and developing complications. Angiopathy

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that develops with a background of diabetes mellitus, even more aggravates the situation, increasing the timings of fracture healing due to slower formation of the osteotylus, also increasing the risks of developing aseptic necrosis or pseudoarthrosis in the distal segment of the radial bone in groups of patients with this disease [25, 26].

Another factor affecting the processes of the consolidation of fractures in the distal segment of the radial bone in patients with diabetes mellitus is the polyneuropathy.

Diabetic neuropathy actually can negatively affect the consolidation of fractures, including the fractures of the radial bone, though its role is no that evident as it is in cases of angiopathy [27]. Neuropathy can impair the normal innervation of the bone tissue, affecting the balance between the osteoblasts and osteoclasts. This can shift the balance towards resorption, weakening the bone and complicating its healing after the fracture [28]. It is important to note that diabetic polyneuropathy leads to a deceleration of the inflammatory response: the inflammation process is a necessary stage of healing the fracture, while the neuropathy can suppress this process, resulting in an insufficient inflammation, which negatively affects the consolidation [29].

In case of the radial bone, these mechanisms can be especially expressed, for this bone is subject to significant loads in everyday life [30].

Diabetes mellitus causes a number of metabolic disorders, significantly affecting the processes of the consolidation of fractures, including the fractures of the radial bone [31].

The metabolic disorders include hyperglycemia, deficit of insulin and deficit of vitamin D. Hyperglycemia provides the environment for the development of diabetic complications. In the settings of elevated glucose levels, glycation of the proteins occurs, due to which, the glycation end-products form and an increase is observed in the production of the active oxygen species and of the factors increasing the number and the activity of osteoclasts: RANK, RANKL, tumor necrosis factor (TNF) [32, 33].

THE EFFECTS OF CHRONIC INFLAMMATION AND CYTOKINES ON BONE REGENERATION IN DIABETES MELLITUS

Diabetes mellitus is characterized by chronic subclinical inflammation, which provides systemic and local effects on the processes of bone tissue regeneration. The key role in this process is played by the pro-inflammatory cytokines, such as TNF, IL-1β, IL-6 and IFN-γ, the levels of which are significantly increased after a long-term hyperglycemia [23].

TNF is one of the central inflammation mediators, affecting not only the differentiation of the osteoclasts via the RANK/RANKL pathway, but also directly suppressing the activity of the osteoblasts, suppressing the expression of bone matrix genes and inhibiting the synthesis of type I collagen [34]. Besides, TNF induces the expression of RANKL in the osteoblast-like cells, increasing the bone resorption.

IL-1β and IL-6 activate the osteoclastogenesis and slow down the reparative function of the osteoblasts. The increased concentration of IL-6 is associated with slowed consolidation of fractures and worse formation of the osteotylus [34].

Diabetes also promotes to the development of an unfavorable inflammatory micro-environment in the fracture zone. The accumulation of AGEs (advanced glycation end-products) activates the RAGE receptors on the cells of the immune system, the osteoblasts and the osteoclasts, inducing the production of cytokines and ROS (reactive oxygen species), which promotes to the persistence of low-intensity inflammation in the area of the trauma.

Additionally, the thing that should be kept in mind is the effects of hyperglycemia on the MSC (mesenchymal stem cells). In the settings of DM, a depletion develops in the population of MSC along with a decrease in their proliferative activity, impaired differentiation to the osteogenic lineage and increased tendency to developing an apoptosis [17, 28]. This leads to a decrease in the regenerative potential of the bone and to the impaired remodeling.

The activation of inflammasomes was also described (for example, NLRP3), induced by glucose and AGEs, which initiate cellular inflammation and a cascade of producing IL-1β and IL-18. These cytokines additionally increase the damage of the bone tissue and intervene with the regeneration.

Thus, the dysbalance between the pro-inflammatory and the regenerative signals in diabetes mellitus leads to the formation of the defective bone matrix, to the impairment of the vascularization and to the complicated consolidation of fractures.

The role of cytokines and growth factors in the impaired regeneration of the bone tissue in cases of diabetes mellitus

Besides the metabolic disorders, chronic inflammation and vascular abnormalities, the important pathogenetic mechanism of impaired consolidation

of the bone tissue in cases of diabetes mellitus includes the changes in the signaling pathways of the key cytokines and growth factors, regulating the osteogenesis, angiogenesis and restoration of the matrix. The abnormalities in the functioning of the TGF-β, IGF-1 and FGF, as well as in the interleukins (IL-1β, IL-6, IL-17) are currently considered as the central element of weakening the regeneration processes in DM patients.

TGF-β: the weakening of the bone tissue response and of the angiogenesis

Transforming Growth Factor Beta (TGF-β) is one of the main mediators of bone tissue regeneration. It regulates the differentiation of osteoblasts, the synthesis of type I collagen, the remodeling and vascularization in the fracture zone. However, in the settings of diabetes, a significant impairment can be observed in the transmission of the signal via the TGF-β/Smad2/3 cascade, which results in the inhibition of the osteogenic activity of the mesenchymal stem cells (MSC) and the delay in the formation of mature bone tissue [17, 35].

According to the data from the research work by M. Becerikli et al. [35], in cases of DM, a hyperglycemia-induced decrease develops in the phosphorylation of Smad2/3 along with the decrease in the expression of TGFBR1/2 receptors. This alters the formation of the osteotylus, decreases the expression of Runx2 and Col1a1 — the key genes of osteogenic differentiation. Moreover, it was found that the decrease in the activity of TGF-β in diabetes is accompanied by the suppression of angiogenesis by means of a decrease in VEGF and HIF-1α production, which additionally worsens the restoration of the bone tissue.

The confirmation for this is the data from the research by R.K. Singh et al. [36], which has shown that the restoration of the activity of the TGF-β/Smad signal pathway by using the nanocarriers transporting the TGF-β1 significantly improves the osteogenesis, stimulates the neo-angiogenesis and accelerates the healing of fractures in the animals with induced diabetes.

IGF-1 and the anabolic signaling deficit

The insulin-like growth factor 1 (IGF-1) plays the key role in the formation of the bone tissue: it increases the proliferation of osteoblasts, the collagen synthesis, the differentiation of MSC and the remodeling of the matrix. In DM patients, the IGF-1 level decreases due to the insulin insufficiency and due to the resistance to the IGF-1/PI3K/Akt signaling pathway, which leads to the decrease in the anabolic activity of the bone tissue [37].

The experimental research works have demonstrated that the administration of IGF-1 or the activation of its signaling cascade promotes to the restoration of the expression of osteogenic factors and accelerates the formation of the osteotylus in diabetic animals [38].

FGF-signals and angiogenesis

The family of Fibroblast Growth Factors (FGF), especially FGF-2, participates in the processes of vascularization, reparation and stimulation of the osteogenic differentiation of MSC. DM impairs the expression of FGFR receptors and the activation of MAPK/ERK pathways, which suppresses the proliferation of stem cells, decreases the vascularization of the damage zone and worsens the quality of the newly formed bone tissue [34].

Interleukins and inflammatory micro-environment

IL-1β, IL-6, IL-17 are the pro-inflammatory cytokines, the level of which is steadily increased in patients with DM. These substances:

- suppress the activity of osteoblasts,
- activate osteoclastogenesis,
- impair the balance between the resorption and the formation of the bone tissue.

IL-6 also hinders the mineralization of the bone matrix, while the IL-17 increases the inflammatory background and the destruction of the bone tissue by means of the activation of Th17-cells [34].

Thus, the decrease in the activity of TGF-β, IGF-1 and FGF, as well as the interleukin dysbalance, lead to the disruption of bone tissue healing in cases of DM, both by means of the suppression of osteogenesis and via the suppression of angiogenesis. These signaling pathways are the promising targets for targeted therapy aimed at the improvement of the consolidation of fractures in patients with diabetes mellitus.

Glycation of collagen

Glycation of proteins and accumulation of glycation end-products play a substantial role in the impaired consolidation of fractures in cases of diabetes mellitus.

In the settings of hyperglycemia, the structure and properties of collagen are altered, which makes it less strong, less elastic and less resistant to enzymatic cleavage. As a result of this, a less strong osteotylus forms, which is susceptible to damage and has a slower healing rate [39].

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Glycation hinders the formation of normal transverse cross-links between collagen molecules, which provide strength and stability of the bone matrix. This even more weakens the bone tissue and complicates the consolidation.

The accumulation of glycation end-products, such as pentosidine, affects the process of mineralization, making the bone tissue more fragile [40]. They also bind to their receptors on various cells, including macrophages and osteoclasts, activating them and stimulating the output of pro-inflammatory cytokines. The activity of pro-inflammatory cytokines in the fracture area impairs the normal healing and promotes to the bone tissue resorption [41].

Glycation end-products directly suppress the functions of osteoblasts, decreasing their ability to synthesize new bone matrix and to participate in mineralization [34].

Vitamin D deficiency

In cases of diabetes mellitus, impaired metabolism of vitamin D was noted. One of the reasons of altered structure of the bones in diabetes mellitus is the deficit of calcium, developing due to the deficit of vitamin D, as well as due to the dysbalance of its absorption and increased washout. During the animals tests, it was shown that the decrease of insulin levels results in an impaired absorption of calcium in the duodenum. Besides, in diabetes mellitus, the increased elimination of calcium with urine was reported, caused by hyperglycemia [42].

An important role in the altered consolidation of the bone is played by vitamin D. The disruption of its metabolism in diabetes mellitus develops due to the damaging of intestinal cells and due to the decrease in their ability to absorb vitamin D from food in the settings of hyperglycemia, as well as due to the development of diabetic nephropathy: in diabetes, the functions of the kidneys may become impaired, which results in a decrease in the production of vitamin D [43].

Impaired vitamin D metabolism in cases of diabetes leads to the suppression of the functions of osteoblasts, promotes to the decreased absorption of calcium and slows the processes of fracture consolidation [44].

The important role in the process of the osteotylus formation is played by insulin, which has a stimulating effect on the bone matrix and the formation of cartilage. Due to this, in the settings of insulin deficit, osteopenia develops. The deficit of this hormone results in decreasing collagen synthesis by the osteoblasts [45]. In rats with untreated diabetes mellitus, the collagen synthesis level in the zones of fractured bones was decreasing by 50–55%, which was resulting in the worsening of the mechanical properties of the newly formed tissue [46].

Insulin also takes part in the paracrine regulation of the process of consolidation of fractures. A decrease in the insulin levels leads to the dysbalance in the synthesis of the growth factors, such as the basal fibroblast growth factor, the insulin-like growth factor-1, the platelet-derived growth factor, the transforming growth factor beta and the vascular endothelial growth factor. These factors are necessary for the normal consolidation of fracture, and in the settings of their deficit, the proper restoration of bone does not take place [46].

Diabetes mellitus significantly increases the risk of developing osteomyelitis due to the combination of factors related to the decrease of the immune protection. Osteomyelitis extremely negatively affects the consolidation of fractures, facilitating the development of complications [47].

The processes affecting the inhibition of the factors of immune protection and promoting the development of infectious complications, include the impaired functions of the neutrophils and macrophages, which promotes to the decrease of the production serum antibodies in the settings of hyperglycemia [48].

As a result of these factors, the consolidation of fractures in patients with osteomyelitis developing with a background of diabetes mellitus, can be significantly hindered. This may lead to the development of such complications as fracture nonunion, pseudoarthrosis and ankylosis [49].

The effects of microangiopathy and diabetic neuropathy on the regeneration of the bone tissue

Among the systemic complications of diabetes mellitus, negatively affecting the consolidation of fractures, special significance is gained by the microangiopathy and the diabetic polyneuropathy. These pathological processes impair the vascularization and the innervation of the bone tissue, worsening the delivery of oxygen, nutrients and growth factors, required for normal bone tissue healing.

Microangiopathy in DM develops with a background of long-term hyperglycemia, leading to the non-enzymatic glycation of the proteins in the vascular wall and in the basal membrane of the capillaries. This promotes to the thickening of the basal membrane, to the decrease in the capillary permeability and to the development of endothelial dysfunctions [21].

In the settings of chronic hyperglycemia, an increase is observed in the production of ROS, which results in the damage of endothelial cells and impaired microcirculation. Simultaneously, the RAGE pathways also show signs of activation related to the accumulation of AGEs, which additionally worsens the function of the vessels [41].

These processes are especially crucial in the zones with anatomically restricted blood supply, such as the distal metaepiphysis of the radial bone. In DM, the microangiopathy significantly decreases the quality and the speed of developing the osteotylus, also increasing the risk of aseptic necrosis [15].

The additional contribution into the impaired blood supply of the bones belongs to the macroangiopathy, associated with the atherosclerosis of major vessels, the dyslipidemia and the activation of the renin-angiotensin-aldosterone system. These changes aggravate the ischemia in the tissues, especially in patients with concomitant diabetic nephropathy [43].

Diabetic polyneuropathy is another important factor, negatively affecting the regeneration of the bone. Impaired innervation of the bone tissue affects the balance between the osteoblasts and the osteoclasts, including the effects induced by means of neuropeptides (for example, CGRP, SP) and inflammation mediators. Upon decreasing the sensitivity and the tone of sympathetic and sensory nerves, the local regulation of circulation also becomes impaired along with the aggravated microcirculation and with a decreased regenerative response [28].

Besides, neuropathy is associated with a decrease of the inflammatory response, required at the early stages of bone tissue healing. The suppression of the activity of macrophages and lymphocytes in the damage zone leads to insufficient inflammation and to the weakened osteoinduction, disrupting the initiation of the reparative processes [29].

The functional activity of osteoblasts also suffers from the deficiency of neurotrophins, the decrease of which is described in cases of diabetic neuropathy, which impairs theirs proliferation and differentiation [30].

Thus, microangiopathy disrupts the blood supply of the bone tissue, decreases the delivery of oxygen and growth factors, while the diabetic neuropathy weakens the neurogenic regulation of osteogenesis and the immune response. In total, these mechanisms significantly decrease the efficiency of reparative processes in cases of fractures in DM patients, increasing the risk of delayed consolidation, pseudoarthroses and other complications.

Immune mechanisms of impairing the bone tissue regeneration in cases of diabetes mellitus

Besides vascular, metabolic and hormonal disorders, the key role in the impairment of the processes of the consolidation of the bone tissue in patients with diabetes mellitus is played by the immune cells participating in the initiation and regulation of inflammation, osteogenesis and remodeling. As of today, it was found that T-lymphocytes, macrophages, NK-cells and other cells of the innate immune response actively interact with the cells of the bone tissue and significantly affect its restoration.

$CD4^+$ T-helpers and $CD8^+$ cytotoxic T-lymphocytes take part in the regulation of inflammation and osteogenesis. In cases of diabetes mellitus, the observed findings include a shift of the subpopulations of $CD4^+$-cells towards the Th1/Th17-phenotype, associated with the increased production of IFN-γ, IL-17 and TNF, which stimulate the bone resorption and suppress the osteoblastogenesis [34].

Special significance has the activation of Th17-cells, increasing the expression of RANKL on the osteoblast-like cells and, as a result, stimulating the differentiation of osteoclasts. This disrupts the balance between bone tissue formation and resorption and leads to the prevailing of destructive processes.

$CD8^+$ T-cells also contribute to the pathological cascade, producing TNF and IFN-γ. Their accumulation in the damage zones in DM patients is associated with an increase in the osteoclastic activity and chronic inflammation [32].

Tissue macrophages play an ambivalent role in bone tissue regeneration. Classically, the activated M1-macrophages provide the initiation of inflammation, producing IL-1β, TNF and ROS, also (alternatively), the activated M2-macrophages take part in the resolution of inflammation and in the initiation of reparative processes (including angiogenesis and osteogenesis).

In diabetes, a dysbalance can be observed towards the M1-phenotype, which results in persisting inflammation, decreased levels of VEGF and TGF-β, inhibition of osteogenic differentiation and poor formation of the osteotylus [36].

Besides, the glycation of matrix proteins and the activation of RAGE receptors on macrophages increase the expression of pro-inflammatory mediators, which supports the chronization of inflammation and aggravates the quality of healing.

Natural killers (NK-cells), as a part of the innate immune response, also take part in the inflammatory

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microenvironment of bone tissue regeneration. In cases of DM, their activity changes with a shift of the cytokine profile towards the increased production of IFN-γ, which aggravates the inflammation and the resorption of the bone tissue [28].

Moreover, NK-cells can interact with osteoclasts and macrophages, increasing inflammation and modulating the immune response in the fracture zone.

Thus, in cases of diabetes mellitus, intensive disorders of the immune homeostasis occur: the predominance of Th1/Th17-profile, the activization of M1-macrophages, the decrease in the activity of M2-cells and the functional shifts in the functioning of $CD8^+$ and NK-cells. These changes support chronic inflammation, promote to bone tissue resorption and suppress the regenerative processes, creating the unfavorable environment for the consolidation of fractures.

Medication treatment effects

Some research works investigate the use of thiazolidinediones, as a factor affecting the processes of healing the fractures, including the ones of the distal metaepiphysis of the radial bone, in patients with diabetes mellitus. However, currently there is no unambiguous opinion from the researchers about the effects of substances of this group on the bone tissue [50].

Negative effects of taking the substances from the thiazolidinediones group:

1. Some research works have demonstrated that the use of these medications may lead to a decrease in the mineral density of the bone tissue and may increase the risk of fractures. Thiazolidinediones simultaneously inhibit the differentiation of osteoblasts and activate the differentiation of osteoclasts, which results in loss of bone mass by means of decreasing the formation of the bone tissue and increasing the bone tissue resorption.

2. The experimental researches in animals have demonstrated that the substances from the group of thiazolidinediones may slow down the formation of the osteotylus and may worsen its mineralization [51].

For the prevention of abnormalities of the consolidation of fractures, including the typical fractures of the radial bone, and the development of complications in patients with diabetes mellitus, it is necessary to apply the measures aimed at the mitigation of risk factors, as well as to create optimal conditions for the healing of the bone tissue (Table 1) [52].

PROPHYLAXIS AND TREATMENT APPROACHES

The main directions of the preventive measures are the following:

1. Control of glycemia. This is the key factor of preventing the abnormalities of the healing of fractures. It is necessary to aim for achieving and maintaining the individual target levels of glycosylated hemoglobin (HbA1c) [53]. By no means unimportant is teaching the patients on the self-control of blood glucose levels. Regular control of the blood glucose levels allows for timely adjusting the treatment and for preventing the hyperglycemia [54].

2. Prevention and treatment of angiopathy. These methods include the control of blood pressure and the

Table 1

The results of clinical research of the consolidation of fractures in cases of DM

Authors (year)	Research design	Population	DM type	Fracture location	Primary findings
Pscherer et al. (2019) [8]	Prospective observation	Patients with DM and without DM (*n*=120)	Type 1 and 2 diabetes	Distal segment of the radial bone	Healing delayed by 3 weeks, the risk of complications is higher 3.4-times
Malige et al. (2022) [16]	Retrospective analysis	Patients with type 2 DM (*n*=87)	Type 2 diabetes	Distal segment of the radial bone	Late surgery (>5 days) — growth of the number infections and nonunion
Tulipan et al. (2021) [31]	Literature review	Summary of research on type 2 DM	Type 2 diabetes	Forearm (tot.)	Decreased remodeling, despite the normal BMD
Wang et al. (2019) [45]	Meta-analysis	Analysis of more than 20 research works with the total *n* >10 000	Type 1 and 2 diabetes	Various zones	Increased risk of nonunion (OR 1.42), repeated fractures

Note. DM — diabetes mellitus; OR — odds ratio.

levels of cholesterol and triglycerides in blood, which helps preventing the development and the progression of angiopathy. Timely detection and treatment of vascular complications of diabetes promotes to the improvement of blood supply in the bone tissue [55].

3. Anatomic reposition of the fractured bone fragments. In order to provide an optimal healing of the fracture, it is necessary to maximally precisely match the bone fragments, restoring the normal anatomy of the bone, creating the favorable environment for the formation of the osteotylus.

Also important is the choice of the optimal repositioning method [56]. In patients with diabetes mellitus, if possible, closed reduction of the fractured bone fragments is more preferable. This type of repositioning minimizes the risk of developing infections, also providing faster healing of fractures. However, closed reduction is not always an effective method, having a number of contraindications, in which open reduction is the only method accessible for the correction of fractures: open or unstable fractures, fractures with the interposition of the soft tissues, fractures with significant displacement of the fractured bone fragments, fractures with a concurrent damaging of vessels and nerves, as well as long-standing fractures. When choosing the open reduction as a method for treating the fractures, it is necessary to thoroughly control the blood glucose level and to provide a prevention of infectious complications [57].

4. Reliable immobilization. In order to prevent the dislocation of fragments and to create stable conditions for the formation of osteotylus, reliable fixation of the fracture is necessary. This is especially important in diabetic patients, in which healing can be delayed. The immobilization method (plaster splint, orthesis, external fixation device, internal fixation) is to be chosen depending on the type of fracture, its location and the status of the soft tissues [58]. In cases of stable fractures, the preferable fixation method is an orthesis. The benefits of this fixation method include the possibility to control the status of the skin above the fracture area, to carry out the hygienic procedures, also applying less pressure to the soft tissues, providing the prevention of circulation disorders, of developing edemas and contractures.

However, in case of unstable fractures or fractures with significant displacement of the fractured bone fragments, the orthesis cannot assure the sufficient fixation for the correct consolidation of the fracture, in such cases it is more practicable to use a plaster splint or other splints.

The external and internal fixation devices shall be used in cases of inefficiency of the conservative methods, however, these methods are accompanied by the risk of infectious complications [59].

5. The correction of vitamin D deficit: All the diabetic patients receive the recommendations to regularly check their blood vitamin D levels. In case of detecting vitamin D deficit, it is necessary to prescribe the corresponding therapy for achieving and maintaining the optimal level [60].

6. Timely treatment of osteomyelitis. When suspecting the presence of osteomyelitis, it is necessary to arrange a combined examination and to initiate treatment as soon as possible. The treatment of osteomyelitis should include the usage of effective antibiotics following the sufficient dosages and duration [61].

4. The optimization of medication therapy: When prescribing the medicinal products for the treatment of diabetes, it is necessary to take into account their potential effects on bone tissue and the risk of fractures.

If possible, priority shall be given to the medicines which do not negatively affect the BMD and do not increase the risk of fractures [62].

The correction of micro-environment as a strategy of improving the consolidation of fractures in cases of DM

In patients with diabetes mellitus, the local microenvironment in the fracture zone is characterized by increased oxidative stress, chronic inflammation, hypoxia, deficit of angiogenic factors and impaired differentiation of the bone lineage cells. This is why in recent years, more and more attention is paid to the active modulation of the tissue microenvironment as a direction for the prevention and treatment of delayed consolidation.

1. Decrease of the oxidative stress

Chronic hyperglycemia induces the formation of reactive oxygen species (ROS), which impair the functions of the osteoblasts, damage the vascular endothelium and increase the secretion of pro-inflammatory cytokines [34].

The correction measures include the following:

- using antioxidants (alpha-lipoic acid, vitamin E, N-acetylcysteine),
- inhibitors of NADPH-oxidase,
- using nanocarriers with antioxidant activity (for example, Cerium nanoparticles [36]).

2. Repolarization of macrophages

The elimination of M1-domination and the stimulation of the transition to M2-phenotype of macrophages promotes to the restoration of angiogenesis and osteogenesis. This can be achieved by the following:

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- local administrations of TGF-β1, IL-4, IL-10,
- using the biomaterial stimulating the M2-response (for example, hydrogels, enriched with antioxidants and growth factors),
- therapy aimed at blocking the RAGE-signaling [35].

3. Improvement of angiogenesis

Angiopathy and hypoxia at the fracture zone in cases of DM impair the reparation. In order to stimulate the neo-vascularization, the following methods are used:

- local delivery of VEGF, FGF-2,
- HIF-1α stimulators,
- PRP (platelet-rich plasma) containing the angiogenic and regenerative factors.

4. Support of osteogenic differentiation

The administrations of IGF-1, BMP-2, TGF-β1 along with using mesenchymal stem cells (MSC) allow for restoring the osteogenic potential and normalizing the processes of remodeling [[37].

5. Biomaterials and carriers

Modern developments include the biocompatible matrices, capable of the following:

- suppression of inflammation,
- delivery of the growth factors and antioxidants,
- formation of supporting environment for cellular migration and differentiation [36].

The correction of the micro-environment is the most important component of the regenerative strategy in cases of impaired consolidation of bones in DM patients It should be combined with the systemic correction of hyperglycemia and of the osteometabolic disorders, but aimed directly at the tissue conditions required for the effective healing.

CONCLUSION

Patients with diabetes mellitus have an increased risk of fractures due to the development of osteoporosis, as well as the high risk of impaired consolidation due to metabolic disorders, circulation and innervation disorders, as well as the risk of developing infectious complications. For the successful treatment of fractures of the radial bone in diabetic patients, it is necessary not only to provide the anatomically correct repositioning and reliable immobilization, but also to correct the systemic disorders characteristic for diabetes, paying special attention to the optimization of glycemic control, to the correction of vitamin D deficit and to the prevention of infectious complications. In case of the absence of competent treatment of fractures of the distal segment of the radial bone in patients with diabetes mellitus, the development of such complications as aseptic necrosis, pseudoarthrosis and ankylosis of the radiocarpal joint is possible. The recommendations include arranging a multidisciplinary management of such patients with the participation of the physicians of the following specialties: internists, endocrinologists and surgeons.

ADDITIONAL INFORMATION

Author contribution. *P.A. Tebeneva* — concept and design of the study, editing of the article; *A.A. Makulova* — scientific revision of the manuscript, collection and analysis of literary sources, preparation and writing of the text of the article. The authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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REFERENCES

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes prevalence and treatment from 1990 to 2022: A pooled analysis of 1108 population-representative studies with 141 million participants. *Lancet.* 2024;404(10467):2077–2093. doi: 10.1016/S0140-6736(24)02317-1
2. Vestergaard P, Rejnmark L, Mosekilde L. Diabetes and its complications and their relationship with risk of fractures in type 1 and 2 diabetes. *Calcif Tissue Int.* 2019;84:45–55. doi: 10.1007/s00223-008-9195-5
3. Wukich DK, Kline AJ. The management of ankle fractures in patients with diabetes. *J Bone Joint Surg Am.* 2008;90(7):1570–1578. doi: 10.2106/JBJS.G.01673
4. Sarodnik C, Rasmussen NH, Bours SP, et al. The incidence of fractures at various sites in newly treated patients with type 2 diabetes mellitus. *Bone Rep.* 2022;17:101614. doi: 10.1016/j.bonr.2022.101614
5. DeGeorge BR, van Houten HK, Mwangi R, et al. Outcomes and complications in the management of distal radial fractures in the elderly. *J Bone Joint Surg Am.* 2020;102(1):37–44. doi: 10.2106/JBJS.18.00561
6. Aguado-Henche S, Morante-Martínez P, Cristóbal-Aguado S, Clemente de Arriba C. Study of human radius construction systematics: Evaluation by DXA in dry bone. *Eur J Orthop Surg Traumatol.* 2019;29(2):389–396. doi: 10.1007/s00590-018-2311-y
7. Chung KC, Spilson SV. The frequency and epidemiology of hand and forearm fractures in the United States. *J Hand Surg Am.* 2001;26(5):908–915. doi: 10.1053/jhsu.2001.26322
8. Pscherer S, Sandmann GH, Ehnert S, et al. Delayed fracture healing in diabetics with distal radius fractures. *Acta Chir Orthop Traumatol Cech.* 2019;82(4):268–273. doi: 10.1007/s43465-023-01049-4
9. Hygum K, Starup-Linde J, Harsløf T, et al. Mechanisms in endocrinology: Diabetes mellitus, a state of low bone turnover. A systematic review and meta-analysis. *Eur J Endocrinol.* 2018;176(3):R137–R157. doi: 10.1530/EJE-16-0652
10. Nypaver C, Bozentka DJ. Distal radius fracture and the distal radioulnar joint. *Hand Clin.* 2021;37(2):293–307.

11. Mehta SP, Karagiannopoulos C, Pepin ME, et al. Distal radius fracture rehabilitation. *J Orthop Sports Phys* Ther. 2024;54(9):CPG1–CPG78. doi: 10.2519/jospt.2024.0301
12. Papaioannou I, Pantazidou G, Kokkalis Z, et al. Systematic review: Are the elderly with diabetes mellitus type 2 prone to fragility fractures? *Cureus.* 2021;13(4):e14514. doi: 10.7759/cureus.12506
13. Patel DS, Statuta SM, Ahmed N. Common fractures of the radius and ulna. *Am Fam Physician.* 2021;103(6):345–354.
14. Chen Y, Chen X, Li Z, et al. Safety and efficacy of operative versus nonsurgical management of distal radius fractures in elderly patients: A systematic review and meta-analysis. *J Hand Surg Am.* 2018;41(3):404–413. doi: 10.1016/j.jhsa.2015.12.008
15. Konarski W, Poboży T, Kotela A, et al. Does diabetes mellitus increase the risk of avascular osteonecrosis? A systematic review and meta-analysis. *Int J Environ Res Public Health.* 2022;19(22):15219. doi: 10.3390/ijerph192215219
16. Malige A, Konopitski A, Nwachuku CO, Matullo KS. Distal radius fractures in diabetic patients: an analysis of surgical timing and other factors that affect complication rate. *Hand (NY).* 2022;17(4):764–771. doi: 10.1177/1558944720944262
17. Ali D, Tencerova M, Figeac F, et al. The pathophysiology of osteoporosis in obesity and type 2 diabetes in aging women and men: The mechanisms and roles of increased bone marrow adiposity. *Front Endocrinol (Lausanne).* 2022;13:981487. doi: 10.3389/fendo.2022.981487
18. Hygum K, Starup-Linde J, Langdahl BL. Diabetes and bone. *Osteoporos Sarcopenia*. 2019;5(2):29–37. doi: 10.1016/j.afos.2019.05.001
19. Prasad TN, Arjunan D, Pal R, Bhadada SK. Diabetes and osteoporosis. *Indian J Orthop*. 2023;57(Suppl 1):209–217. doi: 10.1007/s43465-023-01049-4
20. Holmberg AH, Yonel O, Nelson PM, et al. Risk factors for fractures in middle age. A prospective population-based study involving 33,000 men and women. *Osteoporosis Int.* 2019;17(7):1065–1077. doi: 10.1007/s00198-006-0137-7
21. Zhao J, Liang G, Luo M, et al. Influence of type 2 diabetes microangiopathy on bone mineral density and bone metabolism: A meta-analysis. *Heliyon.* 2022;8(10):e11001. doi: 10.1016/j.heliyon.2022.e11001
22. Ballato E, Deepika F, Prado M, et al. Circulating osteogenic progenitors and osteoclast precursors are associated with long-term glycemic control, sex steroids, and visceral adipose tissue in men with type 2 diabetes mellitus. *Front Endocrinol (Lausanne*). 2022;13:936159. doi: 10.3389/fendo.2022.936159
23. Jiao H, Xiao E, Graves DT. Diabetes and its effect on bone and fracture healing. *Curr Osteoporos Rep.* 2018;13(5):327–335. doi: 10.1007/s11914-015-0286-8
24. Lu H, Kraut D, Gerstenfeld LC, et al. Diabetes interferes with the bone formation by affecting the expression of transcription factors that regulate osteoblast differentiation. *Endocrinology.* 2023;144:346–352. doi: 10.1210/en.2002-220072
25. Saul D, Khosla S. Fracture healing in the setting of endocrine diseases, aging, and cellular senescence. *Endocr Rev.* 2022;43(6):984–1002. doi: 10.1210/endrev/bnac008
26. Schwartz AV, Lane NE. *Diabetes in America.* 3rd ed. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases (US); 2018.
27. Yamamoto M, Yamaguchi T, Sugimoto T. Increased fracture rate in patients with type 2 diabetes mellitus is independent of its bone mineral density. *Clin Calcium.* 2018;16(8):1308–1314.
28. Galiero R, Caturano A, Vetrano E, et al. Peripheral neuropathy in diabetes mellitus: pathogenetic mechanisms and diagnostic options. *Int J Mol Sci.* 2023;24(4):3554. doi: 10.3390/ijms24043554
29. Kayal RA, Tsatsas D, Bauer MA, et al. Diminished bone formation during diabetic fracture healing is related to the premature resorption of cartilage associated with increased osteoclast activity. *J Bone Miner Res.* 2018;22(4):560–568. doi: 10.1359/jbmr.070115
30. Cheng C, Shoback D. Mechanisms underlying normal fracture healing and risk factors for delayed healing. *Curr Osteoporos Rep.* 2019;17(1):36–47. doi: 10.1007/s11914-019-00501-5
31. Tulipan J, Jones CM, Ilyas AM. The Effect of osteoporosis on healing of distal radius fragility fractures. *Orthop Clin North Am.* 2021;46(4):541–549. doi: 10.1016/j.ocl.2021.06.012
32. Candhi A, Liporace F, Azad V, et al. Diabetic fracture healing. *Foot Ankle Clin.* 2019;11(4):805–824. doi: 10.1016/j.fcl.2006.06.009
33. Shah KN, Raskin J, Jones LK, Aaron RK. Pathophysiology and risk factors of osteonecrosis. Current update for the musculoskeletal system. *Mad.* 2019;8:201–209. doi: 10.1007/s12178-015-9277-8
34. Roszer T. Inflammation as death or life signal in diabetic fracture healing. *Inflamm Res.* 2021;60(1):3–10. doi: 10.1007/s00011-010-0246-9
35. Becerikli M, Reinkemeier F, Dadras M, et al. TGF-beta pathway inhibition as the therapeutic acceleration of diabetic bone regeneration. *J Orthop Res.* 2022;40(8):1810–1826. doi: 10.1002/jor.25212
36. Singh RK, Yoon DS, Mandakhbayar N, et al. Diabetic bone regeneration with nanoceria-tailored scaffolds by recapitulating cellular microenvironment: Activating integrin/TGF-β co-signaling of MSCs while relieving oxidative stress. *Biomaterials.* 2022;288:121732. doi: 10.1016/j.biomaterials.2022.121732
37. Fang J, Zhang X, Chen X, et al. The role of insulin-like growth factor-1 in bone remodeling: A review. *Int J Biol Macromol.* 2023;238:124125. doi: 10.1016/j.ijbiomac.2023.124125
38. Raschke M, Wildemann B, Inden P, et al. Insulin-like growth factor-1 and transforming growth factor-beta1 accelerates osteotomy healing using polylactide-coated implants as a delivery system: A biomechanical and histological study in minipigs. *Bone.* 2022;30:144–151. doi: 10.1016/s8756-3282(01)00640-8.
39. Alblowi J, Kayal RA, Siqueira M, et al. High levels of tumor necrosis factor-alpha contribute to accelerated loss of cartilage in diabetic fracture healing. *Am J Pathol.* 2018;175(4):1574–1585. doi: 10.2353/ajpath.2009.090148
40. Cole JB, Florez JC. Genetics of diabetes mellitus and diabetes complications. *Nat Rev Nephrol.* 2020;16(7):377–390. doi: 10.1038/s41581-020-0278-5
41. Rosenberg JL, Woolley W, Elnunu I, et al. Effect of non-enzymatic glycation on collagen nanoscale mechanisms in diabetic and age-related bone fragility. *Biocell.* 2023;47(7):1651–1659. doi: 10.32604/biocell.2023.028014
42. Yamamoto M, Yamaguchi T, Yamauchi M, et al. Serum pentosidine levels are positively associated with the presence of vertebral fractures in postmenopausal women with type 2 diabetes. *J Clin Endocrinol Metab*. 2008;93:1013–1019. doi: 10.1210/jc.2007-1270
43. Cornish J, Callon KE, Reid IR. Insulin increases histomorphometric indices of bone formation in vivo. *Calcif Tissue Int*. 2020;59(6):492–495. doi: 10.1007/BF00369216
44. Papaioannou I, Pantazidou G, Kokkalis Z, et al. Vitamin D deficiency in elderly with diabetes mellitus type 2: A review. *Cureus.* 2021;13(1):e12506. doi: 10.7759/cureus.12506
45. Oei L, Rivadeneira F, Zillikens MC, Oei EH. Diabetes, diabetic complications, and fracture risk. *Curr Osteoporos Rep*. 2019;13(2):106–115. doi: 10.1007/s11914-015-0260-5
46. Liu X, Chen F, Liu L, Zhang Q. Prevalence of osteoporosis in patients with diabetes mellitus: A systematic review and meta-analysis of observational studies. *BMC Endocr Disord*. 2023;23(1):1. doi: 10.1186/s12902-022-01260-8
47. Wang H, Ba Y, Xing Q, et al. Diabetes mellitus and the risk of fractures at specific sites: A meta-analysis. *BMJ Open*. 2019;9(1):e024067. doi: 10.1136/bmjopen-2018-024067
48. Benfield T, Jensen JS, Nordestgaard BG. Influence of diabetes and hyperglycaemia on infectious disease hospitalisation and outcome. *Diabetologia.* 2018;50(3):549–554. doi: 10.1007/s00125-006-0570-3
49. Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). *FEMS Immunol Med Microbiol*. 2021;26(3-4):259–265. doi: 10.1111/j.1574-695X.1999.tb01397.x.
50. Holt RI, Cockram CS, Ma RC, Luk AO. Diabetes and infection: Review of the epidemiology, mechanisms and principles of treatment. *Diabetologia.* 2024;67(7):1168–1180. doi: 10.1007/s00125-024-06102-x

https://doi.org/10.17816/clinpract676866

journal of clinical practice 2025 Vol 16 №1

51. Lecka-Czernik B. Bone loss in diabetes: Use of antidiabetic thiazolidinediones and secondary osteoporosis. *Curr Osteoporos Rep.* 2020;8(4):178–184. doi: 10.1007/s11914-010-0027-y
52. Starup-Linde J, Eriksen SA, Lykkeboe S, et al. Biochemical markers of bone turnover in diabetes patients: A meta-analysis, and a methodological study on the effects of glucose on bone markers. *Osteoporos Int.* 2024;25(6):1697–1708. doi: 10.1007/s00198-014-2676-7
53. Kamml J, Ke CY, Acevedo C, Kammer DS. The influence of AGEs and enzymatic cross-links on the mechanical properties of collagen fibrils. *J Mech Behav Biomed Mater.* 2023;143:105870. doi: 10.1016/j.jmbbm.2023.105870
54. Lee RH, Sloane R, Pieper C, et al. Glycemic control and insulin treatment alter fracture risk in older man with type 2 diabetes mellitus. *J Bone Miner Res*. 2019;34(11):2045–2051. doi: 10.1002/jbmr.3826.
55. Maiorino MI, Signoriello S, Maio A, et al. Effects of continuous glucose monitoring on metrics of glycemic control in diabetes: A systematic review with meta-analysis of randomized controlled trials. *Diabetes Care.* 2020;43(5):1146–1156. doi: 10.2337/dc19-1459
56. Lin MC, Sihota P, Kolibová SD, et al. Fracture characteristics of human cortical bone influenced by the duration of in vitro glycation. *JBMR Plus.* 2024;9(2):151. doi: 10.1093/jbmrpl/ziae151
57. Costigan W, Thordarson DB, Debnath UK. Operative management of ankle fractures in patients with diabetes mellitus. *Foot Ankle Int*. 2022;28(1):32–37. doi: 10.3113/FAI.2007.0006
58. Vukich DK. Diabetes and its negative impact on the results of orthopedic surgery. *Justice Peace Ortop.* 2018;6(3):331–339. doi: 10.5312/wjo.v6.i3.331
59. Lichtman DM, Bindra RR, Boyer MI, et al. Treatment of distal radius fractures. *J Am Acad Orthop Surg*. 2020;18(3):180–189. doi: 10.5435/00124635-201003000-00007
60. Sihota P, Yadav RN, Dhaliwal R, et al. Investigation of mechanical, material, and compositional determinants of human trabecular bone quality in type 2 diabetes. *J Clin Endocrinol Metab.* 2021;106(5):e2271–e2289. doi: 10.1210/clinem/dgab027
61. Tanios M, Brickman B, Cage E, et al. Diabetes and impaired fracture healing: A narrative review of recent literature. *Curr Osteoporos Rep.* 2022;20(5):229–239. doi: 10.1007/s11914-022-00740-z
62. Twito O, Borisovsky G, Ayzenfeld RH. The effect of glycemic control on rehabilitation outcomes of diabetic patients following hip fracture repair. *J Diabetes Treat.* 2018;10:154. doi: 10.29011/2574-7568.000054

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