INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycaemia resulting from the defective action or secretion of insulin. Chronic hyperglycaemia can lead to the damage, dysfunction and failure of various organs. In the context of complications of healing and orthopaedic rehabilitation, vascular (microangiopathy) and nerve (neuropathy) disorders deserve particular attention. About 12% of the patients admitted to orthopaedic departments have diabetes. Studies indicate that there is an indisputable link between diabetes and: an increased risk of fractures, the difficult healing of injuries of bones, ligaments and musculotendinous. It appears that one of the main reasons for this is non-enzymatic glycosylation (glycation) of collagen molecules, a phenomenon observed in the elderly and diabetic populations, as it leads to the formation of advanced glycation end products (AGEs). Collagen is one of the major connective tissue components, and is therefore part of ligaments, tendons and bones. AGEs affect the weakening of its structure and biomechanical properties, and thus also affects the weakening of the structure and properties of the above-mentioned tissues. The aim of the study is to undertake an overview of the current knowledge of the impact of diabetes on the risk of some injuries and subsequent healing and rehabilitation of patients following orthopaedic injuries.

KEYWORDS
advanced glycation end products, bone fractures, diabetes, ligament, orthopaedic injuries, tissue healing
It is recognized that significant morphological changes in diabetes are closely related to its late complications (positive correlation with morbidity and mortality). The onset of these changes is very individual and depends on the degree of diabetes control by the patient. However, in most patients after 10-15 years from diagnosis, morphological changes in the arteries (atherosclerosis), kidneys (diabetic nephropathy), retina (retinopathy), nerves (neuropathy) and other tissues should be expected. 3

Diabetes occurs in about 12% of the patients of orthopaedic departments. 4 It is a problem both with regard to the increased risk of injury and with regard to the subsequent healing and rehabilitation process. The available data show the negative effect of diabetes on the outcome of various orthopaedic procedures. In addition, more frequent occurrences of musculotendinous injuries in this patient population are observed. 5 Considering the orthopaedic complications in people with diabetes, there is an increased incidence of the following disorders: fractures, Charcot neuroarthropathy, dorsi- flexion of the digits of the hands and toes, plantar ulcerations and postoperative infections. 5 It should also be noted that diabetes has a significant effect on the increased risk of infection after orthopaedic procedures. 6 One of the main pathomechanisms involved in joint and bone changes in DM is non-enzymatic glycosylation of collagen (glycation) resulting from chronic hyperglycaemia accompanying diabetes. As a result, so-called advanced glycation end products (AGEs) are formed. Because collagen is one of the main connective tissue components, it is therefore also part of ligaments, tendons, and bones. Advanced glycation end products cause the weakening of its structure and biomechanical properties, and this weakens the above-mentioned tissues and contributes to increasing skeletal fragility. 8 Further clinical studies of this issue are required, as the research results indicate that there is a link between diabetes and the injuries of bones, ligaments and musculotendinous. These issues will be discussed in this paper.

In the context of the complications of healing and orthopaedic rehabilitation, we focused on disorders of the vessels (microangiopathy) and nerves (neuropathy). Detailed characteristics of the pathogenesis and complications of diabetes exceed the framework of this study. Only aspects that directly affect the rehabilitation and healing of orthopaedic injuries are described.

2 | SKELETON AND DIABETES

An increased risk of fractures in DM patients may seem paradoxical, especially in DM type 2, as in general they have a bone mineral density (BMD) within normal limits and a rather high body mass index. In type 1 diabetes, BMD has been reported as being lower compared with healthy controls. 5 In general, these 2 factors have been correlated with a decreased risk of fractures. 8,9 It has been suggested that an increased risk of fractures in DM patients is multifactorial and includes an increased risk of falling, microvascular complications and alterations due to chronic hyperglycaemia (Figure 1). 10 Moreover, skeletal fragility in DM patients is a result of morphological and architectural bone changes such as a smaller cortical area, increased porosity and impaired strength. 6 According to the data, in type 2 DM skeletal dynamics are reduced, assessed on the basis of decreased biochemical markers level of bone metabolism and reduced bone formation rate in histomorphometric studies. 11,12 Furthermore, it has been reported that osteoblast function and maturation may be impaired due to increased circulating levels of molecules such as transforming growth factor β (TGF-β). 13

It has been suggested that a crucial impact on the fragility of the skeleton in DM patients may be due to the accumulation of AGEs. 8 Studies have revealed that AGEs decrease the activity of osteoblasts via impairing the adhesion of these cells to the collagen matrix, inhibiting differentiation and proliferation. Furthermore, a decrease in the mRNA of crucial osteoblast products has been noted. 8 According to the results, there is a negative correlation between AGEs and mechanical bone properties, especially with ultimate strain, stress and fracture toughness. Moreover, in vitro studies have revealed that

![Diagram of Diabetes/Hyperglycemia](image)

**FIGURE 1** Factors that increased risk of fractures in diabetes mellitus. AGEs, advanced glycation end products.
crack-like micro damage is positively correlated with high AGE levels. The level of pentosidine (one of the AGEs) has been reported as 30% higher in DM patients compared with nondiabetic. In terms of increased severity of osteoarthrosis (OA) in DM patients, it has been suggested that it may be explained by the catabolic effect of hyperinsulinemia and hyperglycaemia on cartilage. Furthermore, not only cartilage degeneration but also subchondral bone changes are exacerbated in DM patients. Chen et al reported microstructural deterioration, abnormal bone remodelling and decreased strength in DM patients assessed on the basis of tibial plateaus, compared with non-DM patients and controls (cadavers).

In experimental studies in animal models with type 1 diabetes and type 2 diabetes, it has been observed that the biomechanical properties of the diabetic animals worsened when compared with the control animals. Follik et al demonstrated that femur fractures of type 1 diabetic rats had worse biomechanical properties (defined as stiffness, energy, and the force required to break the bone) after 6 weeks from fracture compared with similar properties in the control animals after 2 weeks from fracture. Although the extreme values of hyperglycaemia and hypoinsulinaemia observed in animals in the type 1 diabetes model poorly reflect clinical reality, they directly indicate the contribution of these factors to the healing process of the fracture. In the model of type 2 diabetes, more common clinically, deterioration of the biomechanical properties (torsional strength) was observed not before 35 days of intervention without significant difference after 2 weeks. According to data, the risk of hip fracture in DM patients is increased. For type 1 diabetes the incidence is 6-7 times higher and for type 2 DM the incidence is 1.4-1.8. It has been suggested, that the reason may be due to the increased risk of falling and antidiabetic drugs, acting both directly on bone metabolisms and indirectly inducing hypoglycaemia, which may result in falls. Ankle fractures are another common injury. It has been suggested that, in a diabetic woman and patients treated with insulin, the risk of ankle fractures is increased, although these results are inconsistent. Nevertheless, if a fracture occurs, the risk of infection, nonunion or amputation is significantly increased compared with nondiabetic patients. According to the results, in 90% of nondiabetic patients, treatment results are reported as good, whereas in DM patients it is 70%. In a study by Kline et al, intrarticular fracture of the distal tibial plateau (pilon type) in diabetic patients was complicated by the lack of or delayed bone fusion in 43% of the patients as compared with 11% of healthy individuals. Shibuya et al in a retrospective analysis of 177 cases involving intervention of foot and shin bones (osteotomy, arthrodesis, fracture setting), looked for a link between pre- and postoperative factors affecting complications that were defined as: delay of bone fusion, absence of bone fusion or abnormal bone fusion. Statistical significance was found for the following: the presence of neuropathy, glycated hemoglobin (HbA1c) above 7%, and length of surgery. It should be noted that the most important prognostic factor was neuropathy.

The question arises - of which predictors are the most accurate in the assessment of the risk of potential fractures in this group of patients. It seems that bone turnover markers may be an important tool. According to the Starup-Linde and Vestergaard study, the level of bone turnover markers is lowered in patients with diabetes. The authors evaluated the concentration of C-terminal telopeptide of type I collagen (CTX), insulin-like growth factor 1 (IGF-1) and sclerostin, procollagen type 1 N-terminal propeptide (P1NP), osteocalcin and bone-specific alkaline phosphatase (ALP). The results seem promising, but researchers underline the need for further research in this area.

Coexisting diabetes is a problem not only because it increases the risk of fractures, but also because it affects the subsequent healing and rehabilitation process. According to the data, blood viscosity in DM patients is increased, leading to hypoxia of tissues. As a result, inflammatory reactions are slowed down, impairing wound healing and increasing infection risk. Pollock et al, in a retrospective study of 1486 patients, reported a risk of hospital re-admission for patients with fractures of the proximal end of the femur (femoral neck fractures, intertrochanteric and subtrochanteric fractures) within 30 days of discharge after primary surgery. According to the results, the rate of re-admission was 9.35%. There was a positive correlation between patients requiring re-hospitalization and the co-existence of either diabetes or respiratory diseases. According to Gortler et al, coexisting DM significantly impairs healing in lower extremity fractures. In a review, it has been reported that the rate of infections, re-operations, malunions and nonunions is significantly higher in DM patients.

In shin bone fractures, Bibbo et al observed an extended wound healing period in people with diabetes (over 50% longer). There is also an increased incidence of complications, especially in patients treated with insulin compared with those treated with oral antidiabetic drugs or dietary diets. Patients with advanced complications of late diabetes are more likely to develop an infection during treatment, bone healing problems and the longer use of orthopaedic orthoses after fractures. Interestingly, the complications described above did not depend on the method of treatment - surgical or nonsurgical. Factors that directly correlate with bone healing disorders are neurogenic neuroarthropathy in the medical history, nephropathy, neuropathy, longer duration of illness, and insulin treatment.

### 3 | Impact of Antidiabetic Drugs on Bones

Although DM itself impairs bone mechanical properties, it should be noted that some drugs administered for DM may negatively impact bone metabolism as well. Table 1 presents the mechanism of action of antidiabetic drugs and their effect on risk of fractures.

The most commonly prescribed drug for increased insulin sensitivity is metformin, which is a biguanide. This drug activates AMP-activated protein kinase (AMPK), causing the reduction of glucose production in the liver and increased glucose uptake in the muscles. It appears, that it is neutral in terms of the risk of fractures and some studies showed a reduced risk of fractures in patients.
treated with metformin. According to studies on animal models, the beneficial effects of metformin on bone metabolism may be due to increased osteoblast differentiation via activating osteoblast-specific runt-related transcription factor 2 (Runx2) with AMPK/USF-1/SHP regulatory cascade. Metformin has also been shown to have an adverse effect on osteoclastogenesis in ovariectomized rats by reducing the expression of the receptor activator for nuclear factor kappa-B ligand (RANKL) and increasing the level of osteoprotegerin also known as osteoclastogenesis inhibitory factor.

Sulfonylureas are other drugs commonly used in DM type 2 patients. Drugs from this group stimulate the pancreatic cells to secrete insulin. It was shown that one of sulfonylureas drug glibenclamide has a positive effect on rat osteoblast cells and promotes their proliferation and differentiation. The ADOPT and Rochester studies indicated that therapy with glibenclamide does not affect bone mass nor increases the risk of fractures. However, another study showed that glibenclamide therapy decreases the level of the serum P1NP, a marker of bone formation. It has also been revealed that in the elderly with type 2 diabetes these drugs have an adverse effect on bones and are associated with an increased risk of hip fractures in both sexes over the age of 65 years.

Glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors are relatively new incretin-based drugs for the treatment of T2DM. In response to nutrients, the endocrine cells of the intestine release incretins - gastric inhibitory peptide (GIP) and glucagon-like peptide 1 (GLP-1). Incretins are quickly inactivated by DPP-4 and these antidiabetic medications are intended to prolong the effect of the incretins by stimulating the release of insulin by the pancreatic cells and inhibiting the production of glucagon in the liver. Most of the animal studies reviewed by Gilbert and Pratley or Charandran indicate a neutral or positive effect of these drugs on bones. The findings of Sun et al show an anabolic effect of GLP-1 receptor agonist to the skeleton in spontaneous diabetic rats. Regarding the clinical data, incretin-based antidiabetic drugs seem to have a neutral effect or a positive effect on reducing the risk of bone fracture.

Thiazolidinediones (TZDs) are antidiabetic drugs that increase insulin sensitivity by activating peroxisome proliferator-activated receptor γ (PPARγ). Due to the many side effects, their use has decreased significantly. Rosiglitazone and pioglitazone, the most well-known TZDs, have been proven to negatively affect the skeleton. According to the review by Gilbert and Pratley, thiazolidinediones increase the rate of bone loss and the risk of fractures in the population of patients with diabetes. Chen et al found that TZDs caused an increased risk of fractures particularly in women under 64 years of age. It seems that thiazolidinediones impair the function of osteoblasts and activate osteoclastogenesis. Moreover, these drugs negatively impact osteoblastogenesis via decreased activity of osteoblast-specific signaling pathways and decreased activity of osteoblast-specific transcription factors. These processes result in a more intense bone loss. By activating PPARγ, TZDs stimulate the differentiation of mesenchymal cells towards adipocytes, increase RANKL expression and osteoclastogenesis, and reduce osteoblastogenesis. Pioglitazone treatment has been shown to reduce the expression of osteoblast-specific Runx2 and ALP and to stimulate the transdifferentiation of human mesenchymal bone marrow stem cells into adipocytes in vitro. Bone loss as a result of the action of TZDs may also be associated with a reduced amount of insulin-like growth factor 1 (IGF-1) and therefore reduced bone formation.
The sodium/glucose cotransporter 2 inhibitors (SGLT2 inhibitors or gliflozins) is another DM drug class, which may negatively affect bone metabolism. Due to the mechanism of action, they may alter the hemostasis of calcium and phosphate, thus inducing secondary hyperparathyroidism. It may potentially affect bone mass and increase the risk of fractures. However, the mechanisms by which SGLT2 inhibitors cause bone loss are not clear.

### 4 | Ligament and Tendon Injuries in Patients with DM

It is known that diabetes affects changes in the joints and ligaments. According to the available data, collagen glycation appears to be crucial. The process of production of the final form of collagen is regulated by the formation of numerous cross bonds between individual filaments that stabilize its structure. Regulation of bond formation may occur in an enzymatic and non-enzymatic manner. It is considered that enzymatic cross-linking of collagen is crucial in connective tissue regeneration. This affects the achievement of proper stiffness, resistance to load, and resistance to injury by the healing tissue. In turn, the process of non-enzymatic cross-linking is a negative phenomenon observed in both elderly and diabetic patients. These bonds are the result of oxidative, non-enzymatic reactions between glucose and collagen. As a result, AGEs are formed. The healing tissues in this mechanism are less resistant to injuries, load and stretching.

Data about the healing process of ligaments in patients with diabetes are limited. There is, however, research on animal models related to the healing process of tendons in diabetes-induced mice. Since the histological structure of the ligaments is similar to the tendon structure, they may be the basis for the study and analysis of ligament healing disturbances in diabetes-inflicted individuals. Disorders of healing are observed at the structural, biochemical and molecular level. Healing tendons in diabetic individuals exhibit worse biomechanical properties: reduced stiffness, reduced tensile stress, reduced maximum load, decreased Young’s modulus. Young’s modulus is also known as the elastic modulus and is defined as the quotient of stress (MPa) and strain (proportional deformation) in a material. In the inflammatory phase of healing, significant reduction of neutrophil and macrophage infiltration at the lesion site was observed. In turn, the proliferative phase is characterized by decreased amounts of fibroblast and lymphocyte infiltration, therefore, cell proliferation is limited. There is also a decrease in vascularization in the early proliferative phase (evaluated on the 7th day after injury, unchanged on the 28th day). Another deviation in the healing process is the decrease of collagen type I, collagen type III and biglycan synthesis within 2 weeks of injury. Molecular studies have shown an increased amount of insulin receptors in the lesion site in both the control group and the group with induced diabetes. Decrease mRNA expression of growth factors, such as vascular endothelial growth factor (VEGF), thymosin β-4 (Tβ-4) and metalloproteinase 3 (MMP-3), has also been detected.

One of the most common orthopaedic problems is Achilles tendon injury. Recently, an attempt has been made to find a link between diabetes (type 1 and type 2) and changes in the Achilles tendon structure that can be observed in ultrasonography (USG). Achilles tendon changes have been shown to correlate with the risk of tendinopathy. It is worth noting that a direct association of the body mass index (BMI) of a diabetic patient with the occurrence of changes in USG was more likely than diabetes alone. The structure of the tendon unit in diabetic patients is generally impaired. Thinning, shortening, and increasing stiffness of tendons are observed. The pathomechanisms of these changes have not yet been fully explained. Non-enzymatic glycosylation of collagen is most likely responsible for increased tendon stiffness in individuals with diabetes. There are numerous studies on animal models.

Boivin et al compared the biomechanical and histological structure of the Achilles tendon in db/db diabetic mice to nondiabetic control mice. In mice with diabetes, the following changes were observed: tendon diameter increase, decrease of maximum load, decrease of tensile stress, decrease of tendon stiffness, and decrease of tendon elastic modulus. In addition, 25% of the diabetic mice were evaluated with the infiltration of the tendon by inflammatory cells (neutrophils). In summary, hyperglycaemia and obesity had a significant effect on the occurrence of pathological lesions within the Achilles tendon in mice. It is likely that similar changes occur in humans, but further research is needed.

Ahmed et al hypothesized that impaired healing in DM may be due to abnormal expression of neurotrophic and angiogenic factors, as neurotrophins play a prominent role in angiogenesis and re-innervation within connective tissue, which is crucial for regeneration and homeostasis. Indeed, in a study on rats with injured Achilles tendons, the authors observed significantly lower levels of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) in rats with induced DM vs healthy controls.

According to the results of Oliveira et al, the Achilles tendon in DM rats displays significant differences in morphology compared with the control group without DM. The tendons were assessed with MRI and Atomic Force Microscopy. The authors observed a significant increase in the coronal and transverse dimensions of the tendon in the DM group. Furthermore, irregularity in the fibre bundles was noted. In the previous study, the authors reported vascular hyperplasia in the vessels of the Achilles tendons and an increase in VEGF, type 1 collagen, and NF-κB expression and mast cell number in comparison with healthy controls.

In the study by Mohsenifar et al, the animals underwent tenotomy of the Achilles tendon. According to the study, the healthy control group displayed significantly higher Young’s modulus and stress tensile load. In the group with streptozotocin induced type 2 DM, the authors noted intensified inflammation and diminished fibrosis.

Also, in vitro studies can be useful in understanding the mechanisms of tendon healing disorders in diabetes. Lin et al determined the effect of various glucose concentrations on tendon-derived stem cells (TDSCs) in vitro. It has been shown that high glucose concentration inhibits the proliferation of these cells, induces apoptosis...
and reduces the expression of markers associated with the tendons (sclerosis and collagen type 1 alpha 1 chain).

Another common orthopaedic injury in the population of people affected by diabetes is rotator cuff disease. In the reconstruction of the rotator cuff, diabetes was one of the preoperative predictors that negatively affected the mobility of the shoulder joint at 3 months postoperatively. However, in the same study, there was no statistically significant difference when lifting the hand forward after 1 year of observation. Dhar et al conducted a study evaluating the outcome of arthroscopic reconstruction of rotator cuff damage after 1 year of observation and showed improvement in movement range and higher scores on the American Shoulder and Elbow Score (ASES) and the Penn Shoulder Score in patients with diabetes and in the control group. Similar results were obtained by Chen et al in a study in which, after an open repair operation, progressive improvement in locomotive performance was observed at the 6th week, the 6th month and the 34th month. It is worth noting that in both studies, patients from the control group had a significantly greater range of movement in postoperative evaluation (forward elevation of the shoulder, external rotation, internal rotation) compared with patients with diabetes, although the difference was not significant in the preoperative evaluation. In patients with diabetes, recurrent damage after rotator cuff repair occurs significantly more often and, importantly, correlates with glycaemia. Among individuals with poorly controlled diabetes (HbA1c >7%), as many as 43.2% were injured again. In an experimental study of tendon attachment of supraspinatus muscle healing in a diabetic mouse model, diabetes was associated with the deterioration of the biomechanical properties, namely - stiffness and maximum load, in DM rats when compared to the controls.

Mubark et al conducted a study evaluating the results of frozen shoulder treatment by the arthroscopic release of the articular capsule. There were 40 patients in the experimental group. Excellent results were noted in 22 patients, good results in 14 patients, and fair results in 4 patients. All of the patients with the fair results (ie, the worst results in the study) were diagnosed with type 2 diabetes. Martinez-Huedo et al report higher rates of mortality in patients with DM vs non-DM after TKAs and THAs. According to Webb et al, patients with insulin-dependent DM were found to be at a greater risk for adverse effects after TKA than the group with non-insulin-dependent DM and the group without DM. Patients with DM are more likely to be readmitted and discharged to a location other than home. DM and preoperative hyperglycaemia have been considered an important predictor and a risk factor for surgical side infections (SSI). Moreover, in orthopaedics, it is a well-known risk factor for postoperative complications. Kremers et al reported an increased risk of surgical side infection after TKA and THA in 1 year postoperatively in patients with DM and preoperative hyperglycaemia, although these effects did not remain statistically significant after adjusting for BMI, operative time and ASA score.

Severe complications of lower limb arthroplasty procedures are venous thromboembolisms (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE). It is hypothesized that DM may increase the risk of these complications as DM has been associated with decreased fibrinolysis, increased blood coagulability and endothelial damage. According to Zhao et al, DVT after TKA was significantly more common in patients with DM.

Not only are the primary THA and TKAs results affected in patients with DM. According to the study by Lopez-de-Andres et al, hospital postoperative complications were significantly more common in patients with DM after revision TKA or revision THA. In the first group, the incidence of acute post haemorrhagic anaemia and urinary tract infections was higher. Postoperative infection, acute post-haemorrhagic anaemia, mean length of hospital stay and hospital mortality were significantly higher in patients with T2DM after revision THA.

5 | IMPACT OF DIABETES ON TOTAL KNEE ARTHROPLASTY (TKA) AND TOTAL HIP ARTHROPLASTY (THA) RESULTS

As mentioned previously, DM impairs bone and cartilage metabolism and biomechanical properties. As a result, severe osteoarthritis and eventually arthroplasty may be expected. It has been reported that DM is a risk factor in patients undergoing arthroplasties and increase the risk for vascular disease, wound infection and myocardial infarction compared with nondiabetic patients. Ghaibeh et al reported a positive correlation between diabetes and acute kidney injury in patients after THA. In terms of direct orthopaedics complications the following are mentioned: periprosthetic fractures, dislocations, aseptic loosening, persistent pain, revision risk and increased re-admission rates.

6 | SUMMARY

Microvascular disorders (microangiopathy) and nerve disorders (neuropathy) deserve particular attention when considering the complications of healing and orthopaedic rehabilitation. The research we have reviewed reveals an indisputable link between diabetes and: an increased risk of fractures, difficulty in bone healing, difficulty in the healing of ligaments and tendons, and difficulty in the healing of musculotendinous injuries. It seems that the non-enzymatic glycosylation of collagen molecules (a phenomenon observed in the elderly and diabetic populations), leading to the formation of AGEs is essential. It should be noted, however, that most of the research on this problem was conducted on animal models. Due to the small number of clinical trials in this area, further studies are needed to understand the exact aetiology of changes at the cytological and histological level.

CONFLICT OF INTEREST

The authors declare no conflict of interest.
REFERENCES


