Diabetes and Alternative Solutions for Diabetic Wounds

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Abstract

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia due to insulin resistance and insufficient insulin secretion. DM maintains its place as a metabolic disorder of increasing importance in the world due to its prevalence and the problems it causes. Its prevalence is constantly increasing due to changes in lifestyles and it ranks fifth among the causes of death because it is a chronic and broad-spectrum metabolic disorder. Acute and chronic complications resulting from poor management of hyperglycemia caused by DM negatively affect the quality of life of individuals. In addition, it increases mortality and morbidity rates in individuals and brings heavy burdens to national economies by increasing health expenditures due to the follow-up and treatment of the disease. Wounds in diabetic patients heal late or do not heal at all, causing significant health complications in patients. In some cases, diabetic wounds can even cause the death of patients. Hyperglycemia caused by diabetes negatively affects the wound-healing process, making wounds susceptible to chronic non-healing wounds. Although the treatment of diabetic wounds includes debridement of necrotic tissue, revascularization surgery, infection control, glucose level control, and foot care, these methods are not sufficient to ensure wound healing. Therefore, potentially effective and painless alternative treatment solutions are needed to shorten the healing process of diabetic wounds.

Keywords: Diabetes mellitus, Complications of diabetes, Wound, Wound healing, Alternative solutions

Cite this Article as: DENİZ M, 2025. Diabetes and alternative solutions for diabetic wounds. In: Ismael SS, Nisa QU, Nisa ZU and Aziz S (eds), Diseases Across Life: From Humans to Land and Sea. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 237-243. https://doi.org/10.47278/book.HH/2025.182

A Publication of Unique Scientific Publishers

Chapter No: 25-034

Received: 29-Jan-2025
Revised: 12-Apr-2025
Accepted: 02-May-2025

Introduction

1. Definition and Importance of Diabetes Mellitus (DM)

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia due to insulin resistance and insufficient insulin secretion (Blair, 2016). DM maintains its place as a metabolic disorder of increasing importance in the world day by day due to its frequency and the problems it causes. Its prevalence is constantly increasing due to lifestyle changes and it ranks fifth among the causes of death because it is a chronic and broad-spectrum metabolic disorder (Yüksel & Bektaş 2020). The International Diabetes Federation (IDF) estimates that 540 million people in the world have diabetes and 643 million people will have diabetes by 2030. It is also expected that 1 in 8 adults will have diabetes by 2045 (Anonymous, 2024a). The IDF reports that 6.7 million adults worldwide die from DM or DM-related complications. (Anonymous, 2024b). Acute and chronic complications resulting from poor management of hyperglycemia caused by DM cause a decrease in the quality of life of individuals, increase mortality and morbidity rates in individuals, increase health expenditures due to follow-up and treatment of the disease, and impose heavy burdens on national economies (Yüksel & Bektaş, 2020). For this reason, DM disease, which is closely related to family and community health and requires continuous care, should be detected at an early stage, and to prevent or delay the complications that may develop due to DM, individuals must manage their diabetes throughout their lives in the best way and with determination. (Aytemur & İnkaya, 2022).

2. Classification of Diabetes Mellitus (DM)

In the 2024 DM guidelines;

i. Type 1 Diabetes Mellitus (T1DM): Diabetes characterized by beta-cell destruction, often leading to absolute insulin deficiency.
ii. Type 2 Diabetes Mellitus (T2DM): Diabetes characterized by progressive insulin secretion defects in the setting of insulin resistance.
iii. Gestational Diabetes Mellitus (GDM): A form of diabetes that occurs during pregnancy and usually resolves with delivery (Anonymous, 2024c).

3. Type 2 Diabetes Mellitus (T2DM)

T2DM is one of the most common metabolic diseases, accounting for 90-95% of diabetic patients worldwide (Izzo et al., 2021; Anonymous, 2024c). T2DM is characterized by relative insulin deficiency and insulin resistance due to dysfunction of pancreatic β-cells (Chatterjee et al., 2017). More than 90% of people with diabetes have T2DM. Although the incidence and prevalence of T2DM varies geographically, 80% or more of people with diabetes reside in areas with low to moderate income. Major factors contributing to the increase in T2DM include urbanization, an aging population, decreasing levels of physical activity, increasing prevalence of overweight and obesity, dietary changes such as increased consumption of processed foods and glucose-containing beverages, and increased fetal exposure to

hyperglycemia during pregnancy (Chatterjee et al., 2017; IDF Diabetes Atlas, 2021; Anonymous, 2024d). Although T2DM usually develops in individuals aged 45 years and older, T2DM is also seen in children, teenagers, and young adults (Anonymous, 2024e). T2DM often develops in individuals with risk factors and genetic predisposition and is caused by the interaction of environmental factors and genetics (Bellou et al., 2018). Individuals with a history of T2DM in first-degree relatives are 2-3 times more likely to develop diabetes. Ethnically, Asian, Hispanic, and black American women are more likely to develop T2DM. Excess adipose tissue distribution is among the important determinants of T2DM risk due to insulin resistance. Children born above the average body mass index have a higher risk of T2DM regardless of birth weight (Robertson et al., 2024). One of the main risk factors for T2DM is abdominal adiposity, which leads to insulin resistance. Other risk factors include low HDL levels, quantity and quality of sleep, exposure to certain environmental toxins and pollutants, unhealthy diet, increasing age, polypharmacy, and smoking (Blair, 2016; IDF Diabetes Atlas, 2021; Robertson et al., 2024). Low testosterone levels have been found to increase the likelihood of developing T2DM in men, while high testosterone levels increase the likelihood of developing T2DM in women and decrease the risk in men. Cardiovascular disease (CVD), hyperuricemia, metabolic syndrome, history of gestational diabetes, and polycystic ovary disease facilitate the development of T2DM in individuals (Robertson et al., 2024). As the disease progresses in T2DM, insulin secretion becomes unable to maintain glucose homeostasis, leading to hyperglycemia. If hyperglycemia is not controlled in the long term, it can lead to complications (Galicia-Garcia et al., 2020). With proper management of diabetes, complications can be delayed or prevented altogether (IDF Atlas of Diabetes, 2021).

i. Clinical Signs and Symptoms of Type 2 Diabetes Mellitus

The symptoms experienced by people with T2DM are similar to those of patients with T1DM, including;

- Polyphagia or anorexia
- Dry mouth
- Polydipsia,
- Polyuria,
- Nocturia,
- Weight loss,
- Blurred vision,
- Numbness in the feet,
- Tingling,
- Don't burn,
- Urinary tract infections,
- Vulvovaginitis,
- Fungal infections,
- Itching,
- Dry skin
- Fatigue
- Late healing wounds (Blair, 2016; Dağdelen et al., 2023).

ii. Complications of Diabetes Mellitus

People with diabetes are at risk of a number of health problems. Good management of blood glucose, blood pressure, and cholesterol can delay or prevent complications of diabetes (Anonymous, 2024f). Complications of diabetes are analyzed in two categories. These are acute and chronic complications of diabetes.

a. Acute complications of diabetes; diabetic ketoacidosis, Hyperglycemic Hyperosmolar Nonketotic Coma and hypoglycemia.

b. Chronic complications; microvascular and macrovascular complications.

- Microvascular complications; diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, sexual dysfunction, diabetic foot
- Macrovascular complications; Coronary artery disease (CAD), Acute Coronary Syndrome (ACS), myocardial infarction (MI), stable or unstable angina, heart failure, hypertension, peripheral arterial disease (PAD) (Blair, 2016; Gedik Çelik, 2017; Dağdelen et al., 2023).

a. Acute Complications of Diabetes

a.1. Diabetic Ketoacidosis (DKA)

Although individuals with T1DM are more prone to DKA, individuals with T2DM are also at risk (Anonymous, 2024g). DKA occurs in infections, inadequate insulin use, continuous insulin administration to the same site, individuals with diabetes who cannot control their diabetes, and eating disorders (Gedik Çelik, 2017). DKA can be prevented by recognizing the problems caused by hyperglycemia in the early period and providing treatment, treating additional disorders in the individual, and maintaining fluid-electrolyte balance (Olgun et al., 2023; Anonymous, 2024g).

a.2. Hyperglycemic Hyperosmolar Nonketotic Coma (HHNC)

It is a condition due to severe hyperglycemia, plasma hyperosmolality, inadequate fluid intake, and altered mental status without DKA (Olgun et al., 2023). It is mostly seen in individuals over the age of 50. 25-35% of cases are patients with T2DM who have not been previously diagnosed (Anonymous, 2024g). It occurs due to inadequate fluid intake of the patients to replace the fluid loss due to hyperglycemic diuresis. HHNC mortality ranges between 12-42%. The diagnosis is made when the blood glucose level is above 600 mg/dl and osmolarity is 320 mOsm/kg and above (Gedik Çelik 2017; Anonymous, 2024g).

a.3. Hypoglycemia

Hypoglycemia is when the blood glucose level is 60 mg/dl and a blood sample taken from capillaries shows a level below 50 mg/dl (Olgun et al., 2023). Excessive intake of insulin or oral hypoglycemic drugs, excessive physical activity or delayed mealtime, insulin that is not selected following daily life activities, insulin injection long before eating, and intramuscular injection where insulin administration is absorbed faster, and symptoms of hypoglycemia are the causes of hypoglycemia (Gedik Çelik, 2017). When an individual is in hypoglycemia, they experience symptoms such as palpitations, nausea, anxiety, hunger, trembling, sweating, fatigue, vision changes, difficulty speaking, headache, and dizziness (Yale et al., 2018; Dağdelen et al., 2023; Anonymous, 2024g).

b. Chronic Complications of Diabetes

b.1. Microvascular Complications

Microvascular complications, which are among the complications of diabetes, are quite common in individuals with diabetes. Chronic kidney disease (CKD), retinopathy and peripheral neuropathy are among the common problems seen in patients with DM. In hyperglycemia, in which early and adequate blood glucose control is not achieved, changes in the microcirculation affect systems and organs. Hyperglycemia lead to low-grade inflammation and atherosclerosis, affecting large and small vessels and nerves, resulting in microvascular problems (Avogaro & Fadini, 2019; Olgun et al., 2023).

b.2. Diabetic Retinopathy

Diabetic retinopathy is a progressive neurovascular disease that develops due to systemic disease and causes both structural and functional changes in the retina (Anonymous, 2024h). Diabetes is the leading cause of severe vision loss and blindness in adults (Mezil & Abed, 2021). Approximately 60% of T2DM patients have retinopathy and 1 in 10 patients have severe vision loss (Yüksel & Bektaş, 2020). To detect these conditions early, patients are advised to undergo annual eye examinations and have their blood sugar and blood pressure monitored (Blair, 2016).

b.3. Diabetic Nephropathy (Diabetic Kidney Disease)

Diabetic nephropathy is observed in 20%-50% of patients with diabetes. Diabetic nephropathy is observed in 5-15% of T2DM and 38% of patients have any stage of CKD (Avogaro & Fadini 2019; Bektaş & Yüksel 2020; Olgun et al., 2023). To prevent the development or progression of nephropathy in T2DM patients, attention should be paid to blood glucose and blood pressure control (Anonymous, 2024g).

b.4. Diabetic Neuropathy

Diabetic neuropathy is a unique neurodegenerative disease of the peripheral nervous system resulting from damage to the capillaries that feed neurons (Gedik Çelik, 2017; Feldman et al., 2019). The prevalence of neuropathy is between 10-90% (Yüksel & Bektaş, 2020). Although the exact cause of neuropathy is unknown, the duration of diabetes and hyperglycemia, HbA1c and triglyceride levels, body mass index (BMI), age, obesity and concurrent peripheral vascular disease, and smoking are important factors in the development of neuropathy (Blair, 2016; Yüksel & Bektaş, 2020). The development of neuropathy is delayed by ensuring optimal glycemic control. It is recommended to repeat neuropathy screening every year after the diagnosis of T2DM (Anonymous, 2024g).

b.5. Diabetic Foot Ulcers (DFU)

Diabetic foot ulcers are injuries that usually occur on the sole due to peripheral neuropathy necrosis or inflammation in all skin layers in patients with diabetes (Mezil & Abed, 2021). Diabetic foot ulcers develop in 15%-25% of individuals with diabetes (Anonymous, 2024g). DFU is one of the problems that reduce the quality of daily life of patients, threaten life, and burden the patients and the national economy (Edmonds et al., 2021; Olgun et al., 2023). Since diabetic foot problems are preventable complications, nurses are in an important position in the prevention of DFU. In the prevention of diabetic foot problems, regular follow-up by nurses after diagnosis, raising awareness of patients about diet and drug treatment, and raising awareness through training for patients with diabetes are important (Aghakhani et al., 2020; Olgun et al., 2023).

c. Macrovascular Complications

Macrovascular complications in DM are caused by atherosclerosis. Macrovascular complications are caused by chronic inflammation and injury to the arterial wall of the peripheral or coronary vascular system, with atherosclerosis occurring as a result of hyperglycemia (HG) disrupting the structure and function of many tissues in the body, especially the vascular system (Lotfy et al., 2017; Olgun et al., 2023). DM is a complicated and persistent condition that involves lifelong medical treatment and carries a high risk of disease in patients with multiple macrovascular complications (Mezil & Abed 2021). CAD, ischemic heart disease (IHD), MI, PAD, and cerebrovascular disease are associated with long-term complications caused by DM (Blair, 2016; Lotfy et al., 2017; Olgun et al., 2023). These complications are the leading cause of death in T2DM. Increased lipid concentration and blood pressure, hyperinsulinemia, diabetic nephropathy, smoking, high BMI, and family history of IHD are conditions that facilitate the development of macrovascular complications (Olgun et al., 2023). Compared to healthy individuals, the risk of macrovascular complications is at least 2-4 times higher and the risk of stroke is 4 times higher in individuals with diabetes. T2DM increases the risk of MI by 2.5-5 times. Every year, 27 out of 1,000 people with T2DM die due to CVD (Yüksel & Bektaş 2020; Anonymous, 2024g). In controlling and preventing complications of diabetes, keeping blood glucose levels at or near normal levels, adhering to medication intake, exercising, and having information about DM are conditions that improve the quality of life of diabetic patients (Lotfy et al., 2017).

4. The Effect of Diabetes on Wound Healing

The disruption of the cellular, anatomical, and functional continuity of living tissue is called a wound (Masson-Meyers et al., 2020).

Wound healing is a set of cellular and biochemical events that develop with trauma, are completed with the formation of new tissue, and involve not only the wound area but all systems (Öztopalan et al. 2017). The restoration of this process and the restoration of tissue integrity is called wound healing (Öztaş, 2021). Wound healing consists of the successive processes of inflammatory reaction, cell proliferation, synthesis of the elements that form the extracellular matrix, and tissue regeneration (Gonzalez et al., 2016). However, inadequate blood flow, infection, high-pressure wound dressing, foreign bodies, necrotic tissue, local steroid use, tissue edema, radiotherapy, anemia, steroids, sepsis, uremia, and diabetes mellitus negatively affect the wound healing process. (Parsak et al., 2017). Patients with diabetes cannot metabolize carbohydrates, proteins, or fats due to inappropriate insulin production or insulin resistance. As a result, due to abnormal insulin metabolism, glucose in the blood cannot be used and hyperglycemia occurs (Kolluru et al., 2012). Wounds in diabetic patients heal slowly or not at all, causing significant health complications in patients. In some cases, diabetic wounds can even cause death in patients (Shi et al., 2024). Hyperglycemia caused by diabetes negatively affects the wound healing process, making wounds susceptible to chronic non-healing wounds. Wound healing occurs by following the processes of inflammation, cell proliferation, angiogenesis, collagen deposition and maturation (Salazar et al., 2016; Pekmezci & Mutlu, 2019). However, due to hyperglycemia caused by diabetes, the wound healing process is stuck in the inflammatory phase as a result of increased levels of proinflammatory cytokines, proteases, increased reactive oxygen species (ROS) and impaired expression of growth factors (Salazar et al., 2016). Due to hyperglycemia, the migration of neutrophils and macrophages to the wound becomes inadequate and chemotaxis decreases. This causes deterioration of leukocyte function and prolongation of the chronic inflammatory phase in the wound (Okur et al., 2020). In addition, hyperglycemia in patients with diabetes leads to overproduction of ROS species, causing oxidative stress, which impairs proliferation, migration, and myofibroblast differentiation, induces apoptosis, and impairs wound healing (Shi et al., 2024). Diabetes disrupts the production of vascular endothelial growth factor, which reduces angiogenesis and consequently reduces capillary density in the wound area, impairing wound healing (Sinno & Prakash, 2013). Hyperglycemia delays wound healing by impairing protein synthesis, migration, and proliferation of keratinocytes and fibroblasts for reepithelialization (Burgess et al., 2021). Transforming growth factor-beta (TGF-β), which plays an important role in wound healing, decreases diabetes and this disrupts the inflammatory response, angiogenesis, reepithelialization, extracellular matrix accumulation, and remodeling (Sinno & Prakash, 2013). Hyperglycemia causes an increase in the expression of MMP, which plays a role in the regulation of the extracellular matrix leading to impaired wound healing (Slavkovsky et al., 2011).

5. Alternative Solutions in Diabetic Wounds

Diabetic wounds can cause amputation or death in patients because they do not heal completely and are prone to recurrence (Çen et al., 2023). Therefore, diabetic wounds are an important medical problem and a significant burden for global health systems in the treatment of chronic and non-healing wounds in patients due to cellular dysfunction and microcirculatory disorders (Qin et al., 2022; Çen et al., 2023). Although the treatment of diabetic wounds includes debridement of necrotic tissue, revascularization surgery, infection control, glucose level control, wound dressing, and foot care, these methods are not sufficient to ensure wound healing (Okur et al., 2020; Qin et al., 2022). Although these treatments provide better control of symptoms, they have a limited therapeutic effect on diabetic wound healing (Qin et al., 2022). Therefore, there is a need for potentially effective and painless alternative treatment solutions to shorten the healing process of diabetic wounds. Studies have been conducted in the literature that have a positive effect on diabetic wound healing (Okur et al., 2020; Qin et al., 2022).

Table 1: Methods used in the healing of diabetic wounds.

Methods Used in The Healing Of Diabetic Wounds	References Supporting These Effects
• Olive leaf extract, Hypericum perforatum extract, Allicin, Clinoptilolite, Lavender oil, Kirenol, Tea tree oil, Bay leaf essential oil,	(Samancıoğlu, 2013[2]; Gökçe, 2015[2]; Toyğar, 2018[2]; Gülpak, 2020[2]; Ren et al., 2020[2]; Sürme et al., 2022[2]; Yoldaş, 2022)[2].
• Oxygen-generating polymeric nanofiber, Symbiotic algae-bacteria cover producing hydrogen, Dressing with hydrogen-rich water	(Zehra et al., 2020[2]; Chen et al., 2021[2]; Deniz, 2024)[2].
• Photobiomodulation, Transcutaneous Electrical Nerve Stimulation (TENS),	(Oyebode et al., 2021[1,2]; Boyacıoğlu, 2022)[2].
• Atmospheric cold plasma application	(Ersözlü, 2024)[2].
• Combined use of lucilia sericata larvae and achillea sintenisii extracts	(Polat, 2024)[2].
• Mad honey, Melatonin loaded lecithin-chitosan nanoparticle, Gallocatechin-silver nanoparticles embedded in cotton gauze patche, Sprayable methacrylic anhydride-modified gelatin hydrogel combined with bionic neutrophils nanoparticle, Cellulose-based pH-responsive Janus dressing	(Malkoç et al., 2020[2]; Correa, 2020[2]; Nagarjuna Reddy et al., 2022[2]; Liu et al., 2022)[2].
• Bioactive glass	(Tang et al., 2021)[2]
• İnsulin-loaded nanoemulsion with Aloe vera gel, Ginkgo biloba extract novel topical cream, Gel formulations of Merremia mammosa (Lour.), Extracellular vesicles from adipose-derived stem cells, Nanoemulsion formulations containing Boron and/or Zinc, Natural okra-based hydrogel, bone marrow mesenchymal stem cell-derived hydrogel	(Chakraborty, 2021[2]; Bardaa, 2021[2]; Marchianti et al., 2021[2]; Liu et al., 2021[2]; Gundogdu et al., 2022[2]; Xin et al., 2023[2]; Xu et al., 2024)[2].
• Nanoclay, Collagen, and Tadalafil	(Ordeghan et al., 2022)[2].
• Lactobacillus bulgaricus and Lactobacillus plantarum	(Mohtashami et al., 2021)[2].
• A novel alginate from Sargassum seaweed	(Lu et al., 2022)[2].

[1]References about human; references about model mice and rats[2]

Conclusion

DM maintains its place as a metabolic disorder that is becoming increasingly important worldwide due to its frequency and the problems it creates. IDF estimates that 540 million people in the world have diabetes and 643 million people will have diabetes by 2030. Complications that arise due to poor management of hyperglycemia caused by DM cause significant health problems and even death. For this reason, potentially effective and painless alternative treatment solutions have been put forward to shorten the healing process of diabetic wounds. Studies conducted to heal diabetic wounds and shorten the wound-healing process show that it accelerates various stages of wound healing. In addition to studies conducted on wound healing in diabetes, new studies are also needed to increase the quality of life.

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