

# A Comprehensive Review on Diabetes Mellitus and Its Relation to Other Diseases

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## Abstract

**Introduction:** The prevalence of type 1 and type 2 diabetes is rising worldwide. Diabetes is a major health issue across the globe and a cause of microvascular and macrovascular complications, including nephropathy, neuropathy, retinopathy, blindness, and cardiovascular disease. Long-term control of blood glucose is an important and determining factor in the prevention of these complications.

**Methods:** In this review study, the databases such as Scientific Information Database, PubMed, SID, ISI, and Scopus were searched for articles published from 1975 to 2019, with emphasis on the articles published within the past 10 years. The used keywords were diabetes, insulin, oxidative stress, microvascular, and macrovascular as well as the diseases and disorders related to diabetes.

**Results:** Considering diabetes, types of diabetes, and its relationship with the organs, it is possible to estimate some degree of prevention, recovery, and timely treatment of diabetes and its effects on other organs

**Conclusion:** Diabetes mellitus (DM) causes numerous diseases and affects the organs due to hyperglycemia, reduced insulin level or insulin tolerance, increased free radicals, and dysfunction of organs. Delay in the diagnosis of diabetes leads to increased diabetes complications that can be prevented by severe glycemic control.

**Keywords:** Diabetes mellitus, Insulin, Oxidative stress, Heart disease, Kidney disease, Diabetes, Organs

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## Introduction

Diabetes mellitus (DM) consists of the two Greek words diabetes meaning fountain and *mellitus* meaning sweet. The two major types of the disease are type 1 and type 2: the former (i.e., type I) is insulin-dependent, while the latter is resistant to insulin. Diabetes is a major health issue with a rising prevalence across the world. By causing chronic hyperglycemia, diabetes can lead to extensive and irreparable damage to other organs of the body.<sup>1</sup> In addition to inducing acute disorders, diabetes causes chronic complications in the eyes, nerves, blood vessels of the heart, and organs. It can ultimately lead to disability and early death in many patients. In diabetic patients, kidney complications, heart disease, brain disorders, the

risk of blindness, and organ gangrene are, respectively, 17, 2, 2, 25, and 5 times more common than in healthy people. This can be due to the glycosylation of the plasma proteins and the cell membrane due to the histochemical changes in diabetes, triggering vascular endothelial damage and the proliferation of smooth muscle cells and inducing the formation of atheromatous plaques in the vessels.<sup>2</sup> In type 1 diabetes, which often occurs at the age of 30 and accounts for 10%-15% of all cases of the disease, insulin production from the pancreas is discontinued due to the loss of insulin-producing cells. Therefore, people with this type of diabetes should receive daily injections of insulin immediately after diagnosis.<sup>3</sup> In type 2 diabetes, which is mainly developed in obese adults over the age of 30 and



accounts for 85-90% of all cases of the disease, the insulin produced from the pancreas does not work well. In fact, the secreted insulin is not usually adequately efficient due to insulin resistance, especially in obese people.<sup>4</sup> One of the main causes of type 2 diabetes is genetics, and around 22% of people carry the gene. The human chromosome q21-q23 is associated with type 2 diabetes.<sup>5</sup> Regarding the severe complications of diabetes and the association between this disease and other organs and its impacts on those organs, this study aimed to review the risk factors for diabetes and the ways for eliminating them, with a further emphasis on the mechanisms involved in the disease and its complications, including increased oxidative stress due to free radicals such as reactive oxygen species (ROS), leading to hyperglycemia. The roles of disease management, lifestyle change, appropriate diet, and exercise as well as the use of hypoglycemic drugs in reducing and delaying the development of diabetes and the associated diseases are also discussed.

### **Epidemiology**

DM is a non-contagious disease that is regarded as an epidemic in the third millennium.<sup>6</sup> More than 250 million people worldwide suffer from the disease. It is estimated that the global population of diabetics will increase by 165% by 2050 compared to that in 2000, so one in three people across the world will develop the disease by 2050.<sup>7</sup> Most diabetic patients are 45-65 years, but in developed countries, adults aged 65 and over increase. Diabetes is the seventh leading cause of death in the United States and accounts for 9% of the world's total deaths. Diabetes was estimated to affect 171 million people worldwide over the age of 20 in 2000. This estimate is expected to reach 366 million by 2030.<sup>8</sup> Although the incidence of type 1 and type 2 diabetes is increasing worldwide, the rate of this increase is expected to be higher for type 2 diabetes, which is due to lifestyle changes and is confirmed by the high prevalence of obesity due to decreased physical activity. The incidence rate of type 2 diabetes is extremely high in some islands of the Pacific Ocean, moderate in countries such as India and the United States, and low in Russia and China. It seems that these differences are due to a combination of environmental and genetic factors. Epidemiological studies have indicated that diabetes has a varied distribution in Iran.<sup>7</sup>

### **Pathophysiology**

DM is a heterogeneous group of metabolic diseases characterized by chronic hyperglycemia and disorders of lipid and protein metabolism. The disease is due to impaired insulin secretion, insulin dysfunction, or both. Diabetes occurs due to three pathophysiological abnormalities, including impaired insulin secretion, peripheral insulin resistance, and increased hepatic glucose production obesity, particularly central is

common in type 2 diabetes. Some of the biological products produced by adipocytes (e.g., leptin, tumor necrosis factor  $\alpha$ , and free fatty acid) interfere with stages such as insulin secretion, insulin function, and body weight modification, and some of them contribute to developing insulin resistance. In the early stages of the disease, despite insulin resistance, glucose tolerance is maintained at normal levels by increased insulin secretion via beta-pancreatic cells. With the progress of insulin resistance, pancreatic beta cells will not be able to maintain and continue increasing blood insulin levels, in which glucose intolerance is developed. Accordingly, the relative reduction in insulin and the increase in hepatic glucose production lead to the development of apparent diabetes with fasting hyperglycemia, and beta-cell failure may also occur over time.<sup>9</sup> In type 1 diabetes, the production of insulin from the pancreas is ceased due to the loss of insulin-producing cells. Moreover, type 1 diabetes is acquired and is more frequently observed in children.<sup>5</sup>

### **Mechanisms of Developing Complications**

Although chronic hyperglycemia is an important factor for complications of diabetes, mechanisms that lead to organ dysfunction remain unknown. Concerning the mechanism of diabetes, it can be argued that increased intracellular glucose results in the production of advanced glycation end products through non-enzymatic glycosylation of cellular proteins. Non-enzymatic glycosylation is the result of glucose reactions with amine groups or proteins. It has been shown that advanced glycation end products, in interacting with proteins, cause the acceleration of atherosclerosis, progression of glomerular dysfunction, reduction in nitric oxide (NO) production, and endothelial dysfunction.<sup>10</sup> Glycosylation of plasma proteins and cell membranes is one of the first histochemical changes due to diabetes. These changes trigger endothelial damage to vessels and the proliferation of smooth muscle cells and induce the formation of atheromatous plaques in the vessels.<sup>2</sup> The second hypothesis is that the cause of chronic complications of diabetes is that hyperglycemia increases glucose metabolism through the sorbitol pathway, and when intracellular glucose increases, a certain amount of glucose is converted to sorbitol by the aldose reductase enzyme. The increased concentration of sorbitol affects cellular physiology, causes cellular dysfunction, and contributes to retinopathy, neuropathy, and nephropathy. The third hypothesis states that hyperglycemia increases the formation of diacylglycerol, which in turn activates protein kinase C, which affects a range of cellular events that lead to diabetes complications. Growth factors also seem to play an important role in the development of diabetes complications. Vascular endothelial growth factor is increased in diabetic retinopathy and transforms

growth factor beta in diabetic nephropathy. It can also be argued that oxidative stress and free radical production, as the outcomes of hyperglycemia, contribute to the developing complications of diabetes.<sup>10</sup>

### **Diabetes and Molecular Sequencing**

Free radicals break down the DNA and, as a result, eliminate the point mutations in it. Since the encoded protein of mtDNA is combined with a nuclear DNA encoded protein within the mitochondria, in the event of a mutation in mtDNA, certain problems with the function or structure of the respiratory chain enzymes will occur, resulting in the reduction in adenosine triphosphate production and free radical (ROS) production that ultimately cause further mitochondrial damage.<sup>11,12</sup> ROS is one of the most important mutagenic factors for mtDNA.<sup>13,14</sup> Some studies have also been done on other mtDNA mutations.<sup>15</sup>

### **Materials and Methods**

A literature search was performed in peer-reviewed databases of PubMed, SID, ISI, Scopus, and EMBASE (the last search was conducted on February 6, 2019 comprising studies from 1975 onwards). The keywords used were diabetes, insulin, oxidative stress, microvascular, heart disease, kidney disease, as well as diseases and disorders related to diabetes. After reviewing the articles, eligible ones were included. Then, the epidemiology and potential effects of diabetes were investigated with respect to increased oxidative stress, decreased NO, and increased parameters of damage to organs as well as regarding lifestyle, proper diet, exercise, and early prevention and treatment of the disease.

### **Results**

Considering diabetes, types of diabetes, and its relationship with the organs, it is possible to estimate some degree of prevention, recovery, and timely treatment of diabetes and its effects on other organs.

### **Free Radicals**

Free radicals play an important role in both health and disease.<sup>16</sup> Most free radicals are produced by mitochondria, and most damage due to radicals occurs on membrane and mitochondrial DNA. Most of the free radicals are biologically derived from oxygen (ROS), but some of the derivatives of free radicals are derived from nitrogen.<sup>17</sup> It has been shown that hyperglycemia, hyperinsulinemia, and insulin resistance increase free radical production and oxidative stress in type 2 diabetes.<sup>18</sup> In obese people, a substantial insulin-mediated decrease in glucose uptake can result in hyperinsulinemia, which in turn increases the production of free radicals. In addition, hypertriglyceridemia and hypercholesterolemia observed in obese individuals can facilitate the production of ROS.

Hyperglycemia may result in the production of ROS via two mechanisms: the activation of the polyol pathway and increasing glucose autooxidation. Increased concentration of ROS, which is the consequence of these mechanisms, can incur general damage to proteins by cross-linking, fragmentation, and fat oxidation. ROS may also mediate certain changes associated with the development of sclerosis. In other words, increased ROS may increase vascular permeability, macrophage migration, impaired endothelin function, and microvascular and macrovascular complications.<sup>19</sup> Thickening, the loss of elasticity, and increased permeability of the blood vessel wall, which is associated with microvascular and macrovascular complications, can be partly related to the glycosylation of vascular proteins. In diabetic patients, oxidative stress plays a key role in the pathogenesis of vascular complications.<sup>20</sup> An early sign of these injuries is the development of endothelial dysfunction.<sup>20,21</sup> Recently, studies have demonstrated that long-term blood glucose control is a major contributor to the prevention of microvascular and macrovascular complications.<sup>22,23</sup>

### **Adrenal Gland**

Diabetes causes changes in the hormonal output of the endocrine glands and thus abnormal metabolic disorders by creating dysfunction in the nervous system and the endocrine system, such as the adrenal gland. Chronic hyperglycemia disrupts the metabolism of carbohydrates, fats, and proteins due to dysfunction of the neuroendocrine system and influence target tissues by disturbing the function of certain hormones such as insulin and cortisol.<sup>24-26</sup> In addition, diabetes-induced neurological damage can interfere with the functioning of the autonomic nervous system, the peripheral nervous system, and the neuroendocrine system, thereby exacerbating the disease and increasing mortality in the patients.<sup>4</sup> In diabetes, increased activity of the hypothalamic-pituitary-adrenal (HPA) axis leads to hypercortisolism and adrenocortical growth. Increased activity of the HPA axis can be due to a decrease in relative sensitivity to negative feedback of glucocorticoids in different parts of this axis (altered activity of  $\beta$ -hydroxysteroid dehydrogenase) and the increased expression of the hypothalamic corticotropin-releasing hormone.<sup>11</sup> It seems that in patients with diabetes, the autonomic nervous system imbalance leads to increased activity of the HPA axis.<sup>26,27</sup> Regarding the neurochemical changes, it appears that the levels of neurotransmitters change in diabetic patients, which can be predisposing to anatomical changes. In this regard, the decreased production of catecholamines in the autonomic nervous system, adrenal, and serum of diabetic rats suggests that the catecholamine system is more affected. Reduced serum levels of these neurotransmitters are probably due to the reduction in the synthesis of catecholamines and

the reduction in their release from nerve terminals.<sup>28,29</sup> Changes in the level of catecholamines in DM reflect the autonomic nervous system imbalance and the onset of autonomic neuropathy.<sup>30</sup> In addition, the reduction in the neuronal volume and the density of the adrenal medulla in diabetic conditions may be due to the production of free radicals, particularly oxygen free radicals, and increased inflammatory factors, followed by intensified damage to the cells of the medulla. Furthermore, the decreased epinephrine level of the plasma reduces the synthesis of epinephrine and norepinephrine in the sympathoadrenal system.<sup>31,32</sup>

## **Diabetes and Heart**

### **Heart Disease**

Atherosclerosis is one of the most important cardiovascular diseases that involves vessels through the development of fatty streaks<sup>33</sup> and plaques. In the last two decades, lipid metabolism disorders in DM have attracted special attention. Today, the abnormal metabolism of lipoproteins and the development of atherosclerosis in diabetic patients are of particular importance.<sup>34</sup> The process of accelerating atherosclerosis in diabetic people can be attributed to the impaired production of NO. NO, which is naturally secreted from the vascular endothelium, causes vasodilatation and proper flow of the blood inside the arteries. Additionally, NO prevents platelets and leukocytes from interacting with the blood vessel walls and subsequently intravascular injuries. In diabetic patients, the amount of NO decreases, and consequently the process of vasodilatation is disrupted, the coagulation cascade becomes difficult, and platelet aggregation increases.<sup>35</sup> Additionally, blood glucose alterations in patients with type 2 diabetes cause an inflammatory response. Zhang et al in their studies found that the percentage of the development of atherosclerosis is higher in diabetic people than in people without diabetes.<sup>36</sup> It seems that diabetic people at any age are more likely to be predisposed to developing atherosclerosis.<sup>37</sup> Increased triglyceride and very low-density lipoprotein cholesterol levels and decreased high-density lipoprotein (HDL) cholesterol levels have also been reported in diabetic patients.<sup>38,39</sup> At a congress regarding new findings on cardiovascular disease, diabetes was introduced as another risk factor for heart disease, and it was reported that every 10 seconds, one death occurs due to diabetes, and two new cases of diabetes occur globally. In addition, it has been indicated that the percentage of triglyceride distribution in very low-density lipoprotein cholesterol is significantly high in diabetic patients with ischemic heart disease.<sup>40</sup>

### **Stroke**

Vascular complications are extremely important in diabetic patients because they can lead to disability and

death. Cerebrovascular microangiopathy is also one of the vascular complications of diabetes. Therefore, the early diagnosis of cerebrovascular complications in diabetic patients is helpful.<sup>41</sup> Diabetes is one of the known risk factors for cerebrovascular disease, and the incidence of stroke is 2-6 times higher in diabetic patients than in people without diabetes.<sup>42</sup> Brain blood flow is regulated by variations in the resistance of the arterioles. The volume of this regulation ranges between vasoconstriction and vasodilation.<sup>41,43</sup> Furthermore, reduced vasomotor reactivity is associated with an increased risk of cerebrovascular disease, and the increase in cerebrovascular diseases will lead to irreversible physical, health, and economic damage. Therefore, decreased brain vasoreactivity is not merely a pathophysiological phenomenon and can serve as a predictor of cerebrovascular disease.<sup>44</sup> It has been found that cardiovascular risk (CVR) in diabetic patients with autonomic neuropathy symptoms decreases or increases in response to CO<sub>2</sub>, depending on the severity of dysautonomia, so CVR in individuals with dysautonomia without orthostatic hypotension is less than that in the control group. Moreover, CVR in people with diabetes is higher than that in diabetics without autonomia as well as in diabetics with dysautonomia and without orthostatic hypotension.<sup>45</sup>

### **Feeling of Pain in Myocardial Infarction**

Diabetes is one of the most important risk factors for coronary artery disease and can increase the incidence of myocardial infarction (MI) and mortality in these patients.<sup>46,47</sup> Thirty percent of patients with coronary artery disease, including MI, chest pain, and cardiac sudden death suffer from type 2 diabetes. Furthermore, the mortality rate has been reported to be two times higher in diabetic individuals with MI than in non-diabetic ones with MI.<sup>48</sup> Although in patients with MI, many signs and symptoms (e.g., shortness of breath, anxiety, restlessness, cold, and moist skin) and increase in heart rate and respiratory rate may occur, chest pain is one of the most important symptoms of the disease and is considered to be an important sign for the early diagnosis and treatment of MI. The complete diagnosis of heart pain is made based on quality, location, duration, release, and exacerbating and soothing factors. MI is frequently seen with discomfort and a lack of typical pain in the chest. These are more evident in patients with diabetes, and diabetes has been reported in some sources to be the cause of painless MI and sudden death, too.<sup>46,49</sup>

## **Diabetes and Kidney Disease**

### **Urinary Stones**

As a major metabolic disorder in type 2 diabetic patients, insulin resistance can lead to impaired renal ammonia genesis and reduced urine pH,<sup>50</sup> both of which lead

to the formation of uric acid stones in the kidneys. Since decreased urinary pH is one of the main causes of idiopathic kidney stones, the prevalence of urinary stones in diabetic patients is significantly increased so that in previous studies, uric acid stones have been reported in 33% of diabetic patients.<sup>51</sup> Obesity itself is an effective factor in increasing the incidence of urinary stones, which has a substantial prevalence in diabetic patients. Insulin also causes a balance between uric acid and sodium reabsorption in proximal tubules. The lack of balance leads to hyperuricemia, decreased urinary sodium, and uric acid excretion. Therefore, hyperinsulinemia causes hyperuricemia and decreases uric acid excretion, thus leading to the development of hypertension. Hyperglycemia also disrupts uric acid exchange by affecting the proximal tubules and changing the reabsorption of sodium and glucose.<sup>52,53</sup>

### *Nephropathy*

Diabetic nephropathy is one of the most common causes of chronic renal failure in the world and is one of the main causes of mortality and morbidity due to diabetes. Proteinuria in diabetic patients is associated with a dramatic reduction in longevity and an increase in CVR factors. Furthermore, the prevalence of nephropathy gradually increases with increasing the duration of suffering from diabetes.<sup>9</sup> Type 2 diabetes may be asymptomatic for years. Therefore, some patients have developed late complications of the disease, including nephropathy, at diagnosis.<sup>54</sup> One study was conducted to investigate microalbuminuria and its risk factors in type 2 diabetes, showing that hyperlipidemia, the duration of suffering from diabetes, and the age of the patient are risk factors for the development of microalbuminuria.<sup>16</sup>

### *Kidney Transplantation*

The definitive treatment for acute kidney failure is kidney transplantation, which is less costly and leads to longer survival and better quality of life for the patient compared to dialysis.<sup>1</sup> Kidney transplantation causes certain complications such as delayed kidney function, transplant rejection, and death, the causes of which can be cardiovascular disease, infections, malignancies, recurrence of the underlying disease, and drug side effects.<sup>2</sup> The development of DM after kidney transplantation also leads to similar complications, including cardiovascular disease due to cytomegalovirus,<sup>2,14,12</sup> reduced patient survival,<sup>2,4,5</sup> and reduced organ transplant survival. It should also be noted that people who have developed diabetes before kidney transplantation will be more likely to develop complications than those who have developed diabetes after kidney transplantation.<sup>55</sup>

### *Cataracts*

Cataracts are still the leading cause of blindness in the

world, and almost 18 million people are affected by it. In addition, at younger ages, diabetic people are 2 to 5 times more likely to develop cataracts than individuals without diabetes.<sup>56,57</sup> Moreover, epidemiological studies showed that cataract is the most common cause of reduced vision in adults with diabetes,<sup>57</sup> and the need for surgery is also proportionately higher in diabetic patients. It is also estimated that 20% of all cataract surgeries are performed on diabetic patients. Some studies even regarded cataract surgery as a cause of the progression of diabetic retinopathy, vitreous hemorrhage, iris irradiation, and reduction or loss of vision.<sup>58,59</sup> Improving surgical equipment and paying attention to the systemic condition of the patient such as blood glucose and blood pressure are important. Overall, the result of cataract surgery in diabetic patients is desirable. These results in diabetic patients who do not have retinopathy or whose retinopathy is mild are similar to those in people without diabetes.<sup>60</sup> However, in patients with advanced retinopathy, the postoperative vision is weaker and may even be disappointing. The presence of clinically substantial macular edema and poor eyesight before surgery are among the risk factors for the postoperative reduction in visual acuity.<sup>61</sup>

### *Liver*

DM and obesity can alter the levels of fatty acids and glycogen in hepatocytes, as the accumulation of glycogen and fatty acids causes hepatomegaly in untreated cases of diabetes.<sup>62</sup> The compaction of hepatocytes, sinusoidal dilatation, vascular congestion, different distributions of glycogen particles in different regions of the hepatocytes, changes in the distribution of acidophil cells, and necrosis in some regions of the liver indicate abnormal cellular changes in diabetic patients. Structural changes in blood vessels that appear as microangiopathy and macroangiopathy in blood vessels are the main causes of mortality in diabetic patients.<sup>63</sup> Increased levels of activity of alanine aminotransferase and aspartate aminotransferase enzymes in diabetes are mainly related to cytosolic cell division. The changes in alanine aminotransferase and lactate dehydrogenase have been reported to be lower than those in aspartate aminotransferase. It seems that cellular changes and the extracellular matrix of the liver in diabetes can pave the way for understanding the enzymatic changes and the course of cellular changes in diabetes.<sup>64</sup>

### *Thyroid*

The prevalence of thyroid disorders is higher in people with diabetes than in the normal population.<sup>65</sup> It has also been established that undesirable metabolic control indicated by high levels of HbA1c is associated with the increased incidence of thyroid dysfunction.<sup>66</sup> Various studies have shown that low T3 syndrome is present in

people who do not have acceptable metabolic control of diabetes, and the observed disorders in thyroid hormones will be resolved by improving glucose control status.<sup>67</sup> In various studies, the high incidence rate of thyroid disorders in patients with type 1 diabetes is notable with respect to the presence of autoimmune disorders; however, it has also been observed in type 2 diabetic patients. For example, abnormal levels of thyroid-stimulating hormone were seen in 91 patients out of 290 patients.<sup>66</sup> Moreover, several issues have been identified as causes of the increased frequency of thyroid dysfunction in diabetic patients, including the presence of an antibody that inhibits thyroid hormone binding, the inhibition of T4 to T3 conversion in peripheral tissues, and HPA axis dysfunction.<sup>68,69</sup> In various studies, changes have been observed in thyroid hormone levels to hypothyroidism due to inappropriate metabolic control of diabetes. It was found that despite the similarity of serum T4 levels in both groups, there was a significant decrease in T3 and thyroid-stimulating hormones in diabetic patients. There was also a significant correlation between HbA1-c level and these variables. Furthermore, low T3 syndrome has been reported in several studies in diabetic patients.<sup>67</sup>

### **Dyslipidemia**

Dyslipidemia disease increases morbidity and mortality when combined with other prevalent diseases such as DM, hypertension,<sup>33</sup> and cardiovascular diseases. HDL particles are complex lipoproteins that contain various proteins that have both receptors with enzymatic properties and different types of nuclei and surface lipids that improve function.<sup>70</sup> As an independent factor, triglyceride also causes diabetes and subsequently kidney disease. Diabetes is also a major contributor to lipid degradation, lipid metabolism disorders, kidney disease, and proteinuria.<sup>71,72</sup> Among diabetic patients, dyslipidemia, an increase in total cholesterol, triglyceride, low-density lipoprotein, and a decrease in HDL are common and increase the risk of developing cardiovascular disease.<sup>73</sup> Increased cholesterol can lead to hypercholesterolemia through an increase in albuminuria morbidity, reduction in glomerular filtration rate, and the progression of chronic kidney disease.<sup>73,74</sup>

### **Hypertension**

Diabetes leads to microvascular and macrovascular complications, heart disease, retinopathy, and nephropathy by developing hypertension. Blood pressure control is an important goal in diabetic patients, and if an intervention can prevent the increase in systolic and diastolic blood pressure in patients with diabetes, it is considered a success and requires healthcare.<sup>75</sup> In diabetic patients with a desirable systolic blood pressure of 130/80 mm Hg and a reduction in diastolic pressure to less than 80 mm Hg, cardiovascular disease and

mortality can be reduced. Extensive and accurate studies are therefore recommended to determine the incidence rate and risk factors for diabetes. Gestational diabetes is one of the complications of pregnancy that results from carbohydrate intolerance at varied severities.<sup>76</sup> Gestational DM creates difficulties for the fetus and puts the mother at risk of developing type 2 diabetes in the future.<sup>76-78</sup> Therefore, it is necessary that the fetus be examined more closely and that the mother be followed up regularly after delivery. The most important issue regarding the fetus is overweight, which is due to the transfer of the mother's excess amounts of blood glucose to the fetus, leading to birth damage.<sup>78,79</sup> In one cohort study, a relationship was observed between gestational diabetes and malignant neoplasms, especially breast cancer.<sup>80</sup> The study by Gillman et al showed a relationship between gestational diabetes and childhood obesity in a mother with gestational DM.<sup>81</sup> In addition, Bryson et al reported a relationship between gestational diabetes and gestational hypertension and a relationship between preterm delivery and gestational diabetes. Moreover, 50%-60% of patients with gestational diabetes will develop type 1 diabetes in the future.<sup>76,78,82</sup> The correct screening method should be considered for all pregnant women or for certain people who are at higher risk of developing gestational diabetes. Screening for 50 grams of glucose is suggested in people at a comparatively higher risk of the disease.<sup>76,78</sup>

### **Skin**

Dermatological manifestations are due to macrovascular complications of diabetes, impaired wound healing, and other unknown mechanisms. Overall, skin manifestations in type 1 and type 2 diabetes do not differ; however, skin infections and skin autoimmune disorders are more common in type 2 diabetes and type 1 diabetes, respectively. Acquired ichthyosis is the most common skin manifestation in young people with type 1 diabetes. Overall, cutaneous manifestations appear in type 1 diabetic patients, and the incidence of cutaneous manifestations in patients with type 1 diabetes depends on the duration of the disease as well as on the incidence of macrovascular complications.<sup>83</sup> Skin symptoms usually appear after the development of diabetes, but they may occur in some cases even years before the diagnosis of diabetes.<sup>84</sup> Diabetes skin problems include necrobiosis lipoidica,<sup>85</sup> diabetic dermopathy,<sup>85</sup> acanthosis nigricans,<sup>86</sup> lichen planus,<sup>87</sup> diabetic thick skin,<sup>88</sup> xanthoma,<sup>89</sup> yellow skin,<sup>90</sup> and rubeosis faciei.<sup>91</sup>

### **Sleep**

Changes in the levels of living and the modernization of society have contributed to the increase in the incidence of diabetes more pronouncedly than that of genetic and ethnic characteristics. Sleep and rest are important constituents of the human lifestyle, and the disturbance of

each of them leads to the disturbance in the other.<sup>92</sup> Sleep disorders weaken the immune system's response and delay wound healing by reducing the amount of phagocytosis, the proliferation of granulocytes, and the number of natural killer cells.<sup>93,94</sup> Additionally, sleep disorders lead to increased insulin resistance and decreased glucose tolerance by increasing sympathetic nervous system activity, cortisol levels at night, and growth hormone.<sup>95</sup> Chaput et al showed that fasting blood glucose was higher in people with sleep duration over 9 hours and less than 5 hours than in those who slept 7-8 hours a night.<sup>96</sup> Reducing the duration of sleep decreases the amount of leptin (fullness factor) and increases ghrelin (appetite stimulant). Moreover, growth hormone and ghrelin decrease insulin sensitivity and impair glucose tolerance by increasing cortisol levels. Increased growth hormone levels due to the transient insulin resistance in muscle cells can increase blood glucose and insulin resistance in other tissues.<sup>97</sup>

### **Diabetes and Sexual Organs**

#### **Polycystic Ovary Syndrome**

Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects women of childbearing age and is characterized by anovulation and hyperandrogenism. Insulin resistance plays an important role in the pathogenesis of this syndrome. Women with PCOS have obesity-independent insulin resistance.<sup>98</sup> They often have certain glucose and lipid metabolism disorders, and the risk of developing type 2 diabetes and cardiovascular disease increases over time in these people. Longitudinal studies on insulin and glucose systems have demonstrated a comparatively higher incidence of glucose intolerance in women with PCOS. It seems that the risk of glucose intolerance is approximately 5-10 times higher in people with PCOS than in healthy people.<sup>99</sup>

#### **Menopause**

The long-term consumption of estrogen in postmenopausal women may increase the risk of developing type 2 diabetes.<sup>100</sup> Glycosylated hemoglobin levels were significantly different between postmenopausal women treated with hormone replacement therapy and those who did not receive hormone replacement therapy.<sup>101</sup> Due to lifestyle changes, physical inactivity, nutrition, genetics, and the like, diabetes is rising in the general population. Reduced insulin sensitivity has been reported in the middle of the luteal phase compared with the mid-follicular phase of the menstrual cycle during normal pregnancy.<sup>102</sup> Furthermore, the short-term use of estrogen replacement hormones has been found to improve glycosylated hemoglobin levels in postmenopausal women with diabetes.<sup>103</sup> Estradiol reduces ROS by producing antioxidant effects, and insulin produces synergistic effects by exerting hypoglycemic

effects; consequently, peripheral glucose absorption, oxidative markers, and plasma malondialdehyde level are reduced.<sup>104</sup> In ovariectomized mice and postmenopausal women, estradiol was found not only to increase insulin secretion from  $\beta$ -cells but also to increase the sensitivity of target organs to insulin.<sup>105</sup>

#### **Spermatogenesis**

The development of diabetes in both genders is associated with certain limitations in reproductive potential. Research has indicated that in the absence of insulin, the ability of the anterior pituitary lobe cells to use glucose decreased, so the level of gonadotropin-releasing hormone reduces. Changes in carbohydrate homeostasis in diabetes are associated with the impairment of reproductive functions, HPA axis function, as well as histopathological pattern of gonads. Moreover, a type of unconventional steroid feedback was developed in the HPA axis, which reduced pituitary sensitivity with respect to the regulation of the axis activity.<sup>106,107</sup> However, what has been documented regarding tissue changes in seminiferous tubules related to this study is that the effective factors due to diabetes are able to reduce and disrupt the process of spermatogenesis. Probably, the decrease in the number of sex cells may be due to cell death, which is owing to failure in their production process caused by diabetes, leading to reduced fertility.<sup>108,109</sup>

#### **Sexual Function**

Sexual dysfunction in diabetic men occurs before the age of 60 in 50% of the cases and appears to be lower in women than in men. Sexual health is an important part of diabetes care, which is neglected, particularly in women. Decreased hemodynamic and metabolic function leads to the loss of the usual supporting mechanisms that can reduce microvascular disease in women. Dyslipidemia, hypertension, and endothelial dysfunction also exacerbate these disorders. The decrease in nitric acid production caused by vascular dysfunction due to diabetes leads to a decrease in the vaginal stenosis.<sup>110</sup> The study by Tyrer et al indicated the effect of diabetes on decreasing vaginal lubrication. Likewise, the study by Schriener-Engel et al in diabetic patients showed a decrease in sexual dysfunction, vaginal lubrication, and orgasm as well as sexual dysfunction in diabetic patients under insulin treatment. Sexual function index (i.e., desire, arousal, vaginal wetness, orgasm, and total sexual satisfaction) is substantially lower in diabetic people than in healthy ones.<sup>111-113</sup>

#### **Elderly**

The most common outcome of type 2 diabetes is fatal vascular complications such as cardiovascular disease, peripheral artery disease, or stroke. In an 11-year study,

the mortality rate of diabetes in older people with a new diagnosis of diabetes was 2.9% higher than that in the non-diabetic group because they had developed more microvascular and macroscopic complications.<sup>114</sup> The lack of awareness of hypoglycemia is common, so about one quarter of insulin-dependent patients develop hypoglycemia without warning signs. Following a drop in blood sugar, changes in blood supply to the brain occur that do not easily appear in diabetic healthy people due to the stiffening of the arteries or nervous system disorders. Increased duration of diabetes can lead to the current lack of awareness and more severe hypoglycemia. Hypoglycemia, dizziness, forgetfulness, pallor, sweating, distraction, irritability, loss of body temperature, nightmares, and insomnia can also be mentioned. The effect of hypoglycemia on the elderly is more severe due to poor physical strength and macrovascular disease. In addition, due to hypoglycemia, these people are at a higher risk of macrovascular events such as heart attack and stroke. Accordingly, desirable blood glucose levels in young people is higher than those in the elderly.<sup>115</sup>

### **Psychological Problems**

In diabetes, psychological conditions and problems including stress, anxiety, and depression have drawn special attention.<sup>116</sup> Although diabetes is reported as a source of stress in diabetic people, the stress associated with diabetes has adverse psychological impacts such as depression, anxiety, and adverse sexual effects.<sup>117</sup> The study by Gonzales et al revealed that in these patients, poor self-care, medication compliance, blood sugar regulation, and severe microvascular and macrovascular complications are associated with psychological problems, especially depression.<sup>118</sup> Depression in diabetic patients can be associated with anorexia, eating disorders, and the patient's refusal to receive insulin, ultimately making it difficult to treat and control the disease. Moreover, stress, depression, and anxiety are risk factors for diabetes or exacerbate it. In addition, mental stress increases cortisol secretion in response to it by affecting the HPA axis. Cortisol, in turn, causes an increase in sugar production, a reduction in its consumption in body tissues, and therefore hyperglycemia by affecting the liver.<sup>119</sup>

### **Oral Diseases**

Oral diseases are considered one of the side effects of diabetes. These diseases are more severe and more common in diabetic people than in the normal people. People with diabetes are more predisposed to developing some of the symptoms of oral disease manifestations such as candidiasis that can lead to poor blood glucose control. Additionally, they are predisposed to dry mouth due to increased glucose levels in oral secretions and the lack of immunoregulation.<sup>120</sup> A study on oral manifestations showed that the most common manifestations are

gingivitis (96%), periodontium (90%), and dry mouth (76%).<sup>121</sup>

### **Serum Iron Level**

Several studies have evidenced an association between increased iron stores in the general population and increased incidence of diabetes.<sup>122,123</sup> These findings suggested that for elevated hemoglobin level to be associated with diabetes, a large or, at least, a sufficient amount of iron store is essential. In people with iron deficiency anemia, the clear relationship between the incidence of gestational diabetes and the presence and absence of anemia has been investigated. In women with iron deficiency anemia, the incidence of gestational diabetes was half its incidence in non-anemic women and women with thalassemia minor.<sup>124</sup> Another study showed that the prevalence of pregnancy is lower in the women with iron deficiency anemia than in the control group.<sup>125</sup> Serum ferritin level was also significantly higher in the group with glucose tolerance and diabetes.<sup>126</sup>

### **Salivation**

Cortisol is a glucocorticoid hormone secreted from the adrenal cortex and contributes to the regulation of mineralocorticoids, immune system function, blood pressure, and metabolism. Cortisol level increases in hypertension, hypercholesterolemia, obesity, and glucose intolerance. Changes in blood cortisol levels also change the level of the hormone in the saliva, and salivary cortisol is an indicator of free cortisol in the blood or biologically active cortisol. The measurement of salivary cortisol has several advantages over the measurement of its level in serum or plasma, including inexpensive and non-invasive sampling.<sup>127,128</sup> Human studies have indicated that high cortisol causes insulin resistance and is likely to contribute to developing type 2 diabetes. Disturbances in cortisol level have been reported in individuals with insulin resistance, predisposition to diabetes, and type 2 diabetes.<sup>128</sup> Similarly, the study by Chiodini et al who aimed to investigate cortisol secretion in patients with type 2 diabetes indicated that the activity of the HPA axis and the secretion of cortisol substantially increase, with its rate being dependent on the complications of the disease.<sup>129</sup> Accordingly, the increased levels of cortisol secretion cause diabetes and make metabolic control difficult.<sup>130</sup>

### **Conclusion**

DM causes numerous diseases and affects the cardiovascular system and other organs due to hyperglycemia, reduced insulin level or insulin tolerance, increased free radicals, and dysfunction of the arteries and organs. Delay in the diagnosis of diabetes leads to increased microvascular and macroscopic complications such as diabetic retinopathy, nephropathy, and



neuropathy, which are directly related to hyperglycemia and can be prevented by severe glycemic control. Increased blood glucose increases glucose autoxidation in a focused manner, which results in the production of free radicals. In this case, the production of free radicals is greater than the ability to regulate them by the defense antioxidants produced by the body, which is due to oxidative stress function, leading to macrovascular and microvascular complications.<sup>131</sup> Therefore, screening for diabetes is essential for the early diagnosis and prevention of chronic complications resulting from it.<sup>92</sup> In diabetes, another important role is played by NO, which is produced by the NO synthase enzyme in endothelial cells and is responsible for the effects of insulin on vessels and the transport of insulin and glucose to skeletal muscles.<sup>132</sup> In addition to acute disorders, diabetes causes chronic complications in the eyes, nerves, and blood vessels of the heart and organs and ultimately death in many patients. Renal complications, cardiovascular and brain diseases, blindness, and gangrene are much more frequent in diabetic people than in people without diabetes. Moreover, the incidence and progression of microalbuminuria are associated with defective endothelial function, and given the essential role of NO in endothelial physiology, incomplete NO activity in diabetic patients has drawn attention. Therefore, improving this trend can play an important role in controlling the effects. Other important factors in diabetes are care, blood glucose control, screening, lifestyle, and diet. The management, lifestyle changes, including diet and exercise, and the use of hypoglycemic drugs should also be taken into account in diabetes.<sup>133</sup> Although oral hypoglycemic drugs are the cornerstone of diabetes care, their side effects, their inability to satisfactorily prevent and control the complications of the disease, and the reduction in their efficacy over time should not be ignored. It should also be noted that in traditional medicine and conventional medicine, lifestyle changes should be first addressed for the treatment of any disease.<sup>134</sup>

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#### Competing Interests

The authors declare no conflict of interests.

#### Ethical Approval

This study does not include any studies with human or animal subjects performed by any of the authors.

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