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Why Diabetes Worsens Patient Prognosis: A Literature Review of Cardiovascular and Renal Complications

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Abstract

Background. Diabetes is considered a serious chronic metabolic disease due to its increasing prevalence worldwide. The main factor worsening the prognosis of patients is cardiovascular complications, which are the main factors of morbidity and mortality in diabetes.

Aim. This review aims to explain why diabetes exacerbates cardiovascular and renal diseases, leading to worse clinical outcomes in affected individuals, focusing on its pathophysiological mechanisms.

Material and Methods. A systematic literature review was conducted using PubMed and Google Scholar databases. Meta-analyses, randomized controlled trials, cohort studies, and systematic reviews regarding the impact of diabetes on arrhythmogenesis, myocardial ischemia, stroke, venous thromboembolism and the development of chronic kidney disease were analysed.

Results. Cardiac arrhythmias have been shown to be promoted by glycaemic variability and autonomic neuropathy. Based on the research, we can conclude that the increased risk of myocardial infarction and ischemic stroke is due to persistent hyperglycaemia, which, by inducing oxidative stress and chronic inflammation, leads to endothelial dysfunction and plaque instability. Based on the accumulated evidence, we know that the association between diabetes and venous thromboembolism remains inconsistent. Diabetes significantly increases the risk and worsens patients outcomes after ischemic stroke, mainly by increasing the risk of ischemic focus haemorrhagic and reducing cortical plasticity. The effect of diabetes on the course of haemorrhagic stroke is not unequivocal. Diabetic kidney disease increases the risk of cardiovascular disease.

Conclusion. The multifactorial effects of hyperglycaemia on both the cardiovascular system and chronic kidney disease synergistically worsen outcomes in diabetes. Early detection, rigorous glycaemic control, and multifaceted management of risk factors are essential to improve survival.

Keywords: diabetes; cardiovascular disease; diabetic kidney disease; arrhythmias; stroke

Contents

1. Introduction

Diabetes is defined as a serious chronic disease. which result from insufficient insulin production or the inability of the body to use it effectively (Hossain et al., 2024a) . It is believed that there are mainly 2 types of diabetes. Type 1 diabetes (T1DM) is an autoimmune disease that causes the destruction of β cells of the pancreas, which results in a rapid decrease

in insulin and the need for constant insulin therapy. Type 2 diabetes (T2DM) develops gradually due to increasing insulin resistance of tissues and initial hyperinsulinemia, which eventually stops due to the depletion of the β cell reserve. It has been noted that T2DM is associated with obesity, improper diet and lack of physical activity and usually manifests itself in middle or old age (Antar et al., 2023) . Thanks to the data collected from the International Diabetes Federation, we know that diabetes is a global problem. It has been shown that in 2021 there were about 537 million people with diabetes, and the healthcare costs amounted to 966 billion dollars. The number of people with diabetes is expected to increase by 643 million in 2030 and 783 million in 2045, which will translate into expenditures exceeding 1 trillion dollars (Hossain et al., 2024b) . It has been shown that the main cause of death in people with T2DM are cardiovascular disease complications. They are responsible for about half of all deaths in this group of patients. It is suspected that people with T2DM have more than twice the risk of death from cardiovascular complications than people without diabetes. It has been proven that the presence of cardiovascular disease in a patient with diabetes significantly worsens the prognosis by increasing overall mortality. This has shown how important it is to detect and control cardiovascular risk factors early (Yun and Ko, 2021) . The priority is to determine the causes of the increase in the incidence of cardiovascular complications, due to the prevalence and tendency to increase the number of diabetes cases. Therefore, the aim of this study is to present the existing knowledge on the impact of diabetes on the increased incidence of cardiovascular complications and patient prognosis.

2. Research materials and methods

A review of the literature available in the PubMed and Google Scholar databases was carried out, focusing on clinical trials, meta-analyses, and systematic reviews related to the impact of diabetes on patient outcomes, primarily caused by cardiovascular complications. The search strategy included keywords such as: diabetes; cardiovascular disease; diabetic kidney disease; arrhythmias; stroke.

3. Research result

3.1. Cardiac arrhythmias

The presence of diabetes significantly increases the incidence of arrhythmias and their associated morbidity and mortality (Gaur et al., 2024) . The ethology of heart rhythm disturbances in diabetes is multifactorial (Grisanti, 2018).

3.1.1. Glucose level fluctuations

In meta-analysis it was shown that hypoglycaemia was associated with an increased incidence of cardiac arrhythmias (Li et al., 2023) . Nocturnal drops in blood glucose promoted the development of arrhythmias such as: bradycardia, atrial ectopic beats and single ventricular beats (Chow et al., 2014).

Hypoglycaemia causes changes in the autonomic nervous system tone, first increasing the sympathetic compensatory response, which manifests itself and then after a few to a dozen or so minutes, compensatory action of the parasympathetic, which results in increased parasympathetic tone and bradycardia at night (Chow et al., 2014; Li et al., 2023) . In an animal study model, it has been shown that the main mechanism of severe, fatal cardiac arrhythmias during hypoglycaemia is not the activation of the sympathetic nervous system, but excessive activation of the parasympathetic nervous system, particularly through acetylcholine acting on nicotinic receptors in the heart (Reno et al., 2019).

On the other hand, arrhythmia induction also involves the sympathetic nervous system. In response to neuroglycopenia, sympathetic nervous system activation raises catecholamine levels, especially norepinephrine, which can provoke a spectrum of arrhythmias (QTc prolongation, premature ventricular contractions, atrio-ventricular block) that may culminate in cardiac arrest. Hypoglycaemia also lowers potassium levels, which increases the risk of arrhythmia; maintaining normal potassium levels significantly reduces mortality. It has also been shown that previous episodes of mild hypoglycaemia attenuate the catecholamine response to severe hypoglycaemia and protect against death, also indicating the involvement of the sympathetic nervous system in the induction of cardiac arrhythmias (Reno et al., 2013).

It was noted that not only the decrease in glucose level causes the increased risk of arrhythmia, but also its fluctuations at high and low concentrations. In an animal model of streptozotocin-induced diabetes, it was shown that significant differences in glucose concentrations were associated with a high susceptibility to the development of atrial fibrillation, caused by a

significant increase in oxidative stress, and consequently apoptosis of cardiomyocytes, muscle and articular fibrosis (Saito et al., 2014).

3.1.2. Autonomic neuropathy

Diabetes affects nerve degeneration in many ways, it has a negative effect through mechanisms such as: the formation of advanced glycation end products, activation of PARP pathways that destabilize proteins and DNA of nerve cells, increasing oxidative stress, leading to microangiopathy, supplying nerves (Diabetic neuropathy, 2019).
Autonomic degeneration can affect patient deterioration by reducing exercise tolerance, caused by impaired rhythm and pressure modulation, causing insufficient adaptation of the heart during exercise, which manifests itself as rapid fatigue and shortness of breath. Damage to the parasympathetic nervous system contributes to the development of resting tachycardia, which does not decrease during sleep (Agashe and Petak, 2018).

3.1.3. Heart remodelling and changes in conduction

The clinical study showed a correlation between the occurrence of high frequency of supraventricular arrhythmias and right ventricular and atrial remodelling at T2DM patients. Ventricular extrasystoles and bradycardia episodes also correlate with structural changes, but they depend to a greater extent on the remodelling of the left side of the heart (Sarapultsev et al., 2017).

3.2. Myocardial ischaemia

T2DM significantly increases the risk of cardiovascular events, including myocardial infarction. Moreover, even if they have not had coronary artery disease before, they are at as high a risk of acute coronary syndrome as those with documented disease, and among those who have already had a heart attack, the probability of a recurrence within 10 years exceeds 40% (Cui et al., 2021).
Individuals with T1DM diabetes face almost a threefold higher overall mortality rate than the general population, and they experience cardiovascular complications on average more than ten years earlier. Even in young adults, the annual likelihood of a cardiovascular event is still around 1–2%. Furthermore, those with suboptimal glycaemic control may see their risk of

dying from cardiovascular causes increase by up to eightfold compared to people without T1DM (Schofield et al., 2019).

3.2.1. Endothelial dysfunction

In diabetes, endothelial dysfunction results from the overlap of several processes: direct toxic effects of hyperglycaemia and free radicals on endothelial cells, metabolic disorders (macrovesicles, unfavourable lipid profile), and concomitant inflammation and hypertension. Together, they lead to reduced NO synthesis and loss of the ability of vessels to properly dilate (Stampouloglou et al., 2023).

Endothelial dysfunction has been shown to independently forecast adverse long-term coronary and cardiovascular outcomes even in patients with angiographically normal coronary arteries: both invasive assessments and non-invasive techniques have consistently linked impaired endothelial responses to a poorer clinical course over extended follow-up. Moreover, pooled analyses demonstrate that flow-mediated dilation performs at least as well and in some studies even better, than conventional risk markers in predicting future cardiovascular events, underscoring its value as an independent prognostic indicator (Hamilton and Watts, 2013).

3.2.2. Atherosclerotic plaque

In diabetics, atherosclerotic plaques are more unstable and inflammatory than in nondiabetics: they accumulate lipid cores earlier and more abundantly and are heavily infiltrated with macrophages, which weakens the fibrous cap. Sharp-tipped cholesterol crystals increase local inflammation and can mechanically damage the plaque surface. Although extensive calcification often occurs, which provides some stiffness, it is accompanied by increased vessel stiffness and uneven stress distribution, which promotes fracture. In diabetics, it is fractures, not surface erosion, that predominate as the cause of incidents, and the risky features of plaques appear earlier and persist throughout life (Suzuki et al., 2023).

On the other hand, it is believed that in patients with T2DM the key factor predisposing plaques to rupture is impaired fibrous repair rather than heightened inflammation. This is evidenced by reduced collagen and elastin levels, which weaken the plaque scaffold, alongside lower platelet-derived growth factor (PDGF) concentrations (limiting smooth muscle cell proliferation and migration) and diminished matrix metalloproteinase-2 (MMP-2)

activity (necessary for proper matrix remodelling). The absence of differences in macrophage content or proinflammatory cytokines compared to non-diabetic patients, together with strong positive correlations between PDGF, MMP-2 and collagen/elastin levels, underscores that the primary issue is a failure of repair mechanisms (Edsfeldt et al., 2014).

3.2.3. Cardiac Autonomic Neuropathy

Cardiac autonomic neuropathy (CAN) is a form of diabetic autonomic neuropathy affecting cardiovascular regulation, is a major contributor to impaired pain perception during myocardial ischemia, leading to a high prevalence of silent myocardial ischemia and "painless" heart attacks in people with diabetes. This neuropathy is associated with higher mortality and a range of serious cardiovascular complications, and by blunting the sensation of coronary pain, it substantially increases the risk of unrecognized and therefore untreated ischemic events (Gogan et al., 2025).

CAN occurs in both T1DM and T2DM, and its severity increases with the duration of the disease. Already at the time of diagnosis, some patients have autonomic disorders, and several years after diagnosis, the problem affects a significant proportion of patients. Moreover autonomic dysfunction often accompanies established cardiovascular disease, longer diabetes duration, and poor glycaemic control, affecting about one-third of people with T1DM (Serhiyenko and Serhiyenko, 2018).

3.3. Venous Thromboembolism

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), affects 1 in 1,000 people and causes thousands of deaths annually in the UK. Moreover PE is the leading cause of inpatient death and the most common cause of death in pregnancy (Roberts and Arya, 2011) . Currently, there are no studies directly indicating diabetes as a direct cause of VTE, differences between studies make the evidence for an association of diabetes with VTE equivocal, but there are studies showing the probable involvement of diabetes in the pathophysiology of these diseases (Bell et al., 2016a). Having that in mind, diabetes tends to have little effect on venous thromboembolism disease (Pastori et al., 2023) . In a meta-analysis including a total population of over 100,000 individuals, a borderline statistically significant increase in the risk of events was observed for DVT/PE in

patients with diabetes compared to those without diabetes. Additionally, due to moderate heterogeneity (I^2 = 59.7%), it was not possible to precisely determine the impact of diabetes on VTE risk (Bell et al., 2016b). Another study found that women with T2DM whose HbA_1c exceeds 7 % may face a slightly elevated risk of unprovoked VTE compared to those with levels between 6.5 % and 7.0 % , also it was noted that men showed no effect of maintaining normal glucose levels on the risk of VTE (R. Charlier et al., 2022). In the retrospective cohort study, it was shown that the study group, patients with diabetes, had a 1.4 times higher risk of VTE compared to the control group. Furthermore, the risk was higher in women than in men, especially in the age group 50–59 years. (Deischinger et al., 2022).

3.4. Stroke

3.4.1. Ischaemic Stroke

Diabetes is one of the most significant risk factors for ischemic stroke, especially in individuals under the age of 65. Epidemiological studies have shown that diabetes alone accounts for 37–42% of all ischemic strokes. Moreover, diabetes markedly increases the incidence of ischemic stroke across all age groups, with the strongest effect observed in younger patients; as a result, individuals with diabetes tend to experience strokes at a younger average age than those without the condition (Kissela et al., 2005) . The mechanisms of diabetes involvement in ischemic stroke are very similar to those in coronary artery disease, they mainly include: endothelial dysfunction, inflammation and impaired plate stability (Maida et al., 2022a). Diabetes is an independent risk factor for poorer return to independence in daily activities. In addition, newly diagnosed diabetics had a more difficult return to independence than patients with a longer history of treatment (Yang et al., 2021).

In addition, there are reports that diabetes worsens the prognosis after stroke in an animal model, specifically mice. Diabetes was induced in them by streptozotocin and then photothrombotic stroke was induced in the somatosensory cortex to assess cortical plasticity and functional recovery after stroke. Studies have shown that diabetes can significantly impair the plasticity of the cerebral cortex after stroke. This phenomenon prevents the remapping of somatosensory function and leads to a reduction in sensorimotor recovery. It turns out that mice with diabetes do not show increased size of lesions. These studies may suggest deficits in plasticity mechanisms, and not, as it might seem, primary damage (Sweetnam et al., 2012).

In another study using a similar animal model, it was also shown that diabetes did not affect the size of the ischemic focus, but intensified the haemorrhagic transformation of the lesion by inducing mitochondrial defects and endothelial cell apoptosis (Mishiro et al., 2014). It has been shown that haemorrhagic transformation of the ischemic focus significantly worsens the prognosis of the patient after stroke. Symptomatic haemorrhagic transformation leads to worse neurological outcomes in the long term, and is also one of the main causes of death in the acute phase of ischemic stroke (Hong et al., 2021).

There is no clear evidence confirming the influence of diabetes on the location of the affected cerebral artery (POP et al., 2021). There are studies indicating that T2DM predisposes primarily to ischemic strokes of the small vessel type (lacunar stroke) and increases the share of posterior circulation strokes, while at the same time reducing the share of cardiogenic and haemorrhagic strokes (Maida et al., 2022b).

3.4.2. Haemorrhagic Stroke

The role of diabetes as a factor increasing the risk of haemorrhagic stroke has not been elucidated yet (Hill, 2014; Lau et al., 2019; Sacco et al., 2024a; Mavridis et al., 2025). Thanks to the conducted meta-analyses, we know that on average 26% of patients with haemorrhagic stroke had diabetes. Studies show, however, that hyperglycaemia occurring during the acute phase of intracerebral haemorrhage was associated with greater hematoma growth and worse clinical outcomes (Lau et al., 2019). Based on the meta-analysis of 102 prospective studies, it was found that diabetes is associated with a statistically significantly increased risk of haemorrhagic stroke (Sacco et al., 2024b). A retrospective cohort study showed that T1DM significantly increased the risk of haemorrhagic stroke in people with T1DM – HR 1.88 (95% CI 1.57–2.26) compared to people without diabetes, whereas T2DM was not associated with a significantly increased risk of haemorrhagic stroke – HR 0.99 (95% CI 0.96–1.02) (Mavridis et al., 2025). Studies focusing on deep brain locations have revealed an association between excessive fluctuations in fasting blood glucose towards hyperglycaemia and hypoglycaemia and an increased risk of intracerebral haemorrhage (Jin et al., 2018). Considering the locations and the association of abnormal fasting glucose levels, it can be hypothesized that diabetes-induced small vessel disease is a potential cause of haemorrhage (Jin et al., 2018; Liu et al., 2018; Mavridis et al., 2025).

3.5. Chronic kidney disease

Diabetic kidney disease (DKD) is the primary cause of the disease and the end-stage cause, because it occurs in 20-50% of patients with T2DM, and also accounts for 50% of all cases. Determining the type of coefficient, in 2-4% of the impact, the result of the estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m² (Hoogeveen, 2022). It is believed that in DKD both microalbuminuria and macroalbuminuria are fundamental, manifest markers of kidney disease. Thanks to the studies carried out, we know that albumin, which indicates the presence of a filtration membrane and the accompanying decrease in eGFR, which occurs as a consequence of the disease, has been excluded. Albuminuria is also used as an independent risk factor for cardiovascular disease, which signals dysfunction of the epithelium. It can be concluded that in the case of T21M, albuminuria may correlate with CKD indicators more strongly than in the case of T2DM, which represents a more specific and warning "diabetic disease" in patients with T1DM (Majeed et al., 2022). Studies showing that the annual incidence of albuminuria is higher in soldiers with T2DM and is about 8% in the known from 2–3% in soldiers with T1DM (Hoogeveen, 2022). An epidemiological study of 15,046 adult participants showed that DKD affects poorer prognosis. As many as 31.1% of patients with T2DM and DKD died within ten years mainly from cardiovascular causes, while without DKD the 10-year cumulative mortality was 11.5%, which was an increase of 3.9 percentage points compared to the reference group without diabetes and DKD (Afkarian et al., 2013).

4. Discussion

This study summarizes the key mechanisms by which diabetes contributes to increased risk of cardiovascular complications. It has been shown that a higher incidence of cardiac arrhythmias is strongly associated with fluctuations in blood glucose levels. From animal and clinical studies, we know that hypoglycaemia activates the autonomic nervous system, first by increasing sympathetic activity and then parasympathetic tone, which can cause bradycardia and other arrhythmias. Acute changes in glucose levels have been shown to increase oxidative stress, promote cardiac remodelling, and facilitate structural changes in the atria and ventricles, which can predispose patients to atrial fibrillation and other arrhythmias. In people

with diabetes, direct damage to the nervous system has also been observed, which can reduce exercise tolerance and contribute to resting tachycardia, which persists even at night.

It has been noted that patients with diabetes are also more susceptible to myocardial ischemia. The researchers found that the resulting atherosclerotic plaques and impaired vasodilation due to epithelial dysfunction are the result of chronic hyperglycaemia, and therefore oxidative stress and the resulting inflammatory process. Due to poor repair mechanisms, often makes diabetic plaques more unstable and more prone to rupture. Cardiac autonomic neuropathy has been shown to mask the typical symptoms of myocardial ischemia, which delays diagnosis and treatment and increases mortality.

There have been studies suggesting that women with poorly controlled T2DM, in particular, have a slightly increased risk of venous thromboembolism. However, current evidence does not clearly support diabetes as a direct cause. Therefore, further research is important to resolve this association. What we do know is that diabetes is a well-known risk factor for ischemic stroke and also worsens outcomes after stroke. Studies have shown that it contributes to endothelial dysfunction and plaque instability in the arteries of the brain, similar to the mechanisms in coronary artery disease. From studies in animal models, we know that diabetes can reduce brain plasticity and regeneration after ischemic injury, which may impede functional recovery. The association of diabetes with haemorrhagic stroke is less clear. Some studies show that T1DM may increase the risk, and that large fluctuations in glucose levels may affect the integrity of small vessels and increase the risk of intracerebral haemorrhage. Finally, diabetic kidney disease remains a major contributor to morbidity and mortality. Albuminuria and declining renal function are common in patients with diabetes and are strong predictors of cardiovascular events and premature death. Effective prevention and treatment of kidney damage are therefore crucial to managing overall cardiovascular risk.

5. Conclusion

In light of the literature review, diabetes significantly worsens the prognosis of patients, exacerbating cardiovascular dysfunction through multiple pathways. It has been proven that the increased risk of myocardial infarction and stroke may be caused by chronic hyperglycaemia and inflammation through endothelial dysfunction and plaque instability. On the other hand, glycemia fluctuations and autonomic nerve damage promote arrhythmia.

Thanks to the conducted studies, we know that diabetes clearly contributes to the progression of chronic kidney disease, although the relationship between diabetes and venous thromboembolism is less documented. In light of the arguments presented, it can be firmly stated that early detection and comprehensive treatment of cardiovascular and renal risk factors remain crucial for improving the survival and quality of life of people with diabetes.

Disclosure

Author's contribution

Conceptualization: [AR], [MR], [UW]
Methodology: [MR], [AR]
Formal analysis: [AR], [UW], [JM]
Investigation: [MR], [AR], [JM]
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