

The impact of type II diabetes on the risk of atrial fibrillation – literature review

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Abstract

Atrial fibrillation (AF) is the most common type of supraventricular arrhythmia, affecting an estimated 40 million people worldwide. Type 2 diabetes mellitus (T2DM) is a common disease among cardiac patients, and hyperglycemia has a significant impact on cardiovascular function. Oxidative stress causes microvascular damage, while the increased production of vascular endothelial growth factor (VEGF) affects the endothelium, leading to its dysfunction. These factors, along with diabetic cardiomyopathy, contribute to hyperglycemia-induced changes in the vessels, and myocardium, thereby predisposing patients to the development of AF. The aim of this review was to discuss and analyse the factors linking AF with T2DM.

Keywords: atrial fibrillation · diabetes mellitus type 2 · hyperglycemia

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Introduction

In patients with atrial fibrillation (AF), we observe irregular stimulation of the atria of the heart, leading to abnormal blood flow from the atria to the ventricles. The factors that predispose a patient to both T2DM and AF overlap and include primarily obesity and hypertension. These factors

lead to pathologies in the vascular system and cardiac muscle. Hyperglycemia increases the activity of many metabolic pathways (e.g. beta oxidation of fatty acids), thereby increasing the production of toxic metabolites, which increase oxidative stress, leading to inflammation and accelerated aging of cells, including heart muscle cells. Hypertension and atherosclerosis, which are often co-occurring conditions in patients

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with T2DM, may contribute to the development of AF. The remodeling of the atrial wall muscles and the increase in their stiffness in the course of diabetic cardiomyopathy contribute to the risk of AF.

Material and methods

Analysis of risk factors for AF in patients with T2DM is presented based on the literature available in PubMed and Google Scholar. The following keywords were used during the literature search: “atrial fibrillation”, “type 2 diabetes mellitus”, “oxidative stress”, “endothelial dysfunction”, “VEGF”, “cardiomyopathy” and “metformin”. The search was limited to scientific articles published in years 2000-2025, written in English or Polish. Inclusion criteria were: original research and review articles addressing the relation between AF and T2DM in adult humans. Articles on type 1 DM, animal-only models and non-peer-reviewed sources were excluded. Due to data heterogeneity, a narrative literature review was conducted, following general systematic review principles without strict adherence to PRISMA guidelines.

Results

A total of 214 abstracts were identified in the initial search. After title and abstract screening, 137 were excluded due to lack of relevance to the topic or failure to meet the inclusion criteria. Full text analysis was conducted for 77 articles, of which 49 were removed because of insufficient data linking T2DM with AF mechanisms, duplication of findings or unclear methodology. Finally, 18 full-text articles were included in the final review. These articles provided detailed information on the role of oxidative stress, inflammation, VEGF signaling, and myocardial remodeling in the development of AF among patients with T2DM.

Discussion

Changes occurring in the atria as a result of chronic exposure to cardiovascular risk factors, including T2DM, can be divided into 3 main types: structural remodeling, functional remodeling, and electrical remodeling [1-4]. Structural remodeling is a process involving the remodeling of the myocardial structure (including the interstitium) and the loss of cardiomyocytes, which manifests itself through increased atrial mass and volume [1]. In patients with AF one can observe an increase in the intercellular space due to the loss of cardiomyocytes and subsequent fibrosis, which reduces the atrial bipolar potential [2]. The decrease in cardiomyocyte

number is compensated by hypertrophy of non-degenerating cells. Fibrosis, accompanied by the accumulation of collagen fibers within the interstitial and perivascular spaces, leads to conduction abnormalities and differences in the efficiency of electrical conduction [2]. Structural remodeling is closely related to electrical remodeling, which creates the so-called AF substrate, i.e. the structural and electrophysiological basis that sustains arrhythmias. The creation of conditions favorable to the stabilization of AF is influenced by a shortened refractory period and a reduced sodium current, which translate into slower conduction [1]. The term autonomic remodeling refers to altered sympathovagal activity and excessive atrial innervation [1]. The imbalance between sympathetic and parasympathetic activity promotes the development of complex reentrant circuits, which are associated with sustained AF. Chronic inflammation, oxidative stress, endothelial dysfunction, increased sympathetic nervous system activity, epicardial fat accumulation, and metabolic disorders within myocytes further enhance the atrial remodeling in patients with T2DM [3]. Obstructive sleep apnea, episodes of myocardial ischemia, hypertension, and increased sinus node cell apoptosis are other factors contributing to the complex pathological process of AF development [3-4]. The most beneficial treatment for patients includes glucose control and treatment of comorbidities [4].

Glucose intolerance and insulin resistance increase the risk of AF in both men and women by 40% and 60%, respectively [5]. Chronic hyperglycemia contributes to glycation of the insulin receptors, which leads to insulin resistance. Poor glycemic control and late diagnosis of DM also have an influence on the potential occurrence of AF. T2DM is characterized by the body's inability to use carbohydrates as an energy source. To meet its energy needs, the body begins to use fatty acids to produce the appropriate amount of adenosine triphosphate (ATP). The consequences of increased fatty acid metabolism are the activation of nuclear peroxisome proliferator-activated receptor-alpha (PPAR- α) and increased β -oxidation, which are not only a source of many toxic metabolites but also of reactive oxygen and nitrogen species that intensify oxidative stress [5]. Furthermore, oxidative stress is a factor that intensifies β -oxidation of fatty acids. These processes trigger each other, leading to further damage to the cardiovascular system. The previously mentioned insulin resistance impairs the ability of vessels to respond to nitric oxide (NO). In addition to the insulin receptor substrate, other proteins are also subject to glycation. As a result of this process, free radicals accumulate as by-products. Abnormalities in the processes occurring inside mitochondria and oxidative stress influence the processes responsible for the adaptation of the heart muscle. Oxidative stress leads to the activation of inflammatory pathways in the cells, which translates into increased C-reactive protein (CRP) levels in patients with

persistent AF. Human mitochondrial DNA is poorly protected against damage associated with hydroxyl radicals, which leads to premature cell aging (including muscle cells) [6].

The aggravating effect of T2DM on patients with AF is supported by the positive effect of hypoglycemic drugs on atrial remodeling [5]. In 2014, Chang et al. published a study that aimed to determine whether metformin, a first-line drug in the treatment of DM, reduces the risk of AF among patients [7]. For this purpose, they analyzed 645710 patients from a subset of the Taiwan National Health Insurance Research Database who were newly diagnosed DM in the years 1999-2010. The patients were divided into a group with metformin as part of their treatment plan (user group) and a non-user group. After 13 years of follow-up it was noticed that the incidence of AF was significantly lower in the group treated with metformin, (hazard ratio of 0.81, 95% confidence interval (CI) 0.76-0.86, $p < 0.001$). The authors concluded that metformin had a protective effect against oxidative stress and myocyte remodeling, thereby reducing the risk of AF among diabetic patients [7]. The beneficial effects of including metformin in the treatment plan likely stem from its influence on adenosine monophosphate (AMP)-activated protein kinase (AMPK) activation and peroxisome proliferator-activated receptor gamma (PPAR γ) modulation, which translates into reduced oxidative stress. By inhibiting transforming growth factor beta (TGF- β) signaling, Metformin limits collagen deposition and reduces atrial stiffness. Calcium homeostasis is particularly important for proper cardiomyocyte function. Metformin increases sarcoplasmic/endoplasmic reticulum Ca $^{2+}$ -ATPase isoform 2a (SERCA2a) expression, which prevents unfavorable Ca $^{2+}$ accumulation in the cytosol and, consequently, the development of early and delayed after depolarizations [8].

Chronic hyperglycemia induces oxidative stress, accompanied by increased concentrations of inflammatory markers, e.g. CRP, fibrinogen and interleukin-6 [9]. Inflammation in the body leads to hypoxia and the release of cytokines, vascular endothelial growth factor (VEGF), factors affecting vascular tone. Oxidative stress induces lipid oxidation, resulting in the formation of OX-LDL, which by acting on macrophages and monocytes, increases the concentration of VEGF in the serum [10]. VEGF-releasing cells include endothelial cells, monocytes/macrophages, platelets, neutrophils, and fibroblasts. In addition to its effects on the cardiovascular system, VEGF also controls hematopoiesis, injury scar formation, and bone formation [11]. Angiogenesis (i.e. the formation of new blood vessels) has a negative impact on the body function, particularly by leading to cardiac hypoxia. VEGF is one of the main pro-angiogenic factors, which additionally participates in the remodeling of muscle tissue at the site of damage.

Zhang et al. indicated a correlation between higher plasma VEGF concentration and hyperglycemia [12]. A platinum EGF-A enzyme-linked immunosorbent assay kit (eBioscience,

Vienna, Austria) was used to check the VEGF concentration in plasma collected from a blood sample. The authors concluded that there is a close interrelation between hyperglycemia, inflammation and VEGF in patients with T2DM, indicating that increased VEGF levels may be the cause of microangiopathy in these patients [12]. The results discussed in this review are consistent with and complement the findings of Zhang et al., who demonstrated that plasma VEGF concentrations were significantly higher in patients with poor glycemic control compared to those with normal glucose levels [12]. The comparison of VEGF levels in patients before and after improvement of glycemic control over a 4-month period confirmed that maintaining stable blood glucose reduces the VEGF concentration. This observation supports the conclusion that hyperglycemia directly stimulates VEGF synthesis, leading to endothelial dysfunction and increased vascular permeability. Pathological endothelial function includes increased secretion of prothrombotic factors into the extracellular matrix, including tissue factor and von Willebrand factor. The hyperglycemia-related endothelial dysfunction affects the function of the organ supplied by dysfunctional vessels. The vascular endothelium is a tissue with versatile effects due to numerous factors modulating the processes occurring in the body. Disturbances in the amount and timing of the secretion of these factors may lead to atherosclerosis and hypertension, which are risk factors for AF.

Diabetic cardiomyopathy is a structural and functional disorder of the left ventricle of the heart. Factors that stimulate cardiac hypertrophy include hyperglycemia and insulin resistance, which is the basis of DM. Diabetic cardiomyopathy is characterized by a pathological structure of the myocardium in the absence of other factors that could lead to it [12]. Glucose transporter type 4 (GLUT4) is responsible for transporting glucose within adipose tissue, liver and muscles. In order to fulfill its role, it must first be incorporated into the cell membrane [13]. In addition to blocking glucose transport within the above-mentioned tissues, disturbances in the pathway responsible for this process, lead to a decrease in the activity of the Ca $^{2+}$ pump in the sarcoplasmic reticulum [13]. The increase in intracellular Ca $^{2+}$, additionally intensified by insulin-stimulated coronary endothelial NO synthase (eNOS) (in the case of T2DM, its activity decreases), leads to myocardial stiffness in people with T2DM. The basis of this phenomenon is, among others, the phosphorylation of titin caused by a reduced concentration of NO [12].

Titin is the largest known human protein, weighing approximately 3 MDa, and occurring in 3 cardiac isoforms (N2A, N2B and N2BA). Phosphorylation of titin leads to an increase in the stiff titin isoform N2B/N2BA (compliant) expression ratio. In addition to the ratio of titin isoforms, the stiffness of the myocardium is also influenced by the phosphorylation of its individual elements carried out by protein kinases.

We distinguish between PKA (protein kinase A)-dependent phosphorylation, CaMKII (calmodulin-dependent protein kinase II delta)-dependent phosphorylation, and PKC (protein kinase C)-dependent phosphorylation. PKA (i.e. cyclic adenosine monophosphate (cAMP)-dependent protein kinase) is involved in the phosphorylation of the N2B titin isoform, which leads to a decrease in myocyte stiffness. Reducing the stiffness of the heart walls stimulates the adrenergic system, which in turn increases heart rate and diastolic filling of the atria [14]. Increased participation of the previously mentioned isoform in the structure of the heart muscle translates into problems with cardiac muscle relaxation and increased stiffness. The role of titin, a type of striated muscle myofilament, is to provide stiffness to cardiac myocytes. Its mutations are responsible for 25% of familial dilated cardiomyopathies and 18% of sporadic cases of non-genetic dilated cardiomyopathy (DCM) [15]. Hyperglycemia contributes to abnormal phosphorylation of titin molecules, which affects titin stiffness. This thesis is confirmed by the positive effect of metformin on the development of cardiac diastolic dysfunction [16].

Studies on a mouse heart model showed a reduction in sarcomere passive stiffness as a result of activation of the phosphorylation of the N2B element [16]. Modifications involving the process of titin phosphorylation in patients diagnosed with diastolic heart dysfunction include changes in the activity of protein kinase A (PKC α) and phosphorylation of individual components of titin (N2B and PEVK).

In the structure of the previously-mentioned protein, we can distinguish the C-terminal anchored in the M band and the N-terminal associated with the Z disk; a single titin molecule stretches from the Z line to the M line. However, the most important part of titin is related to the I band. Titin within the I band has a stretchable region that generates passive tension when the sarcomere is stretched beyond its Slack length [11]. The contraction of myocytes leads to the generation of a recoil force by the compressed titin molecule, thanks to which the myocytes in the relaxation phase can be rebuilt and regain their original diastolic length [17]. DCM is a pathology within the heart muscle that involves the gradual stretching of muscle fibers, which become thinner and weaker. As a consequence, the heart chambers widen. The TTN gene (codes for titin) is one of the sarcomeric genes whose mutations is one of the most common causes of dilated cardiomyopathy.

Analysis of data from a global health research network (mainly from the United States) and concerning 634885 patients diagnosed with cardiomyopathy in the years 2002-2020, revealed the relationship between mortality among patients and cardiomyopathy with co-existing AF [18]. The examined patient group included people diagnosed with dilated, hypertrophic and restrictive cardiomyopathy. The overall

mortality rate in patients with DCM and AF was 7.1%, while in patients with DCM without AF it was 4.9% (odds ratio 1.36, 95% CI 1.27-1.46, $p < 0.0001$). These results were statistically significant and indicate a meaningful difference in mortality between the 2 patient groups. A higher risk of death within 1 year from the diagnosis was observed in patients with AF and DCM compared to those diagnosed with cardiomyopathy without AF. The results of this analysis indicate the frequent occurrence of AF in patients with cardiomyopathy and support a worse prognosis among these patients [18].

Conclusions

The relationship between DM and AF does not appear to result from a single direct mechanism, but rather from the cumulative effect of multiple pathological processes, including structural, electrical and autonomic remodeling. However, people with DM are at a higher risk of developing AF. This is supported by the impact of large fluctuations of glycemia on blood vessels. The resulting inflammation, oxidative stress and endothelial dysfunction lead to both minor and major changes in vascular structure and function. A malfunctioning circulatory system places an additional burden on the heart, which may result in scarring and remodeling. Importantly, AF in patients with T2DM should be regarded less as the consequence of one specific pathway and more as the outcome of numerous overlapping processes. In this context, AF may serve both as a marker of advanced cardiovascular degeneration and as an independent disease entity associated with a worse prognosis. Therefore, reducing the risk of arrhythmic complications depends not only on early diagnosis and treatment of AF itself, but also on comprehensive management of DM. Optimal glycemic control and pharmacotherapy, particularly metformin, may indirectly reduce the incidence of AF by slowing down the progression of adverse cardiovascular remodeling.

Conflicts of interest

None.

Funding

None.

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