REVIEW ARTICLE

ATRIAL FIBRILLATION IN PATIENTS WITH CONCOMITANT DIABETES MELLITUS – WHAT DO WE ALREADY KNOW AND WHAT DO WE NEED TO DISCOVER?

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ABSTRACT

Recently published data indicate the prevalence of atrial fibrillation, the most common cardiac arrhythmia worldwide, in up to 20% of the elderly population. This arrhythmia significantly impacts the quality of life by increasing the risk of stroke, thromboembolism, dementia or heart failure, resulting in a substantial increase in the risk of adverse events and all-cause death. On the other hand, diabetes mellitus is the most predominant metabolic disorder on the globe, which incidence is surging annually, currently affecting over 500 million individuals. Patients with coexisting diabetes have a relevantly elevated risk of atrial fibrillation development. This association have not yet been comprehensively elucidated. Nonetheless, it seems to be a multifactorial, complex relationship comprising mechanisms such as oxidative stress, insulin resistance, hemostasis and fibrinolysis disturbances or endothelium dysfunction, which lead to mechanical and electrical left atrial remodeling. Therefore, this study aims to summarize the evidence regarding the relationship linking diabetes mellitus and atrial fibrillation.

KEY WORDS: atrial fibrillation, diabetes mellitus, epidemiology, anticoagulation

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INTRODUCTION

Atrial fibrillation (AF), the most common cardiac arrhythmia in the general population worldwide, has become a crucial epidemiological and clinical challenge in healthcare worldwide over the past decade. This arrhythmia significantly deteriorates the quality of life by a significant increase in the risk of stroke, thromboembolic events, development and progression of heart failure and dementia, subsequently leading to a substantial increase in the total mortality [1, 2]. Previously published data indicated the occurrence of atrial fibrillation in approximately 1% of the population [3]. However, we observe a rapid rise in the AF prevalence annually and the latest research pointed out the prevalence in over 3% of the general population [4]. In 2010, the number of patients with AF was estimated at 33 million people worldwide, including 8.8 million in the European Union, while by 2060, this number is predicted to double, reaching over 17.9 million just in the European Union [5, 6]. It should also be emphasized that the AF risk surges with age to over 24% in people aged ≥ 85 [6]. Nonetheless, the data seems to be underestimated due to the frequent occurrence of asymptomatic form of the arrythmia – silent atrial fibrillation (SAF). Hence, it is necessary to popularize the methods of non-invasive, long-term monitoring in people at high risk of AF development.

Diabetes mellitus (DM), the most prevalent non-infectious epidemic of the 21st century, is nowadays the most widespread metabolic disease. In 2017, over 450 million patients suffered from DM, with the outlook of an increase to 693 million by 2045 [7]. Similarly, DM, due to micro-and macro-vascular repercussions, contributes to the elevated cardiovascular risk and leads to several disorders such as cardiomyopathy or thromboembolic events, consequently increasing total mortality [8].

THE AIM

The study aims to summarize the current state of knowledge regarding the relationship between DM and AF.

METHODS

The analysis of literature about the relationship between DM and AF.

REVIEW

Concomitant diabetes and atrial fibrillation – what do we already know?

EPIDEMIOLOGY

Considering the prevalence of both disorders mentioned above, it is not surprising that the diseases often coexist. The authors of a meta-analysis based on 7 randomized prospective studies and over 1.6 million participants showed a 40% higher AF risk in DM patients than the population without coexisting DM [9]. Similarly, studies such as Framingham Heart Study, Atherosclerosis Risk in Communities (ARIC), or Valsartan

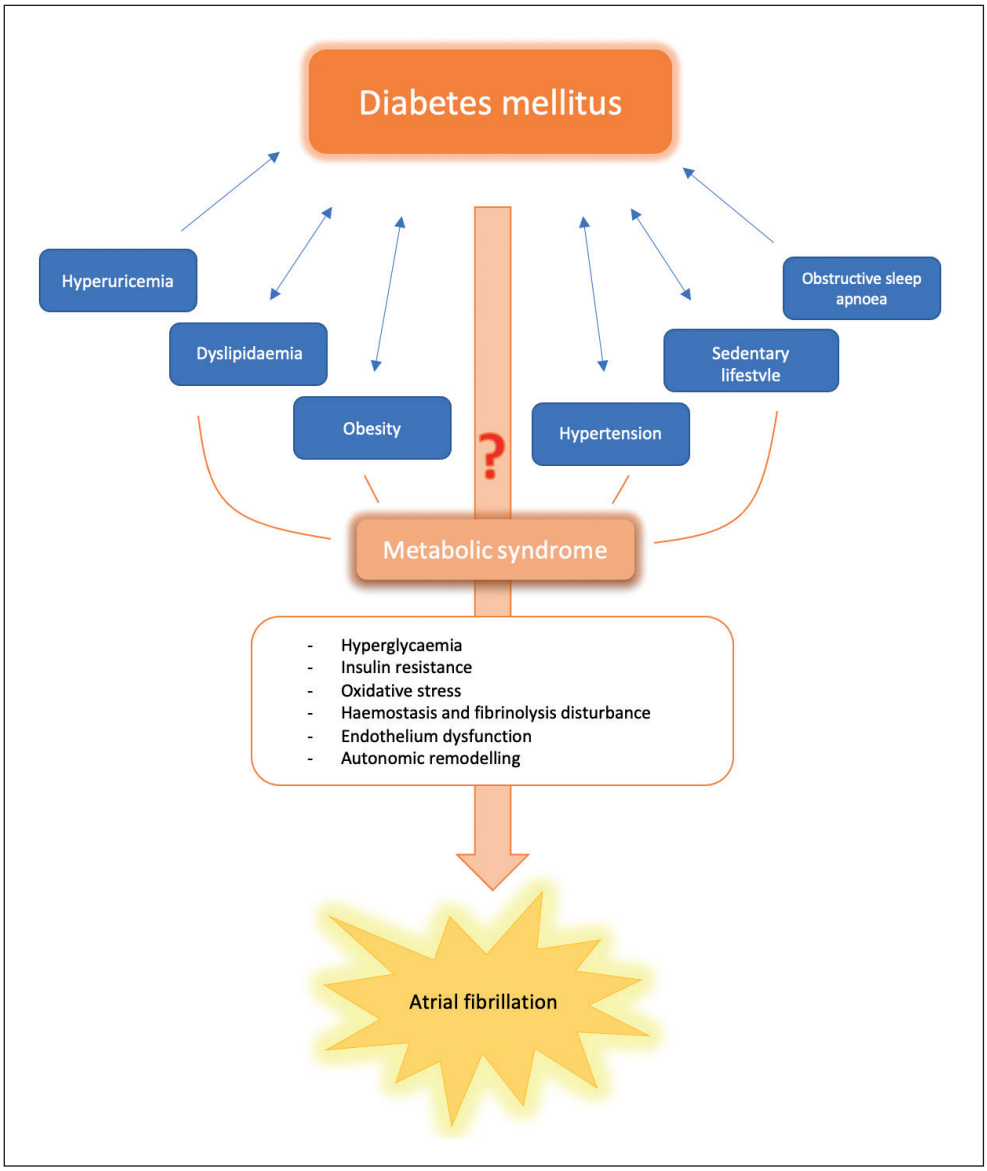

Fig. 1. Multifactorial relationship between diabetes mellitus and atrial fibrillation.

Antihypertensive Long-term Use Evaluation (VALUE) indicated a two- or three-fold higher incidence of this arrhythmia in people with concomitant DM [10-12]. A recently published analysis of the epidemiological study NOMED-AF, using a long-term non-invasive ECG monitoring vest worn by participants for approximately 30 days, demonstrated a substantially higher AF prevalence in DM burdened participants compared to the general Polish population aged ≥ 65 years (25%; 95% CI 22.5-27.8%, *vs* 17%; 95% CI 15.4-18.5%, p <0.001) [13]. SAF affects likewise as much as 9% (95% CI: 7.9-11.4%) of people in the DM group, compared with 7% (95% CI: 5.6-7.5%, p <0.001) in people without diabetes. The arrhythmia occurrence in 25% of the elderly population with concomitant DM underlines the necessity of active screening for AF, especially in the groups of risk.

ETIOLOGY

The relationship between DM and AF has not yet been fully elucidated, however, it seems to be complex and multifactorial. DM has already been proven an independent risk factor for cardiovascular adverse events, leading to a relevant increase in all-cause mortality in this group of patients [7, 14].

The coexistence of DM and AF results in a 68% higher risk of development and progression of heart failure, while the risk of a thromboembolic event, mainly stroke, increases even up to 79%. Hence, the total mortality rises by 61% compared to diabetes only [14, 15].

Despite considerable evidence linking DM and AF in everyday clinical practice, the association between these two diseases remains unclear. Data on the essential factor determining the increased incidence of AF in people with concomitant DM are inconclusive and often contradictory. A Korean study conducted on a population of over 6 million subjects confirmed the hypothesis of increased AF risk along with the duration of DM [16]. In those with impaired glycemic tolerance, the annual risk was 1.04 (95% CI: 1.02-1.05), while in the case of early DM, less than 5 years after establishing the diagnosis, it was already aHR 1.06 (95% CI:

1.04-1.08), and in late diabetes aHR 1.09 (95% CI: 1.07-1.11, p <0.001) [16]. Similar results were presented by Dublin et al. based on a population of 1,410 Americans with AF de novo. The paper described a 3% (95% CI: 1-6%) higher risk for each additional year from diagnosis of diabetes. [17]. On the other hand, the study containing the data of almost 263,000 patients of Spanish nationality did not show a significant effect of the duration of glucose metabolic disorders on the risk of arrhythmia [18].

Another hypothesis is the influence of the metabolic control, expressed as the concentration haemoglobin HbA1c concentration, on the AF prevalence. Studies conducted on the American and Japanese populations confirm this assumption, pointing to a directly proportional increase in the risk of AF development along with the increase in HbA1c value. In people with worse metabolic control, with HbA1c> 9%, the probability of this arrhythmia almost doubles (OR 1.96; 95% CI 1.22-3.14) [19, 20]. On the other hand, Alves-Cabratosa and Schoen et al. described that HbA1c> 7% turned out to be a statistically insignificant AF [18, 21]. Similar results were observed in diabetic patients after cardiac surgery, where the HbA1c concentration had no relevant effect on the AF incidence [22]. Moreover, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study showed that intensive hypoglycemic treatment with the therapeutic target of HbA1c <6% did not reduce the incidence of atrial fibrillation compared to the control group of patients with HbA1c 7-7.9% [23].

Considering the outcomes of the studies as mentioned above and the overall clinical picture of a patient with concomitant DM and AF, it seems that not the DM *per se*, but the whole cluster of comorbidities plays the primary role in promoting arrhythmia in this group. The homeostasis distortion in diabetic subjects might create a suitable environment for developing other disorders such as dyslipidemia, hypertension, obesity or sleep apnea syndrome. Furthermore, in patients with both coexisting diseases, we can observe insufficient control of cardiovascular risk factors. Hence, they often fail to achieve their individual therapeutic goals [24]. The assumption may be confirmed by the fact that hypertension and dyslipidemia occur in more than a half, and obesity in almost 75% of diabetic patients [25-27]. Consequently, such a cluster of comorbidities leads to an increased risk of AF prevalence [28, 29]. The multifactorial relationship between DM and AF is presented in the figure 1.

The mechanisms underlying these relationships appear to be multifactorial and not fully discovered. The etiopathogenesis of more frequent AF prevalence in DM may be affected by metabolic disorders such as insulin resistance, abnormal glucose tolerance, increased synthesis of inflammatory mediators, oxidative stress, hemostasis and fibrinolysis, or endothelial dysfunction, which then lead to atrial remodelling, promoting arrhythmia development. [30-34]. Animal models clearly show structural changes in the left atrium, mainly fibrosis and dilatation of this heart cavity, leading to ionic remodelling, and thus the formation of areas of slow electric potential conduction and the initiation and continuation of the impulse circulation in the reentry loop [32, 35]. Moreover, in the diabetic model, atrial cycle length and activation time were prolonged, and the electrical stimulus induced more repeated atrial responses [32]. In diabetic rats, an increased expression of cathepsin a, a protease involved in the process of atrial tissue fibrosis was also found. Inhibition of this protein resulted in improved left atrial systolic function, a reduction in fibrosis and a lower number of areas of slow conduction were observed in animals [36].

DM also affects the sympathetic and parasympathetic nervous systems. Dimitropoulos et al. proposed a three-stage model of autonomic remodelling comprising parasympathetic denervation followed by sympathetic overload and, consequently, sympathetic denervation [37]. The results seem to be supported by other studies showing an increase in the arrhythmia incidence during sympathetic nervous system stimulation [38]. Nonetheless, further research is needed to thoroughly understand the relationship between diabetic neuropathy of the heart and AF.

DISCUSSION

IMPLICATIONS IN EVERYDAY CLINICAL PRACTICE

Due to the significantly higher risk of cardiovascular events such as stroke, thromboembolic episodes or heart failure, which subsequently increases the risk of death among patients with concomitant DM and AF, a holistic approach seems to be crucial in the everyday care of this particular population of patients [11, 39]. This comprehensive management should begin with active screening for atrial fibrillation in DM individuals, especially those aged ≥65. We should emphasize that this arrhythmia very often remains asymptomatic, which additionally impede the challenge. A clinically useful tool may be the SAF risk stratification scale, which facilitates the selection of patients with the highest probability of SAF development and qualifies them for the next stage of diagnosis establishment, which should contain a long-term, non-invasive heart rate monitoring [40]. This appears to be the only way we can detect short-term, paroxysmal arrhythmia episodes. Another instrument facilitating a holistic approach to AF patients care is the Atrial Fibrillation Better Care - ABC Pathway [37]. It contributes to the improvement of integrated management of a patient suffering from atrial fibrillation. A - is an acronym for avoiding stroke, i.e., reducing the risk of stroke, mainly the oral anticoagulation; B - better symptom management, and therefore better control of symptoms related to arrhythmia; C, on the other hand, is cardiovascular and other comorbidities optimization - optimal diagnosis and treatment of concomitant diseases [37]. The application of this simple and pragmatic treatment path is associated with a significant reduction of both the costs of therapy and, most importantly, the risk of cardiovascular adverse events and total mortality. Its effectiveness has been proven in numerous studies [38-40].

CONCLUSIONS

Atrial fibrillation occurs in every fourth diabetic patient. Most of these patients remain asymptomatic, which additionally hinder the diagnosis. Since the vast majority of DM patients benefit from anticoagulant treatment, this group deserves special attention. The annual growing population of subjects with coexisting DM and AF poses more and more challenges, becoming one of the utmost essential priorities of health care worldwide. Despite the numerous published studies that have unveiled some of the complex, multi-level connections between glucose metabolism disorders and AF, further research is needed to determine whether diabetes *per se* or the natural burden of comorbidities is the primary determinant of the increased risk of AF in this group of patients.

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The Authors declare no conflict of interest.

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