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Diabetes Mellitus and Its Role in the Development and Progression of Atrial Fibrillation: A Review and Recommendations

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ABSTRACT

Millions worldwide suffer from a chronic metabolic disorder called type 2 diabetes mellitus. Atrial fibrillation is the most common persistent arrhythmic condition that increases the risk of heart and brain complications. Recent studies depict that diabetic patients have a higher chance of developing AF, but the exact link between these two conditions is unclear. We discuss the current understanding of how AF and Diabetes are related based on the following aspects: electrical, electromechanical, structural, and oxidative stress changes, connexin remodeling, and glycemic fluctuations. Additionally, we explore other potential mechanisms, including inflammation, autonomic dysfunction, obesity, microvascular disease, metabolic factors, hyperglycemia, and renal dysfunction. We also summarize the clinical studies investigating the outcomes and management of patients with AF and Diabetes. We review the available treatment options, such as anti-diabetic and anti-arrhythmic drugs, and non-pharmacological interventions, such as cardioversion, catheter ablation, and direct current cardioversion. This review provides valuable insights into the multifaceted relationship between Diabetes mellitus and its role in the development and progression of atrial fibrillation, offering recommendations for understanding and managing this complex interplay.

INTRODUCTION

Over recent decades, the coexistence of type 2 diabetes mellitus (DM) and atrial fibrillation (AF) has garnered increasing attention in the field of medicine [1]. These two conditions, each of profound significance, converge to create complex clinical scenarios and challenges for patients and healthcare providers [1]. To thoroughly grasp the intricacies inherent in this connection, it is crucial to explore different facets of DM and AF. [1]. Individuals who have Diabetes face an elevated likelihood of developing AF; however, the exact connection between Diabetes and AF remains uncertain [2]. This article delves into the mechanisms linking AF and Diabetes, including electrical, electromechanical, structural, and oxidative stress factors, connexin remodeling, and glycemic fluctuations [1]. We also review clinical studies involving patients with both conditions, exploring treatment with anti-diabetic and anti-arrhythmic drugs and non-pharmacological approaches such as cardio version catheter ablation and direct current cardio version.

Type 2 diabetes mellitus, marked by persistent high blood sugar levels from insulin resistance and inadequate insulin secretion over time, ranks among the most widespread metabolic disorders globally [2]. In contrast, atrial fibrillation, the most common sustained arrhythmia in clinical practice, disrupts the heart's normal rhythm, leading to irregular and often rapid heartbeat patterns [1].The roots of DM and AF can be traced through the annals of medical history [1]. DM was recognized in ancient civilizations, with early references to "sweet urine" in Indian Ayurvedic texts [2]. On the other hand, AF was first systematically described by the 9th-century Persian physician Rhazes, although the term "atrial fibrillation" emerged in the early 20th century [2]. DM and AF have recently witnessed a surge in prevalence [1]. DM now affects millions globally, with a substantial portion comprising type 2 cases [1]. Similarly, AF is a growing concern, with increasing numbers of individuals affected, especially in aging populations.DM encompasses various types, with type 2 being the most common, while AF can be classified into several subtypes, including paroxysmal, persistent, and permanent forms [3]. These subtypes offer insights into the course and management of AF in DM patients [3]. Differential gender and ethnic predispositions exist in both conditions [4].According to the International Diabetes Federation, 91% of the 415 million patients with DM have type 2 DM [1]. The incidence of type 2 DM has been consistently on the rise. With menopausal women being more affected than men [3]. The estimated mortality rate associated with DM is notably higher in women than men, with vascular complications being more prevalent in women and cancers in men [4]. For example, DM has shown a higher

prevalence in certain ethnic groups, while AF incidence increases with age, impacting a larger proportion of the elderly population [4]. Beyond hyperglycemia, risk factors for DM include obesity, physical inactivity, genetics, and a family history of the disease [3]. On the other hand, AF is associated with a wide array of factors, including hypertension, valvular heart disease, and structural heart abnormalities [3]. The pathophysiology of DM involves insulin resistance and pancreatic beta-cell dysfunction, leading to elevated blood glucose levels [5]. AF, in contrast, stems from complex electrical and structural changes in the heart, including atrial remodeling and inflammation, creating a substrate for arrhythmia [2]. DM and AF exhibit genetic components, with specific gene variants contributing to susceptibility [2].Type 1 DM stems from the lymphocyte-mediated destruction of pancreatic beta islet cells, involving human leukocyte antigen association, particularly with a strong linkage to DQA and DQB genes. The pace at which beta-cell deterioration occurs differs among individuals. of different age groups, limiting the body's ability to maintain physiological glucose levels [5]. Research in this area has shed light on potential targets for personalized treatment strategies [2].Patients with DM may present with symptoms like polyuria, polydipsia, and weight loss, while AF often manifests as palpitations, fatigue, and shortness of breath [6]. The coexistence of these conditions can complicate their clinical courses, raising the risk of heart failure, stroke, and cardiovascular mortality [2,3].DM is diagnosed through criteria such as fasting blood glucose levels, HbA1c, and oral glucose tolerance tests [7], while AF is typically confirmed through electrocardiograms (ECGs) and Holter monitoring [1,3].The diagnostic criteria for DM include a random plasma glucose level ≥200 mg/dL, fasting plasma glucose level ≥126 mg/dL with a fasting time of 8-12 h, and HbA1c ≥6.5% [2]. Managing patients with DM involves a multidisciplinary approach tailored to their age, sex, and lifestyle. Medications such as metformin, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, acarbose, glucagon-like peptide 1 (GLP-1) analogs, dipeptidyl peptidase-4 (DPP-4) inhibitors, and thiazolidinediones (TZDs) are used to manage type 2 DM. At the same time, insulin therapy effectively controls type 1 DM [8]. Additionally, a well-balanced diet, exercise, strong compliance with medication regimens, regular clinic visits, and active avoidance of potential triggers improve the long-term prognosis of DM [9]. Patients with DM are prone to developing cardiovascular and cerebrovascular complications, predisposing them to long-term sequelae. Examples include sudden myocardial infarction and stroke [4]. The coexistence of DM and atrial fibrillation (AF) carries a poor prognosis and increased mortality [1]. Glycemic fluctuations, oxidative stressors, and inflammation tend to trigger structural, electrical, electromechanical, and autonomic changes in the heart, constituting the

pathophysiology of DM-associated AF [1]. DM-associated AF is a causal factor for thromboembolic complications, with a 70% relative risk of aggravating cerebrovascular ramifications, such as stroke and transient ischemic attacks [9].Pharmaceutical therapeutic agents, including TZDs, omega-3 polyunsaturated fatty acids, vitamins, antioxidants, statins, and DPP-4 inhibitors, have been shown to decrease inflammation and adiposity, enhance antioxidant defense mechanisms, reduce fatty acid accumulation, mitigate reactive oxygen species (ROS) damage, improve beta-cell function, enhance cardiac remodeling, and reduce overall cardiovascular risk. These interventions improve prognosis, reduce hospitalizations due to AF, and enhance overall management, positively impacting mortality and morbidity [9]. In conclusion, the intricate interplay between type 2 DM and AF necessitates a multifaceted understanding of these conditions. This review endeavors to comprehensively explore the clinical relationship between DM and AF, shedding light on their implications for prognosis and long-term mortality. By examining their definitions, histories, epidemiological characteristics, clinical features, and management approaches, we aim to contribute to the ongoing discourse surrounding these complex health challenges.

DISCUSSION

PATHOGENESIS OF DIABETES AND ATRIAL FIBRILLATION

The pathogenesis of atrial fibrillation (AF) in the context of diabetes mellitus (DM) continues to be a subject of intense research, shedding light on novel mechanisms and clinical implications. Recent studies have expanded our understanding of the intricate interplay between these two conditions, revealing additional layers of complexity.

Oxidative Stress and Inflammation:

Contemporary investigations emphasize the pivotal roles of oxidative stress and inflammation in mediating AF, particularly when the heart is metabolically stressed by DM [8-10]. Reactive oxygen species (ROS), influenced by mitochondrial metabolism and electron transport, have been identified as critical contributors to heightened oxidative stress within the heart [11]. New findings highlight the involvement of additional ROS sources, such as nicotinamide adenine dinucleotide phosphate oxidase, and the down regulation of ROS-degrading enzymes [11]. These factors collectively exacerbate oxidative stress, further underscoring its role in modifying ion channel activity and ultimately increasing AF

susceptibility [11]. ROS-induced shortening of the atrial action potential duration has been linked to AF initiation and maintenance [11].

NF-κB Pathway:

The signaling pathway known as nuclear factor kappa B (NF-κB)... has gained prominence in AF pathogenesis, particularly in the context of DM. Recent research has elucidated its impact on the cardiac sodium channel SCN5A, located in the promoter region of this critical channel [10-11]. The binding of NF-κB to this site has decreased SCN5A mRNA abundance and reduced protein expression [11]. Consequently, this reduction in SCN5A expression results in diminished sodium current amplitude and slowed conductance, creating a substrate conducive to re-entry and the perpetuation of AF [12,13].

RhoA Pathway:

Another emerging pathway with implications for AF, especially in DM, is the Ras homolog gene family member A (RhoA) pathway [12]. This pathway has been linked to atrial fibrosis, which plays a significant role in AF development [12]. Recent studies have uncovered connections between RhoA pathway activation and DM, shedding light on potential therapeutic targets [12].

Atrial Electromechanical Function:

Investigations into atrial electromechanical function have uncovered critical insights into DM's influence. Recent clinical studies have highlighted impaired atrial electromechanical function in DM patients, including increased atrial fibrosis and intertribal conduction delays [12,13]. These findings have important implications, suggesting that prolonged intra- and inter-atrial electromechanical delays and early diastolic function alterations in ventricles could serve as early diagnostic indicators for DM patients, potentially predicting AF recurrence or development [12,13].

Autonomic Nervous System Imbalance:

DM's impact on the autonomic nervous system continues to be a focus of research [14]. Recent work has delved into the denervation of the parasympathetic system and the upregulation of the sympathetic nervous system in patients with DM, elucidating the imbalances between these two systems that are crucial for AF maintenance [14]. Impaired

vagal responses and reduced parasympathetic tone observed in DM patients have prompted further exploration into the underlying mechanisms [14].

Atrial Structural Remodeling:

The structural aspects of atrial remodeling are gaining attention, particularly concerning fibrosis and connexin 43 protein changes [12,13]. Recent clinical observations have underscored associations between abnormal glucose metabolism, atrial electrical remodeling, and fibrosis [12,13]. The diabetes group exhibited decreased atrial voltages and increased AF recurrence rates, shedding light on the intricate interplay between DM and atrial structural remodeling in AF pathogenesis [12,13].

Advanced Glycation End-Products (AGEs) and RAGEs:

The significant elevation of advanced glycation end-products (AGEs) resulting from prolonged hyperglycemia and oxidative stress is an area of ongoing research [15]. Recent studies have elucidated the covalent crosslinking and modification of protein structures, mainly collagen, by AGEs [15]. This process has been linked to atrial interstitial fibrosis, a pivotal pathological change in DM-induced AF [15]. Additionally, increased AGE and receptor for AGEs (RAGE) expressions in diabetic myocardium have been identified, providing a potential pathway for atrial structural remodeling [15].

In conclusion, recent advancements in our understanding of the pathogenesis of AF in the context of DM have unveiled a complex web of mechanisms involving oxidative stress, inflammation, signaling pathways, and structural changes. These insights contribute to our knowledge of the disease process and open doors to novel therapeutic avenues for managing AF in DM patients. The pathophysiological association between AF and DM is summarized in Figure 1.

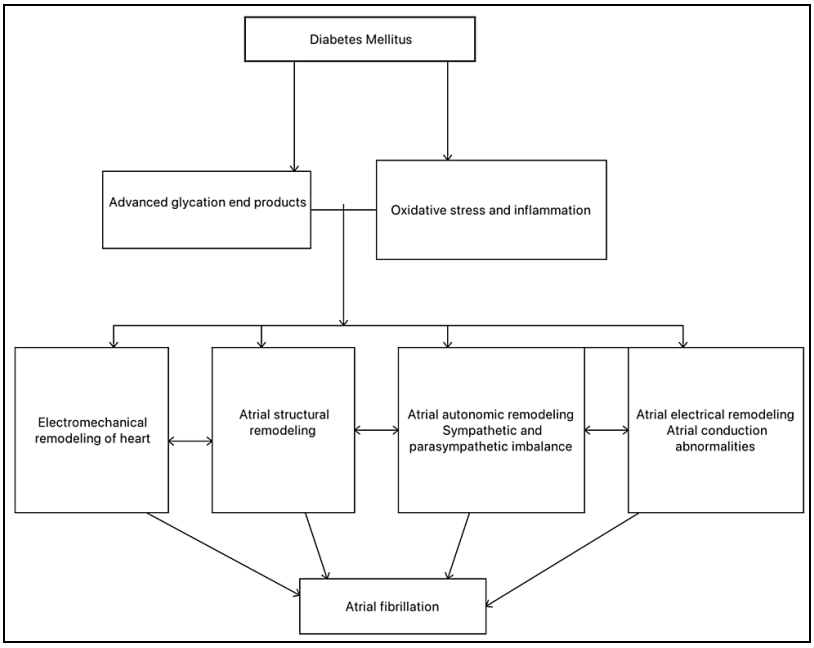

Figure 1: Pathogenesis of Diabetes and atrial fibrillation

CLINICAL CORRELATION OF DM AND AF:

Diabetes Mellitus (DM) presents a significant clinical correlation with Atrial Fibrillation (AF), elevating the risk by 1.4- to 1.6-fold compared to non-diabetic individuals. While AF shares common risk factors with DM, such as hypertension and advanced age, DM introduces unique factors into this clinical equation [16,17]. Meta-analyses conducted by leading researchers in the field consistently underscore DM as an independent risk factor for AF, substantiating this association with robust evidence [16]. These comprehensive studies reveal that DM not only contributes to the risk of AF but does so significantly, underlining its role as a potent catalyst for atrial fibrillation [16]. One compelling meta-analysis by Huxley and colleagues emphasized the formidable link between DM and AF [17]. Their research, encompassing a wide array of data, illuminated a 1.4- to 1.6-fold increase in the likelihood of developing AF for individuals with DM, further strengthening the clinical correlation [17].

Similarly, the work of Watanabe et al. reaffirmed these findings, demonstrating the consistency and reproducibility of the DM-AF relationship across various studies [18]. Their meta-analysis further underscored the robustness of this association, bolstering the evidence for DM's substantial contribution to AF risk [18].

Furthermore, epidemiological studies have consistently documented DM's autonomy as a risk factor for AF [16]. Beyond commonalities with other risk factors, DM introduces unique

pathophysiological mechanisms that heighten the propensity for arrhythmias [16]. These mechanisms include systemic inflammation, autonomic dysfunction, obesity, heart failure, and poor glycemic control [16]. Notably, the duration of DM, or its "long-standing" nature, emerges as a critical factor. Research has confirmed that extended exposure to... metabolic perturbations associated with DM independently elevates the risk of AF [19]. I understand the need for vigilant monitoring and managing DM, particularly in individuals with extended disease duration [19]. Diagnosing AF in DM patients can be challenging since AF's symptoms are not always overt. While irregular pulse patterns might raise suspicion, the definitive diagnosis necessitates electrocardiograms (ECGs) [16]. Alarmingly, nearly one-third of AF cases occur without noticeable symptoms, underscoring the importance of regular cardiac screening for individuals with DM [16]. The clinical correlation between DM and AF is well-substantiated by extensive research, including meta-analyses, epidemiological studies, and clinical investigations. Diabetes mellitus constitutes a separate risk factor for atrial fibrillation, adding unique pathophysiological dimensions to this arrhythmia's development. Vigilant monitoring, early detection, and optimal management of DM are imperative in mitigating the heightened risk of AF in diabetic patients. Some crucial studies depicting clinical interlink between AF and DM are summarized in Table 1 with their characteristic findings.

Table 1: clinical correlation between Diabetes and atrial fibrillation

Author	Type of Study	Patients	AF DIAGNOSIS	DM DIAGNOSIS	MEAN AGE
Ostergren et al. [20]	Retrospective study	793 patients with or without hypertension and type 2 diabetes	ECG	Self-report OGTT	61± 31.5 in men 60 ± 12.5 in women
Dublin et al. [21]	Population-based case study	One thousand four hundred ten patients with new-onset AF and 2203 without AF.	GH electronic data	NA	74 (66-80)
Nichols et al. [19,22]	Retrospective study	7,372 patients with or without Diabetes	NA	NA	58.4 ± 11.5
Schoen et al. [23]	Cox proportional-hazards model	34,720 females with or without Diabetes	ECG	Hb1AC	54.1 (48.9-62.1)

THERAPEUTIC IMPLICATIONS

DM's widespread prevalence necessitates effective therapeutic strategies. Lifestyle adjustments are crucial in lowering blood glucose levels [1], and various medications are commonly used for DM management [1]. Here's a review of some critical drugs and their effects on AF:

Metformin:

This biguanide has been used for 60 years, lowering hepatic glucose production and enhancing peripheral glucose utilization. Metformin's use has been associated with a decreased risk of AF, with studies showing protective effects [24]. Metformin may prevent AF by reducing oxidative stress, inflammation, fibrosis, and hypertrophy in the atria [24]. Metformin is generally well-tolerated but may cause gastrointestinal side effects, lactic acidosis, or vitamin B12 deficiency in some patients [24].

Thiazolidinediones (TZDs):

These insulin-sensitizing agents, such as rosiglitazone, pioglitazone, and troglitazone, act as ligands to the peroxisome proliferator-activated receptor gamma (PPAR-γ), showing potential anti-inflammatory effects and preventing AF development in patients with DM [25]. TZDs may inhibit AF by modulating the expression of genes involved in atrial remodeling, calcium handling, and electrical conduction [25]. However, TZDs may also have adverse effects, such as weight gain, edema, heart failure, or increased fracture risk [25].

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors:

These drugs increase urinary excretion of glucose by inhibiting the SGLT-2 channel. They have shown promise in reducing AF risk, with evidence suggesting mitochondrial function improvement and attenuation of atrial remodeling [26]. SGLT-2 inhibitors may also have cardioprotective and renoprotective effects in patients with DM and cardiovascular or kidney disease [26]. SGLT-2 inhibitors may cause genital infections, urinary tract infections, dehydration, or diabetic ketoacidosis in some patients [26].

Glucagon-like peptide-1 (GLP-1) receptor agonists:

This new class of anti-diabetic drugs includes exenatide, liraglutide, lixisenatide, albiglutide, and dulaglutide. GLP-1 receptor agonists have been linked to lowering cardiovascular risks

[26,27]. GLP-1 receptor agonists may reduce AF by improving glycemic control, reducing weight and blood pressure, and decreasing inflammation and oxidative stress [27]. GLP-1 receptor agonists may cause nausea, vomiting, diarrhea, pancreatitis, or thyroid tumors in some patients [26,27].

Dipeptidyl peptidase-4 (DPP-4) inhibitors:

These oral anti-diabetic drugs, including sitagliptin, saxagliptin, linagliptin, and alogliptin, enhance the effectiveness of endogenous incretin hormones [27]. They have been studied in animal models, indicating potential benefits for AF prevention [27]. DPP-4 inhibitors may suppress AF by improving glucose metabolism, reducing inflammation and fibrosis, and preserving atrial function [27]. DPP-4 inhibitors are generally safe and well-tolerated but may cause hypoglycemia, infections, or allergic reactions in some patients [27]. Non-pharmacological approaches include direct current cardioversion (DCCV) and catheter ablation. DCCV may have reduced success in restoring sinus rhythm in patients with DM due to increased atrial fibrosis and remodeling [28]. Catheter ablation may be more effective than DCCV or anti-arrhythmic drugs in maintaining sinus rhythm and Enhancing the well-being of individuals with diabetes mellitus. And AF [29]. However, catheter ablation may also have complications such as bleeding, infection, stroke, or cardiac tamponade [29].

In summary, the therapeutic implications of DM and AF are complex and multifaceted. Various pharmacological and non-pharmacological interventions are available for managing both conditions. However, the optimal treatment strategy should be individualized and tailored to each patient's characteristics and preferences.

Certainly, here is a revised acknowledgment section for your atrial fibrillation (AFib) and diabetes mellitus (DM) article, considering the absence of patient involvement, third-party funding, or conflicts of interest:

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CONCLUSION

The incidence of combined DM and AF is on a steady rise. Epidemiological evidence indicates an association between DM and AF, but the exact causal relationship remains uncertain. It's unclear whether DM directly causes AF or if DM merely serves as an indicator of an elevated cardiovascular disease burden, leading to increased risk. Nevertheless, DM is a significant risk factor for the development and persistence of AF. The pathophysiological mechanisms contributing to AF occurrence in DM patients encompass autonomic, electrical, electromechanical, structural remodeling, oxidative stress, connexin remodeling, and glycemic fluctuations. While no evidence definitively establishes DM as a direct cause of AF, further studies are needed to understand this relationship better. Researchers and clinicians should focus on identifying the optimal therapeutic strategies for AF in patients with DM and determining the most suitable timing for interventions. Upstream therapies involving anti-diabetic drugs like thiazides, SGLT-2 inhibitors, DPP-4 inhibitors, and GLP-1 receptor agonists have shown potential in reducing the risk of AF. Continued research is essential to refine our understanding and improve the management of AF in individuals with DM.

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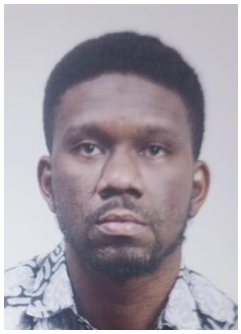	8-Dr. Osatohanmwen Ekomwereren, Senior House Officer, Trauma and Orthopedics, Royal Shrewsbury Hospital, The Shrewsbury and Telford NHS Trust, United Kingdom

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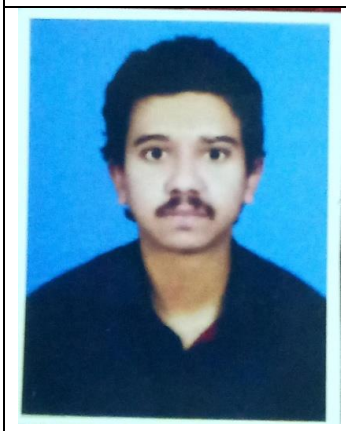	10-Saptarshi Mukherjee MAKAUT UNIVERSITY, WEST BENGAL, NADIA, KOLKATA
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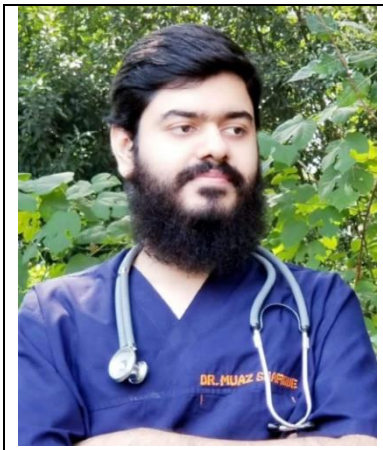	12-Dr. Muaz Shafique Ur Rehman, MBBS Allama Iqbal Medical College Lahore/Jinnah Hospital Lahore

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