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The Relationship between the Incidence of Atrial Fibrillation and Patients with Type 2 Diabetes Mellitus: A Systematic Review

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Abstract

Objectives: To investigate the prevalence and mechanisms of atrial fibrillation (AF) among type 2 diabetes (T2D) patients. ***Methods:*** We conducted a thorough search of PubMed, SCOPUS, Web of Science, Google Scholar, and Science Direct to find pertinent literature. Rayyan QRCI was utilized during the entire process. ***Results:*** We included twelve studies with a total of 587,822 T2D patients and 299,957 (51%) were females. The prevalence of AF among T2D patients ranged from 0.2% to 41.63% with a total prevalence of 44936 (7.6%). The reported risk factors for developing AF among T2D patients were impaired glucose tolerance (IGT), men, obesity, elderly patients, those with lower socioeconomic backgrounds, those who currently smoked, people with reduced renal function, long-term BP fluctuation, and microvascular illness. ***Conclusion:*** Although the exact relationship between T2D and AF is still unclear, there is a significant correlation. Certain glycemic control studies indicate that therapeutic HbA1c levels in conjunction with well-controlled T2D do not significantly reduce the risk of new-onset AF in T2D patients. Further investigation is needed to fully comprehend the connection between T2D and AF. In the interim, healthcare professionals can treat people with T2D, AF, or possibly both illnesses at the same time according to accepted guidelines.

Keywords: Atrial fibrillation; Type2 diabetes; Cardiovascular; Systematic review.

INTRODUCTION

Cardiovascular events and cardiovascular death have been linked to increases in T2D. Although elevated levels of coagulation and atherosclerosis are responsible for the majority of cardiovascular events in patients with T2D, embolization linked to AF accounts for a sizable portion of these events. In T2D, there is a higher incidence and prevalence of AF, the most frequent heart arrhythmia [1].

Diabetes, obesity, hypertension, heart failure, and, on rare occasions, hyperthyroidism is linked to AF [2]. Research indicates that the presence of diabetes increases the incidence of AF by 35% to 60%, even after making the necessary statistical adjustments [3-5].

Although myocardial steatosis, which is commonly seen in conjunction with MS, and the accumulation of intracellular triglycerides lead to elevated levels of free fatty acids and the formation of toxic lipids like ceramide, which in turn lead to accelerated myocardial apoptosis and fibrosis, are the main causes of AF [6]. Atrial dilatation, which results in both structural and electrical remodeling of the left atrium, is brought on by the combination of AF and retrograde pressure from left ventricular diastolic and/or systolic failure. Although myocardial steatosis, which is commonly seen in conjunction with MS, and the accumulation of intracellular triglycerides lead to elevated levels of free fatty acids and the formation of toxic lipids like ceramide, which in turn lead to accelerated myocardial apoptosis and fibrosis, are the main causes of AF [6, 7]. Atrial dilatation, which results in both structural and electrical remodeling of the left atrium, is brought on by the combination of AF and retrograde pressure from left ventricular diastolic and/or systolic failure [7].

The purpose of this systematic review technique is to investigate the prevalence and mechanisms of AF among T2D patients.

METHODOLOGY

Study Design and Duration

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards were followed in the conduct of this systematic review [8]. March 2024 marked the start of this systematic review.

Search strategy

PubMed, SCOPUS, Web of Science, Google Scholar, and Science Direct were the four main databases that were thoroughly searched in order to locate pertinent literature. We looked through exclusively English databases, taking into consideration each one's particular needs. We transformed the following keywords to PubMed Mesh terms in order to locate the pertinent studies; "Diabetes mellitus," "Type 2 diabetes," "T2D," and "Atrial Fibrillation." "OR," "AND," and "NOT," three Boolean operators, matched the necessary keywords. Full-text English publications, freely accessible articles, and human trials were among the search results.

Selection Criteria

We considered the following criteria for inclusion in this review:

- Studies that summarized to investigate the prevalence and mechanisms of AF among T2D patients.
- Studies conducted within the last 5 years (2019-2024).
- Only human subjects.
- English language.
- Free accessible articles.

Data Extraction

Two verifications of the search method's output were conducted using Rayyan (QCRI) [9]. By applying inclusion/exclusion criteria to the aggregated search results, the researchers evaluated the relevance of the titles and abstracts. Every paper that met the inclusion requirements was thoroughly scrutinized by the reviewers. The authors talked about methods for resolving disputes. A pre-made data extraction form was used to upload the approved study. The authors extracted data about the study titles, authors, study year, country, participants, gender, AF prevalence, smoking status, diabetes duration, and main outcomes. A separate sheet was created for the risk of bias assessment.

Strategy for Data Synthesis

By assembling summary tables with information from relevant studies, a qualitative assessment of the research's findings and components was given. After gathering the data for the systematic review, the most efficient way to use the information from the included study articles was chosen.

Risk of Bias Assessment

Using the ROBINS-I risk of bias assessment technique for non-randomized trials of treatments, the quality of the included studies was evaluated [10]. The seven examined themes included confounding, study participant selection, intervention classification, deviation from planned interventions, incomplete data, outcome evaluation, and choice of reported result.

RESULTS

Search Results

The systematic search produced 930 study articles in total, of which 412 duplicates were eliminated. After 518 studies had their titles and abstracts screened, 481 were not included. After 37 reports were requested to be retrieved, 3 articles were found. After screening 34 studies for full-text assessment, 10 were rejected due to incorrect study results, 8 were rejected due to incorrect population type, and 2 articles were editor's letters. This systematic review included twelve eligible study articles. A synopsis of the procedure for choosing studies is provided in **Figure 1.**

Characteristics of the Included Studies

Table 1 presents the sociodemographic characteristics of the included study articles. Our results included twelve studies with a total of 587,822 T2D patients and 299,957 (51%) were females. Five studies were prospective in nature [14-16, 18,19], four were cross-sectional studies [13, 17, 20, 21], two were retrospective in nature [12, 22], and one was a case-control study [11]. Four studies were conducted in the USA [11, 15, 16, 18], two in Japan [20, 21], two in Sweden [19, 22], one in New Zealand [12], one in Thailand [13], one in China [14], and one in Romania [17], **Table 2** presents the clinical characteristics. The prevalence of AF among T2D patients ranged from 0.2% [13] to 41.63% [17] with a total prevalence of 44936 (7.6%). The reported risk factors for developing AF among T2D patients were impaired glucose tolerance (IGT) [12], men [12, 17, 18, 21], obesity [12, 17, 18], elderly patients [12, 18, 21], those with lower socioeconomic backgrounds [12], those who currently smoked [12], people with reduced renal function [12, 14, 20, 22], long-term BP fluctuation [15], and microvascular illness [16].

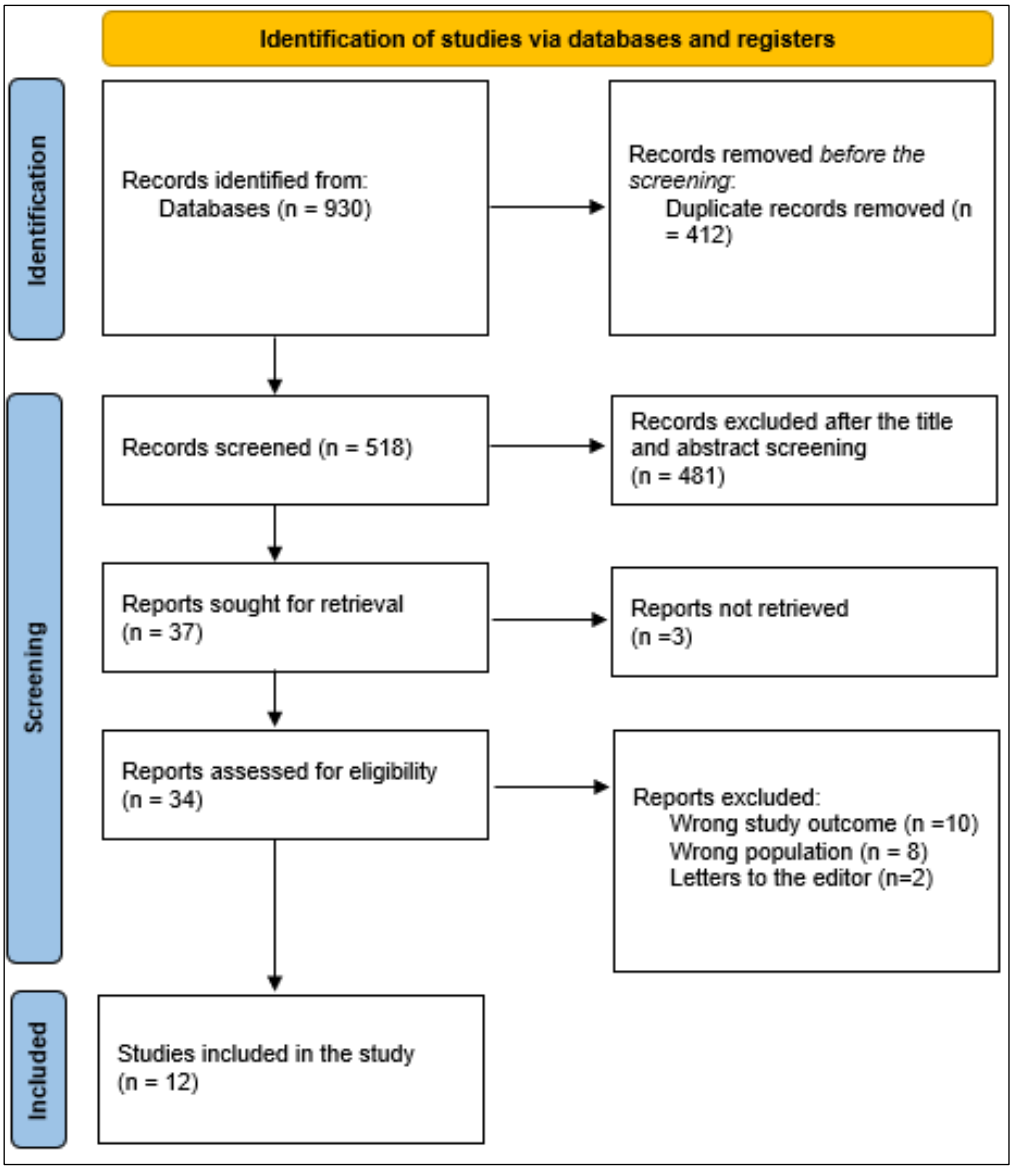

Figure 1: Study selection is summed up in a PRISMA flowchart

Table 1: Sociodemographic characteristics of the included participants

Study	Study design	Country	Participants	Mean age	Gender (Females)
Iqbal *et al.*, 2022 [11]	Case-control	USA	4584	56.7	2746 (59.9%)
Yu *et al.*, 2023 [12]	Retrospective cohort	New Zealand	650	56.7 ± 12.2	348 (53.5%)
Kaewput *et al.*, 2021 [13]	Cross-sectional	Thailand	27,281	60.7 ± 10.5	18,821 (68.8%)
Geng *et al.*, 2022 [14]	Prospective cohort	China	16,551	62.2 ± 5.8	6622 (40%)
Kaze *et al.*, 2023 [15]	Prospective cohort	USA	8399	62.6 ± 6.5	3259 (38.8%)
Kaze *et al.*, 2022 [16]	Prospective cohort	USA	7603	62.5 ± 6.6	2889 (38%)
Gaman *et al.*, 2019 [17]	Cross-sectional	Romania	221	68.7 ± 10.6	116 (52.49%)
Yang *et al.*, 2020 [18]	Prospective cohort	USA	9240	66.7 ± 6.1	3546 (38.4%)
Johansson *et al.*, 2023 [19]	Prospective cohort	Sweden	88,889	49 ± 8.9	72,334 (51.8%)
Honda *et al.*, 2022 [20]	Cross-sectional	Japan	899	69 ± 12.2	381 (42.4%)
Otake *et al.*, 2021 [21]	Cross-sectional	Japan	1650	60 ± 13	588 (35.6%)
Seyed Ahmadi *et al.*, 2020 [22]	Retrospective cohort	Sweden	421,855	64.7 ± 12.5	188,307 (44.7%)

*NM=Not-mentioned

Table 2: Clinical characteristics and outcomes of the included studies

Study	Diabetes duration (years)	Smoking status (%)	AF prevalence (%)	Main outcomes	ROBIN-I
Iqbal *et al.*, 2022 [11]	NM	597 (13%)	238 (5.2%)	Metformin did not appear to have any protective effects on AF once confounders such as age, sex, race, BMI, and co-morbidities were taken into account.	High
Yu *et al.*, 2023 [12]	NM	297(45.7%)	44 (6.7%)	Individuals with T2D who have impaired glucose tolerance (IGT) are more likely to experience AF, and this risk is present over the long run as well as the short term. Men, elderly patients, those with lower socioeconomic backgrounds, those who currently smoked, people with higher metabolic measurements, and people with reduced renal function all showed a stronger correlation.	Moderate
Kaewput *et al.*, 2021 [13]	7.1 ± 4.8	1084 (4%)	48 (0.2%)	Compared to T2D patients overall, the prevalence of significant visual impairment in those with incident AF was almost three times higher. Furthermore, there was an independent link between significant visual impairment and T2D patients who experienced incident AF.	High
Geng et al., 2022 [14]	7.3 ± 8.2	1762 (10.6%)	1394 (9.2%)	Individuals with T2D who experienced AF had markedly higher chances of death, CKD, and subsequent severe cardiovascular events.	Moderate
Kaze *et al.*, 2023 [15]	10	1160 (13.8%)	155 (1.8%)	More long-term BP fluctuation was found to be independently linked to an increased risk of incident AF in a large sample of T2D patients, above and beyond mean BP.	Moderate
Kaze *et al.*, 2022 [16]	9	1057 (13.9%)	137 (1.8%)	Independent of other AF risk factors, they found that the presence and burden of microvascular illness, as measured in several vascular beds, was linked with a higher risk of incident AF in a large cohort of people with T2D.	Moderate
Gaman *et al.*, 2019 [17]	NM	NM	92 (41.63%)	A significant proportion of the study group had obesity, metabolic syndrome, and hypertension—three cardiometabolic risk factors for AF. Compared to women, diabetic men were more likely to experience AF. In patients with diabetes, AF was highly correlated with metabolic syndrome and hypertension.	Moderate
Yang *et al.*, 2020 [18]	10.7 ± 7.7	105 (1.3%)	165 (1.8%)	Individuals who developed AF were more likely to be Caucasian, male, and obese. They also had lower diastolic blood pressure and low low-density lipoprotein cholesterol. Age, gender, race, BMI, heart failure, diastolic blood pressure, triglycerides, hemoglobin A1c, length of diabetes mellitus, serum creatinine, and hypertension medication were all included as significant indicators in the risk prediction model.	Moderate
Johansson *et al.*, 2023 [19]	NM	25,836 (18.5%)	4948 (5.6%)	With the exception of the group with impaired glucose tolerance, there was a significant correlation between glycemic status and the development of AF; the group with known diabetes had the greatest correlation (p-value <0.001).	Moderate

Study	Diabetes duration (years)	Smoking status (%)	AF prevalence (%)	Main outcomes	ROBIN-I
Honda *et al.*, 2022 [20]	12.5 ± 9.7	NM	53 (5.9%)	Among Japanese patients with T2D, AF is more closely associated with impaired kidney function than with the prevalence of proteinuria or albuminuria. Patients with impaired renal function who have T2D may be the target of AF prevention treatment due to their greater AF prevalence.	Moderate
Otake *et al.*, 2021 [21]	4	718 (43.5%)	72 (4.4%)	The age- and sex-adjusted risk ratio for AF was 3.47 (95% confidence interval: 2.77–4.37) when compared to the general Japanese population. As people aged, the prevalence of both nonvalvular and combined nonvalvular/valvular AF rose. Additional pertinent variables linked to both AF and nonvalvular AF were male gender, the existence of hypertension, and a lowered platelet count.	Moderate
Seyed Ahmadi *et al.*, 2020 [22]	NM	NM	37,590 (8.9%)	AF is still at risk due to T2D, which raises risk by about 35% overall. With a threefold extra risk at CKD-5, those with advanced renal problems had significantly larger excess risks. Since glucose regulation is necessary for the development of renal problems, it may have an effect over an extended period of time even though its direct effect on the development of AF is probably somewhat small.	Low

DISCUSSION

This comprehensive review stated that the prevalence of AF among T2D patients ranged from 0.2% [13] to 41.63% [17] with a total prevalence of 44936 (7.6%). A 2017 meta-analysis found that higher serum glycated hemoglobin levels (HbA1c) were linked to incident AF in prospective cohort studies [23]. In 2011 a meta-analysis by **Huxley *et al.*** reported that the risk of getting AF in individuals with T2D was found to be 34% greater than in the non-diabetic population. According to this study, there is a 10-fold increase in the incidence of new-onset AF related to T2D [24]. A recent study from Eastern Norway found a strong positive connection ($r = 0.408$, $p = 0.005$) between the length of AF and HbA1c levels, suggesting that impaired glucose metabolism contributes to an increased burden of AF [20]. In methods intended to lessen the burden of AF and its associated problems, HbA1c levels may be a helpful marker because diabetes raises the risk of thromboembolism in AF and further encourages arrhythmia. Saliba et al.'s recent research supporting this idea demonstrated that glycated hemoglobin is directly linked to stroke risk and that using HbA1c increased prediction accuracy for stroke events in diabetic individuals with AF [21].

It is reasonable to conclude that metabolic syndrome (MS) plays a substantial role in the development of AF in T2D patients based on epidemiological evidence. The disease known as MS causes left atrial fibrosis and structural remodeling along with left atrial dilatation. It is also linked to hyperglycemia, specifically variations in glucose levels, endothelial dysfunction, hypertension, and myocardial steatosis [27].

Moreover, profibrotic growth factors, like transforming growth factor (TGF)-β, which stimulates profibrotic pathways, are expressed more frequently in T2D patients [28]. Furthermore, by upregulating connective tissue growth factors, the elevated synthesis of AGEs and AGE receptors resulting from T2D also leads to atrial fibrosis [28]. Atrial conduction can be slowed down by fibrosis, which also provides the foundation for re-entry [30]. Interestingly, there is significant fibroblast activity and increased collagen synthesis in diabetic hearts [31]. We should also note that structural remodeling may be indicated by the levels of biomarkers for cardiac fibrosis, such as galectin-3 and ST2 [32].

Furthermore, through the TGF-β signaling pathway, the renin-angiotensin-aldosterone system has also been linked to the promotion of fibrosis [33]. Cardiac fibrosis is known to be induced by angiotensin II [34]. In addition to the atria, diabetic patients may also develop myocardial fibrosis in their ventricular myocardium, which can cause the left ventricle to stiffen and dilate abnormally, a condition linked to left atrial enlargement [34].

Additionally, atrial interstitial fibrosis and related conduction problems may be influenced by obesity [34]. T2D and lipomatous metaplasia of the heart are linked to obesity [34]. The findings included an increased susceptibility to both inducible and spontaneous AF, bi-atrial conduction anomalies, and left atrial enlargement in an animal model fed a high-calorie diet [36].

We also found that the reported risk factors for developing AF among T2D patients were IGT [12], men [12, 17, 18, 21], obesity [12, 17, 18], elderly patients [12, 18, 21], those with lower socioeconomic backgrounds [12], those who currently smoked [12], people with reduced renal function [12, 14, 20, 22], long-term BP fluctuation [15], and microvascular illness [16].

Unrelated to AF, poor glycemic management, as evidenced by elevated HbA1c levels, is a risk factor [37]. To explain this relationship, a number of underlying pathophysiological mechanisms have been postulated. First off, due to its lengthy half-life, HbA1c has been proposed as a valid marker for cardiovascular events risk assessment in the absence of diabetes mellitus as well as for the diagnosis of the disease [38]. Elevated HbA1c levels have been linked to low-grade systemic inflammation, the advancement of atherosclerotic disease, and a chronic dysfunction of glycolipid metabolism [39].

Obesity raises the risk of AF by being linked to a pro-inflammatory state, autonomic abnormalities, and atrial enlargement. Even after controlling for a number of factors, a number of sizable epidemiological studies have found a link between obesity and AF [40-42]. However, given that multiple risk factors are typically present in a single patient, some research has questioned whether the modifications can fully account for a wide range of variables. **Wanahita *et al.*** discovered a 49% increase in risk with a BMI above 30 kg/m2 in a meta-analysis of 16 studies [43].

CONCLUSION

Although the exact relationship between T2D and AF is still unclear, there is a significant correlation. Certain glycemic control studies indicate that therapeutic HbA1c levels in conjunction with well-controlled T2D do not significantly reduce the risk of new-onset AF in T2D patients. Further investigation is needed to fully comprehend the connection between T2D and AF. In the interim, healthcare professionals can treat people with T2D, AF, or possibly both illnesses at the same time according to accepted guidelines.

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