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ASSOCIATION BETWEEN DIABETES MELLITUS AND ATRIAL FIBRILLATION A CASE-CONTROL STUDY

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Abstract

Background

Studies have found that both type 1 and type 2 diabetes likely raise your risk of developing Atrial Fibrillation, though the link seems to be greater if you have diabetes mellitus. The prevalence of atrial fibrillation (AF) is increasing worldwide and among factors that aggravate the risk is diabetes mellitus (DM). So, if there is an association between diabetes mellitus and atrial fibrillation, diabetes is a modifiable risk factor for atrial fibrillation. Because of this, we are trying to find if there is an association between diabetes mellitus and atrial fibrillation.The aim of this study was to assess the relationship between Diabetes Mellitus and Atrial Fibrillation.

Methods and Materials: This is a retrospective case-control study. The study consisted of 141 patients suffering from atrial fibrillation with ECG changes in a group of cases and 141 in a group of controls who did not have ECG changes for Atrial Fibrillation. The participants for this study were consecutively elected when identified with AF, and for each subject with AF, the next subjects in sinus rhythm of the same gender were recruited as control subjects.

Results: The study group consisted of 141 patients, ages 19-99 years. The age category 41-60 years comprises most of the patients (70patients, 49.6%). From the 141patients with atrial fibrillation, 41 patients (29%) had Diabetes Mellitus, but in control group only 25 patients had DM, this resulted with OR=1.9.

Conclusion: In conclusion, based on our study undiagnosed DM and among older subjects with AF should pro-actively be assessed if the duration of AF is ≥ 5 years. Further studies are needed to clarify how? Based on pathophysiology of DM and A-fibrillation long-standing DM may in some way induce permanent AF, and glucose lowering strategies reduces the AF burden.

Keywords: Diabetes Mellitus, Atrial Fibrillation, ECG

1. Introduction

Atrial fibrillation is an irregular and often very rapid heart rhythm that affects approximately three percent of the adults. An irregular heart rhythm is called an arrhythmia. Atrial fibrillation can lead to blood clots in the heart. The condition also increases the risk of stroke, heart failure, and other heart-related complications [3,5]. Previous studies have found that both diabetes mellitus (DM) and Atrial Fibrillation (AF) are increasing in epidemic proportions, and are associated with increased cardiovascular and cerebrovascular mortality [3,4;5].

During atrial fibrillation, the heart's upper chambers — called the atria — beat chaotically and irregularly. They beat out of sync with the lower heart chambers, called the ventricles. For many people, Atrial fibrillation may have no symptoms. But Atrial fibrillation may cause a fast, pounding heartbeat, shortness of breath or light-headedness [3,4,5].

Episodes of atrial fibrillation may come and go, or they may be persistent. Atrial fibrillation itself usually isn't life-threatening. But it's a serious medical condition that needs proper treatment to prevent stroke [3].

Male sex, obesity, obstructive sleep apnea, alcohol consumption, and endurance sports increase the risk of developing lone atrial fibrillation. Family history of atrial fibrillation increases the risk strongly and there are several recognized mutations that are causative of lone atrial fibrillation. Common triggers for the origin of atrial fibrillation are the pulmonary veins. The atrial substrate provides the reentry circuits for perpetuating the arrhythmia. The autonomic nervous system is a key modulator and allows the continuation of atrial fibrillation [3,4,5].

2. Literature Review:

A case-control study which was performed in 2009 by GREGORY A. NICHOLS, PHD, et all, shows that Atrial fibrillation prevalence was

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significantly greater among patients with diabetes. Diabetic patients without atrial fibrillation at baseline developed atrial fibrillation at an age- and sex-adjusted rate After full adjustment for other risk factors, diabetes was associated with increased risk of atrial fibrillation among women (odds ratio 1.26,95% CI), but diabetes was not a statistically significant factor among men (1.09 [0.96–1.24])[21].

A case-control study which was performed in 2010 by Sascha Dublin MD, PhD, et all shows that Among people with atrial fibrillation, 252/1410 had pharmacologically treated diabetes compared to 311/2203 of controls. The adjusted OR for atrial fibrillation was 1.40 (95% CI 1.15-1.71) for people with treated diabetes compared to those without diabetes. Among those with treated diabetes, the risk of developing atrial fibrillation was higher for each additional year of diabetes duration (95% CI 1-6%)[9].

A case-control study was conducted in 2005 by Mohammad-Reza Movaheda, et all at the Division of Cardiology, University of California evaluated 293,124 patients with DM and 552,624 control patients hospitalized between the years 1990 and 2000. The mean ages for case and control patients were 65.8T11.3 years and 64.8T12.6 years. There were no significant differences between cases and controls with regard to gender (male 97.8% in DM and 97.4% in the control group) or race (white 65.3% in DM and 68.3% in the control group)[22].

In 2011, Huxley et al. reported the results of a systematic review and meta-analysis examining the association between DM and AF (Huxley et al., 2011). They identified seven prospective cohort studies and four case-control studies that included 108,703 individuals with AF and 1,686,097 control subjects. Overall, DM was associated with a 39% increased risk of AF compared to controls (RR 1.39, 95% CI 1.10–1.75). [23].

A Danish Nation cohort study evaluated the risk of AF in individuals with DM compared to the background Danish population (Pallisgaard et al., 2016). After adjustment for multiple covariates, DM was associated with a relative 19% increased risk of incident AF. Interestingly, the incidence rate ratio was highest in the youngest age group 18–39 years (2.34, 95% CI 1.52–3.60) compared to older patients (1.20, 95% CI 1.18–1.23 age group 65–74)[24].

Objective: Diabetes has long been recognized as a risk factor for atrial fibrillation, but its independent contribution to atrial fibrillation has not been fully evaluated. We sought to find association between DM and atrial fibrillation in age- and sex-matched patients with and without diabetes.

2. Methods and materials

2.1Study Design

This is a retrospective and observational study designed in the format of a case-control study.

2.2 Research Question

Is diabetes mellitus a risk factor for atrial fibrillation?

2.3 Study Population

Our study population includes all patients who were hospitalized in the internal medicine department of Ali Abad Teaching Hospital with the diagnosis of Atrial Fibrillation and for everyone examined FBS, RBS or HbA1c.

2.4 Sampling method

As this is a secondary analysis we include all patients who were diagnosed as Atrial fibrillation based on ECG criteria.

2.5 Sample Size

This study comprises 141 patients in case and 141 in control according to the case-control study statistical evaluation formula.

$N=(r+1/r)\{alfa^2(z_b+z_{a)}{}^2/difference^2)\}$

2.6 Study Sitting

Internal Medicine Department of Ali Abad Teaching Hospital.

2.7 Inclusion Criteria

In case group all patients aged >16yr with evidence of atrial fibrillation in ECG and were admitted in department of internal medicine and in control group, patients with no evidence for atrial fibrillation in ECG who were admitted in department of Internal Medicine for any reason.

2.8 Exclusion Criteria

For the case group, patients aged< 16 years and patients with arrhythmias other than AF.

For the control group, patients aged< 16 years and patients with AF.

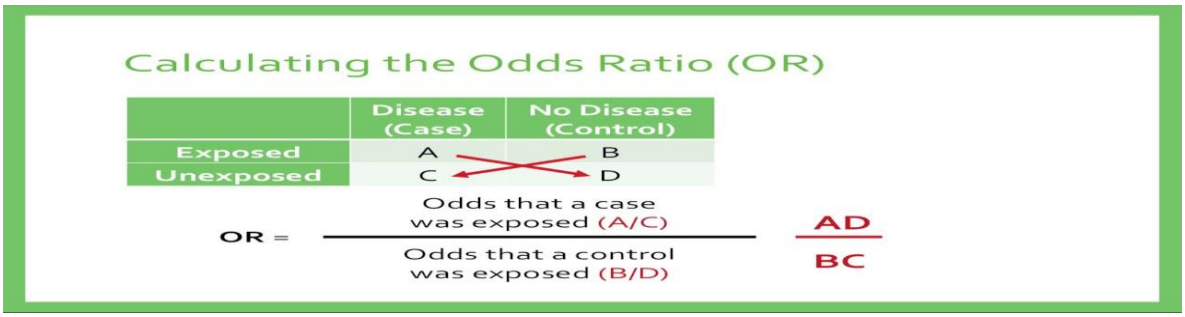
2.9 Data Collection

Medical files, ECG traces, and glycemia reports of patients were reviewed and necessary data were collected according to the study purposes. First, we took an official allowance from the general coordinator of Ali Abad Teaching Hospital who referred us to the archive of the Hospital. Then after, we reviewed the files of the internal medicine department and found 141 patients met our inclusion criteria meaning that these were the patients who had AF and every one of them was examined for glycaemia based on routine glycaemia checking in a hospital lab. Every individual file was reviewed in consecutive steps. In the first step, we reviewed the ECG traces of every patient. In the second step, we carefully reviewed the glycemia report of the individual patient. Finally, we matched the control group with the case group according to age and sex. Also, we extracted all other necessary information. All collected data were written in data collection sheets.

2.10 Statistical Analysis

All data were analyzed by using Microsoft Excel and SPSS 25 software. When applicable, ORs and 95% CIs were calculated using 2 by 2 tables and for finding percentage and age category we used Ms. Excel.

We compared covariates between the non-AF and AF groups using appropriate statistical tests, such as the *t*-test or Mann-Whitney *U* test.



3. .

4. Results

Patient population

The study group consisted of 141 patients, ages 19-99 years. As seen in Table 1-4 the age category 41-60 years comprises most of the patients (70 patients, 49.6%) and the age category 81-99 years has the least patients (3 patients, 2.1%) and males were 52% followed by female 48%.

Table 4.1 shows the age category of patients

Number	Age category	Number of patients	Percentage		Gender
1	19-40	15	10.6%	male	52%
2	41-60	70	49.6%		
3	61-80	53	37.5%	female	48%
4	81-99	3	2.1%		

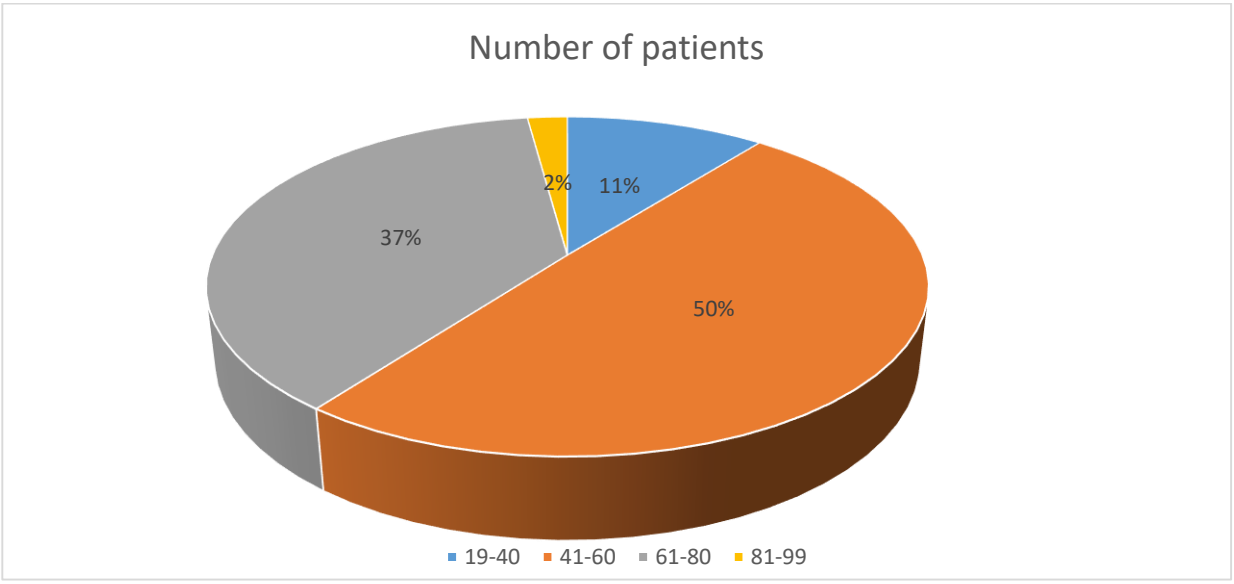


Figure 4.1 shows the age category of patients.

OR= A*D/B*C=41*116/25*100=1.9O

We identified 141 cases of atrial fibrillation during the study period, 41 patients (29%) had diabetes mellitus. 141 controls were selected from GW enrollment lists, stratified by age, sex, calendar year, but in control group only 25 patients had DM, this resulted with OR=1.9.

Cases were slightly older than controls and more likely to have valvular heart disease, coronary artery disease, COPD, cardiomyopathy, hypertension, thyrotoxicosis, or chronic congestive heart failure. Among controls, people with treated diabetes were younger and more often male compared to those without diabetes. Controls with treated diabetes were also more likely to have hypercholesterolemia, coronary artery disease, COPD, hypertension, and congestive heart failure.

Treated diabetes was present in 29% of cases and 17.7% of controls (OR 1.90) with 95% CI adjusted for age, sex, and calendar year. Duration of pharmacologic treatment for diabetes, which we examined as a surrogate for diabetes duration, was available for 91% of people with treated diabetes. The median duration was 8.2 years and was higher for cases than controls

(9.6 versus 7.1 years). At least one measure of blood sugar was available for 99% of people with treated diabetes.

5. Discussion

We identified 141 cases of atrial fibrillation during the study period. 41 patients (29%) had diabetes mellitus and twenty-five patients (25) were in the control group (OR=1.9). Based on our study there is a strong association between DM and A-fibrillation. The overall summary estimate obtained by this study may however be an overestimate of the real association between DM and AF due to the presence of confounding. A case-control study which was performed in 2015 by GREGORY A. NICHOLS, PHD, et all, shows that Atrial fibrillation prevalence was significantly greater among patients with diabetes with OR=1.26 in women and 1.09 in men. The level of adjustment for known and putative risk factors that are associated with both DM and AF, such as elevated BMI and prior cardiac disease, varied across the studies and hence, it was not possible to fully take into account their possible impact on the association. One method by which to ascertain the likely effect of adjustment for such risk factors on the relationship between DM and AF is to compare the crude and multiple-adjusted estimates of the association from the same study population. Three studies did report separate estimates of effect that in the first instance were adjusted only for age and sex and then additionally for other risk factors. In all instances, the impact of adjustment for multiple confounders was to either render the crude estimate non-significant or to have attenuated the estimate by approximately 20%. Furthermore, the summary estimate from those studies that had adjusted for multiple risk factors was lower than that obtained from studies that had adjusted only by age (OR 1.24 versus OR 1.70; p = 0.053). Therefore, the true risk between DM and subsequent risk of AF may be closer to 25% rather than 40% as indicated by the overall summary estimate. Assuming this to be true, then DM would explain approximately 2.5% of the burden of AF [14].

A case-control study which was performed in 2010 by Sascha Dublin MD, PhD, et all shows that Among people with atrial fibrillation, treated diabetes compared to controls, The adjusted OR for atrial fibrillation was 1.40 (95% CI 1.15-1.71) for people with treated diabetes compared to those without diabetes. Among those with treated diabetes, the risk of developing atrial fibrillation was higher for each additional year of diabetes duration (95% CI)[9].

Several possible pathways by which elevated glucose levels and DM may exert a pro-arrhythmic effect have been suggested. Aside from a small number of case-report studies [20], there is no evidence to indicate that type-1 diabetes is associated with an increase in the risk of AF, suggesting that it is not the chronic hyperglycemia associated with DM but rather insulin resistance that might be the mechanism responsible for the observed increased risk of AF among those with DM. Insulin resistance is also considered to be a mechanism by which hypertension and obesity are associated with an increased risk of AF [21]. Ostgren and colleagues attempted to examine the potential pathways mediating the association between DM, hypertension, and AF in a Swedish community-based case-control study among 915 patients with DM and hypertension and 824 control subjects. In that study, individuals with both risk factors had a three times higher risk of prevalent AF compared with normotensive, non-diabetic controls. However, after adjustment for the Homeostasis Model Assessment Index, the association was significantly attenuated and no longer was significant suggesting that insulin resistance the underlying mechanism governing the link between DM, hypertension, and AF: OR 3.3

4.1 Limitations

Several limitations need to be considered when interpreting the findings of this study. First, because of the retrospective study design, we cannot confirm a causal relationship between concurrent AF and diabetes-related complications. Although propensity score (PS) matching was used to reduce confounding factors and falsification analysis was performed to check for significant confounding factors between the study groups, residual bias cannot be entirely ruled out. Second, undetected complications may have existed among the study population before the follow-up started. A sensitivity analysis was performed to address this issue. Third, the accuracy of the operational definitions of diabetes and diabetes-related complications may be a concern. Although a previous study has validated the definitions of microvascular complications and some studies used similar purposes for diabetic retinopathy, diabetic nephropathy, and diabetic foot, the accuracy of outcome definitions may vary across different populations. Regarding diabetic nephropathy, other causes, such as hypertension and glomerular nephropathy, cannot be excluded. Fourth, AF may have been undetected among patients in the non-AF group because of its paroxysmal nature. Some individuals in the non-AF group may have developed new-onset AF during the follow-up period. Fifth, even though we performed PS matching, the differences in the covariates between the study groups may have been confounders. Sixth, adjusting diabetes durations may not have fully balanced the severity and control of diabetes between the study groups. Finally, the Ali Abad Teaching Hospital database used in the study lacked laboratory values, including HbA1c levels and AF burden, which prevented the evaluation of the dose-response relationship between AF burden and the risks of study outcomes.

5. Conclusion

Based on our study there is a strong association between DM and A-fibrillation. There were forty-one patients with DM in the case group and twenty-five patients in the control group (OR=1.9). Both DM and AF are increasing in epidemic proportions, and are associated with increased cardiovascular and cerebrovascular mortality. The relationship between DM and AF is complex and is mediated by structural, electrical, electro-mechanical, and autonomic changes of the atria, triggered by oxidative stress, inflammation, and glycemic fluctuations. Future studies should further elucidate the mechanism of DM-related AF, and evaluate the best treatment strategy for patients with DM and AF. Significant questions remain regarding 1) the role of diabetes medications for AF prevention: 2) the optimal stroke prevention strategy: and 3) the prevention of AF recurrence after control of DM.

Ethical Consideration

As this is a retrospective and secondary analysis, and anonymous so there is no harm or intervention imposed on the patients. Ethically the current

study is approved by the ethical committee of Kabul University of Medical Sciences.

Conflict of interest: The authors declare no conflict of interest regarding the current study.

Authors' contributions: Samiullah Seyal conceptualized, explained, and analyzed the manuscript. Abdulhafiz Rahmati drafted and wrote it, and Inamullah Inam collected the data. Ahmad Wali Ataye edited and corrected the whole manuscript. All authors have reviewed and approved the manuscript

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