4-1-2019

A Literature Review of Type 2 Diabetes Mellitus & the Prevalence of New Onset Atrial Fibrillation

John B. Mills Jr.
University of the Pacific, jmills23_1@hotmail.com

A Literature Review of Type 2 Diabetes Mellitus

& the Prevalence of New Onset Atrial Fibrillation.

By

John B. Mills Jr.

Capstone Project

Submitted to the faculty of the

Department of Physician Assistant Education

of the University of the Pacific

in partial fulfillment of the requirements

for the degree of

MASTER OF PHYSICIAN ASSISTANT STUDIES

APRIL 2019

Introduction

Atrial fibrillation (AF) is one of the most commonly diagnosed cardiac arrhythmias; however, details regarding the risk factors of AF are not necessarily well identified.[1,2] This literature review will investigate the likelihood of a direct correlation between pre-existing type 2 diabetes mellitus (T2DM) and new-onset AF. Highlighting a definitive association between AF and T2DM has been a perplexing pursuit in research studies of epidemiology.[2] The literature review will examine multiple studies and investigate the extent and significance to which T2DM and AF are related. The specific goal will be to assess whether T2DM patients over the age of 55, with Hemoglobin A1c (HbA1c) less than 7% and lifestyle and medication compliance, are less likely to be diagnosed with new onset AF within 5 years of becoming diabetic, than those with poor diabetic control and elevated HbA1c. HbA1c is a blood test used to measure the average glucose levels in the bloodstream over the past three months.

Understanding the relationship between pre-existing T2DM and new-onset AF could greatly benefit and reduce mortality in this patient population. AF is a known risk factor and a common cause of death due to cerebral vascular accidents (CVA).[1] Reducing the occurrence of AF among the vulnerable and immunocompromised T2DM patient population could have immeasurable benefits and lead to significant decreases in patient mortality. This literature review will summarize several studies, including meta-analyses, case-control studies, and retrospective cohort studies.

Does intense glycemic control in T2DM patients reduce the occurrence of new-onset AF?

The role of glycemic control in T2DM patients with new-onset AF has been at the center of many research studies. These studies have focused on glucose levels and HbA1c, in order to establish a correlation between T2DM and new-onset AF, possibly because these are known, measurable, and reliable prognostic indicators of diabetic control.

The strongest piece of evidence investigating this correlation comes from The Action to Control Cardiovascular Risk in Diabetes study (ACCORD study), which was published in 2014. The research study

included 10,082 T2DM patients. The ACCORD study investigated the impact of glycemic control and the incidence of new-onset AF. The study used HbA1c > 7.5% and other inclusion criteria to determine the study groups. Some participants were treated with intensive glycemic control methods, while others were treated with standard control methods to see how glycemic control impacted new-onset AF. The analysis used a randomized double-blind study method, and a multivariate model (weight, age, heart rate, blood pressure and history of heart failure) was used to calculate incidence of AF. The findings were significant because they showed that intensive glycemic control in patients between the ages of 55-79 did not affect the frequency of new-onset AF. In fact, slightly more people in the standard therapy group had new-onset AF compared to the intensive therapy group.[1]

However, it should be noted that only periodic electrocardiogram readings were obtained during appointed clinical site visits, and continuous event monitors, such as Holter monitors, were not utilized for 24-hour observation and recording.[1] Because of this technique of recording results, it is possible that episodes of AF were missed by the research team. Another limitation of the study is that no data were collected regarding inpatient admission or emergency department visits. Most significantly, the ACCORD study only focused on standard vs intensive glycemic control.

Does poor glycemic control in T2DM patients increase the occurrence of new-onset AF?

Unfortunately, it is very common to work with medication non-compliant T2DM patients. Medication compliance is a multifactorial problem, but T2DM patients who ignore their medication regimen and necessary lifestyle changes will likely have poor glycemic control and elevated HbA1c. Some research studies have found that poor glycemic control is associated with an increase in new-onset AF. For example, studies in China that included Holter monitoring identified a link between poor glycemic control, elevated HbA1c, and increased prevalence in new-onset AF. Additionally, one animal study also linked elevated glucose levels to an increased prevalence of new-onset AF.

A retrospective cohort study was conducted at the Shanghai Ninth People's Hospital of 505 T2DM patients from 2008-2015. The incidence of new-onset AF was investigated. Holter monitor or electrocardiogram recordings were obtained from hospital records or medical examinations conducted on a monthly basis. Out of 505 patients, 48 developed new-onset AF. The group with the higher elevation and variability of HbA1c was associated with a greater increase in new-onset AF. These findings suggest that HbA1c variability is, in fact, a predictor of new-onset AF in patients with T2DM.[3] Additionally, increased HbA1c levels were associated with an increased risk of AF in prospective cohort studies but not in case-control studies.[4]

One method to further investigate glycemic control and its relation to new-onset AF is to utilize an animal study. A study published in 2014 by the Department of Cardiology at Otia University in Japan investigated whether or not glucose fluctuations aggravate cardiac fibrosis and increase the occurrence of AF in rats with T2DM. In this study, glucose fluctuations were found to increase the incidence of AF in T2DM rats. A single IV injection of streptozotocin induced T2DM rats were randomly divided into three groups: uncontrolled, controlled, and T2DM rats with variable glucose fluctuations. The rats were administered long-acting insulin according to their group. At the end of a twelve-week period, the rat hearts were excised. They evaluated the hearts for cardiac fibrosis using masson trichrome staining. The inducibility of new-onset AF was significantly higher in uncontrolled T2DM rats when compared to controlled T2DM rats. AF onset was greatest in T2DM rats with high glucose fluctuations. This study links rises in glucose fluctuation to the induction of cardiac fibrosis. Furthermore, this study suggests that increases in reactive oxygen species through increases in Txnip gene expression allow glucose fluctuations to lead to cardiac fibrosis, and eventually AF.[5]

Can medication compliance keep T2DM patients from acquiring new-onset AF?

Metformin is widely considered the medication of choice for the initial treatment of T2DM. Thus, compliance with metformin typically leads to improved glycemic control. The following research study examined the role of medication compliance in lowering AF risk among T2DM patients.

A 2014 study investigated the relevance of metformin compliance and lowering new-onset AF risk amongst the T2DM patient population. This study used a population-based dynamic cohort and in vitro design. Information was gathered from national health care databases such as the Taiwan National Health & Research Institute. This large study followed 645,710 newly diagnosed T2DM patients for 11 years. None of the patients were insulin dependent. Two study groups of oral diabetic medication prescribed patients were created. One group used metformin and the other used a non-metformin oral diabetic medication. The study findings were significant ($P < 0.05$) and identified a decrease in new-onset atrial tachycardia when metformin was used as 1st line T2DM treatment. This finding was likely attributed to metformin's ability to diminish atrial cell tachycardia induced oxidative stress and myolysis.[6] Such results may raise the question, "Is new-onset AF related to not only lack of glycemic control but also medication noncompliance?"

Some patients with AF, whether T2DM or not, are resistant to initial medical treatment and require more invasive procedures such as catheter ablation to convert out of AF and into a normal sinus rhythm. If T2DM patients are in fact at an increased risk of new-onset AF, should they be treated with catheter ablation early after diagnosis, or should all other treatment measures be exhausted first?

A 2015 systematic review examined the etiology of AF through specific molecular pathways, and investigated the effectiveness of treatment plans for AF in T2DM patients. The data were based on the findings of multiple studies pertaining to the correlation between AF and T2DM. For example, The Framingham Heart Study and The ACCORD study were both utilized. This systematic review found that AF in T2DM patients is a significant cause of CVA. Furthermore, the correlation of AF and T2DM largely increases the likelihood of morbidity and mortality in the T2DM population.[7]

But what about treatment modalities and their effectiveness? This systematic review found that patients treated with catheter ablation had less incidence of future AF than those treated pharmacologically for AF.[7] Unfortunately, only a small percentage had T2DM, so it is yet unknown if catheter ablated patients with AF and T2DM would greatly benefit from this treatment modality. Furthermore, the focus of this review was the prevention of AF in the setting of pre-existing T2DM.

What role do lifestyle interventions and risk stratification have on new-onset AF in T2DM patients?

Management of T2DM can be properly optimized when patients take ownership of medication compliance, and perhaps even more importantly, lifestyle choices. Starting a balanced diet and implementing an exercise regimen is crucial to improving glycemic control and T2DM treatment. The following study examined how lifestyle intervention in T2DM patients affected the prevalence of new-onset AF.

In 2015 the Look AHEAD (Action For Health in Diabtets) randomized trial investigated the effects of intensive lifestyle intervention in T2DM patients over a nine-year period. The goal was to see if there was any change in risk of acquiring new-onset AF. The study used 5,067 obese or overweight people with T2DM and no history of AF. The population was divided into two groups randomly, one with intensive lifestyle intervention and the other with only diabetic education and supportive care. The onset of AF was discovered by electrocardiogram and discharge summaries from hospitals. The findings suggested that among overweight and obese T2DM patients there was no reduction in the likelihood of new-onset AF when intensive lifestyle modifications were implemented. In fact, results were similar in both groups. What remained a common factor in this study was that all patients did have T2DM. While lifestyle intervention is paramount in treating T2DM, according to this study, it will not significantly help reduce the likelihood of new-onset AF.[8]

A crucial aspect of treating AF beyond rate/rhythm control is anticoagulation. Due to the known increase in the risk of CVA associated with AF, anticoagulation is a cornerstone of AF management.

Traditionally, comorbidities and age have determined the need for anticoagulation through the CHA2DS2-VASc scoring system. Risk stratification techniques such as CHAD-VASC scoring may help greatly to see if uncontrolled T2DM is linked to increased likelihood of new-onset AF.

In 2017 a retrospective cohort study examined subjects enrolled in a large nationwide dataset that looked at T2DM patients and used the CHADS-VASC score to stratify new-onset of AF. The study population was identified from a longitudinal health insurance database provided by the National Health Research Institute, and it included 69,530 patients. Patients who had a prior diagnosis or history of AF before the index date were excluded from the study. A CHADS-VASC score was calculated for each group using the Kaplan Meier method. Findings from this study suggested the risk of AF among patients with T2DM and no hyperosmolar hyperglycemic state (HHS) increased with increasing CHADS-VASC scores. The incidence of new-onset AF increased significantly ($P < 0.05$) when the CHAD-VASC score increased from 1 to 6 or greater among patients with T2DM and HHS.[9] There is clinical significance to the above findings because of the increasing need for anticoagulation as a CHADS-VASC score rises to prevent the risk of cardiovascular events such as CVA. Furthermore, the findings of this study suggest that new-onset AF is more common in patients with T2DM, comorbid conditions, advanced age, and a history of HHS, further raising suspicion that uncontrolled T2DM may be linked to increased likelihood of new-onset AF.

Hospitalizations and rates of new-onset AF in T2DM patients.

As illustrated by the results of the next two studies, T2DM patients are being diagnosed with new-onset AF. Studies continue to produce conflicting evidence as to why T2DM patients may or may not be more likely to have new-onset AF. Researchers have struggled to determine the cause of new-onset AF in T2DM. It has been challenging for researchers to determine if there are any mitigating factors that can reduce the likelihood of acquiring AF. At a minimum, these studies highlight the need to further investigate the association between existing T2DM and new-onset AF.

A 2011 meta-analysis of cohort and case-control studies investigated T2DM patients with glucose intolerance or impaired fasting glucose and AF through computerized search parameters. The goal of this study was to use a meta-analysis of previously published studies to reliably determine what link exists between T2DM and new-onset of AF. This research study included a population of over 1-million T2DM patients. This study found that T2DM was associated with a 10-time increase in the occurrence of new onset AF Individuals with T2DM have approximately a 40% increase in new onset AF compared to those without T2DM. The strength of this study was simple; it was very large and gathered data from legitimate primary sources. The study findings support the concept that T2DM patients are at increased risk of acquiring new-onset AF. However, the studies limitations included a lack of subtype evidence such as new-onset AF after excessive binge drinking.[2]

In Lombardy, Italy, a large population-based study was conducted from 2000-2010. It focused on T2DM as a risk factor for AF, as well as other cardiovascular diseases. This study was conducted retrospectively and utilized administrative health databases to acquire the entirety of its data. While this study design, and others like it, may have some obvious limitations, it also has the advantage of easily including large numbers of patients. This study utilized 285,428 participants with T2DM and followed them closely to see who would acquire new-onset AF and who would not. The findings were significant because they illustrated that patients with T2DM had more hospitalizations due to new-onset AF than those without T2DM. In fact, T2DM was identified as having a 32% greater risk for new-onset AF. These findings have added importance because they identify T2DM as an independent risk factor for AF. [10]

Discussion

The goal of this literature review was to answer the following question: Are type T2DM patients over the age of 55 with medication compliance and HbA1c less than 7% less likely to be diagnosed with new-onset AF within 5 years of becoming diabetic than those with poor diabetic control and elevated

HbA1c? In this literature review, the incidence of new-onset AF was elevated among the T2DM patient population. These studies were unable to identify with certainty what contributing factors led to the association of the two conditions. Despite in-depth examination of glycemic control, HbA1c levels, lifestyle intervention, medication compliance, and efficacy of various treatment modalities more studies are needed to fully comprehend the relationship between T2DM and new-onset AF.

Conclusions

There is a clear association between T2DM and AF, but to what degree remains somewhat unknown. According to some glycemic control studies, well-controlled T2DM with therapeutic HbA1c levels offers little advantage in decreasing the likelihood of new-onset AF amongst T2DM patients.[1] In contrast, other studies that focused on uncontrolled glycemic levels, or did not focus on glucose control at all signified that T2DM was, in fact, an independent risk factor for AF due to the increased number of new-onset hospitalizations and diagnosis. [2,3,4,10] To further understand the relationship between T2DM and AF, additional research is required. In the meantime, medical providers can follow established principles to manage patients with T2DM, AF, or perhaps both conditions simultaneously.

Awareness that both T2DM and AF are associated is paramount. As a medical practitioner, it is important to understand that lowering HbA1c to a therapeutic level (HgbA1c < 7.0%) is the first step towards controlling T2DM. Being aware of T2DM guidelines and stressing the importance of medication compliance is part of serving the patient population to the best standard of care. Well controlled T2DM may not completely rule out the possibility of new-onset AF. Medical professionals should be aware that new-onset AF is a possibility in T2DM patients, and then survey for signs and symptoms associated with AF. These actions may help greatly reduce the incidence of poor cardiovascular outcomes such as CVA or mesenteric ischemia in the T2DM patient population.

References

1. Fatemi, O., Yuriditsky, E., Tsioufis, C., Tsachris, D., Morgan, T., Basile, J., Bigger, T., Cushman, W., Goff, D., Soliman, E., Thomas, A. and Papademetriou, V. (2014). Impact of Intensive Glycemic Control on the Incidence of Atrial Fibrillation and Associated Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus (from the Action to Control Cardiovascular Risk in Diabetes Study). The American Journal of Cardiology, 114(8), pp.1217-1222.

2. Huxley RR, Filion KB, Konety S, Alonso A. Meta-Analysis of Cohort and Case–Control Studies of Type 2 Diabetes Mellitus and Risk of Atrial Fibrillation. The American Journal of Cardiology. 2011;108(1):56-62. doi: 10.1016/j.amjcard.2011.03.004.

3. Jun Gu, Yu- Qi Fan, Jun- Feng Zhang, Chang- Qian Wang. Impact of long-term glycemic variability on development of atrial fibrillation in type 2 diabetic patients. Anatol J Cardiol. 2017; 18(6): 410-416.

4. Qi W, Zhang N, Korantzopoulos P, et al. Serum glycated hemoglobin level as a predictor of atrial fibrillation: A systematic review with meta-analysis and meta-regression. Plos One. 2017;12(3). doi: 10.1371/journal.pone.0170955.

5. Saito S, Teshima Y, Fukui A, et al. Glucose fluctuations increase the incidence of atrial fibrillation in diabetic rats. Cardiovascular Research. 2014;104(1):5-14. doi:10.1093/cvr/cvu176.

6. Chang S-H, Wu L-S, Chiou M-J, et al. Association of metformin with lower atrial fibrillation risk among patients with type 2 diabetes mellitus: a population-based dynamic cohort and in vitro studies. Cardiovascular Diabetology. 2014;13(1). doi:10.1186/s12933-014-0123-x.

7. De Sensi F, De Potter T, Cresti A, Severi S, Breithardt G. Atrial fibrillation in patients with diabetes: molecular mechanisms and therapeutic perspectives. Cardiovascular Diagnosis and Therapy. 2015;5(5):364-373. doi: 10.3978/j.issn.2223-3652.2015.06.03.

8. Alonso A, Bahnson JL, Gaussoin SA, et al. Effect of an intensive lifestyle intervention on atrial fibrillation risk in individuals with type 2 diabetes: The Look AHEAD randomized trial. American Heart Journal. 2015;170(4). doi: 10.1016/j.ahj.2015.07.026.

9. Hu W-S, Lin C-L. Role of CHA2DS2-VASc score in predicting new-onset atrial fibrillation in patients with type 2 diabetes mellitus with and without hyperosmolar hyperglycemic state: real-world data from a nationwide cohort. BMJ Open. 2018;8(3): e020065. doi:10.1136/bmjopen-2017-020065.

10. Staszewsky, L., Cortesi, L., Baviera, M., Tettamanti, M., Marzona, I., Nobili, A., Fortino, I., Bortolotti, A., Merlino, L., Disertori, M., Latini, R. and Roncaglioni, M. (2015). Diabetes mellitus as risk factor for atrial fibrillation hospitalization: Incidence and outcomes over nine years in a region of Northern Italy. Diabetes Research and Clinical Practice, 109(3), pp.476-484.