Review Article

iMedPub Journals
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Medical and Clinical Reviews
ISSN 2471-299X

2021
Vol.7 No.12:170

DOI: 10.36648/2471-299X.7.12.170

The Association of Cardiac Morbidities in Type 2 Diabetic Patients; A Meta-Analysis

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Citation: Abubakar Shahid Chishti M, Zain-ul- Abiddin, Fida T (2021) The Association of Cardiac Morbidities in Type 2 Diabetic Patients; A Meta-Analysis. Med Clin Rev Vol.7 No.12:170.

Abstract

Diabetes mellitus especially type 2 is one of the most common chronic diseases prevalent in the whole world. It is a metabolic disorder leading to neuropathy and micro vascular lesion. The later when occurring in coronary vessels is the main contributing factor towards the development of cardiac diseases especially CAD. Our study aims to establish a significant association between the two diseases through the meta-analysis of the related researches done in recent years. Two databases i.e. pub med and google scholar were originally searched to gather all the studies with RCT including the association of diabetes and cardiac disease and were further filtered based on well-defined inclusion and exclusion criteria. The relevant data were extracted from the studies and were analyzed. The final analysis included 6 RCTs and 19,350 patients in total both diabetic (experimental group) and non-diabetic (control), out of which 6,909 suffered from any cardiac morbidity. From these 6,9099 patients, 3,739 patients were diabetic thus indicating a considerable fraction of the diabetic patients suffering from cardiac morbidities.

Highlights

The results point towards the conclusion that a significant association exists between type 2 diabetic patients and cardiac morbidities and this association remains unaffected even in the presence of different variables like obesity, blood pressure, etc. Duration of diabetes, baseline maintenance of blood sugar levels by medical treatments also affect the prognosis of diabetes so screening of diabetic patients for cardiac diseases is beneficial.

Keywords: Diabetes mellitus; Coronary artery disease; Randomized study; Screening; Myocardial infarction

Received: November 04, 2021; **Accepted:** December 27, 2021; **Published:** January 03, 2022

Introduction

Diabetes Mellitus refers to a group of metabolic disorders primarily characterized by chronic hyperglycemia which might be a result of absolute pancreatic deficiency or development of insulin resistance in body cells [1]. About 462 million people (6.28% of the global population) across the world were found to have type-2 diabetes in 2017 with a higher prevalence in socio-economically developed countries such as Western Europe and the USA, and a lower prevalence in countries like Ethiopia. The prevalence is expected to rise especially in developed countries due to the increased risk of obesity with global prevalence reaching up to 7.079% in 2030 [2].

The association between Type 2 diabetes and cardiovascular diseases is well established as diabetics have twice as much risk of experiencing coronary heart disease [3] with a recurrence rate of around 6% per year which is higher than that of a non-diabetic [4]. About 65 to 70% of diabetic mortalities are caused by CVD [5]. Apart from the traditional CVD risk factors that diabetics are prone to have (obesity, hypertension, etc.), endothelial dysfunction and dyslipidemia brought about by T2DM further contribute to atherosclerotic development and the risk of CVD [6]. Moreover, the atherosclerotic plaque of a diabetic is more dangerous because of exclusive macrophage invasion and increased lipid content [7]. Also, silent myocardial infarction induced by diabetes remains an explicit cause of cardiovascular problems [8] A higher triglyceride level added with a lower HDL cholesterol level often seen in patients of T2DM suffering from SMI is considered a probable cause of these occurrences especially in cases where the LDL cholesterol levels are high [9].

Moreover, diabetic suffering from CHD has a worse prognosis than a similar patient who does not have diabetes [10] this is because revascularization procedures employed to restore the interrupted blood supply to the cardiac musculature exhibit worse outcomes [11]. The major reason for it is the exhibition of hyperglycemia, the persistence of inflammation, endothelial dysfunction, dyslipidemia, and thrombophilia exhibited by the patients of type 2 diabetes mellitus [12].

It is obvious from the above discussion that a clear association exists between type 2 diabetes and symptomatic/asymptomatic heart diseases. However, it is not clear if routine screening of diabetics for CVD should be made part of the treatment regimen of diabetes. Much work has been done in this regard in the past years which have given rise to different schools of thought. Our goal for this SYSTEMIC REVIEW is to review the recently published articles in this regard and compare their data collected to reach an agreeable conclusion about the extent of association between type 2 diabetes and heart diseases.

Methods

Literature search

We have conducted a systematic search for articles related to our topic that have been published in the various well-recognized journal for the period of 10 years from January 2010 to September 2020 in English. For this purpose, two databases have been used i.e. Pub med and Google scholar which led to our major finding of topic-related articles. The leading keywords for the search were diabetes or diabetics, asymptomatic or subclinical or silent or undetectable or unknown, heart attack or heart failure, prevalence, association, morbidity, and mortalities related. The articles mostly were based on cohort, observational, or randomized control trials. Two investigators separately collected the relevant articles based on the topics and abstracts and the full text of only selected articles were obtained. The unpublished and disputed researches were not included in the review as it leads to discrepancies because of their incomplete and unavailable data.

Study selection

Research articles are selected based on well-defined inclusion and exclusion criteria. The aspects included in inclusion criteria are related to both studies as well as the patients. A) all topic related cohort, observational and trial-based studies. B) articles within the defined period of 10 years up to date, B) No interventions applied on the study subjects, C) patients of both genders, D) adult patients of age from 30 onwards. E) Asymptomatic patients with diabetes and no history of any previous heart-related diseases, F) availability of at least one of the events; death due to asymptomatic heart attack or hospital admission. The exclusion criteria include A) patients with prior cardiac ailments; B) animal subjects based studies, C) studies with overlapping data, D) studies without final and ambiguous results, E) studies without full available articles

Outcomes

Our main terminal point is “any cardiac-related ailment” and it includes both fatal and non-fatal fates like deaths due to heart failure, asymptomatic heart attacks, and its resultant hospitalizations and performed procedures.

Data extraction

Two investigators collected and organized the information extracted under the headings of research title and author names, type of study, publication date, number of patients included in each study, inclusion criteria, exclusion criteria, morbidities observed, mortalities recorded, diagnostic and screening measures, advised treatment protocols, hemoglobin A1C levels, blood pressure, baseline characteristics of the selected study subjects like age, gender, BMI body mass index, cholesterol levels, type of diabetes mellitus along with its duration, treatment of diabetes, controlled or uncontrolled diabetes, use of aspirin and use of statins. Differences were solved by the third author.

Study quality and risk of bias

The quality of the study is based upon the risk of study bias, publication bias, and research bias that may occur in different stages during the conduction of our research and thus deteriorate its quality. The risk of study bias was assessed at the study and outcome level using Cochrane elaboration tools. The publication bias was removed by using the funnel plot.

Data synthesis and statistical analysis

Statistical analysis was carried out with the help of the review manager (RevMan) Version 5.4. The additional plots were developed with the help of Forrest plotting. We performed the meta-analysis of cardiac patients with a 95% confidence interval ($p=0.001$)

Regulatory aspect

Since our study is based upon the analysis of already published and relevant articles and it did not involve any direct contact or dealing with patients or study subjects so there is no absolute requirement of approval from the Institutional review board. However, all the studies that have been used in our research have mentioned the approval from the IRB as well as the informed consent from the study subjects. Our study is in accordance with the declaration of Helsinki. The results presented by us are in the following of PRISMA statements about systematic reviews and meta-analysis. This study did not have any monetary support from any source **(Tables 1 and 2)**.

Results

Search results and study selection

A total of 853 titles and abstracts were screened for eligibility. Titles and abstracts failed to meet the eligibility criteria were excluded 6 population-based studies out of 10. The reason for exclusion: non-randomized studies (n=6), no effective screening procedure for CAD in diabetes patients (n=4), studies having overlapping data (n=3), studies with no control group (n=6). We finally include 6 randomized trials consisting of a comparison of asymptomatic heart diseases in a diabetic with non-diabetic patients. We repeated the search on ISI web knowledge and

Table 1: Study characteristics of the included studies in the meta-analysis.

S. No.	Author name	Type of study	Publication date	Screening method	Sample size	Outcome
1	Ghosal et al. **[13]**	Cross-sectional study	06-Apr-20	QRISK3 score	1538	The median 10-year risk was 22.2%
2	Zellweger et al. **[14]**	Prospective multi-center trial	10-Apr-20	Stress gated MPS	400	22% of patient have silent CAD
3	Rorth et al. **[15]**	Randomized trial	Jun-18	Not mentioned	647	Patient having AVLSD, diabetes associated with increased risk of heart failure
4	Elliot et al. **[16]**	Prospective two-center study	29-Mar-19	MRI	460	19% unrecognized MI
5	Febyan et al. **[17]**	Case study	07-Jul-20	ECG	1	Cardiac autonomic dysfunction appears frequently in diabetic patients
6	Mamudu et al. **[18]**	Case-control study	2018	Coronary artery calcium screening	3000	Atherosclerosis is 68.5% high among diabetic patients
7	Gyldenkerne et al. **[19]**	Cohort study	2019		12030	The presence of coronary artery disease increases the risk of MI in diabetes patient
8	Deepti et al. **[20]**	Cross-sectional study	19-Sep-20	Myocardial perfusion imaging	97	10.3% of patients have abnormal myocardial perfusion.
9	Swoboda et al. **[21]**	Cohort study	2018	Cardiovascular magnetic resonance	94	Ascending aortic distensibility associated with adverse cardiovascular effects
10	Daphale et al. **[22]**	Cross-sectional study	Nov-17	Exercise treadmill test	300	The risk of asymptomatic coronary artery disease was 3.99 times more among the patients with T2DM as compared to the patients without T2DM

Table 2: Patients characteristics of the included studies in the meta-analysis.

S. No.	Author name	Gender	Body mass index (kg/m^2)	Mean age (years)	HBA_{1c}	Blood pressure	Duration of diabetes (years)		Statin use %	Aspirin use %	Smoking %	Registry
1	Ghosal et al. **[13]**	M=897 (58.3)	27.1	54.5 ± 11.2		135.5	<5 years	503 (32.7)			23.9% of smokers	
		F= 641 (41.7)										
							>5-10	552 (35.9)				
							>10-15	297 (19.3)				
							>15-20	120 (7.8)				
							>20	66 (4.3)				
2	Zellweger et al. **[14]**	Two-third males	31 ± 6	65 ± 7	7.4 ± 1.3	141 ± 17	13 ± 9		66		32	
3	Rorth et al. **[15]**	552 (85%)		61 ± 9		130 ± 17					19%	
4	Elliot et al. **[16]**	54%	28 ± 6	52 ± 13	28 ± 6	143 ± 22	17 ± 11		48	43	23	
5	Febyan et al. **[17]**	male		57		70/palpation				yes	0	
6	Mamudu et al. **[18]**	M=1174 (45.8%)		46-74 years							10.10%	
		F=1389 (54.2%)										
7	Gyldenkerne et al. **[19]**	66% males		65					84.1	79.1	26.1	
8	Deepti et al. **[20]**	65 (67%) males	25.5 ±3.9	52.7±8.4	7.9 ± 1.6	74% have >140	5.25		45.9		16.50%	
9	Swoboda et al. **[21]**	M=76 (81%)	28.7 ± 4.3	60.8 ± 11.1	61.6 ± 15.6 mmol/mol	131.1±15.2	5.1±4.5		70%	17%	16%	
10	Daphale et al. **[22]**	61.3% males	24.00 ± 2.74	46.20 ± 12.20		128.66 ± 21.59					36%	

ScienceDirect but we found no studies which met our inclusion criteria. The study selection process is summarized in the PRISMA guideline in **Figure 1.**

Studies and Patients characteristics

Table 1 gives the study characteristics of included studies with type 2 diabetes from the 10 studies. **Table 2** presents the patients' characteristics including blood pressure, body mass index, HBA1c, Duration of diabetes, Smoking, use of aspirin, and statins. 6 population-based studies were included consisting of a total of 10,015 types 2 diabetes patients were included in our meta-analysis. The studies are randomized and only those studies are included which are published after 2016. Only patients with type 2 diabetes were included. The screening procedures were variable with the use of MRI, exercise treadmill test, myocardial perfusion images, and ECG. The treatment plan is also variable. 3739 incident cases of cardiovascular diseases are presented in type 2 diabetes patients after a follow-up of a few years. As shown in **Table 2**, the mean age varied between 46 and 72 years. the proportion of the male population varied between 45% and 76%. The mean duration of DM ranged from 5 to 17 years and the mean HbA1c from 7.4 ± 1.3

Study quality and risk of bias

To determine the publication bias of our study, the funnel plot is drawn. The Funnel plot results for potential publication bias are shown in **Figure 2**. We found no significant asymmetry and hence no publication bias.

Primary outcome

The 6 RCTs selected for our study included a total of 19350 patients which were divided into two groups; a diabetic group (n=10015) and a control group (n=9335). Out of this patient pool, a total of 6909 patients (35.7%) suffered cardiovascular problems. Out of which 3739 belonged to the diabetic group. Even after considering the multivariable adjustment for various vascular risk factors such as smoking, body mass index, antihypertensive treatments, systolic blood pressure, total body cholesterol levels, the association between diabetes and the occurrence of cardiac events remained well established. A significant association was present between the occurrence of asymptomatic heart disease (Z=7.62; p=0.00001, 95%CI) and type 2 diabetes mellitus when the total period of diabetes, glycated HbA1c levels in the blood, and history of past diabetes treatment were added in the multivariable models as shown in **Figure 3**.

Discussion

The performed meta-analysis pooling 6 RCTs was structured to determine whether a significant association exists between diabetes and any kind of heart disease. The overall results containing a study population of 19350 patients strongly support the idea that diabetes directly contributes to the development of heart diseases. All the RCTs included in the study had been performed in the last three years giving us the latest information collected on the given subject. This way any obsolete data from the past can be ignored. All the RCTs included in the study used

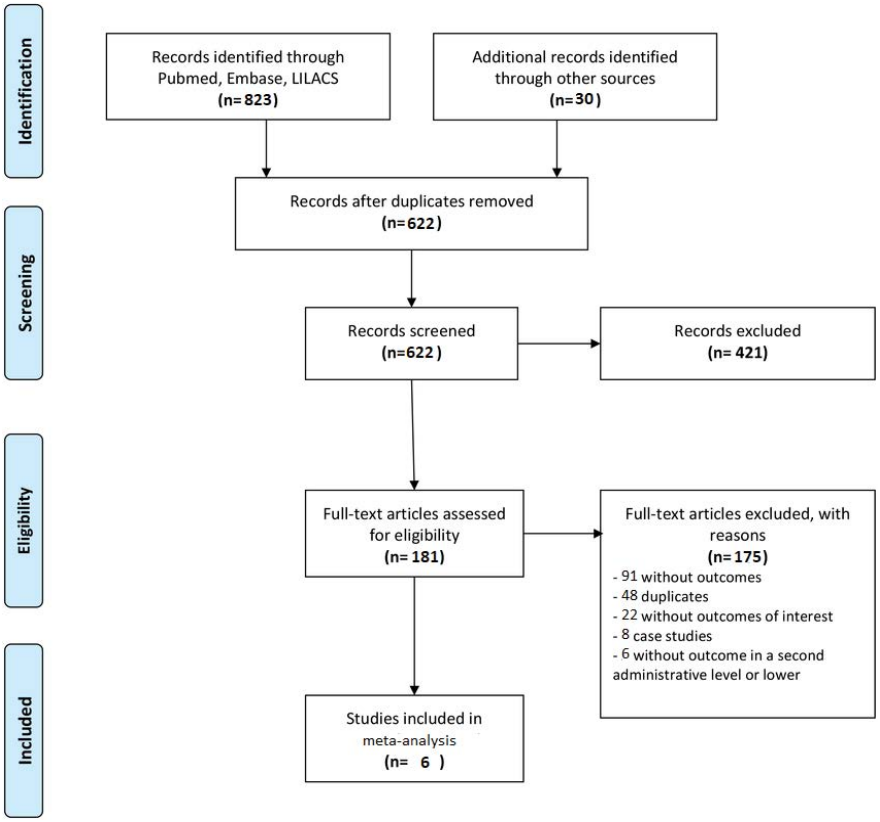

Figure 1 PRISMA Flow chart of literature search and selection of studies.

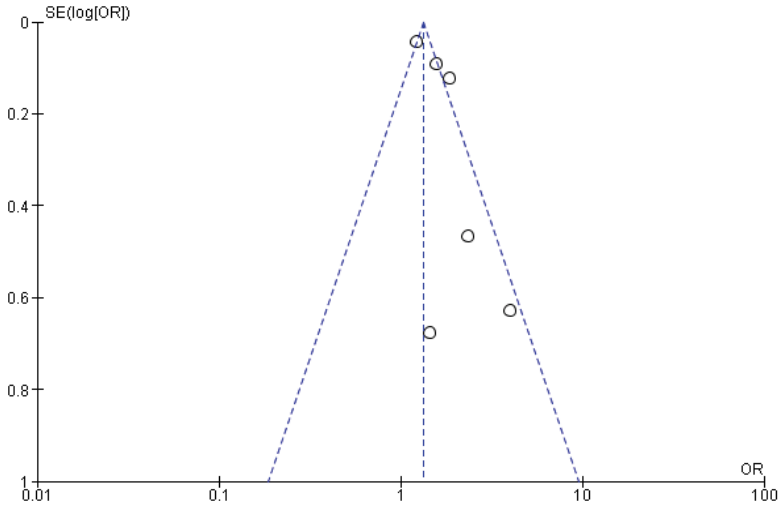

Figure 2 Funnel plot of comparison: 1 comparison of the risk of asymptomatic heart diseases in type 2 diabetes and non-diabetes patients

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Daphale et al 2017	22	200	3	100	0.3%	4.00 [1.17, 13.69]
Elliot et al 2019	14	50	10	70	0.5%	2.33 [0.94, 5.80]
Gyldenkerne et al 2019	3229	8672	1104	3358	77.3%	1.21 [1.11, 1.32]
Mamudu et al 2019	241	352	1189	2211	8.0%	1.87 [1.47, 2.37]
Rorth et al 2018	214	647	861	3576	13.7%	1.56 [1.30, 1.87]
Swoboda et al 2018	19	94	3	20	0.3%	1.44 [0.38, 5.41]
Total (95% CI)		**10015**		**9335**	**100.0%**	**1.32 [1.23, 1.42]**
Total events	3739		3170			

Heterogeneity: Chi² = 19.89, df = 5 (P = 0.001); I² = 75%
Test for overall effect: Z = 7.62 (P < 0.00001)

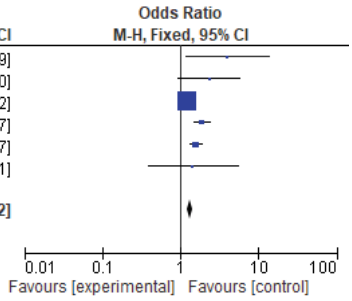

Figure 3 Forest plot of comparison: 1 comparison of the risk of asymptomatic heart diseases in type 2 diabetes and non-diabetes patients.

a different screening method to establish a relationship between diabetes and heart disease. Samit Goshal et al. March 2020 used a Qrisk calculator, Michael J et al. May 2017 used myocardial perfusion scan, Michael D et al. 2019 used DE-MRI, etc. However, all these studies concluded that a well-established association exists between diabetes and heart diseases. This diversity among screening procedures further eradicates any probability of a specific screening procedure affecting the results. Hence the result concluded in the present meta-analysis bypasses any bias that may have developed using a single screening procedure.

Although the Randomized control trials included in the study favored the association between diabetes and heart diseases, the specific variables included/excluded in the study were different. Samit Goshal et al. excluded smoking from the risk score and hence established the link between diabetes and heart disease independent of this variable Rasmus et al. 2018 excluded pre-existing heart diseases (Myocardial infraction etc) from the existing variables in the study by keeping the proportion of baseline MI the same in diabetics and non-diabetics of the study population. All these studies using different variables and still reaching the same overall conclusion further consolidates the idea that diabetes can cause heart disease over time because any bias that may have been produced because of a specific variable can now be eliminated and diabetes can be established as an independent predictor of heart diseases in its patients. Diabetes does not cause heart disease via a single direct way. Diabetes initiates several different pathogenetic mechanisms each of which can result in a different kind of cardiac anomaly. Hence, collecting data about a single kind of heart disease in association with diabetes can never show us the complete picture in this regard. This meta-analysis, however, possesses a unique diversity in its included studies such that an association has been established between different kinds of heart diseases and diabetes. In this way, no kind of heart disease has been left ignored and more accurate analysis of the relationship between diabetes and heart diseases is made possible.

However, this study has its limitations. The studies included exhibiting a marked demographic and age variation which affects the accuracy of the overall results. More singularly focused RCTs in this aspect can rectify this problem. Our study includes only type 2 diabetes patients, so our results cannot be applied to type 1 diabetes patients. Moreover, our study has the strength of low bias risk and overall quality of data.

Conclusion

In conclusion, the results obtained from the analysis of the data of 6 (six) selected randomized controlled trials to indicate that a significant association exists between the occurrence of diabetes mellitus and cardiac morbidities especially coronary artery disease. The probability of the development of cardiac diseases increases in a diabetic person as compared to a non-diabetic person. This occurs mainly because of the micro vascular injuries (endothelial injuries, dyslipidemias, neuropathy) especially in coronary vessels caused by diabetes. The continuation of this association even after the consideration of variables like smoking, blood pressure, obesity, use of anti-hyper lipidemic drugs, and statin explains that the risk factors for the causation of both the diseases are the same. The present analysis shows clear evidence for the benefit of screening the diabetic patients for cardiac diseases in terms of outcomes as the chances of development of cardiac diseases increases with the duration of diabetes, and are more in patients with uncontrolled diabetes, thus timely diagnosis and medical interventions can prevent from much worse outcomes.

Acknowledgments

No acknowledgments.

Disclosure

There is no conflict of interests.

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