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Review Article

A REVIEW ON THE PREDICTIVE RISK FACTORS FOR MAJOR ADVERSE CARDIOVASCULAR EVENTS IN DIABETES PATIENTS

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Abstract

Diabetes is a major public health problem world-wide and is one of the prime risk factors for major adverse cardiovascular events (MACE). Classically,3 points MACE includes non fatal stroke, non fatal myocardial infarction, and cardiovascular death. The present review aims to discuss the mechanism of cardiovascular events in diabetes and the predictors or interventions to mitigate it.Keywords including ('major adverse cardiac events' and 'diabets' or 'diabetes mellitus' or 'type1 diabetes' or 'type2 diabetes' and'predictors' or 'risk factors') were searched through Google Scholar, Pubmed and Scopus databases based on PRISMA guidelines and duplicates were removed.Hyperglycaemia, abnormal lipid profile and oxidative stress are the major factors contributing to cardiac events in diabetes. Various risk factors or predictors for MACE among diabetes patients have been in research to help for the prevention or progression of these cardiac complications, reduce morbidity, mortality and economic burden of the patients.

Keywords: Diabetes, Major adverse cardiovascular events, Predictors, Risk factors.

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INTRODUCTION

Diabetes, one of the oldest known epidemic to the world with first report in Egyptian manuscript about 3000 years ago constitute a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. It is one of the major global health problem with increase in prevalence from 4.7% in 1980 to 8.5% in 2014.. The prevalence of diabetes has been raising more rapidly in middle and low income countries. An estimated 1.6million deaths were directly caused by diabetes in 2016 [2].

The major factor leading to the increasing number of deaths among diabetics is cardiovascular diseases. Relative to the non-diabetic patients, patient with diabetes have 2-3 fold higher risk of suffering from major adverse cardiovascular events(MACE) [3]. MACE has no absolute definition, and various definition based on primary and secondary endpoints have been in use is cardiovascular research since mid 1990.The multiple adverse events comprising MACE are heart failure, Non-fatal reinfarction , recurrent angina pain, re-hospitalization for cardiovascular related illness, repeated percutaneous coronary intervention, coronary artery bypass grafting and all cause mortality [4].

The MACE are majorly seen among people with type 2 diabetes mellitus, which is the most prevalent form of diabetes. Although several new agents recently been proven to reduce cardiovascular system risk in type 2 diabetes mellitus, the residual risk of developing atherosclerotic cardiovascular events despite optimal treatment remain significantly higher in the population when compared to Non-diabetics. [5]While, a large population of the accentuated risk in patients with type 2 diabetes mellitus is attributed to the presence of traditional risk factor, further identification of modulating novel risk factor is crucial to developing novel therapeutic intervention.

A review of all the papers published before with the association between various predictor and MACE in patients with diabetes to help for the early prevention of cardiovascular events and decrease the mortality and health care burden among the individuals is discussed briefly.

APPROACH TO THE LITERATURE

For this purpose, the authors conducted a literature search of Google Scholar, PubMed, and Scopus database regardless of the publication dates of the articles. All search protocols were in accordance with Preferred Reporting items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for systematic reviews.The keywords such as 'major adverse cardiac events' and 'diabets' or 'diabetes mellitus' or 'type1 diabetes' or 'type2 diabetes' and the keyword predictors or risk factors were supplemented. The titles of top 200 articles were then read and the relevant articles were selected. The relevant references of search results were also used to obtain further articles. Duplicates were removed, and the authors proceeded to go through the articles. A further literature survey was conducted to obtain information on mechanism discussed in our review.

MECHANISM OF DIABETES INDUCED MACE IN DIABETIC PATIENTS

There is not clear understanding leading to excess CVS morbidity and mortality among people with diabetes. Certain factors have been identified by researchers over time in people with diabetes than can contribute to the development of MACE.

- Hyperglycemia which is the hallmark of diabetes contribute to myocardial damage after ischemic event.
- Increased level of triglyceride, decrease HDL cholesterol, abnormal lipoprotein particles found in plasma of diabetics are associated with increase myocardial damage.
- The oxidized LDL is pro-atherogenic because once it get oxidized, the immune system recognize them as “foreign particles” and initiate all the steps in the formation of atherosclerotic plaques.
- Dyslipidaemia is due to insulin deficiency and insulin resistance accompanied by increased oxidation, glycosylation and triglyceride enrichment of lipoprotein is also the major mechanism for the occurrence of atherosclerosis among diabetics.
- Dysregulation of vascular tone by decrease nitric oxide production leads to macrovascular damage and diabetes.
- The release of pro inflammatory cytokines associated with vasoconstriction and decrease nitric oxide production increases vascular permeability, programmed cell death and the ROS production.
- Cytokines released from adipose tissue like TNF-alpha, IL-beta, IL-6 and plasminogen

- activator inhibitor 1 are all linked to inflammatory response.
- Numerous studies have demonstrated chronic oxidative stress in diabetic humans and animals. The oxidation stress represent an imbalance between oxidants and antioxidants, that cause damage to cellular macromolecules such as lipids, DNA, protein and is crucial factor leading to CVS complication in diabetes.
- Activated leucocytes that are mediators for inflammation are also responsible for oxidative stress in diabetes.
- Diabetic patient exhibit increase activation of platelet and clotting factor in the blood thereby leading to the formation of blood clots/thrombus/atherosclerotic plaque. Majority of myocardial infarction and stroke in diabetes are due to the rupture of atherosclerotic plaque and the resulting occlusion of a major artery by thrombus.
- Ischaemic and thrombotic events in patients with diabetes lead to increasing number of heart failure. The major contribution being here are endothelial dysfunction, oxidation and glycation of atherogenic lipid and hypercoagulability of the blood. [6,7].

DIFFERENT PREDICTORS TO PREDICT MACE AMONG DIABETIC PATIENTS

AUTHOR	SAMPLE SIZE	FOLLOW UP	MACE OCCURRENCE AMONG DIABETICS	MAJOR FINDING AMONG DIABETICS WITH MACE
Kumar A, et al.2019[5]	12,092 patients	28 months	238(11%)	↑baseline fasting plasma insulin levels
Yiannoulloul, et al.2019[8]	1,699 patients	5 years	(7.8%)	Simaltaneous pancreas and kidney transplantation
Jensen MT, et al.2019[9]	1093 patients	7.5 years	145(13.3%)	Echocardiographic changes
Liao KM, et al.2019[10]	2324 patients	1.8 years	444(19.1%)	High first harmonic of radial pulse wave
Gerbaud E, et al.2019[11]	327 patients	16.9 months	89(27.2%)	High glycemic value >2.7mmol/L
Zhenhua Xing, 2019[12]	10,251 patients	8.8 years	1801(17.8%)	↑ Fat mass
James B.Young, 2018[13]	181,619 patients	12 months	4.7%,6.5% and 1.8% in primary prevention and 16.5%, 24.9% and 8.2% in secondary prevention population	Increase age, siabetes related hospitalization, prior cardiovascular diagnosis, chronic pulmonary disease
Blanc-Blisson C, et al.2018[14]	232 patients	7 years	22(9.4%)	Higher skin autofluorescence
Ioana Simona Chisalita, 2018[15]	741 patients	7 years	74(9.9%)	Low toe brachial index
Lin FJ,et al. 2017[16]	5,483 patients	--	--	Chronic kidney disease stage 4 without beta blocker use, heart failure, higher non HDL-C, higher HDL-C and TG levels
Monseu M ,et al.2015[17]	1,371 patients	69 months	157(11.4%)	Acute kidney injury

Nystrom T, et al.2015[18]	764 patients	4.7 years	334(44%)	↑HbA1C glucose values, poor glycemic control
Kasim M, et al.2013[19]	300	3 years	55(18.3%)	Abnormal myocardial perfusion imaging
Tetsuji Shinohara, et al.2012[20]	82	2 years	11(13.4%)	↑serum interleukin-6 levels
Lee S, et al.2011[21]	1,558 patients	47 months	144(9.2%)	↑hs-CRP levels
Hung WC, et al.2010[21]	193 patients	2 years	58(30%)	↑circulated adinopection levels
Carmine Gazzaruso, et al.2008[22]	291 patients	87 months	49(16.8%)	Erectile dysfunction

1. HYPERINSULINAEMIA

In the study conducted by Kumar A.et al with amedian follow up for 28months in 12,092 patients, MACE occurred in 238patients(11.6%). Of these events, 177 were coronary revascularization.Thetype 2 diabetes mellitus who underwent revascularizationwere noted to have significant higher baseline fasting plasma insulinlevels(p value=0.009) suggesting baseline fasting plasma insulin levels asan independent predictor for MACE [5]. Increase in the insulin levels may directly predispose thepatients to cardiovascular events through inflammatory andprothrombotic state, increasing the synthesis of plasminogen activatorinhibitor-1 which promote thrombus and increase the risk forprogression of atherosclerotic vascular events.

2. SIMULTANEOUS PANCREAS AND KIDNEY TRANSPLANTATION

The study conductedon SPKT recepients with Type 1 diabetes mellitus showed 7.8% of therecepients suffered from MACE.A non fatal cardiovascular events followingtransplantation significantly increases the risk of subsequent allograftfailure; suggesting that those experiencing events should be jointlymanaged by cardiology and transplantation team [8].

3.ECHOCARDIOGRAPHY

Echocardiography significantly and independentlypredicted MACE, including left ventricular ejection fraction(LVEF),impaired global longitudinal strain(GLS), diastolic mitral early velocity(E)or early diastolic tissue Doppler velocity. Monitoring of echocardiograph among diabetics cansignificantly reduce the risk for MACE [9].

4. RADIAL PULSE

Liao KM, et al showed first harmonic amplitude of radialpulse wave C1 is an independent risk marker for MACE and microvascularcomplications.Periodic radial pulse wave measurements and harmonicendpoint can improve the identification of patients with type 2 diabetesmellitus who need CVS treatment [10].

5. HIGH GLYCEMIC INDEX

A glycemic variability cutoff value of greater than2.70mmol/L was the strongest and independent predictive factor formidterm MACE in patients with diabetes [11].

6. LEAN FAT MASS

In a post hoc analysis to investigate the relationshipbetween predicted lean body mass/fat mass end to MACE in patients withtype 2 diabetes mellitus, predicted fat mass had a strong positiveassociation with a higher risk of MACE [12].

7. PREDICTIVE RISK MODELS

James B.Young showed that increase in age,diabetes related hospitalization prior to cardiovascular diagnosis andchronic pulmonary disease are the major predictors for MACE indiabetics patients.[13]

8. SKIN AUTOFLUORESCENCE

Since a marker for the metabolic memory ofhyperglycemia, th SAF plays a major role to predict macrovascular eventswhich are critical for

macroangiopathy in type 1 diabetes mellituspatients. The advanced glycated end products through their opticalproperties allow to estimate their accumulation in tissue by measuringthe SAF [14].

9. TOE BRACHIAL INDEX

In patients with type 2 diabetes mellitus, Toe brachialindex predicted the incidence of MACE independent of other cardio-metabolic as well as atherosclerosis risk factor [15].

10. RESIDUAL RISK FACTORS

A prospective observational study by Lin FJ,et al shows CKD stage 4 without beta blocker use, heart failure, higher non HDL-C,higher HDL-C and triglyceride level can predict the occurrence orprogressive of MACE among diabetics patients [16].

11. ACUTE KIDNEY INJURY

Acute kidney injury predict the risk of chronic non-fatal myocardial infarction, hospitalization for heart failure,lower limbamputation and revascularization, non-fatal stroke and renal failure [17].

12. GLYCEMIC CONTROL

MACE in patients with HbA1C level of 7.1% to8%,8.1%to 9%,9.15 to 10%,were 1.34,1.59,1.73 and 2.23 respectively inpatients with type 1 diabetes mellitus. Therefore, poor glycemic controlcan predict MACE in diabetes [18].

13. MYOCARDIAL PERFUSION INJURY

In the study by Kasim M,et al, abnormalmyocardial perfusion injury post stress left ventricular ejectionfactor(LVEF), can predict the occurrence/progression of MACE indiabetes [19].

14. INTERLEUKIN 6

Tetsujishinohara suggest the measurement of Interleukin 6as a useful tool to identify high risk patients of CVS events in type 2diabetes mellitus [20].

15. ADINOPECTIN

Elevated levels of adinopectin, an anti inflammatory andantioxidative peptide are associated with unfavorable cardiovascularoutcomes in patient with diabetes mellitus [21].

16. ERECTILE DYSFUNCTION

Carmine Gazzaruso showed erectile dysfunction as apowerful predictor of CVS morbidity and mortality in diabetes patients [22].

CONCLUSION

In this review, the known mechanism of diabetes induced cardiovascular events and the potential predictors which can be used to predict MACE among diabetic patients were discussed in detail. As diabetes is a prime risk factor for cardiovascular diseases and patients with diabetes have a 2 to 3 fold higher risk of suffering from cardiovascular event, certain interventions if performed during the diabetes state , can mitigate the risk of cardiovascular events. The further research is imporatnt in this area to add up to the limited literature of interventions or predictive models for MACE in diabetes to reduce morbidity, mortality and economic burden to the patients.

ABBREVIATIONS

MACE: major adverse cardiovascular events
T2DM: type2 diabetes mellitus
HDL: high density lipoprotein
LDL: low density lipoprotein
TG: triglycerides
TNF-α: tumor necrosis factorα
IL-β: interleukin beta
IL-6: interleukin 6
PRISMA: Preferred Reporting items for Systematic Reviews and Meta-Analysis
DNA: deoxyribose nucleic acid
CVS: cardiovascular
HS-CRP: high sensitivity c-reactive protein
HbA1C : glycated hemoglobin
SPKT: simulatenous pancreas and kidney transplatation
LVEF: left ventricular ejection fraction
GLS: global longitudinal strain
SAF: skin autofluorescence

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