A Study on Impact of Glycemic Abnormalities on Coronary Artery Disease

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Abstract

Introduction: Patients with Type 2 Diabetes Mellitus have found to be more susceptible to dysfunctioning of coronary microvessel, leading to the vasoconstriction of coronary micro vessels and hence, the arterial supply decreases significantly, compromising the oxygen and nutritional supply to areas of greater need. Type 2 Diabetes Mellitus causes endothelial dysfunction through a variety of mechanisms, including dyslipidemia, the production of advanced glycated end products, glucose buildup within the endothelium, etc. Endothelial dysfunction, on the other hand, induces or worsens type 2 diabetes mellitus by preventing glucose or insulin from reaching target tissues in a timely manner.

Aims and Objective: To statistically find out the correlation between abnormal variation of glucose level on the endothelial function of coronary vessels.

Materials And Methods: The prospective study has assessed the glucose variability with mean level of glucose and its maximum and minimum level. The study also determined the levels of mean absolute glucose, continuous overlapping net glycemic action and Mean amplitude of glucose excursion. The study employed student t-test and Mann Whitney U-test for statistical analysis.

Result: The study found that Mean Amplitude Of Glycemic Excursions had negative correlation with that of coronary endothelial function (P<0.05). Several parameters were analyzed statistically with other variables of coronary function.

Conclusion: This study has shown that higher the glucose variability, more is the impairment of coronary endothelial function. The study has also concluded that Mean Amplitude of Glycemic Excursions was negative relationship with endothelial function and peripheral endothelial function was not found to have significant association with Glucose Variability.

Keywords: glycemic index, glucose variability, endothelial function, coronary

Introduction

The cardiovascular disease are the leading cause of deaths for decades and there has been sharply increase of these deaths. Among all the cardiovascular associated deaths, 60% has been contributed by congestive type of heart failure and Coronary

Artery Disease (CAD) and in turn, leading to various other cardiovascular and non-cardiovascular complications including diabetes. The mechanism of heart failure and atherosclerosis is exacerbated by hyperglycemia. In addition to chronic hyperglycemia, glycemic variability is also an essential factor for cardiovascular disease [1,2].

Diabetes mellitus causes a wide range of cardiovascular problems. Inflammation, oxidation, vascular remodeling, and endothelial dysfunction are the main contributing factors to atherogenesis. The consequences on the heart, on the other hand, are related to concomitant hypertension and direct effects of diabetes on the myocardium. Coronary artery disease, hypertension, or other known cardiac conditions are not the main cause of diabetic heart disease in patients with diabetes which is known as a myocardial disease [2,3].

Patients suffering from type 2 diabetes shows an increased prevalence of coronary microvascular dysfunction which shows attenuation of microvascular vasorelaxation when there is increased demand for blood supply, which causes ischemia of the vascular system that leads to angina. Diabetes is a leading cause of cardiovascular disease in women than in men. Type 2 diabetes mellitus (T2DM) is linked to a higher risk of cardiovascular disease, which is mostly attributable to the onset of severe atherosclerotic vascular alterations early in life. Endothelial dysfunction has recently gotten a lot of attention as a possible contributor to the etiology of cardiovascular disease in type 2 diabetics. The mechanics underlying this occurrence are unknown, but they are likely to be complex. Type 2 diabetes mellitus causes endothelial dysfunction through a variety of mechanisms, including dyslipidemia, the production of advanced glycated end products, glucose buildup within the endothelium, increased oxidative stress, and low-grade inflammatory responses. Endothelial dysfunction, on the other hand,

induces or worsens type 2 diabetes mellitus by preventing glucose or insulin from reaching target tissues in a timely manner [4,5,6]

There are published works that show nephropathy and Type-1 diabetes are associated which has been proved in several clinical trials and long standing cases have been found with more cardiovascular effects. Poor metabolic level can also act as one of the major risk factor in Type-1 diabetes with or without related with renal causes. Patients with Type-1 diabetes and renal pathologies may also develop elevated cholesterol[7,8].

Acute coronary syndrome (ACS) and coronary artery disease (CAD) contribute in elevation of blood glucose and may cause diabetes mellitus in the long term. Excessive control of glucose targeting lower levels of glycated hemoglobin (HbA1c) has been demonstrated to enhance microvascular endpoints in critical clinical studies. Still, the link between glucose-lowering techniques and decreased occurrence of microvascular consequences is less obvious. In addition to HbA1c levels, glucose variability is also essential. Studies conducted stated that glucose variability shows more adverse effects on endothelial dysfunction than constant hyperglycemia also imaging shows that it is associated with a coronary plaque in patients with coronary artery disease [9,10].

Hypoglycaemic agents are prescribed in Type 2 diabetes to prevent cardiovascular associated complications. While intravenous and subcutaneous insulin is mostly used management option, it is mostly prescribed in type 1 than type 2. Insulin inoculation can lead to hypoglycemia in type 2 as the mechanism of type 2 does not include lowering of insulin hormone, instead, there is receptor pathology. But, in clinical practice, insulin can be prescribed in advanced stage of type 2 diabetes. The objective of management of type 2 diabetes includes prevention of hypoglycemia which can later advance to cardiovascular consequences, as mentioned by few literature [11].

Materials and Methods

This prospective study was conducted between Jan, 2021 to Dec, 2021 and the data was collected from a single center, intended to investigate the effect of Glycemic Variability (GV) on the endothelium. The patients who were included in this study had Chronic Coronary Artery Disease (CAD), patients who had drug eluting stent installed and patients who continuously received treatment in our institution. The patients who were excluded, had other chronic conditions, was on dialysis, Glomerular Filtration Rate (GFR) less than 30 ml/min/1.73 m^2, left ventricular fraction less than 30% and those who did not cooperate with the whole study process.

During the time of follow-up of coronary angiography, low-dose Acetylcholine (ACh) test was done to assess the coronary vasoreactivity. This test is considered to the gold standard diagnostic for evaluating coronary endothelial function.

The study assessed the glucose variability with mean level of glucose and its maximum and minimum level. Along with these, the study has determined the levels of mean absolute glucose, continuous overlapping net glycemic action and Mean amplitude of glucose excursion. The medications were continued while the study was done and Mean amplitude of glucose excursion was considered to be the primary determinant in this study.

Statistics

The study used SPSS 25 software for effective statistical analysis. The data representing continuous variable were presented as mean±standard deviation and data of categorical type were presented as absolute numbers and the corresponding percentages. The authors have used Mann Whitney test and student's *t*-test for effective analysis to find out *p*-value. The study has considered α value (level of significance) to be 0.05.

Results

The study found that the mean age of the sample is 66.25±7.8 years and mean Body Mass Index (BMI) was found to be 24.7±3.3. It was also found that the male and female was 68% and 32%, respectively. There was patients who had diabetes (52%), patients who were smokers (41%) and 26% of them had history of Myacardial Infarction (MI).

Table 1: Demography and Basic characteristics of the study population

Parameters	Value
Number of patients in this study	100
Age (years)	66.25±7.8
Males	68
Females	32
Body Mass Index or BMI (kg/m^2)	24.7±3.3
GFR (ml/min/1.73 m^2)	67.6±15.2
Diabetes	52 (52%)
Current Smoking	41 (41%)
Prior MI	26 (26%)

The study also listed down the current medications on which each patient was. The study found that 96% of them was on statin therapy, 92% of them was receiving antiplatelet therapy, 38% of the patients were on beta blockers while 35% of the patients was receiving calcium channel blockers. Table 2 shows the total number of patients receiving each drug.

Table 2: The current medications with respective number of patients

Medication	Number of patients
Beta Blockers	38
Calcium Channel Blocker	35
Statin	96
Sulfonylurea	15
Metformin	32
Oral hypoglycemic agent	5
Dipeptidyl peptidase 4 inhibitor	6
Antiplatelet agent	92

The study has recorded the findings of glucose monitoring among the study sample. It was found that the mean glucose level of the study sample is 120.5±25.12 mg/dl, Continuous Overlapping Net Glycemic Action was found to be 104.2±26.3 mg.dland Mean Absolute Glucose was 32.2±6.5 mg.dl. The study further found that Mean Amplitude Of Glycemic Excursions was 75.4±28.9 mg/dl. Table 3 shows the findings of glucose monitoring.

Table 3: The findings of glucose monitoring

Parameter	Mean±SD
Glucose (mean value) (mg/dl)	120.5±25.12
Maximum Glucose level	211.2±35.62
Minimum Glucose level	81.2±14.5
Continuous Overlapping Net Glycemic Action (mg/dl)	104.2±26.3
Mean Absolute Glucose (mg/dl)	32.2±6.5
Mean Amplitude Of Glycemic Excursions (mg/dl)	75.4±28.9

As this current study has evaluated the coronary endothelial function by employing the resultant obtained by dividing the difference between coronary vessels diameter exposed to ACh (Acetylcholine) and the initial diameter with that of initial diameter. This was done for the segment of coronary vessel (for both proximal and distal to stent). The same was done in case of assessing nitroglycerin. Reactive Hyperemia Index (RHI) was also assessed.
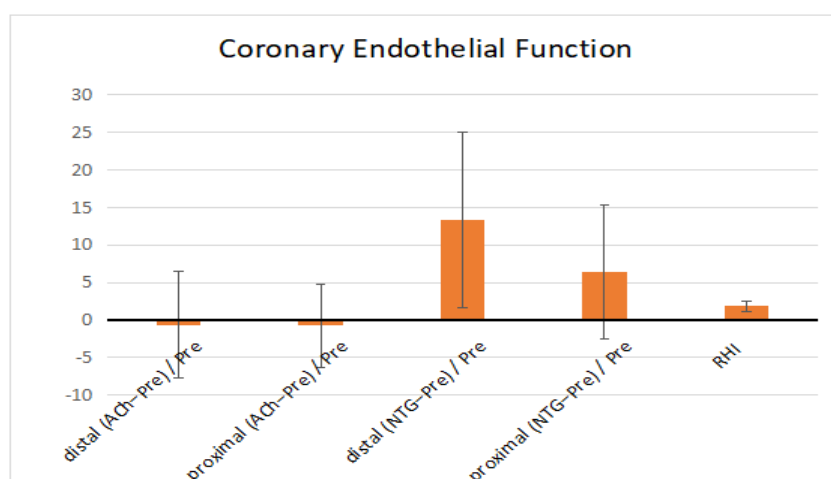

Figure 1: The findings of variables assessing the coronary endothelial function

The study correlated several parameters statistically. Negative correlation was observed between Mean Amplitude Of Glycemic Excursions and coronary endothelial function ($p<0.05$). The study found "r-value" and "p-value" for each parameter. The coronary vessel diameter was assessed distal to the stent placement when exposed to acetylcholine and nitroglycerine. The significance of the test is analyzed and shown. Table 4 shows the detailed findings.

Table 4: The relationship between glucose variability and coronary endothelial function

Parameter		Glucose (mean value)	Continuous Overlapping Net Glycemic Action (mg/dl)	Mean Absolute Glucose (mg/dl)	Mean Amplitude Of Glycemic Excursions (mg/dl)
Distal% (ACh-Pre)/Pre	r-value	-0.05	-0.038	-0.2	-0.39
	*p-value	0.75	0.82	0.24	0.03
Distal% (Nitroglycerin-Pre)/Pre	r-value	0.21	0.22	0.004	-0.02
	*p-value	0.28	0.23	0.96	0.85
RHI	r-value	-0.18	-0.16	-0.06	-0.15
	*p-value	0.3	0.44	0.65	0.32

* α = 0.05; ACh, acetylecholine; RHI, Reactive Hyperemia Index

Discussion

A meta-analysis has pointed out that poor prognosis can be responsible for elevated glycemic variability in patients suffering from CAD. A stratified analysis was conducted which concluded that glycemic excursion and cardiovascular events stay the same in patients with CAD with or without diabetes. The study concluded that the increased variations in the glycemic levels showed poor prognosis in coronary artery disease patients without any association with the sub-type of coronary artery disease and diabetes[9].

Another study which was conducted on chinese subjects with no coronary artery disease had shown that the association between fasting plasma glucose and the mortality of coronary artery disease. After 5 years of follow-up on more than 4000 subjects, coronary artery disease was diagnosed and about 1500 subjects had died [6,9,10]. There are studies which have analytically proved that increased fasting blood glucose is associated with cardiovascular risks and increased mortality due to cardiovascular consequences [10].

A double-blinded randomized trial was conducted in patients suffering from type 2 diabetes who are at high risk of developing cardiovascular disease where the safety of insulin glargine is compared with insulin degludec. The patients were randomized and given 100 units of insulin daily were the first outcome was developing a Major Adverse Cardiovascular Event (MACE). The all-cause mortality, hypoglycemia, and MACE are associated with the glycemic variabilities of day-to-day fasting which states that the higher variabilities in the day to day fasting glycemic levels shows an increase in the risk of developing a high mortality rate and severe hypoglycemia [11].

Another study analyzed the association of blood glucose with the occurrence of cardiovascular conditions. Both normal and

type 2 diabetic individuals developed oxidative stress and endothelial dysfunction at two distinct glucose concentrations (11 and 16 mmol/l). Continuous higher levels of glucose was proved to have greater effect on endothelium and more susceptible to cause oxidative stress. This study concluded that the oscillating glucose shows more adverse effects than constant levels of high glucose on the functioning of endothelial cells and oxidative stress [12].

A study was conducted on 70 cardiovascular disease patients to know the effects of fluctuation of daily glucose on a coronary plaque, evidences show that glucose fluctuation is an important risk factor in developing coronary artery disease excluding dyslipidemia which concluded that daily fluctuations in the glucose show an effect on the vulnerability of coronary plaque in patients priorly treated with lipid-lowering agents [13].

The effective management of type 1 diabetes slowers the microvascular and macrovascular risks. However, regular monitoring of the blood glucose level which can effectively prevent hypoglycemia. There are availability of different glucose monitoring system which can effectively prevent hypoglycemia in the patients with Type 1 diabetes. There is need to conduct further researches for assessing the management profiles of poorly managed patients of diabetes, specially of younger ages [14].

A prospective study was conducted on elderly males to examine the effect of age on cardiovascular disease who are followed up for 9 years. In this period there were 450 deaths due to cardiovascular disease, 370 individuals diagnosed with coronary heart disease, and 1110 people died due to all causes. Men with diabetes and myocardial infarction are excluded from the study and it showed that the late and early onset of diabetes showed an increased risk of developing major cardiovascular diseases. The study concluded that both late and early onset diabetes shows an increase in the risk

of cardiovascular disease and mortality rate but only diabetes with early-onset showed equivalent to coronary heart disease [15].

There are studies conducted in the past which have shown that there was no statistically significance finding between peripheral and coronary function [16]. Some studies have shown positive relationship between RHI and peripheral endothelial function [17]. On the contrary, this current study has found that Mean Amplitude Of Glycemic Excursions is negatively correlated with that of coronary endothelial function which was assessed by the gold standard (low dose ACh) in this study. The subjects of this study had stent installed which had shown to have effect of improvement on both the coronary and peripheral endothelial function. [18]

Conclusion

The study has pointed out some important conclusions. This study has shown that higher the glucose variability, more is the impairment of coronary endothelial function. Even the patients on statin therapy have shown the deteriorating coronary endothelial function. The study concluded that statin therapy has significantly improved peripheral and coronary endothelial function. The study also pointed out that there is a need to develop efficient management approaches for individuals with higher glucose variability. However, this study has some limitations as it was conducted in only single centre and the enrolled patients had CAD and stent implanted. Therefore, there is a need to conduct studies on larger and varied population. Lastly the study has concluded that Mean Amplitude Of Glycemic Excursions was negative relationship with endothelial function as discussed and peripheral endothelial function was not found to have significant association with Glucose Variability.

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