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Research Article

Glycemic Variation in Patients of Acute Coronary Syndrome with Hyperglycaemia and its Relationship with Oxidative Stress: A Pilot Study

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A B S T R A C T

Aim: The aim of this study was to establish the relationship between the glycemic variation in patients of Acute Coronary Syndrome (ACS) with hyperglycemia, oxidative stress and pre-discharge assessment of glycemic status by Oral Glucose Tolerance Test (OGTT).

Materials and Method: Nineteen non-diabetic patients who presented with acute coronary syndrome with random blood sugar ≥200 mg/dl were recruited and glycemic variation was measured using CGMS followed by measurement of 8-isoprostanes PG-2alpha as a marker of oxidative stress, and pre-discharge OGTT was done to know the glycemic status at the time of discharge.

Result: Mean MAGE (A parameter of glycemic variation) was 106.92±22.66 and mean 8-isoprostanes level was 206.05±179.57. There was no relationship between these two values. On doing OGTT, out of 19 non diabetic patients 11 turned out to be frank diabetic and 8 were having impaired glucose tolerance after OGTT, none were euglycemic.

Conclusion: The study highlighted the issue of hyperglycaemia in ACS patients and their abnormal glucose tolerance in the short term, most of them turning to be frankly diabetic and being totally asymptomatic till the time of index event, although no correlation was found between glycemic variability and oxidative stress.

Keywords: Acute Coronary Syndrome (ACS), Continuous Glucose Monitoring System (CGMS), Mean Amplitude of Glycemic Excursion (MAGE), Oral Glucose Tolerance Test (OGTT)

Introduction

At admission, hyperglycemia in patients with Acute Coronary Syndromes (ACS) is a common finding, and it is a powerful prognosticator of survival and increased risk of in-hospital complications in all patients irrespective of diabetic status.

Multiple studies showed that hyperglycaemia may have a direct deleterious effect on ischemic myocardium through a lot of mechanisms e.g., its association with QT prolongation, endothelial dysfunction, elevated systolic blood pressures, platelet aggregation and vascular inflammation. Higher glucose levels in patients with ACS have also been associated with insulin resistance. Recent data from human studies suggest that acute fluctuations in glucose levels i.e. Glycemic variation may have even more powerful impact on oxidative stress than chronic, sustained hyperglycaemia.[1]

Glycemic Variation (GV) means fluctuations in blood glucose level. Reduced or absent glycemic auto regulation or inadequacy of insulin availability is said to be the aetiology for these glycemic jerks. The comprehensive definition of GV considers glycemic excursions include episodes of hyper and hypoglycaemia over the course of the day. The postprandial hyperglycemic excursions too contribute to GV. Various parameters to measure GV are: M value, Mean Amplitude of Glycemic excursion (MAGE), Continuous Overlapping Net Glycemic Action (CONGA), Low Blood Glucose Index (LBGI) and High Blood Glucose Index (HBGI), Average Daily Risk Ratio (ADRR), Absolute mean of daily differences, Mean of Daily Differences (MODD). Out of all these parameters MAGE is considered as one of the best parameters of GV.[2] In one of the studies conducted to measure MAGE as a measure of glycemic instability, value of MAGE was small for normal people (range, 22 to 60 mg/ 100 ml), larger for stable diabetics (67 to 82 mg/ 100 ml), and largest for unstable diabetics (119 to 200 mg/ 100 ml).

In Continuous Glucose Monitoring System (CGMS) the sensor is inserted subcutaneously and it can reliably operate for up to 3 days, followed by replacement with a new sensor at different location, if required. Data are collected after every 5 min by a pager sized monitor device and can be downloaded periodically into a computer for analysis and interpretation.

Oxidative stress is an entity in which the production of free radicals may overrule the scavenging effects of antioxidants. Many studies have reported that increased oxidative stress and depressed antioxidant status have harmful effects on both cardiac structure and function. Oscillating glucose can have more deleterious effects than the constant high glucose on oxidative stress and endothelial dysfunction. Iso-prostanes (IsoPs), isomers of prostaglandins, are bioactive product of arachidonic acid metabolism. 8-iso-prostaglandin F2α (8-iso-PGF2α), as one of the most stable IsoPs, has become a "gold standard" measure of oxidative stress in vivo. 8-isoprostane levels have been associated with several cardiovascular risk factors but they have not been investigated in serum in patients of acute coronary syndrome with glycemic variability to the best of our knowledge.

Hyperglycaemia is seen in up to 50% of all ST Elevation Myocardial Infarction (STEMI) patients, whereas previously diagnosed DM is present in only 20% to 25% of STEMI patients.[3]

Materials And Method

The study was conducted at UCMS and GTB Hospital, Delhi, in the department of Medicine and Biochemistry. Nineteen patients without prior history of diabetes, presenting with ACS and RBS more than 200 mg/dl were recruited from emergency and Coronary Care Unit (CCU). Patients with ketoacidosis, sepsis, chronic liver, pulmonary, renal, cerebrovascular and autoimmune disorders, malignancies, pregnancy, psychiatric illness and patients not giving consent for CGMS were excluded from the study.

Study was conducted after taking informed consent from the patients. Patients presenting to emergency with classical features of chest pain, positive Trop T/CK-MB and ST-T changes were admitted in CCU for cardiac monitoring and anti-ischemic therapy as per ACC guidelines.

After stabilization CGM sensor and machine were applied on the anterior abdominal wall under all aseptic precautions and patients were followed for 48-72 hours.

The Medtronic iPro2 continuous glucose monitoring system consists of the iPro2 recorder and an implanted glucose sensor. The sensor was inserted just underneath the skin using the inserter, and the iPro2 recorder unit was attached to the sensor and adhered to the body with occlusive adhesive dressing. For retrospective CGM data correction and calibration, 4 capillary blood glucose value (before each meal and before bedtime) were also recorded to provide a calibration value. All patients were provided regular diet during the study. The CGM device was worn for approximately 48-72 hours, and after that the iPro2 recorder and sensor were removed. The data from the CGM and SMBG blood glucose meter were uploaded into the Care Link iPro software platform (Medtronic) and exported into Excel (Microsoft, Redmond, Washington).

The mean amplitude of glycemic excursions (MAGE), which has been described by Service et al was used in the study for assessing glucose fluctuations.[5] Glucose profile obtained from continuous monitoring for 48 hours were used. This parameter was designed to quantify major swings of glycemia and to exclude minor ones. For this reason, only increases of more than 1 SD of the mean glycemic values were taken into account. Calculation of the MAGE was obtained by measuring the arithmetic mean of the differences between consecutive peaks and nadirs; measurement in the peak-to-nadir or nadir-to-peak the first qualifying excursion. Calculation of MAGE is of particular interest since the greater the MAGE, the higher the glycemic instability.

On day 5-7 prior to discharge, all subjects underwent 75

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gm Oral Glucose Tolerance Test (OGTT) with standard precautions. Sample for fasting and 2 hr post glucose challenge blood sample were drawn. Results of OGTT was interpreted according to ADA guidelines as shown in the below mentioned Table 1.

Table I

	NGT	IGT	DM
FPG	<100 mg/dl	100-125 mg/dl	>126 mg/dl
2-H PG	<140 mg/dl	140-200 mg/dl	>200 mg/dl
A1C	<5.6 %	5.7-6.4 %	>6.5 %

Serum from the blood drawn was separated by centrifugation and was stored at - 80^{0}C for subsequent estimation of 8-isoprostanes level using ELISA kit (Bioassay Technology).

Statistical Analysis

Nineteen participants were included in the study. Data were entered in Microsoft Excel Spreadsheet and then analysed using SPSS software v 20.0. CGM parameters were analysed using Medtronic MiniMed CGMS Software 3.0. Data were presented as frequencies and percentages for categorical variables and mean±SD for continuous variables. Pearson correlation was done to correlate between glycemic variability (MAGE and 24Hr-MBG) and 8-isoprostanes level. P-value < 0.05 were considered to be significant.

Result

Nineteen patients (mean age 55.95; 11 males and 8 females) were investigated. 52.6% patients were smokers. Hypertension was present in 68.4%, CAD was present in 26.3% and 47.4% patients had dyslipidaemia. 26.3% patients were overweight and 10.5% were obese. Mean MAGE calculated was 106.92±22.66. Mean of 8-isoprostanes level was 206.05±179.57. MAGE did not correlate with 8-isoprostanes level. There was a positive correlation between LDL Level and 8-isoprostanes (r=0.71, p<0.001.) Eleven (57.9%) patients were diabetic and 8 (42.1%%) were having impaired glucose tolerance. There was a positive correlation between admission RBS and OGTT-PP but not between RBS and OGTT-FBS.

Discussion

The present study evaluated the glycemic variability (fluctuations in blood glucose level from peak to nadir) with CGMS, and its correlation with oxidative stress marker in non-diabetic patients presenting with acute coronary syndrome with hyperglycemia (RBS≥200 mg/dl), which were not qualifying for stress hyperglycemia.

It has been observed that hyperglycaemia is a common finding in ICU patients even in non-diabetics. Earlier it was considered as benign but of late it has been realised that it is associated with many complications especially in ACS patients e.g., CHF, reinfarction, arrythmias etc. Hyperglycaemia was associated with higher morbidity and mortality in these patients. Broadly in ACS population hyperglycaemia at admission is a short-term and long-term prognostic marker.

Glycemic variability is intraday glycemic excursions including episodes of hyperglycaemia and hypoglycaemia. It is expected to be more in diabetic patients that too more in type 1 DM than Type 2. GV can now be a better indicator of overall morbidity and mortality when compared with sustained hyperglycemia alone.

Most of the studies done on glycemic variability were on known diabetic patients. There is paucity of published literature on non-diabetic ACS patients. There is limited literature on reference range of glycemic variability in non-diabetic patients. One such study was done by Nathan R. Hill et al in which they estimated normal reference range for MAGE and other parameter of glycemic variability in normal subjects without diabetes in different ethnic groups.[6]

CGMS is gaining acceptance as one of the important tools in management of both Type 1 and Type 2 Diabetes despite its high cost, institutional uses and certain physical characteristics. Advances in technology is helping in increasing its use by physicians for better and advanced management of patients on insulin therapy and reducing the events of hypoglycaemia. Real time picture of various events, hypoglycaemia, timing of insulin therapy etc can be shown to patient's improvements made in the daily regimens.

Konstanty et al have done a study to determine the level of oxidative stress in acute coronary syndrome. They found that 8-iso PGF-alpha level was significantly higher in ACS patients (363.2±45.94) whereas level of 8-isoprostanes estimated was 206.05±179.57 in our study which was quite high in comparison to the previous study.[7]

In this study, the value of serum mean 8-isoprostanes were high but not as high as compared to other studies done in ACS patients. The reason could be other risk factors such as hypertension, regular smoking, hyperlipidaemia, and obesity being also associated with increased isoprostanes.[8-11] We found correlation between only LDL levels and serum isoprostanes and not with any other parameter.

The patients presented to us with hyperglycemia, did not qualify for stress hyperglycemia as in almost all the patients hyperglycemia persisted for more than 48-hours duration and on doing OGTT prior to their discharge none came under normal glucose tolerance category.

Although after adjusting the interval between repeated tests and age in multiple meta-regression model, performing an OGTT in ACS patients was not associated with lower diagnostic accuracy compared to non-ACS patients, which

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implies that it is rational to perform an OGTT to screen for diabetes in patients with ACS prior to discharge, but due to poor reproducibility of the OGTT, it will be appropriate to repeat the test after discharge, which has been recommended in the WHO 1999 criteria, although optimal time to repeat OGTT is still not defined, OGTT could be repeated at 3 months after hospital discharge if necessary.

Small sample size was the major limitation of this study which limited statistical power of most of the results. However, despite the small sample size, the study highlighted the issue of hyperglycaemia and abnormal glucose tolerance in ACS patients in short term as most of them turned out to be frankly diabetic and had been totally asymptomatic till the time of index event. The hyperglycaemia seems to be behaving like a risk factor for subsequent development of diabetes mellitus or impaired glucose tolerance in patients with ACS and therefore it can be recommended that all patients with hyperglycaemia labelled stress-induced or otherwise should have a mandatory OGTT and preferably along with HbA1C for proper diagnosis and management of diabetes in these patients.

Conflict of Interest: None

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