Correlation Of Glycemic Status With Indicators Of Myocardial Oxygen Usage

Asha Shrivastava*, Sanjay Wasnik, Rashmi Dave*****

* Professor, **Senior Resident, *** JR-II, Department of Physiology, Gandhi Medical College, Bhopal, 462003

Abstract: Background: Present study aimed to investigate the correlation between poor glycemic control determined by glycosylated haemoglobin(A1C) and myocardial oxygen demand. Method: Case-control study comprised of three groups of 50 each age matched (30-45 yrs) normoglycemics, prediadetics and type 2 diabetic mellitus (T2DM) as per American Diabetic Association 2011 (ADA) criteria. The haemodynamic determinants of myocardial oxygen demand measured were heart rate(HR), systolic blood pressure(SBP) and rate pressure product(RPP) Result: The observations revealed significant differences in the fasting plasma glucose(FPG) and glycosylated haemoglobin (A1c) in the three groups. The resting HR was significantly higher in patients with T2DM (91.06±4.72 bpm;p=<0.0001) in comparison with controls and prediabetics. The SBP values (mm Hg) were in prehypertensives range in prediabetics and T2DM patients (125.5±4.0; 130.6±5.2). The RPPwas estimated to be significantly higher in T2DM (11922.9±1091.2) compared to prediabetics and controls (10197.6±806.1;8186.8±635.3). Positive correlation was found between resting HR(r=0.97,0.98) and RPP(r=0.98,0.98) with FPG levels in prediabetic and T2DM patients. Similar positive correlation was established between resting HR(r=0.96,0.95) and RPP(r=0.97,0.95) with A1c values. Conclusion: Heightened resting HR and RPP in prediabetics and T2DM patients suggest increased myocardial oxygen demand. These haemodynamic derangements render them vulnerable to adverse outcomes.

Key words-Resting heart rate (HR), Rate pressure product (RPP), Systolic blood pressure (SBP)

Author for correspondence: Dr.Asha Shrivastava, Department of Physiology, Gandhi Medical College, Bhopal–462003.e-mail:drashashrivastava@gmail.com, rdave1987@gmail.com

Introduction: Subjects with T2DM or glucose intolerance are prone to earlier development of coronary and extracoronarymicrovascular and macrovascular complications[1]. Studies have reported that higher cardiovascular risk in patients with T2DM may be due to dysfunctional adrenergic control of myocardial oxygen perfusion and reduction in myocardial oxygen delivery [2]

High resting heart rate reflects an imbalance of the autonomic nervous system, with increased sympathetic activity and/or reduced vagal activity[3]. Heart rate is a major determinant of myocardial oxygen consumption and energy utilization[4]; furthermore, an increase in heart rate reduces the diastolic coronary perfusion time[5].Therefore,increase in heart rate may trigger ischaemic events. Stevens MJ et al and Sayer JW et al reported disturbance of sympathovagal balance evidenced by resting tachycardia in T2DM patients[6,7].The product of HR and SBP is referred to as RPP which is a very reliable indicator of myocardial oxygen demand and is widely used clinically. Epidemiological studies have reported increasing prevalence of hypertension in T2DM patients. Systolic hypertension is known to increase myocardial oxygen demand[8]. Hyperglycemia showed independent association with heightened rate pressure product. These haemodynamic derangements may contribute to undesirable adverse cardiovascular events in T2DM patients3. Epidemiological evidence suggest that complication of T2DM begin early in prediabetic stage[9].As the risk and adverse consequences of high FPG occur at much lower fasting plasma glucose levels. Present study aimed to examine the association of FPG level and A1c with determinants of myocardial oxygen usage.

Material and Method: The study was carried out at the Department of Physiology and Medicine, Gandhi Medical College, Bhopal,Madhya Pradesh (M.P).The study was approved by institutional Ethics Committee Informed consent was obtained from each participating subject.

Study design: Based on the reported prevalence of 2.9% of T2DM in M.P (WHO-2012).Sample size of 43 was calculated using Daniel formulae[10] with alfa error of 0.05 and beta errors of 20%.

A total of 300 adults in the age range of 30-45 years were screened from urban Bhopal. On the basis of ADA 2011 criteria[11]and Joint National Commitee criteria (JNC-7)[12] subjects were classified. After standard exclusion criteria were applied to ensure that any change in heart rate detected were due to hyperglycemia,50 healthy controls,50 prediabetics and 50 newly diagnosed T2DM patients were included in the study. History of prior anti hypertensive and anti diabetic drugs use were excluded from the study.

Study participants were divided into three groups; Controls (groupI) defined as normoglycemics and normotensives (SBP<120 mm Hg, DBP<80 mm Hg); Prediabetics (group II) defined as FPG 100-125 mg/dl or A1c 5.7-6.4% and SBP <140 mm Hg and/or DBP < 90 mm Hg and T2DM (group III) defined as FPG ≥126 mg/dl; A1c≥6.5 gm%

T2DM diagnosed within 1 year and not on any medications were selected for the study. Baseline clinical characteristics, anthropometric measurements and biochemical data were recorded as per the standard procedures[13].Subjects underwent clinical examination under standardized conditions. Resting heart rate was recorded after 5 min rest in supine position by using Electrocardiograph(ECG) machine – (Cardiart 6208 – 12 standard limb lead digital electrocardiogram of BPL Healthcare with recording sensitivity of 5-10-20 mm/mV).The highest heart rate achieved was calculated (1500/R-R interval).

Brachial artery blood pressure (first and fifth Korotkoff Sounds) of right arm was measured three times consecutively with 15 minutes interval on seated participants after they had rested for 5 minutes, with the use of a standardized mercury Sphygmomanometer (Diamond, Industrial Electronic and Allied Products, Pune) and Stethoscope (3M Littman Classic II, German D).The mean of the last two of these measurements was used for estimation of blood pressure. In cases where high blood pressure was recorded for the first time, the blood pressure was checked more than twice and average of two close readings was taken.
Rate pressure product (Robinson Index)[14]is calculated as a product of systolic blood pressure and heart rate (RPP=SBPxHR) and expressed in mm Hg.bpm[15]

Fasting plasma glucose was measured by glucose oxidase peroxidase method (GOD-POD) using autoanalyser (MERCK300) using kits supplied by AGGAPPE diagnostics, Kerela(Product number 11018001). A1c was measured by microcolumn method at recommended temperature (AGGAPPE) and is quantified by direct photometric reading at 415 nm by photocalorimeter.

Statistical analysis: All values were expressed as Mean ±Standard deviation. ANOVA was done to compare groups. Bivariate correlations between variables were evaluated by Pearson's correlation. Statistical analysis was done using SPSS-16.0 (Statistical package for Social science)

Result:

Table 1: Baseline Characteristics Of Study Population

PARAMETERS	GROUP I (n=50)	GROUPII (n=50)	GROUP III (n=50)	F value	P value
AGE (years)	38.5±4.3	38.8±4.6	38.2±4.5	0.234	NS
BMI (kg/m2)	21.9±1.3	25.5±2.2	28.2±3.2	85.03	0.001
SBP (mm Hg)	112.4±5.0	125.5±4.0	130.6±5.2	188.2	0.001
DBP (mm Hg)	73.1±2.9	83.3±4.1	83.9± 2.2	183.2	0.001
HR (bpm)	72.7±4.2	81.2±5.8	91.0±4.7	170.2	0.001
RPP(SBPxHR)	8186.8±635.3	10197.6±806.1	11922.9±1091.2	233.5	0.001

*****Resting values of SBP, DBP and HR were taken.

Table 2: Biochemical profile of study group

Parameter	Group I	Group Ii	Group Iii
FPG(mg/dl)	84.1±8.3	112.4±7.0	149.1±12.3
A1c (%)	4.9±0.5	5.6±0.4	7.7±0.01

Table 3: Correlation of metabolic indicators of oxygen usage with glycemic status

	Group I (R)	Group Ii (R)	Group Iii (R)
FBG vs HR	0.74	0.97	0.98
HbA1c vs HR	0.18	0.96	0.95
FBG vs RPP	0.74	0.98	0.98
HbA1c vs RPP	0.14	0.97	0.95
FBG vs SBP	0.63	0.95	0.95
HbA1c vs SBP	0.09	0.95	0.92
FBG vs DBP	0.51	0.94	0.95
HbA1c vs DBP	0.14	0.94	0.94

As depicted in table1 baseline characteristics are distributed differently in three study groups ($p<0.001$), which is indeed a prerequirement for study.

Prediabetics and majority of T2DM patients were classified as overweight as per WHO criteria[16] (BMI 25-29.99). 2.4% T2DM patients were obese (BMI>30 Kg/m2) and were categorised as prehypertensives as per JNC-7 criteria[12]. No resting tachycardia as identified.
Diabetic patients showed poor glycemic control as evident from the FPG and A1c values as evident from Table 2.

This study does establish a very strong correlation among variables of glycemic status (FPG and A1c) and variables of myocardial oxygen usage (resting HR, SBP, RPP) in prediabetics and T2DM patients compared to normoglycemic participants [Table 3].

Discussion: Elevated heart rate (HR) is a risk factor for cardiovascular morbidity and mortality in healthy people as well as in patients with cardiac diseases is supported by numerous epidemiological association studies.[17-20] Elevated HR is frequently associated with high blood pressure (BP) and metabolic disturbances and increases the risk of new onset hypertension and diabetes[17]. In the present study resting HR was found higher in T2DM patients as compared to healthy normoglycemic controls. No resting tachycardia was found(Table 1) .The pathogenetic connection between HR and cardiovascular disease has been discussed in several reports[18-19,21,22]

The results of two recent longitudinal analyses have shown that elevated HR may predispose to the development of obesity and type 2 diabetes mellitus[23-25]. In the present study heart rate in prediabetics was on higher side than subjects with normal plasma glucose levels. The observation suggests increased future Type 2 diabetic and cardiovascular risk in these subjects. The elevated heart rate in prediabetics might be due to increased sympathetic tone and insulin resistance [26-30].

The prediabetics and T2DM patients were found overweight (BMI>24.5 kg/m^2). Di Carli MF et al studied the role of chronic hyperglycemia in the pathogenesis of coronary microvascular dysfunction in 35 young type 1 and 2 diabetic patients[31]. Positron emission tomography imaging was used to measure myocardial blood flow at rest. They reported reduction in myocardial blood flow and impaired coronary vascular function in patients with DM, suggesting a key role of chronic hyperglycemia in the pathogenesis of vascular dysfunction in diabetes.

An important observation in present study was that SBP was found in prehypertensive range in prediabetics and newly diagnosed T2DM patients. Elevated SBP also increases myocardial oxygen demand and together with elevated heart rate would tend to increase future cardiovascular risk. The elevated RPP is an important indicator of heightened oxygen demand. The higher values of HR, SBP and RPP in prediabetic group indicates increased myocardial oxygen usage much before the beginning of T2DM.

K. Foo, N.Sekhri et al studied the effect of diabetes on heart rate and other determinants

of myocardial oxygen demand in acute coronary syndromes. They found higher values of heart rate, systolic blood pressure and rate pressure product in patients with diabetes than without diabetes. They concluded that in patients with diabetes and coronary artery disease reduction in myocardial oxygen delivery may be compounded by increased myocardial oxygen demand, increasing the risk of regional ischaemia[2].

Glycated haemoglobin has been used to monitor glycaemic control in diabetics for more than two decades. It helps clinicians and their patients to stratify the treatment strategy and avoid long-term complications. In the present study fasting blood glucose (mg/dl) and A1c levels were positively correlated with resting heart rate and rate pressure product.

Elevated A1c increases the risk of micro-vascular and macro-vascular complications in diabetics as well as non-diabetics. As previously reported, A1c levels below the threshold for a diagnosis of prediabetes (<6.5%) are associated with a very high risk of CHD[32].

Park S et al studied the effect of A1c in non diabetic population as a better predictor of cardiovascular disease and coronary heart disease related mortality than fasting or post prandial glucose levels[33]. Poor glycemic control in patients with T2DM as evidenced by their A1c values (>7%) makes them more vulnerable to future cardiovascular complications.

Study Limitation: The autonomic functions were not measured and their relation to haemodynamic parameters were not recorded which was potentially relevant to confirm sympathovagal imbalance. Measurement of A1c was done by microcolumn method not by ADA recommended ELISA method.

Conclusion: Our study concluded that not only diabetics but prediabetics are also equally prone to cardiovascular risk. Thus simple non invasive measures like resting heart rate and rate pressure product in prediabetics and T2DM patients may prove to be beneficial in early detection of autonomic neuropathy and prevention of future cardiovascular mortality and morbidity.

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