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Original Article

Myocardial Work Stress is Linked to the Levels of Glycated Hemoglobin in Indian Prediabetic Population

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ABSTRACT

Background and Aim: Cardiovascular disease and diabetes mellitus are major health concerns In India. Prediabetes shares common pathology with these two diseases. However, the factors contributing to myocardial dysfunction in prediabetes have not been assessed. In this study, we have assessed various cardiometabolic factors contributing to myocardial work stress in in prediabetic subjects. **Methods:** In the present study, the anthropometric parameters, parameters of insulin resistance, inflammation, oxidative stress, glycated hemoglobin (HbA1c), lipid profile, atherogenic lipid risk factors and Rate-pressure Product (RPP), the marker of myocardial work stress were assessed in early middle-aged prediabetes population (n=33) and compared with healthy non-diabetic controls (n=36). **Results:** Prediabetes subjects had increased body mass index (P<0.01), waist-hip ratio (P<0.05), lipid risk factors of atherosclerosis [TC/ HDL-C; P<0.05, LDL C/ HDL-C; P<0.05 and atherogenic index (AI) P<0.05], HbA1c (P<0.001), oxidative stress (increased malondialdehyde; P<0.001 and decreased total antioxidant status, P<0.001) and increased high-sensitive C-reactive protein (P<0.01). They had higher Basal Heart Rate (BHR) (P<0.05) and RPP (P<0.05) denoting increased CV risk in comparison to controls. **Conclusion:** There is myocardial work stress in the form of increased RPP in Indian prediabetic population. The RPP in prediabetes could be linked to increases HbA1c. RPP being a non-invasive risk marker may be studied further to assess its implication as a screening tool for determining CV risks in prediabetes.

Key words: Atherogenic index, Cardiovascular risk, Myocardial work stress, Oxidative stress, Rate pressure product.

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INTRODUCTION

Prediabetes is defined as a stage preceding diabetes mellitus characterized by impaired fasting glucose or impaired glucose tolerance or both. Fasting glucose and insulin assessment are preferred over time-consuming OGTT especially in young people with insulin resistance for evaluation of glycemic status.[1] Accordingly, as per the American Diabetes Association (ADA) criteria, prediabetes is defined as a condition where the Fasting Serum Glucose (FSG) falls within 100-125 mg/dL (5.6 Mm/L- 6.9 mM/L). It has been reported that prediabetes is not only the high risk for future development of diabetes mellitus[2] but also is a potential risk for Cardiovascular Disease (CVD).[3] Coronary atherosclerosis and plaque vulnerability have been reported to be more advanced in prediabetes subjects compared to the non-diabetic patients.[4]

CVD and Diabetes Mellitus (DM)[5,6] are two major health problems In India. Several factors such as insulin resistance, hyperglycemia, dyslipidemia, hypertension, inflammation, etc. have been cited as the mechanisms linking prediabetes and diabetes with CVD.[7] Therefore, considering the morbidity and economic burden of CVD and DM and the underlying common pathophysiological mechanisms shared with prediabetes, presently the emphasis is on early identification of these Cardiovascular (CV) risk factors in prediabetes population as part of preventive and intervention measures in India.

Elevated glycated hemoglobin (HbA1c), a marker of chronic hyperglycemia, is independently associated with Cardiovascular (CV) outcomes in diabetes and even in individuals without a diabetes diagnosis.[8,9] One plausible mechanism by which hyperglycemia may contribute to CVD risk is via the development of hypertension as previous research demonstrates the associations of hyperglycemia with endothelial dysfunction and vascular stiffness, both of which are linked to increased blood pressure and CVD risk.[10,11]

Rate-pressure Product (RPP), the non-invasive marker of myocardial work stress, has been reported to be the indicator of the severity of type 2 diabetes, especially in diabetic neuropathy patients.[12] However, to best of our knowledge, the link of HbA1c to RPP has not been reported in Indian population. Also, no study has been performed till date to assess the association of HbA1c with RPP and other mark-

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ers of CV risks in prediabetes. Therefore, in the present study, we aimed at analyzing the link between lipid risk factors, makers of oxidative stress and inflammation and alteration in HbA1c to RPP to in prediabetes in Indian population.

MATERIALS AND METHODS

Initial Screening and Recruitment of the Subjects

This cross-sectional study was conducted in the departments of Biochemistry and Physiology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry, India, after obtaining the approval of Scientific and Ethics committees of the Institute.

For recruitment of subjects, we selected two municipality areas of Pondicherry city for free health check-up camps and selected apparently healthy subjects who volunteered to participate in our study. These subjects were not under any medication.The study protocol was explained all the subjects and informed written consents were obtained from all before starting the study procedures. After 10 to 12 hr of fasting following dinner, subjects were instructed to report to Biochemistry and Physiology laboratories for the collection of fasting blood sample and recording of physiological parameters.

Grouping of the Subjects

Following the general health examination by a physician from Medicine Department of JIPMER, individuals with the history of smoking, alcoholism, diabetes mellitus, CVD, renal disorder, inflammatory diseases and pregnant or lactating ladies were excluded from the study. Selected volunteers were divided into two groups according to their Fasting Serum Glucose (FSG) values based on American Diabetes Association 2013 criteria.[13]

Control (Normoglycemic) Group (n=36): The normoglycemic volunteers with fasting serum glucose less than 100 mg/dL were included in the control group.

Study (Prediabetes) Group (n=33): FSG values between 100 to 125 mg/dL were categorized as prediabetes subjects.

Anthropometric Measurements and Estimation of Biochemical Parameters

After obtaining written informed consent from subjects, their height and weight were measured to calculate Body Mass Index (BMI). Waist and hip circumferences were measured to determine the Waist-hip Ratio (WHR). Fasting blood was collected by venipuncture from all the subjects under aseptic conditions. The serum was separated into aliquots for storage at −40°C for further biochemical analysis. Estimation of glucose and lipid profile was done by using commercial kits adapted to clinical chemistry auto analyzer (Olympus 400, Beckman Coulter, Orlando, FL, USA). Fasting insulin was measured using INSULIN ELISA (Diametra, M/S biogenix, UP, INDIA) following manufacture instructions. Direct determination of HbA1c was done in human blood by immune-turbidimetry method.[14] MDA was estimated by using TBA method.[15] TAS was measured by using ferric reducing antioxidant power assay (FRAP).[16] hsCRP was measured using CRP ELISA from Cal biotech (Bio diagnosis, Chennai).

Measurement of Blood Pressure and RPP

The systolic and diastolic blood pressures and heart rate were recorded and rate pressure product (RPP) was calculated during the formula, RPP = Systolic pressure × BHR × 10^{-2}.[17]

Statistical Analysis of Data

SPSS version 16 (SPSS Software Inc., Chicago, IL, USA) and Graph Pad In-Stat software (Graph Pad Software Inc., San Diego, CA, USA) were used for statistical analysis. All the data were presented as mean ± SD. Normality of data was tested by Kolmogorov Simonov test. Comparison of the difference in continuous variables between test and control groups was made by student *t*-test for parametric data and by Mann Whitney test for non-parametric data. The association of quantitative data of anthropometric, biochemical and physiological parameters was done by Pearson correlation analysis. Multiple regression analysis was carried out to identify the independent contribution of associated parameters towards the outcome variable. All statistical analyses were performed at 5% level of significance and a P value < 0.05 was considered significant.

RESULTS

There was no significant difference in age between non-diabetic and prediabetes subjects (Table 1). The body weight, BMI and WHR of subjects of the study group, were significantly more compared to that of the control group. The basal heart rate ($p<0.05$), systolic blood pressure ($p<0.01$), diastolic blood pressures ($p<0.05$) and RPP ($p<0.01$) were significantly higher in prediabetic subjects compared to control subjects (Table 1).

Both fasting glucose and insulin levels were higher ($p<0.001$) in prediabetes. The corresponding insulin resistance calculated by HOMA-IR was higher (Table 2). The mean glycated (HbA1c) level was also higher ($p<0.001$) in the test group than control group. Though, fasting lipid profile values had no significant difference between the groups, when we calculated the lipid risk factors such as Triacyl glycerol / HDL-Cholesterol, Total-Cholesterol (TC) / HDL-Cholesterol, LDL-Cholesterol / HDL-Cholesterol and atherogenic index, etc., all these parameters except non-HDL-Cholesterol (NHC) were found to be significantly increased ($p<0.05$) in prediabetes group compared to the control group (Table 2).

There was a significant increase ($p<0.001$) in MDA level and a decrease in total antioxidant status ($p<0.001$) in prediabetic subjects compared to controls (Table 2). When the ratio of MDA to TAS was calculated, it was found to be higher ($p<0.001$) in study group suggesting either an increased rate of oxidation or decreased rate of antioxidant activity in prediabetic subjects. The hs-CRP, the general marker of inflammation was significantly increased ($p<0.01$) in the study group compared to the control group (Table 2).

HbA1c was found to be correlated positively with elevated levels of fasting serum glucose, MAP, RPP and BHR and negatively with a decreased level of TAS and MDA/TAS as well (Table 3). To assess the independent contribution of significantly correlated parameters to HbA1c, multiple regression analysis was performed, which demonstrated the significant association of RPP with HbA1c in prediabetes group (Table 4).

DISCUSSION

The major findings of the present study are significantly increased resting heart rate and RPP (the markers of CV) risks and markers of oxidative stress that were correlated with HbA1c, in prediabetes subjects (Table 3). Multivariate analysis demonstrated the independent association of RPP, the marker of myocardial work stress, with HbA1c (Table 4). As RPP is the product of heart rate and SBP, the close association of HbA1c with RPP in prediabetes subjects indicates that HbA1c might be a predictor of CV risks in prediabetes.

The present study compared the anthropometric, cardiovascular, glycemic, biochemical, oxidative stress and inflammatory parameters between apparently healthy prediabetes subjects with healthy non-diabetic volunteers of similar age and gender from the community. The study also analyzed the association of these parameters with glycated hemoglobin

Table 1: Comparison of age, anthropometric indices, heart rate, Blood Pressure (BP) parameters and RPP between healthy control (normoglycemic subjects) and prediabetis subjects.

	Control Group (*n*=36)	Prediabetes Group (*n*=33)
General parameters		
Age (Years)	37.25±7.82	38.54±6.98
Body Weight (Kg)	59.85±10.40	69.46±11.45***
BMI (Kg/m^2)	23.80±3.41	27.44±4.28**
Waist-Hip ratio	0.87±0.05	0.91±0.06*
Cardiovascular parameters		
BHR (beats per min)	75.38 ±7.34	81.53 ±8.56*
SBP (mmHg)	117.50 ±11.90	125.24 ±10.87*
DBP (mmHg)	68.80 ±8.58	73.90 ±7.86*
RPP (mmHg/min)	89.94 ±10.32	101.24 ±12.91**

*P<0.05; **P<0.01; ***P<0.001 by Student's unpaired '*t*' test. BHR: basal heart rate; SBP: systolic blood pressure; DBP: Diastolic blood pressure; RPP: rate pressure product.

Table 2: Comparison of glycemic and biochemical parameters and lipid risk factor between normoglycemic and prediabetes groups.

	Control Group (*n*= 36)	Prediabetes Group (*n*= 33)
Glycemic parameters		
Hb A1c (g% of Hb)	5.24±0.22	6.12±0.28***
Glucose (mM/L)	85.20±7.80	111. 10±7.55***
Insulin (µU/mL)	7.92 ±5.22	12.90 ± 9.10ΨΨΨ
HOMA-IR	1.67±1.10	3.54 ± 2.80ΨΨΨ
Lipid profile		
TC (mg /dL)	170.86 ± 34.20	181.34±39.77
LDL C (mg /dL)	105.22 ± 30.12	111.63 ± 31.57
TG (mg /dL)	103.80 ± 58.10	121.45 ± 67.30
VLDL C (mg /dL)	20.60 ± 8.20	24.82 ± 10.86
HDL C (mg /dL)	48.10 ± 9.25	45.56 ± 9.30
Lipid risk factors		
Non HDL-C	125.60±32.56	135.20±34.45
TG/ HDL- C	2.32±1.49	2.88±1.56 Ψ
TC/ HDL-C	3.66±0.84	4.10±0.82*
LDL-C/ HDL-C	2.21±0.65	2.45±0.77*
Atherogenic index	0.28±0.22	0.39±0.25*
OS and inflammatory parameters		
Serum MDA (µm/L)	6.10±1.82	11.70±2.15***
TAS (µm/L)	2550.90±325.70	1245.00±450.10ΨΨΨ
MDA/TAS	0.002±0.0006	0.011±0.004***
HsCRP (mg/L)	2.22 ± 1.35	3.10 ± 1.42**

The values are expressed as Mean ± SD. *P<0.05; **P<0.05; ***P<0.001 by Student's unpaired '*t*' test and ΨP<0.05; ΨΨΨ P<0.001 by Mann Whitney U test. Atherogenic index: $\log_{10}$(TG/HDL-C).MDA: Malondialdehyde; TAS: Total antioxidant status; hsCRP: high sensitive C reactive protein; OS: Oxidative stress.

Table 3: Pearson correlation analysis of serum HbA1c with other anthropological and biochemical parameters between healthy control and prediabetic subjects (*n*= 33).

Parameters	Prediabetes Group	
	r	*P*
BMI	0.184	0.233
WHR	−0.162	0.300
MAP	0.341	0.048
BHR	0.373	0.030
RPP	0.466	0.005
FSG	0.291	0.021
Non HDL-C	0.113	0.376
TG/ HDL- C	0.077	0.548
TC/ HDL-C	0.078	0.542
LDL-C/ HDL-C	0.024	0.852
AI	0.124	0.331
TAS	−0.332	0.008
MDA/TAS	0.366	0.003
hsCRP	0.062	0.631

FSG : Fasting serum glucose; TAS: Total antioxidant status; MAP: Mean arterial pressure; BHR: Basal heart rate; RPP: Rate presuure product = SBP × HR/100. P < 0.05 was considered significant

Table 4: Multiple regression analysis of RPP (dependent variable) with biochemical and physiological parameters in prediabetes subjects (*n*= 33).

Independent	B	95% CI of B	β	*P*
Variable				
HbA1c	26	(11- 41)	0.516	0.001
Waist-hip ratio	152	(45- 258)	0.414	0.006

RPP: Rate presuure product = SBP×HR/100. P < 0.05 was considered significant. β: Standardized regression coefficient; 95% CI: 95% confidence interval of unstandardized regression coefficient B.

level in middle adult age group (30-45 years) subjects in Indian population.

The mean BMI and waist-hip ratio were both significantly more in prediabetes subjects. As per the Asian criteria, the mean BMI of the prediabetes group was in the overweight range (>23.5 Kg/m^2). Traditionally obesity has been associated with insulin resistance as in many studies. In the present study, the prediabetes subjects demonstrated significan-thyperinsulinemia and increased HOMA-IR even though both insulin (<30 IU/mL) and HOMA-IR (<3.8) values were within physiological range (Table 1). This finding suggests that the study group subjects are in the early phase of commencement of insulin resistance with the onset of prediabetes and the hyperinsulinemia observed may be a coping mechanism of the body trying to keep serum glucose in range.

All the CV parameters such as BHR, SBP, DBP and RPP were significantly increased in prediabetes group. BHR is an index of vagal tone and increases in resting heart rate indicates the CV risk.[17] RPP is a measure of myocardial oxygen load and contractility and increased RPP indicates myocardial work stress.[17,18] Increased heart rate and RPP are reportedly associated with increased CVD risk.[17,18] Thus the finding of the present

study suggests that the onset of prediabetes heralds the onset of deterioration of CV health.

Though hyperlipidemia is a traditional risk factor for CVD, in our study, we did not find any difference in the fasting lipid profile. However, when individual lipid risk factors were calculated, we found four out of five parameters were significantly raised in the study population. Lipid risk factors that take into consideration of the ratio of bad to good cholesterol are better indices than the lipid profile per se. These include Non-HDL-Cholesterol (NHC), Triacyl Glycerol (TG) / HDL-Cholesterol, Total-Cholesterol (TC) / HDL-Cholesterol, LDL-Cholesterol / HDL-Cholesterol and atherogenic index. Moreover, NHC and TC / HDL- Cholesterol is even better indicators for predicting CVD than Apo-lipoprotein fractions.[19] Atherogenic Index (AI) is a plasma marker of pathological atherogenesis due to its close relationship with coronary artery disease and its inverse relationship with LDL particle size.[20] In our study, all lipid risk factors except NHC were significantly higher in prediabetes, which indicates that in prediabetes individual with sugar and lipid profile apparently more are at higher CV risk compared to the age and gender-matched the non-diabetic individual.

Among several indirect measures of oxidative stress, malondialdehyde (MDA) is used as a common parameter as it indicates the degree of lipid peroxidation.[21] Similarly, though there are several antioxidants in the body, estimation of the Total Antioxidant Assay (TAS) is indicative of general pool of antioxidant defense. Increased TG is reported to increase OS.[21] In our study, MDA was significantly higher with a significant depletion in TAS in prediabetes subjects. Oxidation of lipid converts lipid into peroxide products such as MDA which is a very common indicator of oxidative stress. There are several antioxidant molecules in the body such as glutathione, glutathione peroxidase, catalase, etc. TAS assay estimates the overall antioxidant capacity of serum. Therefore, the ratio of MDA/TAS was very high in the study group, indicating a deteriorating antioxidant defense against the ongoing oxidant assault. As such, ratio of MDA/TAS has been reported as a better determinant of oxidative stress.[22] In our study, the rise in TG level was not statistically significant and this may be due to a wide standard deviation of this parameter. This may suggest that in prediabetes subjects despite normal TG level compared to non-diabetic controls, the rate of oxidation is higher and antioxidant defense is lower resulting in higher net oxidative stress.

Among several parameters of inflammation, hs-CRP is not only considered as the most common marker but also is an independent predictor of cardiovascular risk.[23] According to serum CRP level, risks of CVD are categorized into mild (CRP <0.1 mg/L), moderate (CRP 0.1 – 0.3 mg/L) and high (CRP >0.3 mg/L).[20,24] Hence, the prediabetic subjects in our study appear to be in the moderate CV risk category. Hence, observation of an increase in both hs-CRP and lipid risk factors in our study along with increased OS (Table 2) indicate the impending cardiovascular risks of prediabetes individuals.

Though HbA1c can also be taken as a parameter for diagnosing prediabetes, in our study, we did not use it for diagnosis of prediabetes, as it can also be influenced by other factors such as hemoglobin structural abnormality and oxidative stress. The mean HbA1c in our test group was between 5.7 to 6.4% of total Hb. Glycated hemoglobin is produced by the attachment of sugar to globin part of circulating hemoglobin. Therefore, estimation of HbA1c is an indicator of glycemic status over past 8-12 weeks.[25] However, we analyzed the factors having an association with the HbA1c level in both the groups. The positive correlation of HbA1c with RPP in our study may indicate that the persistence of glycemic load above its normal range is linked to the rise in the CV risk in prediabetes individuals. Though traditionally, the degree of glycation is dependent on glucose concentration and the half-life of the protein, increased oxidative stress also has been linked with an increased rate of glycation.[25] Increased MDA/TAS indicates an increased rate of oxidation but decreased effective antioxidants in our study. The positive correlation of MDA/TAS with increased HbA1c in prediabetes subjects in the present study (Table 3) corroborates with previous observation.

RPP is the product of heart rate and systolic BP denoting myocardial work stress. It is a non-invasive risk factor and can be used for large scale screening and monitoring tool. The findings of the present study establish the close association of HbA1c with RPP (Table 3), the indicator of myocardial work stress and the marker of CV risk. Thus, from the findings of the present study, we may conclude that the prediabetes population has the decrease in antioxidant defense and increase in CV risk, by virtue of their increased glycation load.

The multiple regression analysis (Table 4) further demonstrated that increase in RPP is independently associated with increase in HbA1c and a rise in their waist hip ratio but not BMI in prediabetes subjects. As per previous study waist hip ratio is a better predictor of risk of heart disease compared to BMI.[26] But glycation load and waist hip ratio were not associated in our study. Therefore, our findings suggest both glycation load and waist circumference rise are associated with higher cardiovascular risk independently.

Limitations of the Study

Major limitation of the study is the smaller sample size. Also, cardiovascular risk assessment with use of echocardiography or blood pressure variability has not been done.

CONCLUSION

The present study demonstrated an increased resting heart rate and RPP that are the markers of CV risk and myocardial work stress, in prediabetes. The CV risk as increased RPP was associated with elevated glycation load. Therefore, further studies are required exploring RPP as a screening test in early middle adult age group for determining CV risks in prediabetes.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

HbA1c; Glycated hemoglobin; **RPP:** Rate-pressure Product; **BHR:** Basal Heart Rate; **OGTT:** Oral glucose tolerance test; **FSG:** Fasting Serum Glucose; **CV:** Cardiovascular; **BHR:** Basal heart rate; **WHR:** Waist hip ratio; **AI:** Atherogenic Index; **MDA:** Malon dialdehyde; **TAS:** Total antioxidant status; **OS:** Oxidative stress; **hs-CRP:** High-sensitive C-reactive protein.

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