Original Article

Association of Prehypertension Status with Sympathovagal Imbalance in Young First-Degree Relatives of Type 2 Diabetics in Indian Population is Linked to Body Mass Index

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Abstract

Background and Aim: As reports indicate that autonomic imbalance and hypertension in first-degree relatives (FDR) of type 2 diabetics predispose them to cardiovascular (CV) risks, in the present study, we have assessed contribution of body mass index (BMI) to sympathovagal imbalance (SVI) and prehypertension status in these patients. **Methods:** BMI, basal heart rate (BHR), blood pressure (BP), prehypertension status, rate pressure product (RPP), and spectral indices of heart rate variability (HRV) were reordered and analyzed in FDR of type 2 diabetics (Study group, $n = 63$) and in individuals with no family history of diabetes (Control group, $n = 87$). **Results:** BMI and low-frequency-high-frequency (LF-HF), the ratio of LF to HF power (LF-HF ratio) of HRV, a sensitive marker of SVI was significantly increased ($P < 0.001$) in the study group compared to control group. The SVI in the study group was due to concomitant sympathetic activation (increased LF) and vagal inhibition (decreased HF). In the study group, BMI was significantly correlated with LF-HF ratio, BHR, BP, and RPP. Multiple regression analysis demonstrated an independent contribution of BMI to prehypertension status and bivariate logistic regression revealed significant prediction of prehypertension status by LF-HF and BMI in the study group. **Conclusion:** BMI is more in FDR of type 2 diabetics and SVI in the form of increased sympathetic and decreased parasympathetic activity is present in them. Increased resting heart rate, elevated prehypertension status, decreased HRV, and increased RPP in these participants make them vulnerable to CV risks. BMI in these participants could be the link between SVI, prehypertension, and CV risks.

Keywords: Body mass index, first-degree relatives of type 2 diabetics, heart rate variability, low-frequency-high-frequency ratio, prehypertension status, sympathovagal imbalance

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Introduction

Hypertension and diabetes mellitus have recently been reported to be prevalent in younger age group, especially in in Indian subcontinent due to abrupt change in lifestyle.[1,2] Diabetes and hypertension share many common risk factors for various morbidities.[3] Therefore, early screening, detection, and management of diabetes and hypertension in younger age have been the major goal to prevent the occurrence of morbidity and mortality.[4,5] The first-degree relatives (FDR) of diabetics are more prone to develop diabetes, hypertension, and diabetic heart disease.[5,6] Prehypertension has recently been reported to be associated with autonomic imbalance and cardiovascular (CV) risks.[7] Recently, we have reported the associated of decreased baroreflex sensitivity as a marker CV risk with sympathovagal imbalance (SVI) in FDR of diabetics.[8] However, to the best of our knowledge, till date, no study has been conducted to elucidate the physiological mechanisms for development of prehypertension status that predispose the FDR of type 2 diabetics to increased CV risks.

SVI has recently been reported to be associated with various morbidities in many metabolic diseases,[9] and SVI has

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also been suggested as the major mechanism of metabolic alterations in diabetes mellitus.[10,11] A recent report has linked autonomic imbalance with sympathetic hyperactivity in FDR of diabetics.[12] Nevertheless, autonomic imbalance has been reported in FDR of type 2 diabetics,[12,13] but the mechanisms of increased CV risks and contribution of autonomic imbalance to these increased risks have not been assessed yet. We have reported that SVI occurs in the form of sympathetic overactivity and vagal inhibition in FDR of type 2 diabetics, and SVI is associated with CV risks in these participants.[14] However, prehypertension status as a marker of CV risks has not been assessed in these participants. Recently, spectral analysis of heart rate variability (HRV) has been documented as a tool for assessment of autonomic dysfunction in health and diseases.[15] Recently, we have reported the increased body mass index (BMI) as the major contributor to CV risks in younger- and middle-aged Indian population.[16,17] Therefore, in the present study, we have assessed autonomic functions in FDR of diabetics using HRV analysis, and we have analyzed the association of BMI with SVI in these participants.

Materials and Methods

Study design and subjects

After obtaining the approval of Research Council and Institutional Ethics Committee, of Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India, 150 individuals were recruited for this cross-sectional study from undergraduate medical and paramedical courses of JIPMER of 2013–2014 batches. They were classified into two groups.

1. Control group (n = 87): Normal healthy individuals without family history of diabetes
2. Study group (n = 63): Normal healthy FDRs of patients with type 2 diabetes mellitus.

The participants of the study group (FDR of type 2 diabetics) was defined as the participants having either of the parents or siblings diagnosed to have type 2 diabetes mellitus for at least 1 year and receiving treatment for the same. This was done as part of a hypertension-diabetes research project, in which family history of diabetes was one of the questionnaires in the data sheet. The participants were also interviewed and hospital records examined to confirm the presence of diabetes in their family.

All individuals were examined clinically by a physician to rule out the presence of any acute or chronic illness. Healthy individuals (subjects without illness) were included in the study. Individuals receiving any medication, individuals with history of diabetes, smoking, hypertension, and hypertensive patients receiving medication were excluded from the study. As the level of physical fitness is a major determinant of sympathovagal tone,[18] individuals performing regular athletics and body building exercises were excluded from the study.

Recording of anthropometric and heart rate variability parameters

Individuals were asked to report to AFT laboratory of physiology department at about 8 AM following overnight fast. The temperature of the laboratory was maintained at 25°C for all the recordings. Their age, height, body weight, and BMI were recorded.

After 15 min of supine rest, electrocardiogram (ECG) was recorded for short-term HRV analysis following the procedures recommended by Task Force,[19] using BIOPAC MP-100 data-acquisition system (BIOPAC Inc., Goleta, CA, USA). For the purpose, ECG electrodes were connected and lead II ECG was acquired at a rate of 1000 samples/second during supine rest using BIOPAC MP-100, continuously for 10 min. The data were transferred from BIOPAC to a Windows-based PC with AcqKnowledge software version 3.8.2 (BIOPAC Inc., Goleta, CA, USA). Ectopics and artefacts were removed from the recorded ECG. The RR tachogram was extracted from the edited ECG using the R wave detector in the AcqKnowledge software. HRV analysis was done using the HRV analysis software version 1.1 (Biosignal Analysis group, Kuopio, Finland). Frequency domain indices of HRV, such as total power (TP), normalized low-frequency power (LFnu), normalized high-frequency power (HFnu), and ratio of LF to HF power (LF-HF ratio), and time-domain indices, such as square root of the mean of the sum of the squares of the differences between adjacent NN intervals (RMSSD), standard deviation of normal to normal interval (SDNN), number of interval differences of successive NN intervals greater than 50 ms (NN50), and the proportion derived by dividing NN50 by the total number of NN intervals (pNN50), were recorded.

Recording of blood pressure and rate pressure product

Blood pressure (BP) was recorded using the automatic noninvasive BP monitor, Omron, HEM 7203 model (Omron Healthcare Co., Kyoto, Japan). Heart rate, systolic BP (SBP), and diastolic BP (DBP) were noted from the display screen of BP monitor, and mean arterial pressure (MAP) was calculated. Rate pressure product (RPP) was calculated using the formula, RPP = systolic pressure × heart rate × 10^{-2}.[20]

Statistical analysis

SPSS version 13 (SPSS Software Inc., Chicago, IL, USA) and GraphPad InStat Software (GraphPad Software Inc., San Diego, CA, USA) were used for statistical analysis. All the data were expressed as mean ± standard deviation. Normality of data was tested by Kolmogorov–Smirnov test. For parametric data, the level of significance between the groups was tested by Student's unpaired t-test, and for nonparametric data, Welch's corrected t-test was used. The association of SVI with BMI and CV parameters was assessed by Pearson's correlation analysis. The independent contribution of BMI, basal heart rate (BHR), and prehypertension status to LF-HF ratio was assessed by multiple regression analysis. Independent prediction of prehypertension status to LF-HF ratio and BMI

was determined by bivariate logistic regression. The $P < 0.05$ was considered statistically significant.

Results

There was no significant difference in age between the participants of control group and study group [Table 1]. The BMI, waist–hip ratio, BHR, SBP, DBP, MAP, and RPP of study group participants were significantly more ($P < 0.0001$) compared to that of control group participants [Table 1]. Among the frequency domain indices of HRV [Table 1], TP, HF, and HFnu were significantly reduced ($P < 0.0001$), and LF, LFnu, and LF-HF ratio were significantly increased ($P < 0.0001$) in study group participants compared to the control group participants. All the time-domain indices (mean RR, RMSSD, SDNN, NN50, and pNN50) were significantly less ($P < 0.0001$) in study group participants compared to that of control group participants [Table 1]. Although there was no significant correlation of BMI with any of the parameter in control group, the correlation was significant for all the parameters in study group [Table 2].

Multiple regression analysis revealed significant individual contribution of LH-HF ratio, BHR, and prehypertension status to BMI in the study group [Table 3]. Bivariate logistic regression revealed significant prediction of prehypertension status by LH-HF ratio and BMI in study group [Table 4].

Table 1: Age, anthropometric, and basal cardiovascular parameters of control group (participants with no family history of diabetes) and study group (first-degree relatives of type 2 diabetics) participants

Parameters	Control group ($n=87$)	Study group ($n=63$)	*P*
Age (years)	20.52±2.84	20.78±2.90	0.1340
BMI (kg/m^2)	21.32±3.51	25.47±4.18	<0.0001
BHR (/min)	68.76±7.80	80.42±8.62	<0.0001
SBP (mmHg)	112.83±8.21	128.10±6.58	<0.0001
DBP (mmHg)	70.50±6.10	84.78±7.32	<0.0001
RPP (mmHg/min)	82.45±7.73	108.50±8.52	<0.0001
FDI			
TP (ms^2)	1056.20±432.76	768.28±376.10	<0.0001
LF (ms^2)	383.52±148.30	435.45±156.40	<0.0001
HF (ms^2)	637.30±278.86	298.90±102.31	<0.0001
LFnu	40.28±17.27	55.70±24.68	<0.0001
HFnu	59.72±21.70	44.30±18.32	<0.0001
LF:HF ratio	0.67±0.32	1.34±0.76	<0.0001
TDI			
Mean RR (s)	0.856±0.130	0.712±0.140	<0.0001
RMSSD (ms)	60.84±24.58	42.37±18.32	<0.0001
SDNN	48.47±19.35	27.85±14.14	<0.0001
NN50	40.86±17.66	28.24±15.65	<0.0001
pNN50	24.65±13.10	16.18±7.38	<0.0001

Data presented are mean±SD. $P<0.05$ was statistically considered significant. BMI: Body mass index, WHR: Waist–hip ratio, BHR: Basal heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, RPP: Rate pressure product, TP: Total power, LF: Low-frequency power, HF: High-frequency power, LFnu: Normalized LF power, HFnu: Normalized HF power, LF-HF ratio: Ratio of low-frequency to high-frequency power, Mean RR: Mean heart rate (mean of R to R intervals), RMSSD: The square root of the mean of the sum of the squares of the differences between adjacent NN intervals, SDNN: Standard deviation of normal to normal interval, NN50: The number of interval differences of successive NN intervals >50, pNN50: The proportion derived by dividing NN50 by the total number of NN intervals. SD: Standard deviation, FDI: Frequency domain indices, TDI: Time-domain indices

Table 2: Correlation of body mass index with body mass index, waist–hip ratio, basal heart rate, blood pressure, and rate pressure product of control group (participants with no family history of diabetes) and study group (first-degree relatives of type 2 diabetics) participants

	Control group		Study group	
	r	*P*	*r*	*P*
BHR	0.130	0.102	0.305	0.010
SBP	0.190	0.062	0.677	0.000
DBP	0.140	0.087	0.458	0.001
RPP	0.134	0.092	0.490	0.000
LH-HF ratio	0.098	0.172	0.380	0.006

$P<0.05$ was considered significant. BMI: Body mass index, BHR: Basal heart rate, WHR: Waist–hip ratio, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, RPP: Rate pressure product, LF-HF ratio: Ratio of low-frequency to high-frequency power

Discussion

In the present study, the BMI in the study group was significantly increased compared to control group [Table 1], and BMI was significantly correlated with LH-HF ratio [Table 2], the marker of SVI, indicating the SVI in FDR of type 2 diabetics could possibly be linked to their body adiposity. As there was no significant difference in age between study group and control group [Table 1], the alteration in BMI and autonomic functions between the groups is not attributed to the effect of age. In FDR of type 2 diabetics, LF-HF ratio was significantly increased compared to the control participants [Table 1] indicating a considerable enhancement in sympathetic activity in these participants as increase in LF-HF ratio indicates increased sympathetic activity and decrease in this ratio represents acceleration of parasympathetic activity.[15,19] Since, LF-HF ratio is a sensitive measure of sympathovagal balance,[15,19] increase in this ratio confirms presence of SVI in FDR of type 2 diabetics.

SVI in these participants is due to alterations in both sympathetic and parasympathetic activities. The increase in sympathetic activity in study group participants was revealed by increase in both LF and LFnu as increase in these two HRV indices reflect increased sympathetic drive to the heart.[15,19] Decrease in parasympathetic activity in participants of study group was reflected by decrease in both HF and HFnu ($P < 0.0001$), as decrease in these two parameters represent decreased vagal modulation of cardiac drive.[15,19] In the present study, findings of increased sympathetic activity in FDR of type 2 diabetics corroborate with the reports of earlier studies.[15,19] Further, HRV was found to be considerably decreased in FDR of type 2

Table 3: Multiple regression analysis of body mass index (as dependent variable) with basal heart rate and prehypertension status (as independent variables) in study group participants

Independent variables	Standardized regression coefficient *B*	95% CI		*P*
		Lower bound	Upper bound	
BMI	0.230	0.015	0.856	0.028
BHR	0.230	0.000	0.017	0.072
Pre-HTN status	0.572	1.214	1.856	0.000

P<0.05 was considered significant. BMI: Body mass index, BHR: Basal heart rate, Pre-HTN status: Prehypertension status, CI: Confidence interval

Table 4: Bivariate logistic regression analysis of prehypertension status (as dependent variable) with ratio of low-frequency to high-frequency power and body mass index (as independent variables) in study group participants after adjusting for gender

Parameters	OR (95% CI)	*P*
LF-HF ratio	2.02 (0.965-5.578)	0.012
BMI	3.28 (1.260-7.890)	0.004

P<0.05 considered significant. OR: Odds ratio, LF-HF ratio: Ratio of low-frequency power to high-frequency power of heart rate variability, BMI: Body mass index, CI: Confidence interval

diabetics. The TP not only represents the magnitude of HRV but also the vagal drive of cardiac modulation.[15,19] The decrease in time domain indices of HRV (RMSSD, SDNN, NN50, and pNN50) further confirms decreased vagal tone in FDR of diabetics, as TDI represents parasympathetic modulation of cardiac activity.[15,19] Thus, findings of the present study reveal that the SVI (alteration in LF-HF ratio) in FDR of type 2 diabetics is due to concomitant increased sympathetic activity and decreased vagal activity, which could be linked to BMI.

Although the cause of SVI cannot be fully determined from the present study, it appears that obesity may contribute to it as BMI was significantly more increased ($P < 0.0001$) in study group [Table 1] and was significantly correlated with it [Table 2]. Further, multiple regression analysis revealed independent contribution of BMI to LF-HF ratio [Table 3]. Obesity has been reported to be more prevalent in individuals with family history of diabetes that contributes to metabolic dysfunctions in this high-risk population.[21,22] Thus, increased adiposity in FDR of diabetics could be among the potential contributors to SVI in these participants as obesity has been reported to cause autonomic imbalance.[23,24] Resting heart rate is an index of vagal tone,[25,26] and increased heart rate has recently been reported to be associated with increased CV risks.[27-28] It has also been reported that BHR >70 beats per min increases the risk for major CV events.[29] As BHR was significantly high in study group participants compared to control group participants [Table 1], the FDR of diabetics are at an increased risk of adverse CV events. The most important finding of the present study is that SBP and DBP of many of study group participants were in prehypertension range, and BMI was correlated with prehypertension status, indicating that increase BP is linked to BMI. Further, RPP, the indirect measure of myocardial work stress, was also significantly correlated with BMI in study group [Table 2]. Therefore, it is expected that the increased BMI in FDR of type 2 diabetics is linked to increased myocardial energy load expenditure, which could be a CV risk. Obesity *per se* can increase BP and excess adiposity is a known to increase BP and CV risks.[30,31] BMI had independent contribution to prehypertension status as revealed by multiple regression analysis [Table 3], further increasing the risk of CV morbidity in these participants. Moreover, the level of BMI and LF-HF ratio had significant prediction of prehypertension status in study group participants. Thus, it appears that the SVI that contributes to prehypertension in FDR of type 2 diabetics could be linked to their level of BMI.

Limitations of the study

The limitation of the present study is that we have not assessed the association of SVI with blood glucose, insulin, lipid profile, and inflammatory markers in FDR of type 2 diabetics. However, this preliminary study demonstrates the link of SVI to CV risks in FDR of type 2 diabetics, which could be linked to their degree of adiposity.

Conclusion

In the present study, FDR of type 2 diabetics were young adults, who had significant SVI, increased BMI and increased BP in the prehypertension range. BMI and SVI had significant prediction of prehypertension status. As such prediabetes and prehypertension in young adults remain for a longer duration exposing them to premature CV risks before clinically manifesting as full blown diabetes and hypertension during their adulthood.[32,33] Moreover, FDR of type 2 diabetics are more prone for developing hypertension and CV morbidities. Therefore, studies should be conducted to assess if decrease in BMI can decrease the level of SVI, BP, and CV risk in FDR of type 2 diabetics.

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Conflicts of interest

There are no conflicts of interest.

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