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RESEARCH ARTICLE

A study of heart rate variability among non-diabetic offspring of type 2 diabetic parents

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ABSTRACT

Background: Type 2 diabetes mellitus is an inheritable condition that runs in families as a disorder of impaired glycemic control and its complications. Among the complications of diabetes, autonomic neuropathy contributes to the development of cardiovascular disease states besides diabetic vascular complications. Sympathovagal imbalance is reported to be observed among the non-diabetic first-degree relatives of diabetic population. **Aims and Objectives:** To assess the heart rate variability (HRV) parameters in non-diabetic normotensive offspring of diabetic parents and infer the impairment in sympathovagal balance in them by comparing with the HRV findings of non-diabetic offspring of non-diabetic parents. **Materials and Methods:** This cross-sectional observational study was conducted on 30 healthy non-diabetic, normotensive volunteers with parental history of Type 2 diabetes and 30 non-diabetic normotensive volunteers without parental history of diabetes. The volunteers were between the age of 17 and 25 years with normal body mass index and no health condition that could influence the cardiovascular health. The basal cardiovascular parameters and a 5 min lead II electrocardiogram for short-term HRV analysis were recorded to assess the sympathovagal balance. **Results:** The HRV analysis reveals a statistically significant increase in the sympathetic components and decreased parasympathetic components in the non-diabetic offspring of diabetic parents when compared to the non-diabetic offspring of non-diabetic parents. **Conclusion:** From our study, it could be observed that the non-diabetic offspring of diabetic parents have enhanced sympathetic activity and attenuated vagal activity even in their non-diabetic state, thus inferring an early onset of sympathovagal imbalance that could predispose them to hypertension and its sequel.

KEY WORDS: Heart Rate Variability; Parental History of Type 2 Diabetes Mellitus; Sympathovagal Imbalance

INTRODUCTION

Type 2 diabetes mellitus is an inherited metabolic condition with a global prevalence of 422 million adults aged above 18 years being diabetic in 2014.[1] Diabetes is expected to be the seventh leading cause of death by 2030.[2] Type 2 diabetes mellitus is a heterogeneous polygenic metabolic disease condition that develops as a result of interplay of genetic and environmental factors and it is highly prevalent among Asian population.[3] As Type 2 diabetes mellitus is multifactorial in origin, no specific cause could be attributed to its development, but its property of being inherited makes the role of genes an inevitable factor for the development of the disease state as inferred from the observations among family members with positive family history of diabetes.[4]

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The role of genetic mechanism in the development of inheritable diseases involves gradual impairment in systemic functions that slowly transcends health to disease with gene expression. In contrast to the concept of impaired glucose metabolism predisposing to systemic involvement as a complication, recent observations of systemic involvement preceding glycemic dysregulation by unexplained genetic mechanisms have been reported. Such an observation of altered systemic function among the genetically vulnerable non-diabetic offspring of diabetic parents is the observation of autonomic neuropathy that stands an evidence to the evolution of diabetic spectrum by mechanisms of genetic inheritance even in the absence of diabetes.[5]

The offspring of diabetic parents are genetically prone to develop diabetes and their transition from non-diabetic to diabetic state should happen through the frames of insulin resistance and compensatory hyperinsulinemia, a condition of relative insulin excess which is capable of causing sympathetic overactivity.[6] In contrary to the above finding, Fiorentini *et al*. reported that autonomic impairment could occur independent of insulin resistance in such vulnerable population.[7]

As diabetes has become a universal pandemic making a major contribution to global morbidity and mortality of the youth and the middle aged, early detection of such changes in autonomic regulation could help reduce the impact of this universal health threat on the quality of life by timely implementation of appropriate intervention. Moreover, as controversial observations of sympathovagal imbalance and non-involvement of cardiac autonomic regulation have been reported, this study has been designed with an aim to assess for any change in the autonomic regulation of the cardiovascular system by assessing the heart rate variability (HRV) among non-diabetic normotensive offspring of Type 2 diabetic parents and infer the impairment in the sympathovagal balance in them by comparing the variables with that of non-diabetic offspring of non-diabetic parents.[8-10]

MATERIALS AND METHODS

This cross-sectional observational study was conducted in the research laboratory of the Department of Physiology, Sri Venkateshwaraa Medical College Hospital and Research Centre, Puducherry, after obtaining the Institutional Ethical Committee clearance, for a period of 4 months. 30 non-diabetic normotensive volunteers with parental history of Type 2 diabetes mellitus and 30 non-diabetic normotensive volunteers without parental history of Type 2 diabetes mellitus, between the age group of 17 and 25 years were recruited from the campus as subjects for this study. and, depending on their parental history of diabetes they were classified into two groups as follows:

Group 1 (study): Non-diabetic, normotensive offspring of Type 2 diabetic parents (n = 30).

Group 2 (control): Non-diabetic, normotensive offspring of non-diabetic parents (n = 30).

The volunteers were selected based on the following inclusion and exclusion criteria.

Inclusion Criteria

Volunteers with no parental history of hypertension and those who were in the normal range of body mass index (BMI) (18.5–22.9 kg/sq. m.) were recruited for study and control groups.

Exclusion Criteria

Smokers, alcoholics, hypertensives, and those with a history of metabolic, renal, and endocrine diseases as well as any acute or recent illness were excluded. Yoga practitioners and those who were on any medication that affects autonomic nervous system were not included.

Study Design

The subjects were informed about the procedures briefly and an informed written consent was obtained from all the subjects. The subjects were requested not to participate in any exercise or heavy physical activity and to avoid eating a heavy meal 2 h before the test. The subjects were made to come half an hour before the commencement of testing procedure, to allow the familiarization with the environment and to establish a resting state and the procedures were explained before recording the variables. The anthropometric parameters were recorded to calculate the BMI. After 15 min of rest in supine posture, the basal cardiovascular parameters such as blood pressure (BP) and heart rate were recorded and a 5 min lead II electrocardiogram (ECG) recording was done in supine posture for short-term HRV analysis (room temperature maintained at 20–25°C). The recording was done in accordance to the recommendation of the task force on HRV.[11] The HRV recording was done by connecting the ECG electrodes and lead II ECG was acquired using the instrument PHYSIOPAC-PP4, Medicaid System, Chandigarh, and data analysis was then done using the Kubios HRV analyser. The spectral indices of HRV assessed were as follows:

1. Time domain measures:
   a. Mean RR interval (Mean RR)
   b. Standard deviation of normal-to-normal RR intervals (SDNN)
   c. Root mean square successive difference (RMSSD)
   d. The proportion of NN50 to the total number of NN intervals (pNN50).

Mean RR, SDNN, RMSSD, and pNN50 are measures of parasympathetic activity.

2. Frequency domain measures:
a. Normalized low-frequency power (LF_{nu})
b. Normalized high-frequency power (HF_{nu})
c. Ratio of LF_{nu} to HF_{nu} (LF-HF ratio)
d. Total power (TP).

HF_{nu} and TP are measures of parasympathetic activity and LF_{nu} is a measure of sympathetic activity and FH-HF ratio reflects the sympathovagal balance.[12]

Statistical Analysis

The data were expressed as mean ± SD. To test the significance between study and control groups, unpaired *t*-test was done (using SPSS version 17). The statistical probability $P < 0.05$ was considered to be significant.

RESULTS

The above table [Table 1] displays the basic parameters of the subjects of both the groups. There is significant difference observed between the study (Group 1) and the control groups (Group 2) in the parameters of BMI, basal heart rate, systolic, and diastolic BP.

In the above table [Table 2], the comparison of various frequency domain parameters reveal statistically significant difference between the groups, making the inference that the offspring of diabetic parents have enhanced sympathetic component of HRV (LF_{nu}) when compared to offspring of non-diabetic parents, and the parasympathetic component (HF_{nu}) is decreased in the same group with a significant $P = 0.0057$. The sympathovagal balance as inferred by LF-HF ratio also differs significantly between the groups with $P = 0.0049$ and the TP (TP [m^2]) that expresses the overall parasympathetic activity is significantly attenuated in the study group when compared to controls with $P = 0.0001$.

From the above table [Table 3], it could be inferred that the time domain indices which reflect the cardiac vagal activity is decreased in Group 1, thus making the inference that parasympathetic attenuation exists in them which is demonstrated by the significant decrease in the variables of mean RR, SDNN, RMSSD, and pNN50.

DISCUSSION

In our study, it is observed that the basal parameters of BMI, basal heart rate, systolic, and diastolic BP differed significantly between the groups though they were in the normal range. The observation of higher BMI within normal range in our study is in accord with the findings of Khanna and Sarup, who reported that the healthy children with positive parental history of either diabetes or hypertension had a higher BMI and higher waist–hip ratio which is genetically predisposed.[13] The assessment of HRV among the normotensive, non-diabetic offspring of diabetic parents revealed that they had sympathovagal balance shifted toward sympathetic pronouncement as observed by the statistically significant increase in LF_{nu} in the study population and parasympathetic decline as reflected by a significant increase in LF: HF ratio and by the decrease in the TP (vagal potency of cardiac modulation) of the frequency domain parameters in the study population. The study group had a significant decrease in the time domain measures which are the indices of parasympathetic function such as mean RR (ms), SDNN RR intervals (ms), RMSSD (ms), and pNN50(%). All these observations suggest that the genetically susceptible non-diabetic offspring of diabetic parents, even in their euglycemic state, have alterations

Table 1: Comparison of age, BMI, and basal cardiovascular parameters between the study and control groups

Parameters	Group 1	Group 2	*P* value
Age (years)	20	20	-
BMI (kg/m^2)	20.09±1.23	20.7±0.7	0.0216*
Basal heart rate (beats/min)	74.32±4.15	72.07±2.8	0.0168*
SBP (mmHg)	106.18±4.52	104.09±2.46	0.03*
DBP (mmHg)	71.04±5.18	68.9±2.35	0.044*

SBP: Systolic blood pressure, DBP: Diastolic blood pressure; *P<0.05; **P<0.01. BMI: Body mass index

Table 2: Comparison of frequency domain indices of HRV between the study and control groups

Parameters	Group 1	Group 2	*P* value
LF_{nu}	49.57±4.312	46.69±3.39	0.0057**
HF_{nu}	50.43±4.312	53.31±3.4	0.0057**
LF: HF ratio	0.997±0.181	0.88±0.123	0.0049**
TP (m^2)	907.67±124.26	1095±132.13	0.0001***

*P<0.05; **P<0.01; ***P<0.001. HRV: Heart rate variability, LFnu: Low-frequency power, HFnu: High-frequency power, TP: Total power

Table 3: Comparison of time domain indices of HRV between the study and control groups

Parameters	Group 1	Group 2	*P* value
Mean RR (ms)	824.85±181.26	968.77±164.11	0.0021**
SDNN (ms)	40.83±8.14	53.46±12.38	0.0001***
RMSSD (ms)	20.38±6.9	27.76±7.38	0.0002 ***
pNN50 (%)	7.25±3.3	12.92±3.1	0.0001***

*P<0.05; **P<0.01; ***P<0.001. HRV: Heart rate variability, SDNN: Standard deviation of normal-to-normal, RMSSD: Root mean square successive difference

in the autonomic regulation of cardiovascular system. Our findings were similar to the observations of Laitinen *et al*., Anshu *et al*. and De Angelis *et al*., who reported an altered sympathovagal balance in similar subjects even in their euglycemic state[8,14,15] Goel *et al*. and Tuppad and Jangam reported such similar observation of shifted sympathovagal balance with the assessment of sympathetic and parasympathetic components of autonomic function tests.[16,17] This shift toward sympathovagal imbalance could be due to hyperinsulinemia along with insulin resistance which is the familial traits of the first degree relatives of Type 2 diabetics, who are at the increased risk of developing the condition.[18] The role of elevated insulin levels in the genesis of hypertension could be attributed to enhanced sympathetic outflow through insulin's effect on hypothalamus and it also contributes to decrease in vagal tone.[19,20] Hyperinsulinemia may not be the only reason for the sympathetic enhancement related to insulin resistance, but also additionally, the insulin-resistant state itself could be associated with sensitization of the autonomic nervous system to insulin. In addition to the above mechanisms, increased BMI which predisposes to obesity can lead to insulin resistance by the mechanism of weight gain.[21] Increased adiposity leads to higher free fatty acids in circulation which leads to the development of insulin resistance indirectly by enhancing sympathetic activity and by activation of hypothalamo-pituitary-adrenal axis.[22] Moreover, Fiorentini *et al*. reported that autonomic disturbance occurs in the vulnerable population independent of insulin resistance and this imbalance gets more pronounced with the development of insulin resistance.[7] Therefore, from the above discussion, it could be inferred that non-diabetic offspring of Type 2 diabetic parents can develop dysautonomia either secondary to insulin resistance or independent of it, which is genetically determined and as these people are genetically prone to develop obesity which in turn predisposes them to insulin resistance there could be hyperinsulinemia in them that has enhanced their sympathetic outflow.

Strength of the Study

The observations of our study reveal an early onset of sympathovagal imbalance among the genetically susceptible non-diabetic offspring of diabetic parents. Therefore, periodic monitoring of HRV in the vulnerable population could help detect early changes in the sympathovagal balance and help implement measures to postpone the disease onset.

Limitations of the Study

In spite of being a pilot effort, our study has revealed significant observation of altered sympathovagal balance and a large population study could help establish this observation an early detectable evidence for developing diabetes.

CONCLUSION

Therefore, from the observation of our study, it could be concluded that non-diabetic offspring of diabetic parents have sympathetic overactivity and attenuated cardiac vagal regulation even in their non-diabetic state. Early diagnosis of such alterations in autonomic functions could help institute early intervention like lifestyle modification measures to avert its long-term effects on health.

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