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Research Article

Study of Nerve Conduction Velocity in Normal Subject Having Parental History of Diabetus Mellitus

Dr. Pallavi H. Pandhare[1*], Dr. Mahendra K. Varthi[2], Dr. Jaya Surendra sawarkar[3]
[1*]MBBS MD Physiology, Assistant Professor, Department of Physiology, Indira Gandhi Govt Medical College and Hospital, Nagpur, Maharashtra.
[2]MBBS MD Community Medicine, Assistant Professor, Department of Community Medicine, Chirayu Medical College and Hospital, Bhopal, MP.
[3]MBBS MD Physiology, Assistant Professor, Department of Physiology, Indira Gandhi Govt Medical College and Hospital, Nagpur, Maharashtra.
Corresponding Author: Dr. Pallavi H. Pandhare
Assistant Professor, Department of Physiology, Indira Gandhi Govt Medical College and Hospital, Nagpur.
Email: pallavipandhare4@gmail.com
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ABSTRACT
Background: Hyperglycemia in type 2 diabetes is associated with micro- and macro-complications and causes autonomic nervous dysfunction. Severe autonomic failure due to sympathetic and parasympathetic dysfunction typically occurs in patients with long-standing and poorly controlled diabetes. Heart rate variability (HRV) is a standard screening parameter for diagnosis of autonomic dysfunction. Analysis of 5 minutes measurements of heart rate variability (HRV) has been shown to be a good predictor of physiological distress and mortality, especially for cardiovascular disease.
Aim and Objectives: 1. To evaluate heart rate variability and nerve conduction velocity in off-springs of diabetic and nondiabetic parents using autonomic test. 2 To study and compare autonomic nervous activity in off-springs of diabetic and non-diabetic parents. 3 To study BMI in off-springs of diabetic parents.
Methodology: Present study was a cross sectional study done at Department of Physiology, Grant Government Medical College Mumbai during a period of December 2014 to October 2016. The study involved randomly selected 100 students of first year MBBS students, these can be divided in two groups (50 study groups and 50 Control groups) depending on family history of diabetes mellitus and children with parents having diabetes mellitus were taken as study group.
Result: Mean age, height, weight, and BMI in study group and control group Age (years) mean and SD in study group 19.30±1.13 control group 19.22±1.02 p value-0.7104. Height (meters) study group mean, SD- 1.59±0.04 control group SD-1.59±0.07, BMI (Kg/m2) 21.49±1.94 21.89±2.17. Mean systolic blood pressure of study and controls are 110±11.55 and 108.2±6.09 mmHg respectively. There is no significant difference between systolic blood pressure of study group and controls. Mean diastolic blood pressure of study and controls are 76±10.69 and 74.28±5.08 mmHg. There is no significant difference between mean diastolic blood pressure of study and controls. Mean resting heart rate in study and control are 76.74±10.67 and 75.92±9.49 bpm respectively. The resting heart rate in study group was higher but it was not statistically significant. There was no statistically significant post test difference in mean DBP of study and controls, no statistically significant difference in SBP. Mean of time domain indices of HRV in study group and Control group. Mean RR (ms) study group mean SD-0.79±0.07 Control mean and SD-0.75±0.051. Mean nerve conduction velocity in median nerve in study group and control group Motor study group mean and SD-61.08±10.14 Control group mean and SD-65.48±4.97
Conclusion: HRV is reduced in nondiabetic offsprings of diabetic parents. Offsprings of diabetic parents showed increased sympathetic as well parasympathetic activity. Impaired vagal activity was found in offsprings of diabetic parents. Decreased HRV is associated with greater risk for developing diabetes mellitus. Further our study suggests that the tendency to developing diabetes mellitus sets in an early age.

Keywords: Nerve Conduction, Diabetes Mellitus, Off-Springs Of Diabetic Parents, Body Mass Index, Neuropathy.

INTRODUCTION

Diabetes Mellitus (DM) is defined as a metabolic abnormality characterized by hyperglycaemia and disturbances of carbohydrate, fat and protein metabolism that are associated with absolute or relative

deficiency in insulin secretion and/or insulin action[1-5]. When fully evolved, it is characterized by fasting hyperglycaemia but it can also be characterized in the less overt stages and before fasting hyperglycaemia appears, most usually by the appearance of glucose intolerance [6]. Once regarded as a single disease entity, diabetes is now seen as a heterogeneous group of disease, resulting from a diversity of aetiologies, environment and genetic, acting jointly. Type 2 diabetes is much more common than type 1 diabetes. It is often discovered by chance. It is typically gradual in onset and occurs mainly in the middle aged and elderly, frequently mild, slow to ketosis and is compatible with long survival if given adequate treatment [7].

The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. In the United States, DM is the leading cause of end stage renal disease (ESRD), non-traumatic lower extremity amputations and adult blindness. It also predisposes to cardiovascular diseases. With an increasing incidence worldwide, DM will be a leading cause of morbidity and mortality for the foreseeable future3. The two most important determinants of diabetes are firstly, genetic background (family history) and secondly, obesity. It has been very aptly said that for diabetes, "genetics loads the cannon and obesity finally fires it". As for IHD, the risk factors may be grouped as "Non Modifiable"(Age, Sex, Genetic and Racial factors) and "Modifiable" (Obesity, physical activity, nutritional factors, stress, drugs, infections and chemical toxins, etc)1.

Type 2 Diabetes Mellitus has a strong genetic component. Type 2 diabetes is a familial disease with a lifetime risk of 40% if one parent has type 2 diabetes. The concordance of Type 2 Diabetes Mellitus in identical twins is 70% to 90%. Now a day Type 2 Diabetes Mellitus is being diagnosed more frequently in children and young adults, particularly in obese adolescents [7,8].

Type 2 diabetes mellitus (DM) is a widespread disease and increases the risk of cardiovascular disease, perioperative hypotension and intra-operative morbidity [8-10]. Hyperglycemia in type 2 diabetes is associated with micro- and macro-complications and causes autonomic nervous dysfunction. Severe autonomic failure due to sympathetic and parasympathetic dysfunction typically occurs in patients with long-standing and poorly controlled diabetes.

Heart rate variability (HRV) is a standard screening parameter for diagnosis of autonomic dysfunction. Analysis of 5 minutes measurements of heart rate variability (HRV) has been shown to be a good predictor of physiological distress and mortality, especially for cardiovascular disease. The total power reflects the overall autonomic modulation and is considered an estimation of the balance between sympathetic and parasympathetic nerve activities. Current interest centres on the development of a new generation of tests of autonomic nerve function that are simple, non- invasive, reproducible and allow precision in diagnosis and accurate quantization. Most of them are based on cardiovascular reflexes and abnormality in them is assumed to reflect autonomic damage elsewhere [10].

Neuropathy is one of the most common complications of diabetes. Silent myocardial infarct is more common in diabetics due to involvement of cardiac autonomic nerves. At an early stage autonomic dysfunction may be asymptomatic or mildly symptomatic. Symptomatic autonomic neuropathy carries worst prognosis, so early diagnosis is essential for maximum benefit more so in diabetes. Heart rate variability monitoring plays a vital role in prevention and early diagnosis of cardiac autonomic neuropathic complications [7].

Type 2 Diabetes Mellitus (DM) in relatives indicates that some individuals have an inherited susceptibility to development of disease & pathogenesis of type 2 diabetes may vary among populations. A recent study has confirmed one locus and identified four other novel loci that account for substantial portion of risk for development of Type 2 diabetes.

Reduced heart rate variability (HRV) is the earliest indicator of CADN. Though, cardiovascular reflex tests of HRV standardized by Ewing et al are non invasive, they require patient co-operation to a greater extent. They may not be sensitive enough to reveal subtle effects of interventions on autonomic nerve function [11]. Sympathetic and parasympathetic components of neuro-vegetative system regulate cardiac activity. Spectral analysis of heart rate variability (HRV) is a non invasive method used to assess cardiac autonomic activity.

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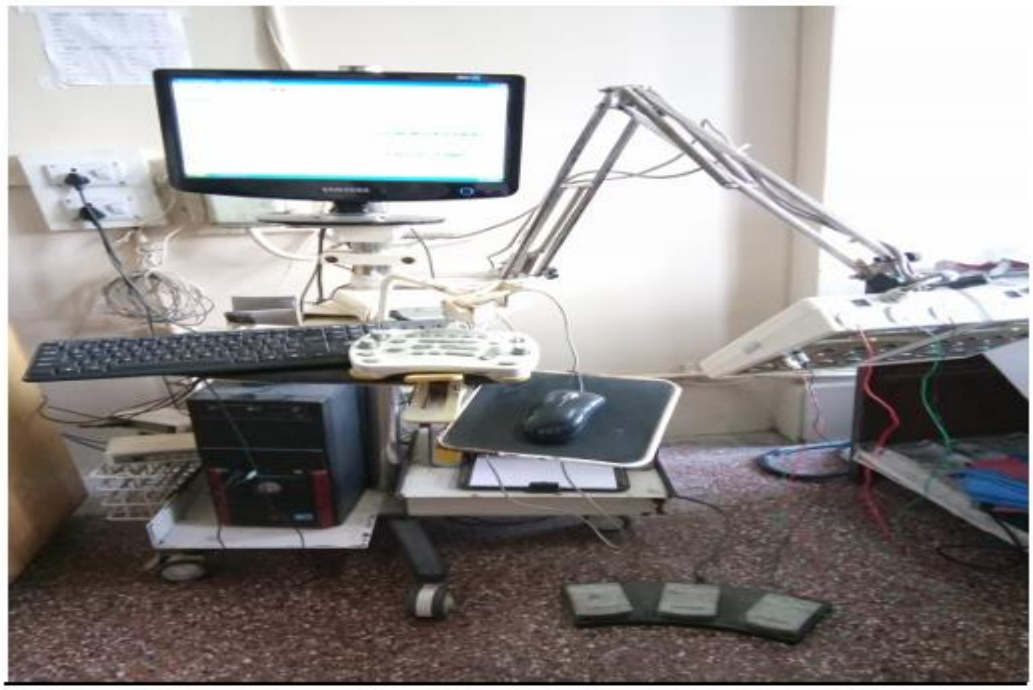
Nerve Conduction Machine



Aims and Objectives

1. To evaluate heart rate variability and nerve conduction velocity in off-springs of diabetic and non-diabetic parents using autonomic test.
2. To study and compare autonomic nervous activity in off-springs of diabetic and non-diabetic parents.
3. To study BMI in off-springs of diabetic parents.

MATERIAL AND METHODS

The present study was conducted after approval was taken from the Institutional Ethical Committee.

Study Design: cross sectional study. **Study Site:** Department of Physiology, Grant Government Medical College Mumbai. **Study Period:** December 2014 to October 2016

Sample Size: 100 (50 study group and 50 Control group) The study involved randomly selected 100 students of first year MBBS studied in Grant Govt Medical College Mumbai. These students can be divided in two groups depending on family history of diabetes mellitus and children with parents having diabetes mellitus were taken as study group.

Study Group: normal offsprings of diabetic parents (n=50). **Control Group:** age and sex matched offsprings of non-diabetic parents (n=50).Written informed consent (Annexure C) was taken before doing the clinical examination of the subject.

Inclusion Criteria

1. Healthy Adults with one of the parent affected by diabetes,
2. Age between 18-21 years,
3. Normoglycemic,
4. Normotensive,
5. Non-smokers and
6. Non-alcoholic

Exclusion Criteria

1. Subjects with history of diabetes mellitus, hypertension, obesity,
2. History of smoking, alcoholism, receiving any medication,
3. History of any clinical signs and symptoms related to renal and endocrinal disorder,
4. History of any acute illness,
5. Subjects who were professionally engaged in heavy physical activity,
6. Athletes,
7. Subjects on treatment of antiretroviral therapy, anti tubercular drugs

Procedure

The subjects were asked to refrain from ingesting any beverages like tea or coffee and alcohol for at least 12 hours prior to the

study. They were asked to have adequate sleep at night and to refrain from any medications throughout the study period. They were asked to report between 10a.m-12p.m. in the lab with light breakfast.
Details of procedures were described to each subject before the tests so that subject was without any anxiety at the time of the tests. The purpose, procedure and non invasive nature of the study were explained and written informed consent for the study was taken from each subject. Their height was measured in centimetres and weight in kilograms. Body mass index was calculated. They were asked to rest for minimum of 15 minutes in supine position.

Electrode Placement for Nerve Conduction Study

Median Nerve

Motor Conduction Velocity

Recording electrode: placed on the motor point of Abductor Pollicis Brevis i.e. midway between the distal wrist crease and the first metacarpo-phalangeal joint.
Reference Electrode: placed 3cm distal to recording electrode at the first metacarpo-phalangeal joint.
Ground Electrode: placed on the forearm.
Stimulating Electrode
Distal stimulation point: placed 3cm proximal to distal wrist crease near the tendon of Palmaris longus.
Proximal stimulation point: placed at the elbow near the volar crease of the Brachial Artery pulse.

Sensory Conduction Velocity

Recording Electrode: placed 3cm proximal to the distal wrist crease slightly radial to the tendon of Palmaris longus.
Reference Electrode: placed 3cm proximal to recording electrode.
Ground Electrode: placed on forearm.
Stimulating Electrode: Cathode placed at proximal inter-phalangeal joint of the second digit (middle finger)
Anode: placed 3cm distal to the cathode.

MATERIALS

Weighing machine, Neuro MEP machine, measuring tape, bold marker

Statistical Analysis

HRV from the recorded ECG was analysed by using Kubios HRV version 2.1 software. Statistical analysis of the observations was carried out using Graph-Pad in Stat version 3.10. The data was expressed in terms of mean and standard deviation and statistics was determined using unpaired t test. Statistical significance was tested at 5% & expressed in terms of 'p' value with $p < 0.05$ = statistically significant.

OBSERVATION AND RESULTS

Table No.1: Mean Age, Height, Weight, and BMI in Study Group and Control Group.

	Study	**Control**	**P Value**
	Mean ± S.D.	Mean ± S.D.	
Age(years)	19.30±1.13	19.22±1.02	0.7104
Height (meters)	1.59±0.04	1.59±0.07	0.7186
Weight(kg)	55.30±4.33	55.38±4.34	0.9268
BMI(Kg/m^2)	21.49±1.94	21.89±2.17	0.3325

< 0.001	**Extremely Significant**	***
0.001 to 0.01	Highly Significant	**
0.01 to 0.05	Significant	*
> 0.05	Not Significant	NS

RESTING BLOOD PRESSURE AND HEART RATE:-

Table No. 2. Mean Resting Heart Rate and Blood Pressure in Study and Control Group

	Study	**Control**	**P Value**
	Mean ± S.D.	Mean ± S.D.	

Systolic blood pressure (mm Hg)	110±11.55	108.2±6.09	0.3652
Diastolic blood pressure (mm Hg)	76±10.69	74.28±5.08	0.3067
Heart Rate (bpm)	76.74±10.67	75.92±9.49	0.6856

- **Systolic Blood Pressure (Sbp)**

Mean systolic blood pressure of study and controls are 110±11.55 and 108.2±6.09 mmHg respectively. There is no significant difference between systolic blood pressure of study group and controls.

Diastolic Blood Pressure (Dbp)

Mean diastolic blood pressure of study and controls are 76±10.69 and 74.28±5.08 mmHg. There is no significant difference between mean diastolic blood pressure of study and controls.

RESTING HEART RATE (Bpm):-

Mean resting heart rate in study and control are 76.74±10.67 and 75.92±9.49 bpm respectively. The resting heart rate in study group was higher but it was not statistically significant.

Cold Pressor Test:-

Table No. 2. Mean BP Response To Cold Pressor Test In Study Group And Control Group.

		Study	Control	P Value
		Mean ± S.D.	Mean ± S.D.	
SBP	Before	109.96±11.55	106.84±6.96	0.1052
	After	107.96±9.65	110.36±9.84	0.2211
DBP	Before	76±10.69	72.42±7.04	0.0508
	After	77.8±7.64	75.88±8.88	0.2493

Mean difference in blood pressure in study group and control group in cold pressor test

Pre Test: SBP 109.96±11.55 and 106.84±6.96 with no statistical difference.

DBP 75±10.69 and 72.42±7.04 with no statistical difference

Post Test: SBP 107±9.65 and 110.36±9.84 with no statistical difference DBP 77.8±7.64 and 75.88±8.88 with no statistical difference

There was no statistically significant post test difference in mean DBP of study and controls, no statistically significant difference in SBP.

Hrv Analysis:

Table No.3 Mean of Time Domain Indices of HRV in Study Group and Control Group.

	Study	Control	P Value
	Mean ± S.D.	Mean ± S.D.	
Mean RR (ms)	0.79±0.07	0.75±0.051	0.0037
RMSSD (ms)	31.12±26.54	20.78±7.32	0.0092
SDNN (ms)	0.04±0.03	0.03±0.01	0.0145

Table No. 4 Mean Frequency Domain Indices of Hrv of in Study Group and Subjects.

	Study	Control	P Value
	Mean ± S.D.	Mean ± S.D.	
LF (n.u.)	70.83±10.81	72.45±4.31	0.3287

HF (n.u.)	29.17±10.81	25.28±3.35	0.0169
LF/HF ratio	2.82±1.14	2.89±0.48	0.7239

Nerve Conduction Velocity Study:-

Table No. 5 Mean Nerve Conduction Velocity in Median Nerve in Study Group and Control Group

	Study	**Control**	**P Value**
	Mean ± S.D.	Mean ± S.D.	
Motor	61.08±10.14	65.48±4.97	0.0069
Sensory	49.87±4.72	52.47±5.24	0.0106

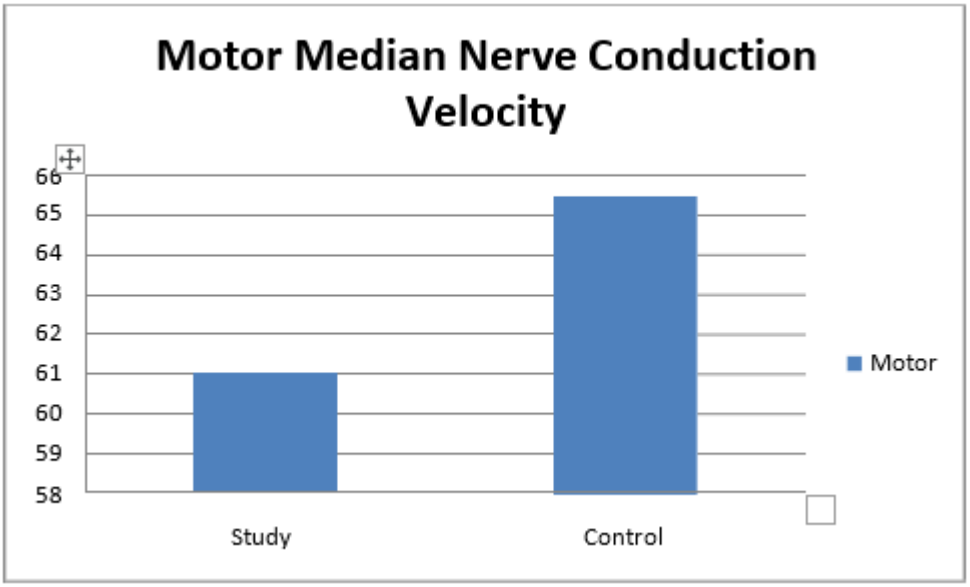


Figure No 1. Mean Motor Nerve Conduction Velocity Study Group and Control Group

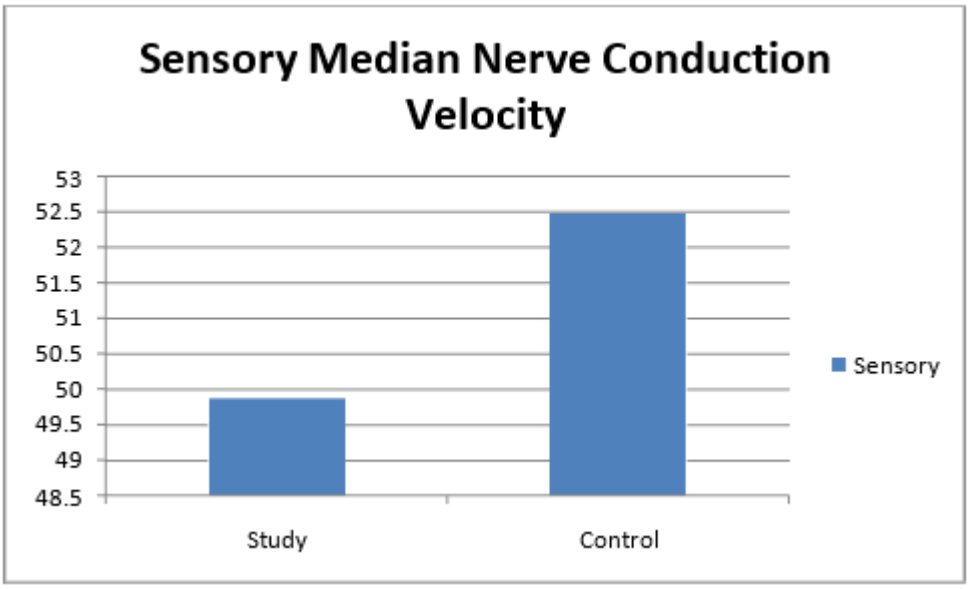


Figure No 2. Mean Sensory Nerve Conduction Velocity Study Group and Control Group

DISCUSSION

Prevention of diabetes remains main goal and effort must be continued to make its primary prevention a realistic public goal. Autonomic dysfunction as primary pathological factor is associated with the increased risk of future diabetes and therefore may be an important factor in determining diabetes risk. Many studies have shown that children of diabetic parents are

more likely to develop diabetes, but very few studies have been done to find out early outcome of genetic transmission.

Therefore, present study aims to assess and compare cardiovascular autonomic activity in healthy offspring with and without parental history of type 2 diabetes. Cardiac autonomic activity was measured by assessing HRV, since HRV analysis is recommended as currently the test of choice when using traditional cardiovascular reflex test in clinical evaluation of autonomic nervous function. All the subjects were in the age group of 18-21 years. The two study groups i.e., healthy offspring's of healthy parents and healthy offspring's of diabetic parents were matched for age, sex and BMI. They differed only in the genetic propensity for developing diabetic in later life.

The study groups were comparable in terms of age and other physical parameters. There was no significant difference in mean ± S.D. of height, weight, Body mass index (BMI) between study group and controls

Resting Heart Rate and Blood Pressure

Arterial pressure is thought to be under sympathetic control. Systolic arterial pressure variability is marker of sympathetic modulation of vasomotor activity, the results of present study revealed that the resting heart rate and resting blood pressure show no significant difference among the study groups but there is minimal changes in mean value score of resting heart rate and blood pressure. Overall the results proved there are no early changes of resting BP and heart rate in offspring's of diabetic parents.

In current study Mean resting heart rate in study and control are 76.74±10.67 and 75.92±9.49 bpm respectively. The resting heart rate in study group was higher but it was not statistically significant, Mean systolic blood pressure of study and controls are 110±11.55 and 108.2±6.09 mmHg respectively. There was no significant difference between systolic blood pressure of study group and controls, Mean diastolic blood pressure of study and controls are 76±10.69 and 74.28±5.08 mmHg. There was no significant difference between mean diastolic blood pressure of study and controls. Similar result observed in the study of Sona Bajaj et al (2010) concluded physical activity level and Basal heart rate did not show any difference between the study groups [4]. Khatri Anshu et al (2012) in his study stated that there were no significant differences in the Age, Body Mass Index (BMI) and Blood pressure between cases and controls. Basal Heart Rate (BHR) was significantly higher in offsprings of diabetic parents compared to control group [5].

In current study Mean difference in blood pressure in study group and control group in cold pressor test Pre test: SBP 109.96±11.55 and 106.84±6.96 with no statistical difference. DBP 75±10.69 and 72.42±7.04 with no statistical difference. Post test: SBP 107±9.65 and 110.36±9.84 with no statistical difference DBP 77.8±7.64 and 75.88±8.88 with no statistical difference. In this study there was increase in the DBP in study group compared to control group but no statistically significant post test difference in mean DBP of study and controls. Also there was no statistically significant difference in SBP.

Hrv Analysis

The HF spectral component of HRV reflects parasympathetic nervous control of heart, LF component of HRV thought to be under sympathetic control, whereas the LF:HF ratio probably reflects sympathovagal balance. HF and LF normalized components P values were 0.0169 and 0.3287 respectively. P value for the LF/HF ratio is 0.7239. This indicates that there are not much predictable changes in cardiovascular autonomic activity in the early age group of 18-21 years of offspring's with the parental history of diabetes. This is been supported by the study done by F.J. Nerves et al stating family history of type 2 DM in the absence of concomitant metabolic disorders, does not impair resting HRV [12].

Longitudinal studies have revealed significant correlation between autonomic dysfunction and risk of developing type 2DM. A Fiorentini et al stated that the sympathetic overactivity in offsprings of type 2 diabetic parents especially in nocturnal period, demonstrated by increase of LF and LF/HF which were supporting our mean score of heart rate variables [13]. It has been supported by Illeamo et al that, first degree relatives (FDRs) have enhanced efferent sympathetic outflow as a primary characteristics [14]. One such study done by A Fiorenitini et al found familiarity of type 2 DM is related to a global reduction and alteration of circadian rhythm of autonomic activity are present in offspring of type 2

diabetic parents, dysautonomia increases if offsprings are insulin resistant [13]. Cahn JN et al states that sympathetic activation is important in the pathogenesis and progression of the clinical syndrome and raised plasma levels of norepinephrine are markers of severity and adverse prognosis [15]. Tomi Laitinen et al have suggested that autonomic dysfunction is one of the early pathophysiological changes to the development of an insulin resistant subgroup of type 2 diabetes and might be genetically determined [16]

In this study, though the components of HRV did not differ significantly between the groups, it was shown a decreasing trend in total variability as well as HF absolute power spectrum among healthy offsprings with parental history of diabetes. Further, it was also revealed that there was a increasing trend in the sympathovagal balance among healthy subjects with parental history of diabetes which was indicated by higher LF/HF. Underlying explanation for not having significant difference for the cardiovascular autonomic activity could be due to the age group of our study population where it is too early to identify the changes. Longitudinal studies might reveal alteration in cardiovascular autonomic activity in same subjects with later stages of their life.

CONCLUSION:

- HRV is reduced in nondiabetic offsprings of diabetic parents. Offsprings of diabetic parents showed increased sympathetic as well parasympathetic activity. Impaired vagal activity was found in offsprings of diabetic parents. Decreased HRV is associated with greater risk for developing diabetes mellitus. Further our study suggests that the tendency to developing diabetes mellitus sets in an early age. We did not find any association of autonomic neuropathy and somatic neuropathy. As Heart Rate Variability (HRV) test is simple to perform, non-invasive, and the autonomic function tests could be used as a screening tool to detect diabetes mellitus, which will facilitate dietary and lifestyle modifications to prevent or postpone the development of diabetes mellitus.

LIMITATATION

The results of the present study should be interpreted in light of some limitations.

1. Less number of subjects made difficult to identify the cardiovascular autonomic changes
2. HRV obtained at rest may not reflect autonomic function in other physiological conditions that cause sympathetic activation and vagal withdrawal such as exercise.
3. Subjects were evaluated at one stage of age to check the autonomic activity and not at the different stages of age.
4. HRV can be significant if recorded for longer duration.

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