CARDIAC AUTONOMIC NEUROPATHY IN ASYMPTOMATIC ADOLESCENTS WITH *TYPE 1* DIABETES MELLITUS.

Original Research Article

ISSN CODE: 2456-1045 (Online)
(ICV-MDS/Impact Value): 3.08
(GIF) Impact Factor: 2.174

Journal Code: ARJMD/MDS/V-12.0/I-1/C-3/APRIL-2017
Category : MEDICAL SCIENCE
Volume : 12.0 / Chapter- III / Issue -1 (APRIL)
Website: www.journalresearchijf.com
Received: 12.04.2017
Accepted: 20.04.2017
Date of Publication: 05-05-2017
Page: 12-16

Name of the Author:

Musharaf Bashir[1], Himani Ahluwalia[1], Raj Kapoor[1], Geeta Kampani[2] and Krishna Biswas[3].

[1]Department of Physiology, VMMC & Safdarjung hospital, New Delhi, India- 110029.

[2]Department of Medicine, VMMC & Safdarjung hospital, New Delhi, India- 110029.

[3]Department of Endocrinology, VMMC & Safdarjung hospital, New Delhi, India- 110029.

Citation of the Article

Bashir M; Ahluwalia H; Kapoor R. ; Kampani G & Biswas K. (2017, April). Cardiac autonomic neuropathy in asymptomatic adolescents with Type 1 diabetes mellitus, Advance Research Journal of Multidisciplinary Discoveries.12.0,C-2(2017):12-16 ISSN-2456-1045. http://www.journalresearchijf.com

ABSTRACT

Cardiac Autonomic Neuropathy (CAN) is one of the lethal complications of diabetes mellitus which is associated with a variety of adverse cardiovascular outcomes like lethal arrhythmias and sudden death. CAN results from damage to the autonomic nerve fibers that innervate heart and blood vessels which leads to reduced heart rate variability (HRV). We examined HRV, a measure of autonomic activity, in adolescents aged 12 to 19 years with type 1 diabetes mellitus (T1 DM) and healthy controls using BIOPAC MP 150. Thirty three adolescents with T1 DM (age 16.15 ± 2.66 years) who were diagnosed to have T1 DM for more than 2 years and thirty one, aged and sex matched, healthy controls (age 17.13 ± 1.34 years) were recruited for this study. We studied different indices of HRV for 5 minutes (standard deviation of all N-N intervals: SDNN, the square root of the mean of the sum of the squares of difference between adjacent N-N intervals: RMSSD, N-N 50 count divided by the total number of N-N intervals: pNN50, very low frequency: VLF, low frequency: LF, high frequency: HF, total power: TP and LF/HF ratio). We found that there was a significant difference between the HRV analyses of T1 DM patients and healthy controls. All the indices of HRV were significantly lower in T1 DM patients as compared to the healthy controls. However LF/HF ratio was higher in T1 DM patients but it was not statistically significant. Our findings suggest reduced overall HRV in adolescents with T1 DM which could be attributed to the presence of CAN in them.

Keywords :-

Heart rate variability,
Type 1 diabetes mellitus,
adolescents,
cardiac autonomic neuropathy,
heart rate.

I. INTRODUCTION

Worldwide prevalence of diabetes is showing a significant increase with 382 million people living with diabetes, half of them still undiagnosed [1]. Although the proportion with T1 DM is small i.e. 5-10%, incidence of T1 DM has been steadily increasing in the past two decades [2].The developing countries are also facing the brunt of this metabolic disorder ,however the focus on early detection of complications of T1 DM after the detection of disease needs to be prioritized globally.

It is a well known fact that the metabolic derangement associated with diabetes mellitus (DM) causes secondary physiologic changes in multiple organs that impose a tremendous burden on the individual with DM and on the healthcare system [3]. The chronic hyperglycemia of diabetes is associated with long term damage of various organs especially the eyes, kidneys, nerves, heart and blood vessels and ultimately results in retinopathy, nephropathy, peripheral neuropathy and autonomic neuropathy [4]. Diabetic autonomic neuropathy (DAN) is one of the serious and long term complications of DM which can involve the entire autonomic nervous system (ANS) [5] and this type of autonomic neuropathy may be evident clinically and subclinically. Clinically it manifests as dysfunction of one or more organ system e.g. cardiovascular, gastrointestinal and genitourinary [5]. However subclinical autonomic dysfunction can occur within 2 years of diagnosis in T1 DM [6] and in some cases, DAN has been seen at the time of diagnosis itself [7]. Because of its adverse cardiovascular outcomes like arrhythmias and deaths, CAN is the most important and well studied form of DAN [8] which results from damage to the autonomic nerve fibers both parasympathetic and sympathetic that innervate the heart and the blood vessels and ultimately leads to altered HRV [9]. Furthermore CAN leads to as resting tachycardia, exercise intolerance, orthostatic hypotension, loss of day and night variation in blood pressure, arrhythmias, silent myocardial infarct and sudden death [10]. The development of these autonomic complications depend on the duration of disease, glycaemic control and patient's age. It has been seen that pubertal spurt , a period of major endocrinal changes, leads to rapid progression of CAN. Hormonal changes during puberty and prolonged periods of poor glycaemic control could induce irreversible neuropathic changes and this emphasizes the significance of early detection of CAN and motivation of the patients to improve their diabetes control. Thus early detection and intervention with strict follow up during the pubertal stage could delay the development of complications in these patients [11]. Early detection of CAN may be done with the help of HRV which is a sensitive, reproducible and non-invasive method. It is one of the first indices of cardiac dysautonomia observed in young diabetics [11]. Thus reduced HRV is the earliest indicator of CAN [9].

To the best of our knowledge there have been very few studies investigating cardiac dysautonomia in asymptomatic adolescents with T1 DM [12] from the Asian subcontinent There is paucity of studies investigating the presence of early DAN in the adolescent population suffering from T1DM in the Indian subcontinent. The emerging picture of T1DM in a country like India is more complex where the adolescents from affluent class suffer from sedentary lifestyle, obesity and unhealthy food habits and those from the lower socioeconomic strata face the challenges of malnutrition and infections. This is the first study of its kind to investigate and detect the presence of CAN in adolescents with T1 DM in India.

II. MATERIALS AND METHODS

Materials

This cross sectional study was conducted in the Department of Physiology and Endocrinology, VMMC & Safdarjung hospital, New Delhi, India. The study was commenced after obtaining clearance from institutional ethical committee. The subjects were informed of the prerequisites of this study and written informed consent was obtained from each subject prior to the study.

This study included adolescents (age 12 to 19 years) who had been diagnosed with T1 DM for more than 2 years. We enrolled 33 adolescents with T1 DM [(13 males and 20 females(age 16.15 ± 2.66 years)]and 31, age and sex matched, healthy controls [(19 males and 12 females (age 17.13 ± 1.34 years)] for this study. Subjects on any medication known to affect ANS, having any acute complications of DM (diabetic ketoacidosis), chronic disorder, any major neuropsychiatric illness known to affect ANS, and smokers were excluded from this study. All the subjects were instructed to refrain from tea/ coffee or any medicine that could affect the outcome of AFT. They were advised to take a light breakfast 3 hours prior to testing. The temperature of the AFT lab was maintained at 23°C to 25°C.

Methods

All the subjects were called to the Department of Physiology and their anthropometric measurements (height, weight and BMI) were recorded. The subjects were requested to lie down supine on a table for about 10 to 15 minutes following which their resting blood pressure was measured with the help of an aneroid sphygmomanometer. Resting heart rate was measured manually. The HRV was recorded in a well controlled condition and in a semi darkened room. The electrodes for recording of electrocardiogram (ECG) in lead II were placed in the supine subject .The autonomic affect on resting HRV was evaluated on the basis of short term recordings of electrocardiogram (ECG) in lead II. The subjects were again allowed to rest for 10 to 15 minutes. ECG was recorded for 5 minutes. HRV was analyzed with the help of Kubios HRV Pro Version Software (University of Kuopio, Finland). Each QRS complex was meticulously checked for any artifacts or ectopic beat. Time Domain and Frequency Domain were analyzed respectively. For Time Domain, we calculated mean R-R interval (MRR), mean heart rate (MHR), standard deviation of all N-N intervals (SDNN), the square root of the mean of the squared successive differences in R-R intervals (RMSSD), NN 50 count divided by total number of NN intervals (p NN50). Frequency Domain analysis was calculated by the power spectrum using the Fast Fourier Transform (FFT) method. Very low frequency (VLF), low frequency (LF), high frequency (HF), total power (TP) and LF/HF ratio were calculated.

Statistical analysis

The data was analyzed by statistical software SPSS version 22. Chi square test was used for the association between sex in the study group. Differences of mean of values of age, height, weight and BMI between two study groups were assessed through unpaired t test. All the HRV parameters were checked if they followed normal distribution using Kolmogorov Smirnov test. Differences of mean values of those parameters that were normally distributed between case and control groups were assessed through t test. Mann-Whitney U test was used for parameters that did not follow normal distribution. However, for the sake of simplicity mean values along with stand errors were presented for both normally distributed and non-normally distributed parameters. P value of < 0.05 was taken as significant.

III. RESULTS

There was no statistically significant difference found in age and sex between the two groups, therefore the groups were comparable for the study as shown in Table 1 and Table 2. The number of males in the control group was 19 (61.29%) and that of females was 12 (38.71%) whereas in the diabetic group the number of males was 13 (39%) and that of females was 20 (61%),(p value= 0.08). The mean age of the control group and T1 DM was 17.13 ± 1.34 vs 16.15 ± 2.66 years, (p value < 0.071). Height, weight and BMI were recorded in both the groups as shown in Table 2. The mean height of T1 DM (151.92 ± 11 cms) was significantly lower as compared to the control group (166.81 ± 9.97 cms),(p value< 0.01). The mean weight of T1 DM (43.46 ± 11.73 kgs) was significantly lower as compared to the control group (59.06 ± 9.73 kgs), (p value < 0.01). The mean BMI of T1 DM (18.49 ± 3.25 kg/m²) was significantly lower as compared to the control group (21.16 ± 1.91 kg/m²), p< 0.01. The minimum duration of diabetes in case group was 25 months and the maximum duration was 144 months (54.9 ± 5.76 months).

Table 1. Sex wise distribution in case and control group

	TYPE1 DM (n= 33)		CONTROL (n= 31)		p value
SEX	N	%	N	%	
MALE	13	39.39	19	61.29	0.080
FEMALE	20	60.61	12	38.71	

[a] By Chi square test.
[b] N= number of subjects.
[c] *p value < 0.05 Significant, **p value < 0.01 Highly Significant, ***p value < 0.001 Very Highly Significant.

Table 2. Age and anthropometric data of healthy controls and type 1 diabetics

PARAMETERS	CONTROLS(n= 31)	TYPE 1 DM (n=33)	p value
AGE (years)	17.13 ± 1.34	16.15 ± 2.66	0.071
HEIGHT (cms)	166.81 ± 9.97	151.92 ± 11	<0.001***
WEIGHT (kg)	59.06 ± 9.73	43.46 ± 11.73	<0.001***
BMI (kg/m²)	21.16 ± 1.91	18.49 ± 3.25	<0.001***

[a] By unpaired t test.
[b] Result was expressed in terms of mean ± SE (standard error).
[c] *p value < 0.05 Significant, **p value < 0.01 Highly Significant, ***p value < 0.001 Very Highly Significant.
[d] BMI= body mass index.

The mean resting heart rate (RHR), systolic blood pressure (SBP) and diastolic blood pressure were recorded in both the groups as shown in Table 3. The mean RHR in T1 DM (86.76 ± 13.27 bpm) was significantly higher as compared to the control group (76.80 ± 12.23 bpm), p= 0.001. The mean resting SBP in T1 DM (110.79 ± 9.39 mmHg) was significantly lower as compared to the control group (117.94 ± 10.88 mmHg), p= 0.007. The mean resting DBP in T1 DM (69.61 ± 8.79 mmHg) was lower as compared to the controls (73.23 ± 8.68 mmHg) but the difference was not statistically significant, p= 0.599.

Table 3.Resting blood pressure and heart rate of controls and type 1 diabetics

PARA METERS	CONTROLS (n= 31)	TYPE-1 DIABETICS (n=33)	p value
HR (bpm)	76.80 ± 12.23	86.76 ± 13.27	0.001**
SBP (mmH)	117.94 ± 10.88	110.79 ± 9.39	0.007**
DBP (mmH)	73.23 ± 8.68	69.61 ± 8.79	0.599

[a] By unpaired t test.
[b] Result was expressed in terms of mean ± SE (standard error).
[c] HR= heart rate, SBP= systolic blood pressure, DBP= diastolic blood pressure.
[d] *p value < 0.05 Significant, **p value < 0.01 Highly Significant, ***p value < 0.001 Very Highly Significant.

Results of HRV analysis were recorded in both the groups as shown in Table 4. In the Time Domain, MRR of T1 DM (692 ± 21.27 ms) was significantly lower as compared to the control group (782.71 ± 20.54 ms), p= 0.03. The SDNN of T1 DM (31.09 ± 2.97 ms) was significantly lower as compared to the controls (56.33 ± 3.44 ms), p< 0.001. The RMSSD of T1 DM (29.65 ± 3.81 ms) was significantly lower as compared to the control group (50.96 ± 4.21 ms), p< 0.001. The pNN50 in T1 DM (13.46 ± 3.21%) was significantly lower as compared to the control group (30.44 ± 4.36%). However, MHR in T1 DM (88.76 ± 2.45 bpm) was significantly higher as compared to the control group (78.11 ± 1.90 bpm), p= 0.001. In Frequency Domain, VLF in T1 DM (284.06 ± 64.34 ms²) was significantly lower as compared to the control group (1055.97 ± 99.96 ms²), p <0.001. The LF in T1 DM (195.31 ± 27.80 ms²) was significantly lower as compared to the control group (1272.90 ± 125.41 ms²), p< 0.001. The HF in T1 DM (515.52 ± 125.49 ms²) was significantly lower as compared to the controls (1566.90 ± 125.41 ms²), p< 0.001. The TP in T1 DM (997.58 ± 182.59 ms²) was significantly lower as compared to the control group (3891.19 ± 305.51 ms²). However, LF/HF ratio was higher in T1 DM (1.47 ± 0.37) as compared to the control group (0.98 ± 0.08) but was not statistically significant.

Table 4. Comparison between HRV parameters *Time Domain and Frequency Domain* of type 1 diabetics and control group.

HRV parameters	CONTROLS		TYPE 1 DM		p value
	Mean	SE	Mean	SE	
MRR(ms)	782.71	20.54	692.45	21.27	0.003**
MHR(bpm)	78.11	1.90	88.76	2.45	0.001**
SDNN (ms)	56.33	3.44	31.09	2.97	<0.001***
RMSSD (ms)	50.96	4.21	29.65	3.81	<0.001***
pNN50(%)	30.44	4.36	13.46	3.21	<0.001***
VLF(ms²)	1055.97	99.96	284.06	64.34	<0.001***
LF (ms²)	1272.90	125.41	195.31	27.80	<0.001***
HF (ms²)	1566.90	166.06	517.52	125.49	<0.001***
LF/HF ratio	0.98	0.08	1.47	0.37	0.48
TP(ms²)	3891.19	305.15	997.58	182.59	<0.001***

[a] By unpaired t test.
[b] Result was expressed in terms of mean ± SE (standard error).

[c] HRV= heart rate variability, MRR= mean R-R interval, MHR= mean heart rate, SDNN= standard deviation of all N-N intervals, RMSSD= the square root of the mean of the squared successive differences in R-R intervals, p NN50= NN50 count divided by total number of N-N intervals, VLF= very low frequency, LF= low frequency, HF= high frequency, TP= total power, LF/HF ratio= sympathovagal balance, bpm= beats per minute, ms= milliseconds, ms^2= milliseconds squared.

[d] *p value < 0.05 Significant, **p value < 0.01 Highly Significant, ***p value < 0.001 Very Highly Significant.

IV. DISCUSSION

We observed statistically significant lower values of anthropometric parameters (height, weight and BMI) in T1 DM as compared to the controls. Impaired growth is a well documented complication of diabetes [13]. Several studies have clearly documented impaired pre-pubertal and pubertal growth in children and adolescents with T1 DM [14]. Gimenez et al [15] observed that the patients with T1 DM had a lower BMI than the reference population in all age groups at diagnosis. Vaman V et al [13] found a compromised growth pattern in young diabetic population who were shorter and lighter in comparison to the normal young population. We also observed that 15 of our diabetic patients had a resting heart rate of more than 90 bpm (86.76 ± 13.27 bpm). Resting tachycardia is a late finding in diabetic patients with vagal / parasympathetic impairment [16]. Elamin et al [17] found higher and statistically significant heart rate ($p<0.05$) in children with T1 DM. The same was also reported by Barkai L et al [11].

Increased RHR in T1 DM indicates a decreased parasympathetic activity that leads to decreased vagal inhibition of heart. As a result of this there is a sympathetic overdrive leading to the increased RHR in almost all age groups.

The resting SBP was significantly lower in T1 DM as compared to the controls. DBP of T1 DM was also lower as compared to the controls but was not statistically significant. In our study, the significantly lower SBP can be attributed to a significantly decreased BMI in T1 DM. The same has been documented by Rescnikov K et al [18]. They examined the relationship between BMI and SBP as a criteria for blood pressure screening in 11,370 school children. They also found that the children with higher BMI had elevated SBP. Mungreiphy NK et al [19] studied the association between BMI, blood pressure and age in 257 Naga males of Northeast India. They found that minimum blood pressure was found among the people who had reduced BMI.

We observed in our study that Time Domain parameters of T1 DM such as SDNN, RMSSD and p NN50 were significantly lower in adolescents with T1 DM as compared to the healthy controls. Frequency Domain parameters such as VLF, LF, HF and TP were significantly lower in adolescents with T1 DM as compared to the controls. However, LF/HF ratio was higher in T1 DM as compared to the controls but was not statistically significant. The observations of significantly reduced indices of parasympathetic activity i.e. RMSSD and pNN50 in Time Domain and HF in Frequency Domain imply that T1DM have significantly reduced parasympathetic activity as compared to the healthy controls. A higher LF/HF ratio inspite of a significantly lower LF in T1 DM also suggests that the parasympathetic derangement was more as compared to the sympathetic [20]. A significantly lower value of SDNN in Time Domain and TP in Frequency Domain as observed can be explained on the basis of an overall reduction of all the component parameters of HRV due to sympathetic and parasympathetic neuropathy. Significantly depressed HRV parameters in children ≥ 11 years has also been documented by Massin M et al [16] whose results suggested that early puberty is a critical period for the development of diabetic cardiac autonomic dysfunction. Jaiswal M et al [21] made similar observations of reduced overall HRV in youth with mean age of 18.8 years and concluded that youth with T1 DM have signs of early cardiac autonomic neuropathy.

Thus our findings of reduced overall HRV indicate towards the presence of clinically significant CAN involving both parasympathetic and sympathetic components. A pattern of parasympathetic loss with a relative sympathetic overdrive, depending on the extent of autonomic neuropathy as indicated by a higher RHR, MHR and a lower MRR in our study, is similar to previous studies.

V. ACKNOWLEDGEMENTS

I am extremely grateful to my supervisor Dr.Himani Ahluwalia and Dr.Raj Kapoor for their valuable guidance and contributions towards this study.

REFERENCES

[1] **International Diabetes Federation.** IDF Diabetes Atlas, 6th Edn. International Diabetes Federation 2013. http:// www.idf.org/diabetesatlas.

[2] **Onkamo P, Vaananen S, Karvonen M, Tuomilheto J.** Worldwide increase in the incidence of type 1 diabetes. The analysis of the data on published incidence trends. *Diabetologia,* 1999; 42: 1395-1403.

[3] **Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL , Loscalzo J.** Harrison's principles of Internal Medicine. 17thed. New York, McGraw Hills 2008: 2305-2475.

[4] **Diagnosis and classification of diabetes mellitus. American Diabetes Association.** *Diabetes Care,* 2004; 27(1): 55-60.

[5] **American Diabetes Association and American Academy of Neurology:** Report and recommendations of the San Antonio Conference on diabetic neuropathy.*Diabetes,* 1998; 37: 1000-1007.

[6] **Pfeifer MA et al.** Autonomic neural dysfunction in recently diagnosed diabetic subjects. *Diabetes Care,* 1984; 7(5): 447-453.

[7] **Ziegler D, Cicmir I, Mayer P, Wiefels K, Gries FA.** Somatic and autonomic nerve function during the first year after diagnosis of type 1 (insulin-dependent) diabetes. *Diabetes Resi*, 1988; 7: 123-127.

[8] **Vinik AI, Maser RE, Mitchell BD, Freeman R.** Diabetic Autonomic Neuropathy. *Diabetic Care,* 2003; 26: 1553-1579.

[9] **Schumer MP, Joyner SA, Pfeifer MA.** Cardiovascular autonomic neuropathy: testing in patients with diabetes. *Diabetes Spectrum,* 1998; 11: 227-231.

[10] **Pop-Busui R.** Clinical Autonomic Neuropathy in Diabetes. *Diabetes Care,* 2010; 33(2); 434-439.

[11] **Barkai L, Madacsy L.** Cardiovascular autonomic dysfunction in diabetes mellitus. *Archives of Diseases in Childhood,* 1995; 73: 515-518.

[12] **Turker Y[1], Aslantas Y, Aydin Y, Demirin H, Kutlucan A, Tibilli H, Turker Y, Ozhan H.** Heart rate variability & heart rate recovery in patients with type 1 diabetes mellitus. *Acta Cardiol,* 2013 Apr; 68(2):145-50.

[13] **Vaman V et al.** Groth status of children and adolescents with type 1 diabetes mellitus. *Indian J Endocrinal Metab,* 2013; 17(6):1057-1060.

[14] **Gionanni C, Angelika M, Chiarelli F.** Growth Abnormalities in Children with Type 1 Diabetes, Juvenile Chronic Arthritis, and Asthma. *International Journal of Endocrinology,* 2014: 1-10.

[15] **Gimenez M et al.** Relationship Between BMI and Age at Diagnosis of Type 1 Diabetes in Mediterranean Area in the Period of 1990–2004. *Diabetes Care,* 2007; 30(6): 1593-1595.

[16] **Martial M Massin et al.** Cardiac Autonomic Dysfunction in Diabetic Children. *Diabetic Care,* 1999; 22(11): 1845-1850.

[17] **Elamin A, Rajesh K, Tuvemo T.** Cardiac Autonomic Dysfunction in Children and Adolescents with type 1 diabetes mellitus. *Sudan JMS,* 2007; 2(2); 95-100.

[18] **Rescnikov K, Futterman R, Vaughan RD.** Body mass index as a predictor of systolic blood pressure in a multiracial sample of US schoolchildren. *Ethin Dis,* 1993; 3(4): 351-361.

[19] **Mungreiphy NK, Kapoor S, Sinha R.** Association between BMI, Blood Pressure and Age: Study among Tangkhul Naga Tribal Males of Northeast India. *Journal of Anthropology,* 2011; 11: 1-6.

[20] **Billman GE.** The LF/HF ratio does not accurately measure cardiac sympatho-vagal balance. *Frontiers in Physiology,* 2013; 4(26): 1-5.

[21] **Jaiswal M et al.** Reduced Heart Rate Variability Among Youth with Type 1 Diabetes. *Diabetes Care,* 2013; 36: 157-162.

*****

Corresponding Author :
Dr.Musharaf Bashir.
Room no: 312, Department of Physiology, VMMC & Safdarjung hospital, New Delhi, India- 110029.
Phone no: +917042272380.
Email id: dr.musharaf.mb@gmail.com