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A comparative study of anxiety levels and its relation with heart rate variability indices in adolescents with type 1 diabetes mellitus

Tip 1 diabetes mellituslu adolesanlarda anksiyete düzeyleri ve bunun kalp tepe atımı değişkenliği ile ilişkilisini inceleyen karşılaştırmalı çalışma

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ABSTRACT

The aim of this study was to reveal the correlation between anxiety levels and heart rate variability (HRV) indices in adolescents with type1 diabetes mellitus (T1 DM). Sixty-four subjects were recruited for this study which included 33 patients with a diagnosis of T1 DM and 31 controls. Subjects were invited to the autonomic function testing laboratory (AFT lab), in the department of Physiology, for HRV analysis and anxiety level determination using a simple questionnaire called Hamilton's scale of anxiety. Anxiety levels were negatively correlated with percentage of normal-normal interval pNN 50 (r= -0.380, p<0.05), Standard deviation of normal-normal interval (r= -0.349, p<0.05), square root of the mean squared deviation (r= -0.384, p<0.05), very low frequency (r= -0.586, p< 0.01), low frequency LF (r= -0.048, p<0.01), high frequency HF (r= -0.351, p<0.05), total power (r= -0.468, p<0.01). Anxiety level was positively correlated with LF/HF ratio (r= 0.349, p<0.05) were found as indicated. There was no correlation between anxiety levels and biochemical parameters such as fasting blood glucose and glycated hemoglobin (HbA1c). Since HRV is a marker of parasympathetic activity, a negative correlation of anxiety levels with HRV parameters indicates reduced parasympathetic activity in patients with T1 DM. A positive correlation between anxiety levels and sympathovagal balance (LF/HF ratio) was observed because of reduced parasympathetic activity which is attributed to reduced HF. The outcomes of this preliminary suggest that anxiety appears to play an important role in reducing HRV in patients with T1 DM.

Keywords: *Anxiety, heart rate variability, type 1 diabetes mellitus, Hamilton's scale, total power*

ÖZ

Bu çalışmada, tip 1 diabetes mellituslu (T1 DM) adolesanlarda anksiyete düzeyleri ve kalp tepe atımı değişkenliğinin (KTAD) korelasyonunu ortaya koymak amaçlandı. Çalışmaya 33'ü T1 DM tanılı ve 31'i kontrol grubunda olmak üzere 64 olgu dahil edildi. Tümü Fizyoloji biriminde bulunan Otonom Fonksiyon Testleri Laboratuvarında KTAD'yi saptamak üzere Hamilton anksiyete ölçeği kullanılarak basit bir ankete tabi tutuldu. Anksiyete düzeyleri ile normal-normal aralık yüzdesi pNN (r= -0,380, p<0,05) arasına negatif korelasyon bulundu. Normal-normal aralığın standart sapması (r= -0,349, p<0,05), kare sapmanın karekök ortalaması (r= -0,384, p<0,05), çok düşük frekans (r= -0,586, p<0,01), düşük frekans LF (r= -0,048, p<0,01), yüksek frekans (r= -0,351, p<0,05), toplam güç (r= -0,468, p<0,01) olarak bulundu. Anksiyete düzeyi ile LF/HF oranı arasında pozitif korelasyon bulundu (r= 0,349, p<0,05). Anksiyete düzeyleri ile açlık kan şekeri, glikozile hemoglobin (HbA1C) gibi biyokimyasal parametreler arasında korelasyon bulunmadı. KTAD parasempatik aktivitenin bir göstergesi olduğu için anksiyete düzeyleri ile KTAD parametreleri arasındaki negatif korelasyon T1 DM'li hastalardaki azalmış parasempatik aktiviteyi göstermektedir. HF azalması ile gözlenen parasempatik aktivite azalması nedeni ile anksiyete düzeyleri ile sempatovagal denge (LF/HF oranı) arasında pozitif bir korelasyon gözlenmiştir. Bu ön çalışmanın sonuçları, anksiyetenin T1 DM'li hastalarda KTAD'yi azaltmada önemli bir rol oynadığını düşündürmektedir.

Anahtar kelimeler: *Anksiyete, kalp tepe atımı değişkenliği, tip 1 diyabetes mellitus , Hamilton ölçeği, toplam güç*

INTRODUCTION

Type I Diabetes Mellitus (T1 DM) ranks third in terms of chronic childhood disorders and has the ability to cause both acute and chronic complications as well as events that can put patient's life at risk[1]. T1 DM at

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any age especially in adolescence increases the possibility of psychological disorders such as anxiety and depression[1]. It has been seen that most of the patients have either depressive or anxiety symptoms at the time of diagnosis[1]. It is established that psychological factors such as anxiety and depression have a great influence on the course of diabetes mellitus (DM) including glycemic control and the management of disease[2]. There is a greater morbidity related to psychiatric conditions in T1 DM with depression being the commonest followed by anxiety[3]. Children and adolescents suffering from T1 DM are at increased risks for psychological disturbances such as anxiety[4,5]. Many studies have found that anxiety leads to poor diabetes management, glycemic control and consequently unfavorable medical outcomes[6,7]. The likelihood of anxiety is increased manifold as the glycemic control worsens[8]. Research has demonstrated that decreased psychological adjustment due to anxiety leads to poor glycemic control in these patients[9,10]. The symptoms of anxiety are widespread in young people with T1 DM with approximately 13% to 21% of young people with T1 DM screening positive for anxiety symptoms[11]. There is a direct association of anxiety with poorer quality of life, self-management, and glycemic control in young people with T1 DM[12].

Anxiety disorders increase the risk of cardiovascular morbidity and mortality[13]. One of the causes for this enhanced risk is the imbalance in the regulation of the autonomic control of the heart[14,15]. Anxiety causes an imbalance between sympathetic and parasympathetic activity leading to a reduced parasympathetic activity and hence reduced heart rate variability (HRV)[16]. Furthermore, low parasympathetic activity has been found to be associated with decreased concentration in adolescents[16].

Limitations of the studies that have been done so far are that they could not take into consideration possible confounders of the relationship between anxiety and HRV[15].

Thus this study was aimed to see correlation between anxiety levels as derived from Hamilton's anxiety scale (HAMA) and various HRV indices in patients diagnosed with T1 DM.

MATERIALS and METHODS

This study was conducted in the Department of Physiology, Medicine and Endocrinology, VMMC & Safdarjung Hospital, New Delhi, India. The study was commenced after obtaining clearance from the institutional Ethical Committee. Thirty- three (33) adolescents aged 12 to 19 years and diagnosed with T1 DM from the Endocrinology outpatient department of Safdarjung Hospital were recruited in this study. Duration of diabetes ≥ 2 years was taken into consideration for this study. Thirty-one (31) age and sex- matched healthy controls were recruited for this study. Subjects on medications that tend to influence heart rate and blood pressure such as β agonists, β blockers etc, those having any medical or comorbid condition, smokers and those with acute complications of T1DM such as diabetic ketoacidosis were excluded from the study.

Anthropometric measurements i.e. height, weight, BMI and other biochemical parameters such as fasting blood glucose and glycated hemoglobin were recorded in the Endocrinology OPD from all the subjects. All the subjects were called to the department of Physiology in morning hours and the investigations were performed between 9a.m and 11:30a.m in the autonomic function testing (AFT) laboratory. The prerequisites for AFT were explained to all the subjects prior to testing. Subjects were instructed to have a light breakfast three hours prior to testing, refrain from caffeine/tea ingestion on the day of investigations. The ambient temperature of the AFT lab was maintained between 23°C to 25°C. Standardized protocol was followed.

All the subjects were tested under similar laboratory conditions. They were allowed to adapt to environmental conditions for 15 minutes. Informed consents were obtained from all the subjects or their guardians. All the subjects were made to lie down in supine

position. The electrodes were placed for recording lead II ECG. The subjects were allowed to rest for 10-15 minutes before ECG examination which lasted for 5 minutes. HRV was calculated from lead II ECG using BIOPAC MP I50. Resting HRV was evaluated on the basis of short-term recordings of an electrocardiogram (ECG).

HRV was analyzed with the help of Kubios HRV Pro Version software (University of Kuopio, Kuopio, Finland). Time Domain and Frequency Domain were analyzed respectively.

Anxiety levels were measured with the help of HAMA. The scale contains 14 questions, each question inquired a succession of symptoms. Each element of anxiety is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0-56, where <17 indicates mild severity, 18-24 mild to moderate severity and 25-30 moderate to severe.

Each parameter of the HAMA was explained to the subjects by the examiner in English/Hindi. Depending on the severity of symptoms they were instructed to rank the symptoms in the scale. The score was calculated by adding up the scores. This scale was filled at the end of all the tests.

The data were analyzed by statistical software SPSS version 22. Fisher's exact test was used to study the distribution of anxiety among patient and control groups. Pearson's correlation coefficient was used to study the correlations in normally distributed parameters and Spearman's correlation coefficient was used for the correlation between all non-normative parameters. Correlations of anxiety levels with various HRV indices were sought for. p value of <0.05 was taken as statistically significant.

RESULTS

Hamilton's anxiety scale was used to determine the levels of anxiety in which all the subjects were asked questions related to the anxiety symptoms by the examiner. Anxiety score was obtained from the questionnaire and depending on the anxiety score, anxiety was divided into mild, moderate and severe level. In subjects with T1 DM, 14 patients (42.42%) showed "mild ", 8 patients (24.24%) "mild-moderate " and 11 patients "moderate-severe anxiety levels" as shown in Table 1. All the controls (100%) showed "mild anxiety levels" as shown in Table 1. The anxiety levels in patients with T1 DM were significantly higher than the controls (p<0.001). Anxiety level between two groups was compared using Fisher's exact test.

Table 1. Comparison of anxiety levels of controls and patients with T1 DM.

	Controls (n=31)		T1 DM (n=33)		
Anxiety level	**N**	**%**	**N**	**%**	**p value**
Mild	31	100	14	42.42	<0.01**
Mild-moderate	0	0	8	24.4	
Moderate-severe	0	0	11	33.3	

Fischer's exact test
*** means highly significant.*
T1 DM : type 1 diabetes mellitus.

We observed a significant negative correlation of anxiety with p NN50% (r= -0.380, p<0.05), Standard deviation of normal-normal interval (SDNN) (r= -0.349, p<0.05), square root of the mean squared deviation (RMSSD) (r= -0.384, p<0.05), very low frequency (VLF) (r= -0.586, p<0.01), LF (r= -0.448, p<0.01), HF

Table 2. Correlation of heart rate variability (HRV) indices with anxiety level in patients with T1 DM.

HRV indices	Anxiety level
p NN50 (%)	r= - 0.380, p<0.05*
SDNN (ms)	r= - 0.349, p<0.05*
RMSSD (ms)	r= - 0.384, p<0.05*
VLF (ms^2)	r= - 0.586, p<0.01**
LF (ms^2)	r= - 0.048, p<0.01**
HF (ms^2)	r= - 0.351, p<0.05*
LF/HF	r= + 0.349, p<0.05*
TP (ms^2)	r= - 0.468, p<0.01**

pNN50: NN50 count divided by the total number of NN intervals, SDNN: Standard deviation of all NN intervals, RMSSD: Square root of the mean of the sum of the squares of differences between adjacent NN intervals, VLF: very low frequency, LF: low frequency, HF: high frequency, LF/HF ratio: sympathovagal balance, TP: total power.
ms: milliseconds, ms2: milliseconds squared.
** means significant, ** means highly significant.*

(r= -0.351, p<0.05), and TP (r= -0.468, p<0.01). A significantly positive correlation of anxiety levels was observed with LF/HF ratio (r= 0.349, p<0.05) as shown in Table 2. However there was no correlation of HRV indices with anxiety level in control group. In our study we did not find any correlation between anxiety levels with biochemical parameters such as fasting blood glucose (r= 0.143, p=0.427) and glycemic control (r=0.144, p=0.423) as shown in Table 3.

Table 3. Correlation of fasting blood glucose and glycaemic control with anxiety level in patients with T1 DM.

Biochemical parameters	Anxiety level
FBG	r=0.143, p=0.427
HbA1c	r=0.144, p=0.423

FBG= fasting blood glucose, HbA1c= glycaemic control.
p value >0.05 Not Significant.

DISCUSSION

To the best of our knowledge, this is the first study of its kind in Indian adolescents with diagnosed T1DM in which the HRV has been studied along with anxiety levels. In our study we compared the anxiety levels of type 1 diabetic adolescents and healthy controls using HAMA. We found that the anxiety levels were significantly high in patients with T1 DM (p<0.001) as compared to the controls. Furthermore in the diabetic group (n=33), 14 patients had “mild” symptoms, 8 patients had “mild-moderate” symptoms and 11 had “moderate-severe” symptoms of anxiety. In the control group (n=31) all the subjects had “mild” symptoms of anxiety.

Adolescence sometimes may be accompanied by psychiatric disorders such as anxiety and depression and the anxiety level in adolescents is usually higher than that of depression[17].

Many studies have been put forward which suggest that T1 DM leads to anxiety in adolescents.

Collins MM et al.[18] had findings similar to our study. They carried a cross-sectional study of 2049 people with type 1 and type 2 diabetes mellitus. They studied the symptoms of anxiety and depression in these patients using the Hospital Anxiety and Depression Scale (HADS). They found high levels of anxiety and depression symptoms in patients with diabetes. They concluded that the prevalence of anxiety and depression symptoms in diabetics was much higher as compared to the general population. Herzer M et al.[19] in their study of anxiety symptoms in T1 DM adolescents observed comparable state and trait anxiety scores with that of otherwise medically healthy children. They found that 17% of 276 adolescents with T1 DM which were included in this study had trait anxiety symptoms. Peyrot M et al.[20] and Tuncay T et al.[21] observed that rates of anxiety were higher for diabetics than in general population. In our study, we also observed elevated anxiety levels in patients with T1 DM.

Sato E et al.[22] examined 13 adolescents with T1 DM. In their study they inquired about the psychosocial aspects of anxiety. It was concluded that all these aspects have an important impact on the emotional state of patients with T1 DM[22]. Elizabeth HB et al.[23] had similar findings. They found significant correlations between anxiety and depression with HbA1C.

The findings in our study have been supported by the findings of Sharma et al.[16] who observed significantly reduced HRV in both Time as well as Frequency domain in a group of 34 children and adolescents who were diagnosed with anxiety disorder. Their findings indicated diminished HRV at rest. Carmilla MM et al.[15] measured the time domain and respiratory sinus arrhythmia (RSA) in 2059 subjects who volunteered to participate in The Netherlands Study of Depression and Anxiety (NESDA). They found that anxious subjects had a significantly lower HRV than controls. The results of these studies focus on the same significant issue that anxiety is an important factor that must be taken into consideration in glycemic control programs.

Findings similar to our study were also reported by Chalmers et al.[24]. They studied 2086 patients with

anxiety disorders and 2294 controls. They found that the patients with anxiety had lower HRV especially high frequency index (HF) was significantly lower as compared to the controls.

In our study, we observed a positive correlation between anxiety and LF/HF ratio (r= 0.349, p<0.05). We also observed a negative correlation between anxiety and Time Domain parameters such as SDNN (r= -0.349, p<0.05), RMSSD (r= -0.381, p<0.05), p NN50 (r= -0.380, p<0.05) and Frequency Domain parameters such as VLF (r= -0.586, p<0.01), LF(r= -0.448, p<0.01), HF (r= -0.351, p<0.05), and TP (r= -0.468, p<0.01). We did not observe any correlation between anxiety levels and FBG (r=0.143, p=0.427) and HbA1c (r=0.144, p=0.423). This suggests that with the increase in the severity of anxiety in T1 DM adolescents, both sympathetic and parasympathetic activity are severely reduced. However it can be said that parasympathetic activity is severely reduced in these patients as shown by significantly reduced RMSSD, p NN50 and HF which are the indices of parasympathetic activity. In our study positive correlation between anxiety and sympathovagal balance i.e. LF/HF ratio shows that greater the anxiety levels more is the LF/HF ratio that can be attributed to decreased parasympathetic activity (HF). In contrast to other studies, we did not observe any correlation between anxiety levels and FBG and HbA1c. So it may be said that in these patients anxiety may have played an important and a direct role in reducing HRV significantly. In conclusion our study shows a negative correlation between the severity of anxiety levels and HRV indices in patients with T1 DM. Our findings of reduced HRV with the increase in anxiety levels in patients with T1 DM could be of clinical importance. It may be said that patients with T1 DM who have high levels of anxiety are very susceptible to reduced HRV which may be prevented by proper counseling. Further research needs to be carried out in this area.

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