

Greater Prevalence of Depression in Type I Diabetic Patients: Correlation with Decreased Plasma Tryptophan

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ABSTRACT

The present study was designed to determine the frequency of major and minor depression in type I Diabetes and to relate the occurrence of depression with plasma tryptophan levels. Study was conducted during the period January 2011 to September 2011 at two private hospitals of North Nazimabad in Karachi; Hanif hospital and Haleem hospital. 100 diabetic subjects were selected out of which 50 were males and 50 were females. Likewise the controls were also in the same number. Patients with type II diabetes mellitus and hypertension were excluded from the study. The study was done to evaluate major and minor depression in diabetic and control subjects. Blood samples from all the participants were collected in fasting from anticubital vein to determine plasma TRP levels. Plasma TRP levels were measured by HPLC-UV method. Our data showed that among the control male subjects 5% were having minor depression while 95% were with no depression, while among test subjects 34% were having major depression, 66% were with minor symptoms of depression. However, among the female controls 13% were suffering with minor depression while 87% were with no depression. Among the female test subjects, 50% were having major depression and 50% were having minor depression. Present study showed a significant ($p < 0.01$) decrease in plasma tryptophan levels in both male and female diabetic patients as compared to healthy non-diabetic controls. The present finding suggests that frequency of major and minor depression is increased in diabetes. Present findings indicate that decreased plasma TRP levels and lowered brain 5-HT levels may be responsible for depression seen in diabetics.

Keywords - 5-HT, Depression, Diabetes, Plasma TRP

1. INTRODUCTION

Depression is a psychological state caused by sad mood, agitation, lack of interest and feelings of worthlessness. The causes of depression are many like the death of a loved one, unhealthy environmental condition, seasonal variations and during post partum state. It is well known that individuals with diabetes experience more depression and diminished health status compared to those

without diabetes [1]. Depression is suggested to be prevalent in persons with type I diabetes and may negatively affect self-management and glycaemic control and increase the risk of diabetic complications [2]. In depression it has been studied previously that the neurotransmitters are altered in the brain namely the monoamines. The most notable monoamine that plays a vital role in the depression is serotonin also known as 5-HT. Alterations in serotonin levels and neurotransmission is associated with depressive disorders. Role of 5-HT in depression is well documented [3]. Decreased brain 5-HT has been associated with depression [4]. It is also noted that the levels of serotonin is

decreased profoundly in those people suffering from uncontrolled diabetes [5].

In diabetes the level of insulin is decreased. Insulin is the hormone that maintains the blood glucose level and helps in the gluconeogenesis in the body. Besides gluconeogenesis insulin also helps in the transport of large neutral amino acids including tryptophan, the precursor of serotonin [6]. A decrease in insulin lowers the TRP/LNAA ratio [7-9]. Synthesis of serotonin depends upon the uptake of tryptophan to the brain. Decrease uptake of tryptophan results in the decreased synthesis of serotonin in brain which leads to agitation, depression, mood swings and memory loss [10].

Based on the above consideration, the present study was designed to initially investigate the prevalence of depression in local population suffering from diabetes. Data from both male and female subjects were calculated to monitor the sex related differences. The present study also determine plasma TRP levels and relates it with the occurrence of major and minor depression commonly observed in the diabetic subjects.

2. METHODOLOGY

2.1 Study design and setting:

A case control study was conducted between January 2011 to September 2011 in Hanif hospital and Haleem hospital, North Nazimabad, Karachi.

2.2 Target Population:

The target population of the study was 100 diabetic type I patients and 100 non diabetic healthy individual. Both the groups had 50 male and 50 female subjects with the age between 35 and 55 years. The patients coming to the diabetic clinic in these hospitals with blood sugar levels more than 120 mg/dl fasting and 200 mg/dl in random were chosen as diabetic and it was also considered that diabetics taken as test were on the hypoglycemic drugs. Similarly the controls were free of signs and symptoms of diabetes and also have the negative deranged blood sugar levels. Patients with type II diabetes mellitus and hypertension were excluded from the study. All the research involving human subjects and material derived from human subjects in this study was done in accordance to the ethical recommendations and practices of these hospitals.

2.3 Data Collection:

Consent was taken and a questionnaire was asked from the participant. This questionnaire was about the personal information that is name, age, sex, race, dietary habits and also asked for the symptoms of depression. Characteristics of all the subjects participating in the study are shown in the table 1. Type I diabetes was already diagnosed by the standardized examination conducted by the specialist. The non diabetics were of same age as of diabetics with normal glucose tolerance test and they were not on any drug treatment during the course of study. Blood samples from all the participants were collected in fasting from anticubital vein. Plasma was separated and used for the determination of plasma TRP levels. Plasma TRP levels were measured by HPLC-UV method. Samples for analysis were stored at -70°C.

2.4 Analysis of depression:

In the questionnaire the patients were asked to answer about depression. This was evaluated by asking them about the persistent feeling of sadness, anxious and/or empty mood with feelings of hopelessness, guilt, loss of interest in daily tasks, easily fatigability, loss of appetite and weight, thoughts of death and suicide and irritability. If five or more symptoms are present daily affecting the routine activities for two weeks then the person is labeled with depression. Those with the long term depression and with almost all of the signs of depression are listed as the cases of major

depression, those with five or less symptoms of depression that do not occur daily nor consecutive for two weeks are labeled cases of minor depression.

2.5 Statistical analysis:

Data are presented as means \pm S.D. Neurochemical and behavioral data were analyzed by student's *t*-test.

3. RESULTS

Table 1 shows general characteristic parameters of the subjects which include age, sex, body weight, and blood pressure and fasting blood glucose levels in both diabetic and non-diabetic subjects.

TABLE 1: Age, sex, body weight, blood pressure and fasting blood glucose level of participants suffering from diabetes type I and controls (non-diabetics)

Parameters	Non-diabetic patients (n=100)		Diabetic patients (n=100)	
	Males	Females	Males	Females
Age (years)	45 \pm 3.6	44 \pm 4.0	44 \pm 4.2	46 \pm 4.6
Weight (Kg)	75 \pm 3.6	70 \pm 3.5	69 \pm 3.5	67 \pm 3.5
Systolic BP (mm Hg)	120.7 \pm 3.5	119.2 \pm 3.2	130.4 \pm 4.2	135.0 \pm 3.4
Diastolic BP (mm Hg)	76.4 \pm 1.3	71.5 \pm 1.5	83.3 \pm 2.8	79.5 \pm 2.5
Fasting Plasma glucose (mg/dl)	77 \pm 5.0	75.9 \pm 4.5	250.6 \pm 3.7	234.4 \pm 3.0

Effect of type I diabetes mellitus on depression in male and female participant are shown in fig. 1. Our data showed that among the control male subjects 5% were having minor depression while 95% were with no depression, while among test subjects 34% were having major depression, 66% were with minor symptoms of depression. However, among the female controls 13% were suffering with minor depression while 87% were with no depression. Among the female test subjects, 53% were having severe depression and 50% were having minor depression.

Effect of type I diabetes mellitus on plasma tryptophan levels in male and female participants are shown in fig. 2. Data analyzed by student's *t*-test showed a significant ($p < 0.01$) decrease in plasma tryptophan levels in both male and female diabetic patients as compared to healthy non-diabetic controls.

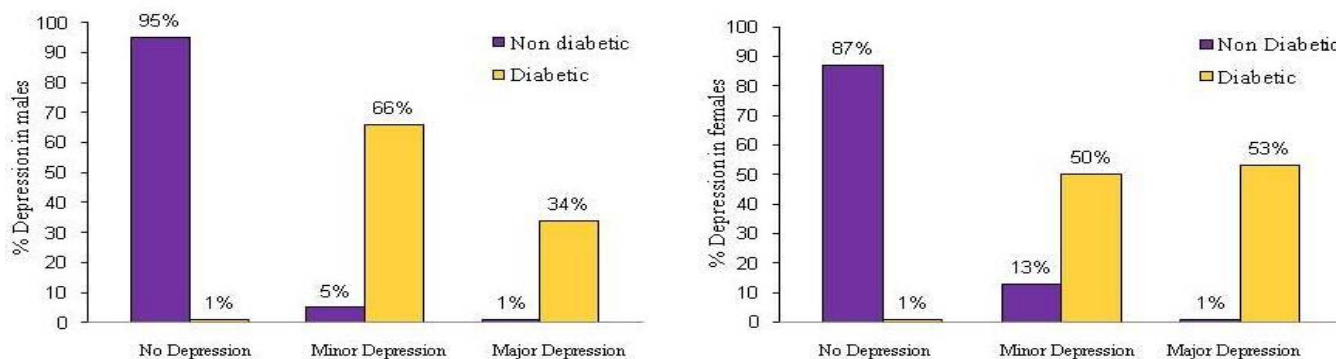


Fig. 1 Shows the occurrence of depression in terms of percentage in diabetic and non-diabetic subjects evaluated by questionnaire.

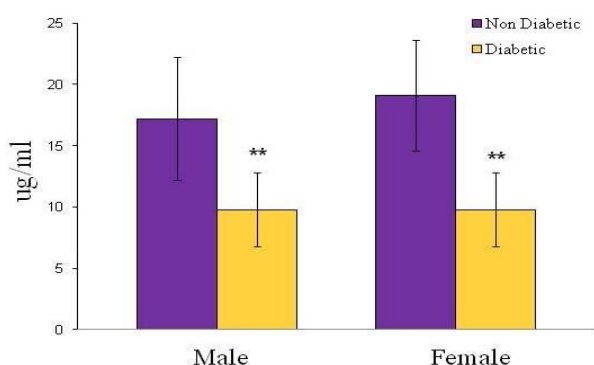


Fig. 2 shows the Plasma tryptophan ($\mu\text{g/ml}$) in diabetic and non-diabetic subjects analyzed by HPLC-UV. Values are presented as mean \pm SD and significant differences are represented as $**=P<0.01$

4. DISCUSSION

Increased depression is one of the most common and dangerous complication of diabetes [11]. Studies have been shown that the rate of depression in diabetics is much higher than in the general population [12-14]. This study showed increased risk of major and minor depression in both male and female diabetic patients as compared to the normal population. The frequency of major and minor depression was similar in male and female diabetic patients. It was also found in this study that plasma tryptophan levels were significantly decreased in male and female diabetic participants as compared to the normal participants. The present results provide a strong evidence for the association between low plasma TRP levels and occurrence of major and minor depression observed in diabetic patients as compared to controls.

Tryptophan depletion might affect various behaviors by affecting brain TRP levels, thereby decreasing 5-HT synthesis. The present study has demonstrated a decrease in plasma TRP levels in both male and female diabetic patients and these patients also exhibited a greater incidence of major and minor depression compared to healthy controls. Several investigators have suggested that brain tryptophan levels vary with the changes in free plasma TRP [15-17]. It has also been reported that brain TRP levels are more sensitive to the changes in total plasma TRP or to the ratio of total plasma TRP to the sum of large neutral amino acids

(LNAA) that compete with TRP for entry into brain [8]. Evidence exists that diabetes is responsible for elevation of the plasma levels of LNAA [18] that reduces brain tryptophan uptake [19] due to which brain serotonin synthesis rate declines.

Previous studies in humans and animals show that brain 5-HT synthesis is altered by the supply of TRP to the brain [20, 21]. At normal circumstances, the brain enzyme TRP hydroxylase is only 50% saturated with TRP therefore an increase in brain TRP will automatically increases the production of brain serotonin [22] and decreased plasma TRP results in decreased 5-HT synthesis [23]. The decrease in plasma TRP levels in the present findings may also be attributed to the greater metabolism of TRP by alternative pathways. Evidence shows that activity of liver TRP oxygenase enzyme is increased in diabetes [24, 25]. Indeed such metabolic alterations in diabetes may ultimately result in decreased synthesis of brain 5-HT in diabetic patients. Reports have shown that tryptophan uptake by brain was decreased in diabetic condition leading to reduction in brain tryptophan levels due to which synthesis and turnover of 5-HT in brain was also decreased [26]. The pathogenesis of depression is closely related to the monoaminergic system, and particularly involves serotonergic mechanism [3, 27, 28]. Decreased brain 5-HT has been associated with depression [29, 30]. Evidence exist suggesting low levels of 5-HT metabolism in depression [31, 32]. Several lines of evidence have indicated that the prevalence of depression in diabetic subjects is higher than in the general population. In the present study, we report that patients with diabetes are at increased risk of developing depression due to the alteration in indoleamine levels. The study also shows that in diabetic females the frequency of minor and major depression was comparable but in male diabetics the frequency of minor depression (66%) was more while major depression (34%) was lower.

5. CONCLUSION

The present finding of decreased plasma tryptophan levels suggests that greater prevalence of major and minor depression commonly observed in diabetics may be due to an altered brain 5-HT metabolism.

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