

Original research article

## CORRELATION OF ANXIETY DISORDER WITH SERUM TSH, CORTISOL LEVEL, MHPG AND INSULIN LEVEL IN ADULTS

<sup>1</sup>Dr. Mohammed Nadeem, <sup>2</sup>Dr Sonali kalvade, <sup>3</sup>Dr. Sheya Nagosker, <sup>4</sup>Ravi Shankar

<sup>1</sup>Research Scholar, Department of Biochemistry, Malwanchal University, Indore, Madhya Pradesh, India

<sup>2</sup>Professor, Department of Biochemistry, Malwanchal University, Indore, Madhya Pradesh, India

<sup>3</sup>Assistant professor, Department of Biochemistry, Index Medical College, Indore, Madhya Pradesh, India

<sup>4</sup>Assistant professor, Department of Biochemistry, GMCH, Udaipur, Rajasthan, India

### Corresponding Author:

Ravi Shankar

### Abstract

**Background:** Anxiety disorders refer to a group of mental disorders characterized by feelings of anxiety and fear, including generalised anxiety disorder (GAD), panic disorder, phobias, social anxiety disorder, obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD). Variations and hormonal level also play significant role in GAD.

**Aim:** Significance of TSH, Serum Cortisol, MHPG and insulin level in patient of generalised anxiety disorder in young adults

**Materials and Methods:** This prospective study was conducted in the department of neuro psychiatry in a tertiary hospital, India. The anxiety disorder patient diagnosed according to DSM criteria detailed data was collected regarding age, gender, residential status, occupation, marital status, special habits, smoking and alcohol intake, dietary habit, family history, associated complications, associated medical and surgical conditions, and drug intake. Serum TSH, Cortisol, MHPG and insulin level was detected by standard procedure taking sample from patients under study

**Results:** A total of 60 participants (30 GAD cases and 30 age related control) were analysed in our study, all (100%) participants were 15-30 years of age in this study. Most (45.7%) of the participants belonged to age group of 25-30 years, 65.7% of individuals were male, while 34.2% were females. Male predominance was seen. Mean RBS of cases was  $116.32 \pm 17.14$  while in control mean RBS is  $113.17 \pm 18.07$ . Mean value of TSH in cases is  $1.32 \pm 0.32$  and in control mean TSH is  $2.48 \pm 0.99$ . Mean value of Serum Cortisol in cases is  $295.83 \pm 100.27$  and in control mean Cortisol is  $122.76 \pm 77.10$ . The difference between values of Serum Cortisol and Serum TSH in case and control is found statistically significant ( $p < 0.05$ ).

The vast majority of patients with hyperthyroidism will display a psychiatric disorder such as anxiety, mania, or depression and Cortisol level also play important role in the

same.

**Conclusion:** Thus it can be concluded that low level of TSH and high level of cortisol responsible for anxiety disorders in adults under study some of the socio-demographic factors like family history.

**Keywords:** GAD, serum cortisol, TSH, insulin, MHPG

### **Introduction**

Anxiety disorders are common and distressing medical conditions, which typically arise in adolescence or early adult life. Anxiety disorders refer to a group of mental disorders characterized by feelings of anxiety and fear, including generalised anxiety disorder (GAD), panic disorder, phobias, social anxiety disorder, obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD). The duration of symptoms typically experienced by people with anxiety disorders makes it more a chronic than episodic disorder<sup>[1-2]</sup>. The World Health Organization (WHO) classifies the following conditions as mental disorders: depression, bipolar disorder, schizophrenia and other psychoses, dementia and developmental disorders, autism<sup>[3]</sup>. The ongoing pandemic, with the related stress and isolation, has significantly contributed to an increase in the number of cases. Other risk factors for developing mental disorders include genetic factors, perinatal infections, and inadequate nutrition<sup>[4-5]</sup>. The increasing incidence of mental disorders has causing decreased productivity and function of individuals in their daily activities, loss of economic resource and higher treatment costs. Therefore, a comprehensive program of chronic disease management should be considered for the effective treatment of these disorders<sup>[6-7]</sup>. Prolonged exposure to stress causes changes in the body, such as an activation of the hypothalamic-pituitary-adrenal axis (HPA), which results in an elevated secretion of Cortisol and many other hormonal changes<sup>[8-9]</sup>. Similarly, anxiety states frequently occur in association with thyroid diseases including hyper- and hypo-thyroidism and thyroiditis in addition to other endocrine disorders such as Cushing's disease, hyperparathyroidism, hyperglycemia and so on<sup>[10]</sup>. Some studies have shown that elevated glucose levels can contribute to the development of anxiety and depression. 7 These disorders may also lead to a worsening in the course of diabetes, with complications such as weight gain, increased mortality, and functional disability<sup>[11-12]</sup>. There have been numerous anxiety disorder studies the levels of the nor epinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) contribute important role in the anxiety-depression<sup>[13]</sup>.

**Aims & Objectives:** The present study attempt has been made to determining the relationship between GAD and long-term integrated Cortisol secretion, TSH level, MHPG and insulin level.

### **Materials and Methods**

This case control study was conducted in department of neuro psychiatry in a tertiary care hospital, Dungarpur district, Rajasthan India. Study period was March 2020 to march 2022.

The patients with GAD were selected by DSM 5 criteria<sup>[14]</sup>. According to these criteria we diagnosed anxiety with the three of the following physical or cognitive symptoms:

1. Edginess or restlessness.

2. Tiring easily; more fatigued than usual.
3. Difficulty in concentration or feeling as though the mind goes blank.
4. Irritability (recognized by others).
5. Increased muscle aches or soreness.
6. Difficulty sleeping (due to trouble falling asleep or staying asleep, restlessness at night, or unsatisfying sleep).

#### **Inclusion criteria**

- Age between 15 and 30 years, both males and female.
- GAD diagnosed by DSM 5 criteria.
- Who given consent for the study.

#### **Exclusion criteria**

- Subjects below 15 and above 30 years of age.
- Subjects with metabolic diseases, malnutrition and cancer patients.
- Diabetes mellitus, liver or kidney diseases or infection patients.
- Pregnant women.
- Who not given consent for the study.

A total of 60 participants (30 cases diagnosed with GAD and 30 healthy controls) divided in two groups

**Group I:** It were consist of GAD subject case (n=30), have symptoms which is diagnosed by DSM 5 criteria.

**Group II:** It were consist of healthy control subjects (n=30). All the subjects included in this group were healthy and there are no signs and symptoms or history of chronic diseases.

We have compared the correlation between cases and control group in terms of serum Cortisol level, Serum TSH level, MHPG and insulin level in different socio-demographics variables

Blood Cortisol level, TSH level, MHPG and insulin level in serum was determined by competitive enzyme immunoassay (CEIA) method using commercially available ELISA kit.

**Statistical analysis:** Data thus collected was incorporated to Microsoft Excel sheet in the form of master chart and was analyzed by using standard statistical software (SPSS version 20). Significance testing for Mean  $\pm$ SD difference of two groups was done by student T-test (unpaired t-test). Qualitative data was compared using chi square test. p-value  $<$  0.05 was considered statistical significant.

#### **Results**

Present study comprised of 30 cases of GAD and 30 controls, who attended the neuropsychiatry department in our tertiary hospitals, all (100%) participants were young adults of 15-30 years of age.

**Table 1:** Correlation of socio-demographics variables and TSH Levels in Case and Controls

| Socio-demographics variables |            | Cases |      | Control |      | P value |
|------------------------------|------------|-------|------|---------|------|---------|
|                              |            | Mean  | SD   | Mean    | SD   |         |
| Age group (in yrs)           | 15-19      | 1.42  | 0.63 | 2.45    | 0.96 | 0.022   |
|                              | 20-24      | 1.20  | 0.67 | 1.93    | 1.10 | 0.196   |
|                              | 25-30      | 1.52  | 0.67 | 2.57    | 1.08 | 0.003   |
|                              | Total      | 1.39  | 0.65 | 2.43    | 1.04 | <0.001  |
| Gender                       | Female     | 1.37  | 0.80 | 2.52    | 1.22 | 0.015   |
|                              | Male       | 1.40  | 0.59 | 2.36    | 0.93 | 0.001   |
| Marital status               | Married    | 1.51  | 0.71 | 15.00   | 2.58 | <0.001  |
|                              | Unmarried  | 1.27  | 0.59 | 30.00   | 2.20 | <0.001  |
| Occupation                   | Working    | 1.33  | 0.44 | 2.94    | 1.12 | 0.001   |
|                              | Student    | 1.34  | 0.70 | 2.36    | 1.04 | 0.009   |
|                              | Housewife  | 1.53  | 0.82 | 1.89    | 0.66 | 0.350   |
| Diet                         | Vegetarian | 1.28  | 0.47 | 2.33    | 0.98 | <0.001  |
|                              | Non-Veg.   | 1.51  | 0.82 | 2.63    | 1.17 | 0.016   |
| Smoking                      | Yes        | 1.22  | 0.40 | 2.39    | 0.81 | 0.007   |
|                              | No         | 1.45  | 0.72 | 2.44    | 1.10 | 0.001   |
| Alcoholic                    | Yes        | 1.27  | 0.59 | 13.00   | 2.73 | <0.001  |
|                              | No         | 1.48  | 0.70 | 34.00   | 2.30 | <0.001  |
| Sleep                        | Good       | 1.30  | 0.67 | 2.52    | 1.08 | <0.001  |
|                              | Poor       | 1.47  | 0.64 | 2.18    | 0.93 | 0.067   |
| Family History               | Yes        | 1.53  | 0.69 | 2.78    | 1.03 | 0.013   |
|                              | No         | 1.25  | 0.60 | 2.34    | 1.04 | <0.001  |

**Table 2:** Correlation of socio-demographics variables and Cortisol Levels in Case and Controls

| Socio-demographic variables |            | Cases  |        | Control |        | P value |
|-----------------------------|------------|--------|--------|---------|--------|---------|
|                             |            | Mean   | SD     | Mean    | SD     |         |
| Age group (in yrs)          | 15-19      | 309.30 | 105.48 | 95.03   | 34.68  | <0.001  |
|                             | 20-24      | 277.95 | 95.07  | 180.05  | 72.38  | 0.045   |
|                             | 25-30      | 276.95 | 114.36 | 133.97  | 58.10  | <0.001  |
|                             | Total      | 284.83 | 103.47 | 129.97  | 60.17  | <0.001  |
| Gender                      | Female     | 243.99 | 152.03 | 161.77  | 70.64  | 0.131   |
|                             | Male       | 305.25 | 63.85  | 108.77  | 41.93  | <0.001  |
| Marital status              | Married    | 268.77 | 111.56 | 15.00   | 152.41 | <0.001  |
|                             | Unmarried  | 300.89 | 95.81  | 30.00   | 96.30  | <0.001  |
| Occupation                  | Working    | 312.27 | 51.00  | 113.51  | 41.51  | <0.001  |
|                             | Student    | 306.66 | 102.72 | 97.80   | 36.88  | <0.001  |
|                             | Housewife  | 218.50 | 128.12 | 198.79  | 55.44  | 0.696   |
| Diet                        | Vegetarian | 292.90 | 105.14 | 16.00   | 138.56 | <0.001  |
|                             | Non-Veg.   | 275.60 | 104.67 | 28.00   | 112.79 | <0.001  |

|                |      |        |        |        |        |        |
|----------------|------|--------|--------|--------|--------|--------|
| Smoking        | Yes  | 200.75 | 96.91  | 89.91  | 38.79  | 0.012  |
|                | No   | 315.40 | 89.35  | 139.98 | 60.95  | <0.001 |
| Alcoholic      | Yes  | 238.68 | 90.57  | 105.24 | 41.43  | <0.001 |
|                | No   | 320.12 | 101.00 | 140.56 | 64.58  | <0.001 |
| Sleep          | Good | 249.74 | 111.78 | 135.65 | 65.97  | 0.001  |
|                | Poor | 319.92 | 83.93  | 114.33 | 39.54  | <0.001 |
| Family History | Yes  | 333.29 | 82.77  | 15.00  | 126.97 | <0.001 |
|                | No   | 236.37 | 101.46 | 30.00  | 130.72 | <0.001 |

**Table 3:** Correlation of socio-demographics variables and Insulin Levels in Case and Controls

| Socio-demographic variables |            | Cases |      | Control |       | P value |
|-----------------------------|------------|-------|------|---------|-------|---------|
|                             |            | Mean  | SD   | Mean    | SD    |         |
| Age group (in yrs)          | 15-19      | 14.82 | 9.73 | 19.42   | 2.75  | 0.245   |
|                             | 20-24      | 16.70 | 6.61 | 16.14   | 3.41  | 0.832   |
|                             | 25-30      | 19.44 | 8.91 | 18.97   | 3.82  | 0.861   |
|                             | Total      | 17.45 | 8.35 | 18.63   | 3.55  | 0.479   |
| Gender                      | Female     | 14.74 | 6.16 | 18.85   | 4.14  | 0.087   |
|                             | Male       | 18.80 | 9.09 | 18.49   | 3.20  | 0.887   |
| Marital status              | Married    | 19.54 | 8.39 | 18.58   | 3.91  | 0.686   |
|                             | Unmarried  | 15.36 | 8.04 | 18.71   | 3.08  | 0.150   |
| Occupation                  | Working    | 19.73 | 9.95 | 9.00    | 19.19 | 0.139   |
|                             | Student    | 17.44 | 8.17 | 26.00   | 18.52 | 0.154   |
|                             | Housewife  | 14.90 | 6.85 | 24.00   | 18.11 | 0.205   |
| Diet                        | Vegetarian | 16.67 | 9.62 | 18.63   | 3.70  | 0.446   |
|                             | Non Veg.   | 18.35 | 6.86 | 18.64   | 3.42  | 0.893   |
| Smoking                     | Yes        | 19.04 | 8.51 | 8.00    | 17.90 | 0.188   |
|                             | No         | 16.87 | 8.41 | 44.00   | 18.82 | <0.001  |
| Alcoholic                   | Yes        | 20.43 | 7.60 | 13.00   | 18.54 | 0.269   |
|                             | No         | 15.17 | 8.38 | 34.00   | 18.67 | <0.001  |
| Sleep                       | Good       | 16.76 | 7.93 | 18.36   | 3.51  | 0.468   |
|                             | Poor       | 18.14 | 8.97 | 19.39   | 3.78  | 0.645   |
| Family History              | Yes        | 18.62 | 9.12 | 19.90   | 2.51  | 0.624   |
|                             | No         | 16.28 | 7.63 | 18.32   | 3.74  | 0.341   |

**Table 4:** Correlation of socio-demographics variables and MHPG Levels in Case and Controls

| Socio-demographic variables |            | Cases |      | Control |      | P value      |
|-----------------------------|------------|-------|------|---------|------|--------------|
|                             |            | Mean  | SD   | Mean    | SD   |              |
| Age group (in yrs)          | 15-19      | 5.62  | 4.81 | 5.69    | 2.05 | 0.972        |
|                             | 20-24      | 6.84  | 4.35 | 6.36    | 2.43 | 0.789        |
|                             | 25-30      | 8.46  | 5.39 | 6.08    | 2.72 | 0.159        |
|                             | Total      | 7.26  | 4.90 | 6.01    | 2.42 | <b>0.215</b> |
| Gender                      | Female     | 5.18  | 3.62 | 6.38    | 2.35 | 0.378        |
|                             | Male       | 8.30  | 5.21 | 5.76    | 2.50 | 0.060        |
| Marital status              | Married    | 8.50  | 5.22 | 6.08    | 2.56 | 0.111        |
|                             | Unmarried  | 6.02  | 4.39 | 5.91    | 2.30 | 0.934        |
| Occupation                  | Working    | 8.87  | 5.84 | 5.46    | 2.72 | 0.128        |
|                             | Student    | 7.26  | 4.68 | 5.72    | 2.05 | 0.292        |
|                             | Housewife  | 5.45  | 4.01 | 7.14    | 2.47 | 0.327        |
| Diet                        | Vegetarian | 6.99  | 5.36 | 6.40    | 2.38 | 0.685        |
|                             | Non-Veg.   | 7.57  | 4.50 | 5.24    | 2.44 | 0.117        |
| Smoking                     | Yes        | 8.15  | 5.37 | 7.00    | 2.00 | 0.588        |
|                             | No         | 6.94  | 4.82 | 5.76    | 2.49 | 0.309        |
| Alcoholic                   | Yes        | 8.80  | 4.86 | 5.86    | 2.88 | 0.091        |
|                             | No         | 6.08  | 4.74 | 6.08    | 2.27 | 1.000        |
| Sleep                       | Good       | 6.52  | 4.57 | 5.87    | 2.47 | 0.618        |
|                             | Poor       | 8.00  | 5.27 | 6.40    | 2.39 | 0.329        |
| Family History              | Yes        | 8.11  | 5.19 | 5.90    | 2.07 | 0.179        |
|                             | No         | 6.41  | 4.62 | 6.04    | 2.54 | 0.778        |

## Discussion

Anxiety disorders have been linked to many chemical imbalances in the body, along with other physiological factors such as sleep, diet, and exercise etc. Also, hormonal imbalances can also reduce or increase anxiety.

Our Results showed that mean value of TSH in cases and control was  $1.39 \pm 0.65$  and  $2.43 \pm 1.04$  respectively. The difference between values of TSH in case and control was found to be statistically significant ( $P=0.001$ ), similar finding reported by N Sahi *et al.* [15].

Present study found the correlation Gender and age had substantial influence on thyroid function and MS. Females with high TSH and high FT3 had higher MS risks than males was a risk for MS, especially for females, concordance with the Walter *et al.* [16] and Meng *et al.* [17]. Aging was a risk for GAD, especially for females. Hence there is an urgent need to initiate interventional programs.

Generalized Anxiety Disorder (GAD) is a common and impairing anxiety disorder in older adults and it has been associated with elevated cortisol in this age group our finding are similar to Bryant *et al.* [18] and Wetherell *et al.* [19].

Our study observed that important risk factors and family history to correlate any socio-

demographic characteristic making difference in Pathophysiology of GAD. But only family history was found statistically significantly related. Serum TSH and Serum Cortisol were measured and we found significantly low levels of serum TSH and raised level of serum Cortisol in GAD cases, our finding comparable with Mantella *et al.* [20] and Lenze *et al.* [21].

The lack of a consistent association between MHPG and various anxiety measures in the current study is in agreement with some previous studies that have examined this issue, Buchsbaum *et al.* [22]. In contrast, Roy *et al.* [23] found plasma MHPG to be associated with both the psychic and somatic anxiety items from the HRSD. Our inability to find an association between MHPG and GAD suggests that the discrepancies noted in previous studies are not likely to be explained by choice of the specific anxiety measurement.

In analyzing the data concerning anxiety disorders, we observed a higher prevalence of anxiety among patients with diabetes, accordance to Chaudhry R *et al.* [24] and Grigsby *et al.* [25].

There was a lower rate of comorbid generalized anxiety and diabetes than in the present study, but this discrepancy can be explained by the fact that the review analyzed all recognized anxiety disorders, while the present study examined only generalised anxiety disorders.

### **Conclusion**

In conclusion, the results give confidence to the observations that examination stress was high in the students. Various metabolic and hormonal variation was observed in GAD: increased the TSH and cortisol level and also effects the heart rate, blood pressure, depressed the enzymatic activities, altered MHPG level and decreased insulin level.

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### **References**

1. Szpunar MJ, Parry BL. A systematic review of cortisol, thyroid-stimulating hormone, and prolactin in peripartum women with major depression. *Arch Womens Ment Health.* 2018;21(2):149-161. Doi: 10.1007/s00737-017-0787-9
2. Abidin Z, Syafiq A, Rahim RA, *et al.* Current and potential developments of cortisol aptasensing towards point-of-care diagnostics (POTC). *Sensors.* 2017;17(5):11-80.
3. Mental Disorders. Available online: <https://www.who.int/news-room/factsheets/detail/mental-disorders> (accessed on 18 June 2021).
4. Owen L, Corfe B. The role of diet and nutrition on mental health and wellbeing. *Proc Nutr. Soc.* 2017;76:425-426.
5. Jacka FN. Nutritional psychiatry: where to next? *E Bio Medicine.* 2017;17:24-29.
6. Chisholm D, Sweeny K, Sheehan P, Rasmussen B, Smit F, Cuijpers P, *et al.* Scaling-up treatment of depression and anxiety: a global return on investment analysis. *Lancet Psychiatry.* 2016;3:415-424.

7. Lim GY, Tam WW, Lu Y, Ho CS, Zhang MW, Ho RC. Prevalence of Depression in the Community from 30 Countries between 1994 and 2014. *Sci Rep.* 2018;8:28-61.
8. Katzung BG, Kruidering-Hall M, Tuan R, Vanderah TW, Trevor AJ. Adreno corticosteroids & Adreno cortical Antagonists. In Katzung & Trevor's Pharmacology: Examination & Board Review, 13<sup>th</sup> ed.; Katzung BG, Kruidering-Hall M, Tuan R, Vanderah TW, Trevor AJ. Eds.; McGraw-Hill: New York, NY, USA, 2021.
9. Mantella RC, Butters MA, Amico JA, *et al.* Salivary cortisol is associated with diagnosis and severity of late-life generalized anxiety disorder. *Psychoneuroendocrinology.* 2008;33(6):773-781.
10. Hall RCW, Hall RCW. Anxiety and Endocrine Disease. *Seminars in Clinical Neuropsychiatry*, 1999. Available at [drrichardhall.com](http://drrichardhall.com)
11. Wang MY, Tsai PS, Chou KR, Chen CM. A systematic review of the efficacy of non-pharmacological treatments for depression on glycaemic control in type 2 diabetics. *J Clin Nurs.* 2008;17:2524-30.
12. Katon WJ, Rutter C, Simon G, Lin EH, Ludman E, Ciechanowski P, *et al.* The association of comorbid depression with mortality in patients with type 2 diabetes. *Diabetes Care.* 2005;28:2668-72.
13. Fava C, Daanese E, Montaganna M. Serine/threonine Kinase 39 is a candidate gene for primary hypertension essentially in women, results from two cohort studies in Swedes. *J Hypertens.* 2011;29(3):484-489.
14. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)*. Washington, D.C.: American Psychiatric Association, 2013.
15. Dr. Nita Sahi, Dr. Sangeeta Gurjar, Dr. Jafar Khan, Dr. Ashutosh Meena, Dr. Gautam Kumar Sharma. Correlation of anxiety disorder with serum TSH and Cortisol level in young adults, *International Journal of Applied Research.* 2019;5(12):52-56.
16. Walter KN, Corwin EJ, Ulbrecht J, *et al.* Elevated thyroid stimulating hormone is associated with elevated cortisol in healthy young men and women. *Thyroid Res.* 2012;5(1):13. Published 2012 Oct 30. Doi: 10.1186/1756-6614-5-13
17. Meng Z, Liu M, Zhang Q, *et al.* Gender and Age Impacts on the Association between Thyroid Function and Metabolic Syndrome in Chinese. *Medicine (Baltimore).* 2015;94(50):e21-93.
18. Bryant C, Jackson H, Ames D. The prevalence of anxiety in older adults: methodological issues and a review of the literature. *J Affect Disord.* 2008;109(3):233-250.
19. Wetherell JL, Thorp SR, Patterson TL, Golshan S, Jeste DV, Gatz M. Quality of life in geriatric generalized anxiety disorder: a preliminary investigation. *J Psychiatr Res.* 2004;38(3):305.
20. Mantella RC, Butters MA, Amico JA, *et al.* Salivary cortisol is associated with diagnosis and severity of late-life generalized anxiety disorder. *Psychoneuroendocrinology.* 2008;33(6):773-781.
21. Lenze EJ, Mantella RC, Shi P, *et al.* Elevated cortisol in older adults with generalized anxiety disorder is reduced by treatment: a placebo-controlled



- evaluation of escitalopram. *Am. J Geriatr. Psychiatry.* 2011;19(5):482-490
22. Buchsbaum MS, Muscettola G, Goodwin FK. Urinary MHPG, stress response, personality factors and somatosensory evoked potentials in normal subjects and patients with major affective disorders. *Neuropsychobiology.* 1981;7:212-224.
  23. Roy AR, Jimerson DC, Pickar D. Plasma MHPG in depressive disorders and relationship to the dexamethasone suppression test. *American Journal of Psychiatry.* 1986;143:846-851.
  24. Chaudhry R, Mishra P, Mishra J, Parminder S, Mishra BP. Psychiatric morbidity among diabetic patients: A hospital-based study. *Ind Psychiatry J.* 2010;19:47-9.
  25. Grigsby AB, Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. Prevalence of anxiety in adults with diabetes: a systematic review. *J Psychosom Res.* 2002;53:1053-60.