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Prevalence of Psychiatric Disorders in Diabetes Mellitus: Revisiting Psychodiabetology

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ABSTRACT
Physical and psychiatric symptoms occur commonly together in patients who consult doctors. Psychiatric disorder often presents with physical complaints and psychological symptoms are a frequent consequence of acute and chronic organic illness. Higher prevalence rates of depression and anxiety disorders in people with diabetes compared with the general population. Depression is associated with hyperglycaemia in people with both type 1 and type 2 diabetes according to well established studies. To estimate the prevalence of psychiatric morbidity in type 2 diabetes mellitus in patients attending medical outpatient department. To study the relation of the psychiatric morbidity with socio demographic and clinical variables in these group. Type 2 male and female diabetic patients attending medical outpatient department at Trichy with age ranging from 18-80 years were recruited for the study with specified inclusion and exclusion criteria. ICD 10 checklist and General Health Questionnaire were used to assess the patients. Psychoactive substance disorders were found in 8.2%, psychotic disorders in 0.8-12.3% patients were diagnosed with mood disorders and behavioral disorders. Neurotic and behavioural syndromes were seen in 16.4% patients. Sexual dysfunction and sleep disorders were also seen in a significant number of patients.

INTRODUCTION

Physical and psychiatric symptoms occur commonly together in patients who consult doctors. Psychiatric disorder often presents with physical complaints and psychological symptoms are a frequent consequence of acute and chronic organic illness. At least a quarter of patients with physical complaints can be diagnosed as suffering from psychiatric disorder.

A "diabetes epidemic" is underway with a worldwide estimate of people having diabetes mellitus (DM) being 30 million in 1985, 135 million in 1995 and 171 million in 2000 and a predicted figure of 366 million by the year 2030 (Fig. 1). The corresponding figures for India are 31 million in 2000 and 79 million by the year 2030[1].The prevalence of diabetes is higher in men than women.

DM is the sixth leading cause of death above 60 years, and seventh across all age groups in developed countries and is an important risk factor the leading causes of mortality i.e., ischemic heart disease, hypertensive heart disease and cerebrovascular disease according to WHO, 2003 reports.

Globally, neuropsychiatric conditions account for 19% of disease burden among adults. Unipolar depressive disorder, schizophrenia and bipolar affective disorder come in first, sixth and 10th positions respectively among the 10 leading causes of YLD (years lost in disease) estimate for 2002. Increasing burden of non-communicable diseases, accounting for more than nearly half of the global burden of disease (all ages) is occurring mostly in the middle-income countries[2-4].

During the last years the co morbidity of mental disorders with chronic health conditions has emerged as a topic of considerable clinical and policy interest. Diabetes is considered one of the most psychologically demanding of the chronic medical illnesses because it requires strict daily management of the treatment by the patients themselves[5]. The presence of psychiatric co morbidity can result in difficult clinical courses, because it may affect adherence to medication and self-care regimes[6]. On the other hand, poor diabetes control might cause or exacerbate depression via direct effects on brain functions or indirectly through complications, functional impairment, or decreased quality of life[7].

There has been a growing interest in the study of psychological distress and mental disorders in diabetes. Some epidemiological studies have found higher prevalence rates of depression and anxiety disorders in people with diabetes compared with the general population[8,9-12]. Studies evaluating the relationship between depression and diabetes have yielded mixed results. For example, the prevalence of depression in people with diabetes ranges from 3.8%[13] to as high as 49.5%[14].

Some studies suggested that depression is associated with hyperglycaemia in people with both type 1 and type 2 diabetes[15], whereas other studies did not find any correlation at all[16]. Concerning treatment of prevalent depression in people with diabetes the results of Lustman and colleagues[17,18] suggest that glycemic control can be improved by appropriate treatment of the co morbid mental disorders.

Diabetes and etiopathogenesis of psychiatric disorders At the molecular level the enzyme glycogen synthase kinase-3 (GSK-3) is a direct target of lithium, has an essential role in many signaling pathways, regulates the function of transcription factors and cytoskeletal elements and has critical effects on cellular resilience and neuronal plasticity. It is unique in that it exhibits significant activity, even in resting, unstimulated cells but is potently inactivated in response to signals such as insulin and polypeptide growth factors and provides obvious opportunities for cross-talk. Its inhibition by lithium and its implication in several human disorders including Alzheimer's disease, bipolar disorder, cancer and diabetes has lead to a tremendous interest in GSK-3 inhibitors as novel therapeutic agents and selective, small-molecule compounds are rapidly being developed for a broad range of disorders (e.g., diabetes, Alzheimer's disease, stroke and inflammatory conditions). But its therapeutic potential is likely to be compromised by multiple unwanted side effects since the enzyme has a broad spectrum of functional roles[19].

Wolfram syndrome, a rare autosomal recessive neurodegenerative disorder, was originally described as a combination of familial juvenile-onset diabetes mellitus and optic atrophy. Later, Wolfram syndrome patients were demonstrated to be highly prone to psychiatric disorders. But mutations in exon 8 of the Wolfram syndrome gene that accounts for 88% of the patients with the syndrome was not detected in a study conducted in patients with psychiatric disorders[20].

Psychotropic medications may further increase the risk of the development of diabetes, either directly or as a result of weight gain. Thus the association between these disorders is clinically relevant and underscores the importance of screening for diabetes mellitus in the bipolar population[21].Increased release of counter-regulatory hormones (i.e., catecholamine, glucocorticoids, growth hormone and glucagon) in the stress response and in depression can mediate hyperglycemia and perhaps leads to insulin resistance seen in major depression[21].

Alteration in cerebral glucose utilization in depression (decreased in the left lateral prefrontal cortex often showing a significant correlation with severity of depressive symptoms) is reversed with

successful antidepressant treatment[23-25]. Possible role of alterations in glucose transporter (GLUT) function in this phenomenon, similar to that reported in Huntington's disease and Alzheimer's disease[26] needs investigation.

The proinflammatory cytokines (IL-1, IL-6 and TNF-a), through their neural effects, also induce "sickness behaviour" (a constellation of nonspecific symptoms including fatigue, anorexia, anhedonia, decreased psychomotor activity and disappearance of body care activities), which overlap with the symptoms of major depression[27]. IL-6 is elevated in many patients with major depression[28,29] Hippocampus might be an important mediator in the complex interrelationship between stress, diabetes and depressive disorders[30]. Psychological reactions at the time of diagnosing Diabetes Differences have been found in the way patients with type 1 diabetes and type 2 diabetes cope with and adapt to their diagnosis[31]. A variety of psychological reactions may occur at the time of diagnosis of diabetes[32].

Prevalence of psychiatric disorders in diabetes mellitus has been studied using different methodologies. Lifetime and 6-month prevalence of simple phobia was more in female patients with diabetes compared to other two groups[33]. Lustman and colleagues[34] found a 71% lifetime prevalence of at least one psychiatric disorder among 57 patients each of type 1 and type 2 diabetes.

In a recent study, Almawi and co-workers[35] who examined 143 type 2 diabetic patients with 132 healthy controls using depression anxiety stress scale (DASS). Logistic regression analysis showed that anxiety, depression and stress were associated with Type2 Diabetes Mellitus after adjusting for all variables, while age was the only significant variable associated with stress. In another study by F de Mont-Marin and co-workers[36] who assessed a sample of 46 diabetic patients using The Composite International Diagnostic Interview (CIDI) according to DSM-3 stated that 52.2% of subjects presented atleast one psychiatric diagnosis in life time and 41.3% did so less than six months before the study. Affective and anxiety disorders consists of 83% of psychiatric diagnoses.

In study by shehnaz and collegues[37] they assessed psychiatric prevalence in a sample of 50 diabetics and 50 healthy controls using a screening test and present status examination. They found 54% of psychiatric disorders using ICD-10 criteria compared to 24% of controls (p = 0.0038).

Kovac's *et al.*[38] in their study in a sample of 92 diabetics using clinical interview found 47.6% of patients with psychiatric diagnoses. In another study by Weyerer *et al.*[39] which was done in community setting of 1536 sample assessed self reporting diabetics with clinical interview schedule. They found 43.1% psychiatric disorders compared to healthy controls. Common problems in diabetes mellitus include Worries of future complications, Food concerns, Guilt feelings/or shame, Fear of hypoglycemic episodes, Diabetic burn-out, women with diabetes appear twice as likely to experience psychological distress as men[40-44]. Impact of adjustment disorders in those diagnosed with diabetes is most marked in case of children and adolescents with type 1 diabetes. Robinson *et al*.[36] in their controlled study with 130 diabetic patients reported 8.5% of depression according to ICD-9. Well's *et al*.[37] with sample of 154 diabetics using DSM-3 reported 9.6% depression. Wilkinson *et al.*[38] in 194 medical out patients of type 1 diabetes reported 16.5% depression. Higher prevalence of moderate to severe depressive symptoms (mean = 32%, range 22-60%) were reported in studies utilizing self-report depressive symptom scales[49,50]Women with diabetes appear twice as likely to experience psychological distress as men[12,51] Young women with diabetes were at nine times greater risk for recurrent depression than their male counterparts[52].

Anxiety disorders: Hermann and co-workers[55] in their study on four hundred and twenty diabetic patients found 5.9% prevalence of anxiety disorders. The prevalence of elevated symptoms was significantly higher in women compared to men and similar in patients with type 1 vs. type 2 diabetes[57] Patients with blood-injection-injury phobia had higher than expected rates of macro vascular complications[60].

Sexual dysfunction: Ralf and co-workers[63] in a study of psychological contributors or correlates of sexual dysfunction in diabetic men (in 40 diabetic men and 40 age-matched healthy volunteers), patients had significantly lower levels of erotic drive, sexual arousal, enjoyment and satisfaction which coexisted with alterations in sexual attitudes and body image.

Insomnia: Sridhar[68] recently reported that sleep problems were directly associated with health-related QOL (Quality of life). They studied the prevalence of sleep disturbances in 184 persons with diabetes and 99 controls matched for age and sex. Sleep disorders were more common in diabetics (33.7% vs. 8.2% in controls, p<0.01)[69]. Diabetics had higher rates of insomnia (50 vs. 31%, p = 0.04) and used more hypnotics (25.9 vs. 6.0%, p = 0.02) than controls. Sleep complaints and restless legs syndrome in adult type 2 diabetics were more common[70].

Substance use disorders: In a study by Desai and colleagues[73] among adult diabetic patients they found 23%-Psychiatric disorders, 1.3%-substance abuse, 2.6%-dual diagnosis.

Eating disorders: In a cross-sectional study of 152 adolescents with type 1 diabetes, female patients aged 13-14 years were at greatest risk for developing disordered eating patterns. Patients with both diabetes and eating disorders had significantly higher levels of co morbid anxiety, panic attacks, and alcohol use disorders, compared with those with one but not both[78].

Cognitive dysfunction in diabetes: Potential for brain damage and cognitive dysfunction in diabetes arises from episodes of recurrent and severe hypoglycaemia, metabolic complications like ketoacidosis and non-ketotic coma. Diabetes could also influence cognitive function by leading to cardiovascular events, transient ischemic attacks and strokes or by repeated hypoglycaemic events and related metabolic and vascular disruption[80].

Factitious disorders: Factitious hypoglycaemia as a manifestation of Munchausen's syndrome was assessed in a study which detected a second generation of the sulfonylurea oral hypoglycaemic agent in 17% of 129 patients who had unexplained severe hypoglycaemia[81].

Objectives:

- To estimate the prevalence of psychiatric morbidity in type 2 diabetes mellitus in patients attending medical outpatient department
- To study the relation of the psychiatric morbidity with socio demographic and clinical variables in these group

MATERIALS AND METHODS

Sample consists of patients both male and female diabetic patients attending medical OPD who are between the age group of 18-80 years. ICD-10 checklist for mental disorders version1.1[82,83] is used to record assessment of psychiatric symptoms and syndromes in F0-F6 categories of ICD-10 classification of mental and behavioural disorders. These patients were initially screened by General Health Questionnaire (GHQ)[84-96]. Duration of study was 6 months (January-June of 2010).

Study area: Study area was outpatient department of medical hospital from Tiruchirapalli.

Study population: Study population is type 2 diabetic patients attending medical outpatient department both males and females with age ranging from 18-80 years.

Sample size: Total 490 patients were screened between January 2010 to June 2010 who were attending medical outpatient department on two days in week. Among 490 patient only 122 patients satisfied inclusion and exclusion criteria. Total 368 patients excluded (135 did not give consent, 93 had severe foot ulcers, 85 had hyperglycaemia with ketoacidosis, 55 excluded due to other causes like retinopathy, infection etc.).

Inclusion criteria:

- Age 18-80 years
- Diagnosed patients with type 2 diabetes mellitus
- Patient who gave informed consent
- Five years of formal education
- Comorbid hypertension

Exclusion criteria:

- Age less than 18 and more than 80 years
- Complications of type 2 diabetes mellitus (e.g. retinopathy, nephropathy etc.)
- People with cardiovascular diseases (except hypertension which is a common comorbidity)
- Cerebrovascular accidents

RESULTS

Out of total 122 subjects 89 (73%) were males and 33 (27%) were females. In 122 diabetics, 61 (50%) of them met criteria for one or the other psychiatric diagnosis, of which 39 (43.8%) were males and 22 (66.7%) were females (Table 4). Eighty nine (70.5%) of study subjects were aged between 40-59 years and 36 (29.5%) were aged between 60-80 years. Among age group of 40-59 years 45 (52.3%) subjects had psychiatric morbidity while 16 (44.4%) subjects among 60-79 age group were psychiatrically ill.[Table 4, Fig. 2]. 45(36.9%) subjects had completed their primary schooling of which 25(55.6%) had evidence of psychiatric illness. 56 subjects (45.9%) studied upto plus two that is upto 12th standard of which 27 (48.2) had psychiatric morbidity. 2 out of 4 diploma holders had psychiatric illness and among 17 (13.9%) graduates 7 of them that is 41.2% had psychiatric illness. (Table 4) Among 122 people 119 (97%) were married, only one was unmarried and two were widows. 60 (50%) of the married diabetics had psychiatric illness while one widow was psychiatrically ill (Table 4).

The occupation of 36(29.5%) subjects was clerical job of which 18, that is 50% had psychiatric morbidity. 30 (24.6%) of the subjects were housewives of which 19 (63.3%) had psychiatric illness. Out of 26(21.3%) farmers 11(42.3%) of them had psychiatric illness. 11 (9%) subjects were retired from job; out of them 4 (36.4%) had psychiatric illness. The psychiatric morbidity among 10 (8.2%) businessmen and 2 (1.6%)

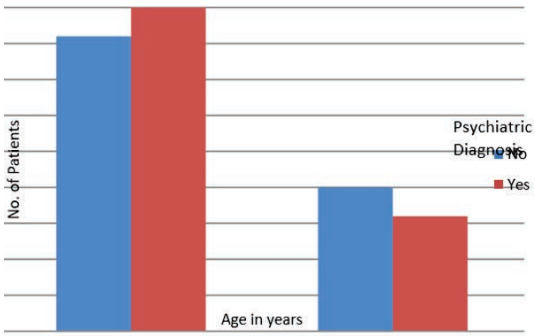

Fig. 1: Age distribution data

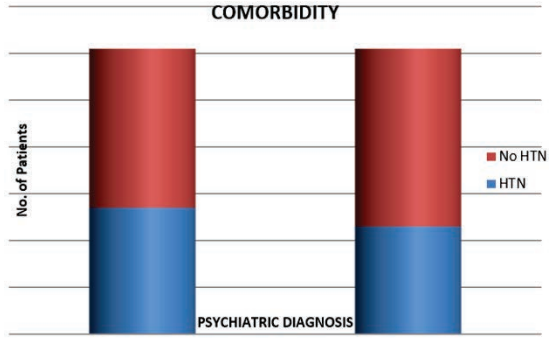

Fig. 2: Comorbidity in diabetic patients

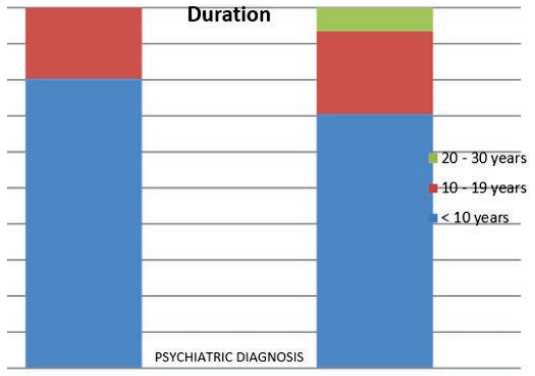

Fig. 3: Treatment duration among diabetics

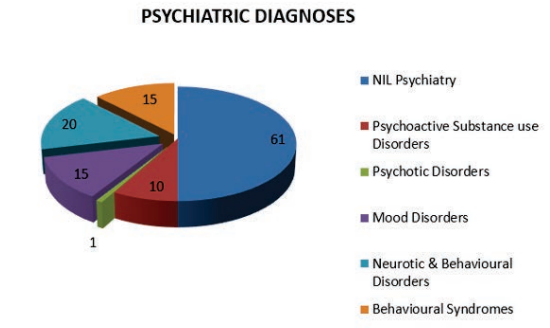

Fig. 4: Psychiatric morbidity in type 2 diabetes patients

professionals was 30% (3) and 50%(1) respectively. At last among 7 (5.7%) skilled workers 5 (71.4%) subjects had psychiatric illness (Table 4).

Among 122 diabetic patients 106 (86.9%) subjects were living in urban areas out of which 55 subjects that is 51.9% had psychiatric morbidity. Comparatively among 16 (13.1%) rural living subjects 6 (37.5%) had psychiatric illness (Table 4). One hundred Eleven subjects were living in nuclear families out of which 53 (47.7%) had psychiatric morbidity. Small number that is 11 (9%) subjects were living in joint families out of which 8 (72.7%) subjects had psychiatric illness (Table 4).

There were 93 (76.2%) Hindus , 14 (11.5%) Muslims and 15 (12.3%) were Christians. 46 (49.5%) of Hindus had psychiatric morbidity and psychiatric morbidity of 46.7% (7), 57.1% (8) was seen among Muslims and Christians respectively (Table 4). Fifty five subjects were earning between Rs.5000-9999 of which 27 subjects that is 49.1% had psychiatric morbidity. 27 (22.1%) subjects were earning between Rs.10000-14999, among which 12 (44.4%) had evidence of psychiatric illness. FiFty (12.3%) subjects were earning less than Rs.5000 out of which 10 (66.7%) were having psychiatric morbidity. only 13 (10.7%) subjects were earning between 15000-19999 and 12 (9.8%) were earning more than Rs. 20000, in these groups psychiatric morbidity was 61.5% (8) and 33.3 % (4) respectively (Table 4).

Ninety nine(80.3%) of diabetics were on treatment with oral hypoglyceamics, exercise and diabetic diet out of which 48 (49%) subjects had evidence of psychiatric illness. Twenty four (19.7%) were on combination of insulin and hypoglyceamics, diet and exercise in which 13 subjects that is 54.2% were psychiatrically ill. (Table 5, Fig. 3). Seventy eight (63.9 %) patients had controlled diabetes and 44 (36.1%) patients had uncontrolled diabetes. In these groups, psychiatric morbidity was 52.6 %(41), 45.5% (20) between controlled and uncontrolled diabetes group respectively (Table 5). Fifty(41%) subjects with diabetes had comorbid hypertension with 23(46%) subjects having psychiatric illness. Seventy two(59%) subjects had only diabetes out of which 38 (52.8%) subjects had evidence of psychiatric illness. (Table 5, Fig. 4).

In 122 subjects, 92 (74.6%) diabetics had duration of illness for less than 10 years, among which 43 (46.7%) patients had psychiatric morbidity. Twenty six (21.3%) subjects had 10-19 years of illness duration and only 4 (3.3%) people with duration of illness lasting for 20-30 years. Psychiatric morbidity was found to be 53.8% (14) and 100% (4) in groups of 10-19 years and 20-30 years of illness duration respectively. (Table 5, Fig. 5). Overall out of 122 diabetics depressive disorder and anxiety disorders had high prevalence. There were total 50% (n = 61) psychiatric morbidity in

Table 5: Psychiatric diagnoses in type 2 diabetes patients

	Frequency	Percentage
NIL Psychiatry	61	50.0
Psychoactive substance use disorders	10	8.2
Psychotic disorders	1	0.8
Mood disorders	15	12.3
Neurotic and behavioural disorders	20	16.4
Behavioural syndromes	15	12.3
Total 122	100.0	

which psychoactive substance use disorders were 8.2% (n = 10), mood disorders about 12.3% (n = 15), neurotic and behavioural disorders account for 16.4% (n = 20), and at last behavioural syndromes in which majority of patients had insomnia were 12.3% (n = 15) (Table 5, Fig. 6).

DISCUSSIONS

Globally around 60% of people are suffering from chronic medical illness which includes arthritis, diabetes mellitus, cardiovascular diseases etc. Psychiatric morbidity is highly prevalent among patients with chronic medical illness. Both Indian and western studies have shown high prevalence of psychiatric morbidity ranging from 14-50% among patients with chronic medical illness[89,90].

The size of present study sample (n = 122) is comparable to previous studies of Lustman and colleagues[51], Bagadia and colleagues[102] who used sample of 114, 100 respectively in evaluating psychiatric morbidity. Though sample size of present study is sufficient for statistical comparison a larger sample would have had a better impact on the statistical power.

Majority of patients in our study were between age group of 40-60 years. According to WHO report maximum people with diabetes fall under this group[1]. Kovacs[38] has already showed in his study on young diabetic that they have high emotional distress and psychiatric morbidity. Similarly elderly are more prone to psychiatric illness either due to cognitive problems or decreasing social support as age advances. Even though our study sample had maximum patients under less than 10 year duration there is no significant association (p = 0.207) with psychiatric morbidity. Reason could be different age of onset; less associated co morbidity and may be good psychosocial support which was not included in our study. Anne and colleagues[106] found in their study that psychiatric morbidity in diabetes is high only in association with co morbidity.

There is no significant association with treatment pattern (p = 0.649) comparable to study by Anne[106]. Reason being the number of patients on insulin in our study is too low to have any statistical significance in results. As it is reported in study by Aiken's that patients who are on insulin have more psychiatric morbidity[107]. Depression has been studied extensively in diabetic patients. Many prevalence studies focussed on prevalence of depression in diabetes and its impact and outcome. In current study prevalence of depression is 12.3%. This is again comparable to previous studies which show prevalence range of 10-15%[103].

Anxiety disorders and their impact on diabetes have been widely studied. The current study has found prevalence of neurotic and stress related disorders are 16%. Reported prevalence of anxiety disorders in diabetics varies from as low as 5.9% to as high as 41.7%[59]. Our study result is comparable to study done by Shehnaz and colleagues[37] which found 12% prevalence of anxiety disorders. Meta-analysis also showed that anxiety disorders were more common in women than in men[61].

Another important finding was increased prevalence of insomnia (behavioural syndromes) which is found to be 12.3%. This was not included in many previous studies and very few have mentioned. Study done by Sridhar and colleagues[68] found that sleep disorders were more common in diabetics (33.7% vs. 8.2% in controls, p<0.01). There was a significant association of sleep disturbances with the presence of cough, dyspnoea, nocturnal cramps, parasthesia and burning of soles. None of our patients had cough, dyspnoea, cramps.

Substance abuse disorders were also around 8.2% which is high compared to older studies. Here, this group also includes benzodiazepine abusers who were prescribed benzodiazepines as treatment for their sleep disturbances.

Limitations: Major limitation of our study is the small sample size. Most previous studies had larger sample. The nature of study is cross-sectional study. Another important limitation is including comorbid illnesses like hypertension, which could bias results because we know that hypertension is independent predictors of depression.

Treatment aspects are not being considered which could have confounded in causing psychiatric illness (for eg.oral hypoglycaemias causing insomnia, and antihypertensive causing depression). Prevalence studies conducted in medical settings typically report a higher association between depression and diabetes (>2 times). The elevated odds ratios found in clinical studies of patients with diabetes and depression may reflect a sampling bias of studying persons who use health care services. The failure to document the onset

of each medical and psychiatric condition raises the possibility that psychiatric disorders may have been present before the onset of a medical illness. This study is also limited by failing to assess the degree of functional impairment associated with disease.

Future studies are recommended to use larger sample sizes. Concentration should be on prevalence of other psychiatric symptoms like insomnia and not just only anxiety and depression. More comprehensive tools like MINI or SCID will reveal clearer data on psychiatric disorders. Adding a scale on quality of life (QOL) is also recommended. In future even treatment aspects of diabetes should be considered which may bias results. Studies in community sample are necessary to avoid biases seen in clinical setting. Furthermore, future studies might include longitudinal designs and an examination of functional impairment (e.g, disease burden, quality of life, ambulatory status etc.) when examining prevalence rates of psychiatric disorders in type 2 diabetes mellitus.

CONCLUSION

Overall results suggest that psychiatric morbidity is high in type 2 diabetes mellitus. The high prevalence of psychiatric disorders will add on to suffering of patients who are already suffering from devastating metabolic disease. This finding highlights the need for mental health screening in patients with type 2 diabetes mellitus for the early diagnosis of psychiatric disorders and use psychiatric interventions like education, counselling and treatment to decrease the suffering and improve the quality of life.

REFERENCES

1. Wild, S., G. Roglic, A. Green, R. Sicree and H. King, 2004. Global prevalence of diabetes. Diabetes Care, 27: 1047-1053.
2. Mathers, C.D. and D. Loncar, 2006. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med., Vol. 3. 10.1371/journal.pmed.0030442
3. Das-Munshi, J., R. Stewart, K. Ismail, P.E. Bebbington, R. Jenkins and M.J. Prince, 2007. Diabetes, common mental disorders, and disability: Findings from the uk national psychiatric morbidity survey. Ovid Technologies (Wolters Kluwer Health), Psychosomatic Med., 69: 543-550.
4. WHO, 2002. Fact sheet 236. Diabetes: the cost of diabetes. Washington. World Health Organization, https://www.who.int/news-room/fact-sheets/detail/diabetes
5. Cox, D.J. and L. Gonder-Frederick, 1992. Major developments in behavioral diabetes research. J. Consult. Clin. Psychol., 60: 628-638.
6. Blumenthal, J.A., S.R. Williams, A.G. Wallace, R.B. Williams and T.L. Needles, 1982. Physiological and psychological variables predict compliance to prescribed exercise therapy in patients recovering from myocardial infarction. Psychosomatic Med., 44: 519-527.
7. Talbot, F. and A. Nouwen, 2000. A review of the relationship between depression and diabetes in adults: Is there a link? Diabetes Care, 23: 1556-1562.
8. Anderson, R.J., K.E. Freedland, R.E. Clouse and P.J. Lustman, 2001. The prevalence of comorbid depression in adults with diabetes. Diabetes Care, 24: 1069-1078.
9. Ciechanowski, P.S., W.J. Katon and J.E. Russo, 2000. Depression and diabetes. Arch. Internal Med., 160: 3278-3285.
10. Peyrot, M. and R.R. Rubin, 1997. Levels and risks of depression and anxiety symptomatology among diabetic adults. Diabetes Care, 20: 585-590.
11. Eaton, W.W., H. Armenian, J. Gallo, L. Pratt and D.E. Ford, 1996. Depression and risk for onset of type ii diabetes: A prospective population-based study. Diabetes Care, 19: 1097-1102.
12. Lustman, P.J., 1988. Anxiety disorders in adults with diabetes mellitus. Psychiatric Clin. North Am., 11: 419-432.
13. Zhang, J., K.S. Markides and D.J. Lee 1991. Health status of diabetic Mexican Americans: results from the Hispanic HANES. Ethn. Dis., 1: 273-279.
14. Leedom, L., W.P. Meehan, W. Procci and A. Zeidler, 1991. Symptoms of depression in patients with type ii diabetes mellitus. Psychosomatics, 32: 280-286.
15. Lustman, P.J., R.J. Anderson, K.E. Freedl and M. Groot, R.M. Carney and R.E. Clouse, 2000. Depression and poor glycemic control: A meta-analytic review of the literature. Diabetes Care, 23: 934-942.
16. Trief, P.M., W. Grant, K. Elbert and R.S. Weinstock, 1998. Family environment, glycemic control, and the psychosocial adaptation of adults with diabetes. Diabetes Care, 21: 241-245.
17. Lustman, P.J., L.S. Griffith, R.E. Clouse, K.E. Freedland and S.A. Eisen *et al*., 1997. Effects of nortriptyline on depression and glycemic control in diabetes. Psychosomatic Med., 59: 241-250.
18. Lustman, P.J., 1998. Cognitive behavior therapy for depression in type 2 diabetes mellitus. Ann. Internal Med., 129: 613-621.
19. Gould, T.D., H. Einat, R. Bhat and H.K. Manji, 2004. Ar-a014418, a selective gsk-3 inhibitor, produces antidepressant-like effects in the forced swim test. Int. J. Neuropsy. chopharmaco., 7: 387-390.

20. Torres, R., E. Leroy, X. Hu, A. Katrivanou and P. Gourzis *et al*., 2000. Mutation screening of the wolfram syndrome gene in psychiatric patients. Mol. Psychiatry, 6: 39-43.
21. Cassidy, F., E. Ahearn and J. Carroll, 1999. Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. Am. J. Psychiatry, 156: 1417-1420.
22. Winokur, A., G. Maislin, J.L. Phillips and J.D. Amsterdam 1988. Insulin resistance after oral glucose tolerance testing in patients with major depression. Am. J. Psychiatry., 145: 325-330.
23. Baxter, L.R., 1985. Cerebral metabolic rates for glucose in mood disorders. Arch. Gen. Psychiatry, 42: 441-447.
24. Baxter, L.R., 1989. Reduction of prefrontal cortex glucose metabolism common to three types of depression. Arch. Gen. Psychiatry, 46: 243-250.
25. Yirmiya, R., 1996. Endotoxin produces a depressive-like episode in rats. Brain. Res., 711: 163-174.
26. Simpson, S.A., J.C.S. Dean and N.E. Haites, 1994. Genetic prediction of adult onset disease. BMJ., 308: 535-535.
27. Maes, M., 1999. The inflammatory response system activation model of major depression. Psychiatry. Psych. Viruses., 711: 55-62.
28. Miller, G.E., C.A. Stetler, R.M. Carney, K.E. Freedland and W.A. Banks, 2002. Clinical depression and inflammatory risk markers for coronary heart disease. J. Cardiol., 90: 1279-1283.
29. Musselman, D.L., D.H. Lawson, J.F. Gumnick, A.K. Manatunga and S. Penna *et al*., 2001. Paroxetine for the prevention of depression induced by high-dose interferon alfa. New. Engl. J. Med., 344: 961-966.
30. McEwen, B.S., A.M. Magariños and L.P. Reagan, 2002. Studies of hormone action in the hippocampal formation. J. Psychosomatic Res., 53: 883-890.
31. Szydlo, D., van, P. Wattum, J. Woolston, 2003. Psychological aspects of diabetes mellitus. Child Adolesc Psychiatry. Clin. N. Am., 12: 439-458.
32. Sridhar, G. R. and K., Madhu, 2002. Studies of hormone action in the hippocampal formation. Ahuja, M. M. S. Edn., RSSDI., Hyderabad,, Pages: 775.
33. Popkin, M.K., 1988. Prevalence of major depression, simple phobia, and other psychiatric disorders in patients with long-standing type i diabetes mellitus. Arch. Gen. Psychiatry, 45: 64-68.
34. Lustman, P.J., L.S. griffith, R.E. clouse. and P.E. cryer, 1986. Psychiatric illness in diabetes mellitus. The J. Nervous Mental Dis., 174: 736-742.
35. Almawi, W.Y., H. Tamim, N. Al-Sayed, M.R. Arekat and G.M. Al-Khateeb *et al*., 2008. Association of comorbid depression, anxiety, and stress disorders with type 2 diabetes in bahrain, a country with a very high prevalence of type 2 diabetes. J. Endocrinological Invest., 31: 1020-1024.
36. de Mont-Marin, F., P. Hardy, J. Lepine, P. Halfon and A. Feline, 1995. Six-month and lifetime prevalences of psychiatric disorders in inpatients with diabetes mellitus. Eur. Psychiatry, 10: 245-249.
37. Rauf, S., Z. Rehman and K. Abrar, 2005. Frequency of Psychiatric morbidity amongst patients with diabetes mellitus in a medical outpatient. Pak. Armed. Forces. Med. J. Mar., 55: 14-18.
38. Kovacs, M., D. Goldston, D.S. Obrosky and L.K. Bonar, 1997. Psychiatric disorders in youths with iddm: Rates and risk factors. Diabetes Care, 20: 36-44.
39. Weyerer, S., W. Hewer, M. Pfeifer-Kurda and H. Dilling, 1989. Psychiatric disorders and diabetes results from a community study. J. Psychosomatic Res., 33: 633-640.
40. Snoek, F.J., F. Pouwer, G.W. Welch and W.H. Polonsky, 2000. Diabetes-related emotional distress in dutch and u.s. diabetic patients: Cross-cultural validity of the problem areas in diabetes scale.. Diabetes Care, 23: 1305-1309.
41. Welch, G.W., A.M. Jacobson and W.H. Polonsky, 1997. The problem areas in diabetes scale: An evaluation of its clinical utility. Diabetes Care, 20: 760-766.
42. Delahanty, L.M., R.W. Grant, E. Wittenberg, J.L. Bosch, D.J. Wexler, E. Cagliero and J.B. Meigs, 2007. Association of diabetes-related emotional distress with diabetes treatment in primary care patients with type 2 diabetes. Diabetic Med., 24: 48-54.
43. Lustman, P.J., L.S. Griffith and R.E. Clouse, 1988. Depression in adults with diabetes: Results of 5-yr follow-up study. Diabetes Care, 11: 605-612.
44. Lloyd, C.E., K.A. Matthews, R.R. Wing and T.J. Orchard, 1992. Psychosocial factors and complications of iddm. the pittsburgh epidemiology of diabetes complications study. viii. Diabetes Care, 15: 166-172.
45. Kovacs, M, H.o V. and M.H. Polloc, 1995. Criterion and predictive validity of the diagnosis of adjustment disorder: a prospective study of youths with new-onset insulin-dependent diabetes mellitus Am. J. Psychiatry., 152: 523-528.
46. Robinson, F.A and Floyd, 1993. training and support group for elderly diabetes. Jr. specialists. group. works.,., 18: 127-136.

47. Wilkinson, G., D.Q. Borsey, P. Leslie, R.W. Newton, C. Lind and C.B. Ballinger, 1988. Psychiatric morbidity and social problems in patients with insulin-dependent diabetes mellitus. Br. J. Psychiatry, 153: 38-43.
48. Gavard, J.A., P.J. Lustman and R.E. Clouse, 1993. Prevalence of depression in adults with diabetes: An epidemiological evaluation. Diabetes Care, 16: 1167-1178.
49. Musselman, D.L., E. Betan, H. Larsen and L.S. Phillips, 2003. Relationship of depression to diabetes types 1 and 2: Epidemiology, biology, and treatment. Bio. Psychiatry, 54: 317-329.
50. Grey, M., E.A. Boland, M. Davidson, J. Li and W.V. Tamborlane, 2000. Coping skills training for youth with diabetes mellitus has long-lasting effects on metabolic control and quality of life. J. Pediatr., 137: 107-113.