

Psychiatric co-morbidity & diabetes

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Diabetes mellitus as well as psychiatric disorders are common. These may occur with one another and/or one may worsen the other. Psychological stress may follow screening for diabetes, as well as when diabetes is first identified. Acting through the hypothalamo-pituitary-adrenal axis, stress may initiate or worsen hyperglycaemia. Depression may be a risk factor for the development of diabetes; it also commonly occurs in subjects with diabetes. Identification and management are both important in preventing the disability. A variety of antipsychotic medications, especially the newer agents can induce weight gain, dyslipidaemia, insulin resistance and diabetes. Therefore in choosing a drug, one must consider the risk factors and screen for metabolic syndrome. Subjects with type 1 diabetes can have cognitive dysfunction, eating disorders and developmental disturbances. Physicians caring for people with diabetes must be trained to recognize and manage co-morbid psychiatric conditions that commonly occur. A biopsychosocial disease model for both conditions can leverage the social strengths and medical knowledge in developing countries.

Key words Antipsychotic drugs - depression - diabetes

The number of people with diabetes mellitus in India is increasing across geographic, ethnic and administrative boundaries¹⁻⁵. Neuropsychiatric disorders account for 12.7 per cent of the global burden of disease⁶. Psychiatric problems are common; a recent population based study of 4319 individuals in US⁷ has shown that nearly a third had mental disorders. In another large New York City study, serious psychological distress (depression, anxiety and other disorders) was reported by 10.4 per cent of persons with diabetes (80/857)⁸.

In India, morbidity due to mental disorders is comparable to global rates⁹. In an epidemiological study from rural north India, psychiatric morbidity was higher in the elderly (43.32%) when compared to those below the age of 60¹⁰. Another survey in a rural community, when repeated after 20 yr¹¹, has shown that the prevalence of psychiatric morbidity did not change significantly, although the pattern of morbidity differed from the earlier study. In a hospital based survey in New Delhi, nearly one third of 209 subjects above the age of 60 had a psychiatric illness¹². Despite comparable prevalence of

psychiatric diseases, attitudes and concepts may vary across cultures¹³. In UK, the rate of common mental disorders were similar in women of Indian origin compared to others; differences in conceptualizations of the disease led to lower frequency of medical consultation¹⁴. Given that both diabetes and psychiatric morbidity are common, they are likely to co-exist, or one may worsen the other¹⁵. This review examines these aspects, with a focus on epidemiology, aetiology, diagnosis and treatment.

Co-existence of diabetes and psychiatric illness

There is little published data from the Indian subcontinent on the co-existence of diabetes and psychiatric illness. At Dhaka, in a study 27.88 per cent (n=29) subjects with newly diagnosed diabetes had depressive illness as assessed by Hamilton Rating Scale for Depression¹⁶. Diabetes is difficult to manage as such, but patients with mental health disorders receive even less intensive medical care for diabetes^{17,18}. Self care behaviour in diabetes was adversely affected by the occurrence of natural calamities¹⁹. Lesser degree of psychological distress not amounting to psychiatric morbidity is more common²⁰. Women with type 2 diabetes mellitus reported poorer quality of life compared to men. Persons aged below 40 yr reported better satisfaction with management, and had better quality of life. Gender differences were apparent in well being: men reported better adjustment, particularly with coping and integration of the illness²¹. Counselling for psychological distress and treatment of depressive disorder would improve the well-being and/ or metabolic control in diabetes mellitus²².

There is recent intriguing evidence that maternal pre- and peri-natal depression can adversely impact the health of their infants, leading to poorer growth²³. People with schizophrenia have greater mortality than controls²⁴. Among 370 patients with schizophrenia followed for 13 yr, standardised mortality ratio (SMR) was above that for the general population. The SMR from diabetes was also increased (996; 95% confidence interval 205-2911)²⁵.

Lifestyle factors such as smoking and poor compliance to treatment may have contributed to the mortality. In addition antipsychotic medications also cause obesity, metabolic syndrome and type 2 diabetes mellitus.

Psychological distress caused by screening for diabetes and reactions at diagnosis

As the onset of both type 1 and type 2 diabetes can be predicted, one must consider the impact it makes in those who are screened for risk of developing diabetes. It is important ethically as well as clinically to manage the resultant anxiety. When screening leads to high stress among those with a positive result, or false reassurance in those with a negative result, the subjects are less likely to take appropriate corrective action²⁶. Similarly one must not falsely assume that lifestyle changes can minimize the risk of developing type 1 diabetes mellitus²⁰.

At the next step, a variety of psychological distress can occur when diabetes mellitus is first diagnosed: denial, anger, guilt, reactive depression and finally acceptance. Physicians must be aware of these reactions which are anticipated with chronic conditions. They must be trained to manage these²⁶, which may take months to resolve.

Management of common mental disorders

Common mental disorders describe states of anxiety and depression; they were previously termed neuroses. Patel *et al*²⁷ have shown that patient models of common mental disorders may evolve from somatic to psychological as the illness becomes chronic and severe. When mental disorders occur in the face of a heavy patient load in outpatient department, how do doctors cope? In a teaching general hospital, physicians and surgeons tended to underestimate the occurrence of psychiatric morbidity in clinical practice²⁸. Even with high degree of awareness that patients with physical disorders have psychological morbidity, doctors felt

it was 'impractical for them to assess and treat emotional problems'²⁹. A redeeming feature is that in developing countries, people with schizophrenia fare better due to the 'healing power of social interventions'³⁰.

Central obesity, hypothalamo-pituitary-adrenal axis (HPA) and stress

Cortisol and obesity are closely associated and may be linked by stress³¹. Other contributing factors could include conversion of cortisol to its metabolites, and the programming of the HPA axis. Central obesity has been called the 'Cushings disease of the omentum': *viz.*, constant exposure of glucocorticoids specifically to the adipose tissue in the omentum may be responsible for central obesity. Bjorntop and Rosmond³² postulated that stress could be responsible for sympathetic nervous system activation, hormone abnormalities and obesity. Different persons may show 'eustress' and 'distress' responses to the same stimulus.

HPA activation and obesity

HPA axis is more active in centrally obese men; central obesity in women was associated with differential cortisol secretary response to meal. Fat may also be preferentially deposited in the abdomen due to activity of enzymes that metabolize glucocorticoids. The activity of 11-beta hydroxysteroid dehydrogenase (HSD) activity was highly related to body fat distribution and with central obesity³³.

Depression and diabetes

Depression in the cause of diabetes: Depression could double the risk of developing type 2 diabetes mellitus, and can be considered a risk factor for its development^{34,35}. The Hoorn study evaluated if psychological stress was positively associated with, among others, prevalence of diabetes mellitus³⁶. The number of stressful life events during the preceding five years was assessed in 2,262 adults aged

50-74 yr without known diabetes. A glucose tolerance test was done after the stressful-event questionnaire was answered. The events included death of a loved one, retirement, moving from a house and ending an intense relationship. Five per cent had previously undiagnosed diabetes. Among single stressful events unrelated to work, death of a partner or moving from a house was related to greater percentage of undetected diabetes (10.6 and 6.9%). Similarly more the number of stressful events reported, the greater the prevalence of undetected diabetes. This study suggested that stressful life events could lead to the onset of diabetes mellitus.

The causal roles are unclear, although impaired central nervous system glucose metabolism, sedentary lifestyle, diet and smoking may all contribute³⁷. A recent study has shown that leptin, originally studied in relation to adipose tissue, has receptors in the limbic system and could have a potential role in emotional processes. Increasing the leptin signals in brain may be a new approach to treat depressive disorders³⁸.

Depression in the course of diabetes: A meta-analysis of studies on the prevalence of co-morbid depression in adults with diabetes was published recently³⁹. Medline and PsycInfo search engines were used to identify studies that measured point prevalence or lifetime prevalence or both, of depression in adults with diabetes; 39 studies were included, with a total combined of 20,218 subjects. The principal conclusion was that diabetes doubled the odds of depression³⁹; *i.e.*, persons with diabetes were twice as likely to have depression compared to those without diabetes. The odds of depression occurring in women were higher than in men. Depression may be related to complexities in management of diabetes, or to neurohormonal abnormalities⁴⁰.

In clinical practice, identification of depression in diabetes is often overlooked for a variety of reasons: societal disapproval of depression, complicity between physicians and patients not to discuss depressive symptoms, and wrongly

considering depression as a 'normal consequence of difficult medical illness'⁴¹. The potential benefits of treatment are thereby missed. It may be suspected by history of depression, mental health treatment, family history of depression, symptoms out of proportion to medical explanation, persistent focus on bodily complaints, innocuous medical symptoms not responding to reassurance, sexual dysfunction or chronic pain as a dominant complaint⁴¹.

Management of depression

Once diagnosed, depression can be managed by cognitive behaviour therapy, antidepressant medications or electroconvulsive therapy. In cognitive behaviour therapy, patients are reinvolved in pleasurable social and physical activities; stressful circumstances are resolved and cognitive techniques are used to identify distorted patterns; they are replaced with adaptive and useful ways of thinking⁴¹. Before starting formal therapy, depressive symptoms must be reassessed after hyperglycaemia is corrected. However, depressive attitude and affective symptoms (*e.g.*, pessimism or crying spells) are unlikely to be only due to poorly controlled diabetes⁴⁰.

Use of antidepressant medications can disturb glycaemic control: tricyclic antidepressants stimulate appetite, whereas selective serotonin reuptake inhibitors suppress appetite, enhance insulin sensitivity and lead to hypoglycaemia if diet is not regulated. Besides, once depression is treated eating habits exercise and drug compliance may change, leading to unstable metabolic control. In the presence of autonomic neuropathy tricyclic antidepressants may worsen orthostatic hypotension, induce constipation and urinary retention⁴⁰.

Psychotic disorders, obesity, metabolic syndrome and type 2 diabetes mellitus

Even before neuroleptic drugs were introduced, schizophrenia was believed to be a predisposing factor to diabetes; diabetes was considered to be an integral part of the disease⁴². Currently used

antipsychotic drugs lead to obesity, diabetes, insulin resistance and metabolic syndrome. One must integrate the role of metabolic factors, medications and lifestyle factors in its pathogenesis; newer evidence indicates that there could be an interaction of orexin peptides and dopamine systems in the prefrontal cortex⁴³. A recent study showed that even after antipsychotic drugs were stopped, insulin resistance and hyperleptinaemia may persist⁴⁴. Patients with severe mental illness had higher prevalence of metabolic syndrome⁴⁵; similarly outpatients with bipolar disorder had greater severity of illness with increasing number of co-morbid conditions including diabetes mellitus⁴⁶. Remission from borderline personality disorder was poor when associated with chronic physical conditions such as obesity or diabetes mellitus⁴⁷. There is evidence for type 2 diabetes and Alzheimer's to occur together, because of common underlying pathogenetic mechanisms⁴⁸.

Antipsychotic drugs and metabolic changes

Antipsychotic drugs are used in the management of schizophrenia, bipolar disorders, dementia and delirium, and other conditions⁴⁹. Earlier agents (chlorpromazine, thioridazine, haloperidol) were called 'typical or conventional'; though they were effective, and they commonly induced neurological adverse effects and hyperprolactinaemia. More recently introduced agents, called 'atypical,' include clozapine, risperidone, olanzapine, ziprasidone and others; they have fewer neurological side effects and better relief of negative cognitive and affective syndromes⁵⁰. They are more effective in preventing relapse.

Metabolic effects of atypical antipsychotic drugs

Atypical antipsychotic drugs have a propensity to induce weight gain in the following order: clozapine > olanzapine > thioridazine > quetiapine > chlorpromazine > risperidone > haloperidol > fluphenazine > ziprasidone⁴⁹. The average short-term weight gain varies from a mean of 0.43 to 4.45 kg,

with its attendant effects on carbohydrate and lipid metabolism. Clozapine and olanzapine, with a greater propensity to induce weight gain seem to be frequently associated with type 2 diabetes mellitus⁵⁰. A similar hierarchy exists for hyperlipidaemia: high for clozapine and olanzapine; low for risperidone. However a recent study from India which compared the use of olanzapine and haloperidol/trifluoperazine for 12 wk did not find a change in glycaemic status, weight or body mass index among the three drugs⁵¹.

Mechanism of action

Weight gain: The atypical antipsychotic agents can increase body weight by either the direct stimulation of appetite via feeding areas of the brain, or indirectly by endocrine effects such as hyperprolactinaemia, decreased gonadal levels and hypercortisolism⁴⁹. Environmental factors also contribute⁵².

Using a candidate gene approach, polymorphisms of genes controlling weight regulation pathway, as well as functional imaging studies of the brain would provide further leads into the pathogenesis of weight gain⁵². Studies were carried out on polymorphisms of histamine H1 receptors and dopamine D2 receptors, polymorphisms in beta 3 adrenergic receptor genes. Even though definite conclusions cannot yet be drawn leptin and ghrelin levels are also being evaluated⁵².

Effect on beta cells and insulin sensitivity: Other postulated mechanisms of action put forward were drug-induced insulin resistance, either directly or via stimulation of cytokine production, and interference with glucose transport across membranes⁵⁰.

Recently the effect of clozapine and of haloperidol on electrical and secretory activity of pancreatic beta cells was studied: while at lower glucose concentrations, clozapine had little effect on membrane potential, at higher doses, it led to marked depolarization of the membrane potential, despite differing glucose concentrations⁵³. Similarly clozapine and olanzapine were shown to increase

basal insulin release, in contrast to conventional antipsychotics⁵⁴. These two drugs also led to hyperinsulinaemia, hyperglycaemia, hyperlipidaemia and hyperleptinaemia⁵⁵. Studies in dogs showed that olanzapine caused weight gain, trunkal obesity and insulin resistance⁵⁶. A possible impedance of neural regulation of beta-cell compensation was suggested.

Clinical implication

Considering the epidemiological and biochemical association of adverse metabolic effects, one must be careful in choosing the antipsychotic agent - efficacy, side effects and patient profile must all be seen on a case to case basis⁵⁷. Weight gain at three to six weeks is a robust clinical indicator for predicting total weight gain: gain is rapid in the first month and stays constant after several months⁵⁸. Other risk factors to consider are activity level, family history of obesity/ diabetes and ethnicity⁵⁹.

A flow chart for screening is available from the consensus statement published on 'Diabetes, psychotic disorders and antipsychotic therapy'⁶⁰.

Management of obesity does not differ in principle from obesity due to other causes: calorie restriction in diet, physical exercise to induce negative calorie balance, cognitive-behaviour therapy, and where necessary, use of drugs to reduce weight (appetite suppressant, lipase blockers⁶¹).

Psychiatric co-morbidity in type 1 diabetes mellitus

Even though childhood diabetes comprises a small percentage of reported diabetic population in India, it is stressful for the child, the family and the health-care team^{62,63}.

Cognitive dysfunction

Diabetes mellitus can affect learning, memory, mental speed and eye-hand co-ordination⁶⁴. Electrophysiological tests can identify cognitive

dysfunction even before psychometric tests. There are few published Indian studies except for the report of Jyothi *et al* and our observations^{65,66}. Children with diabetes scored less compared to controls on all scores (Wechsler's coding, digit span test and Raven's coloured progressive matrices). Lower scores were attributed to both metabolic control and psychosocial factors⁶⁵. It was shown that cognitive function was poorer, reaction time longer, memory scale poorer, although intelligence quotient was comparable with control children⁶⁶. Central nervous system vascular or metabolic dysfunction, emotional influence of the chronic illness or a central neuropathy (analogous to peripheral neuropathy) may all contribute. Children tend to miss school more often, and obtain lower scores⁶⁷. Therefore one must consider educational skills in diabetic children when planning diabetic treatment regimens.

Diabetes and child development

Development in childhood diabetes may be compromised at different stages:

Infancy and toddlers: The difficulties arise from irregular meal schedule, poor conception to understand the need for injections and testing, and finally conflict with other siblings who may resent unequal sharing of parental attention. Parents may need psychosocial support along with medical advice⁶⁶. Diabetes care groups may offer fellowship and advise. It is 'ultimately a balance of the ideal with the practical and realistic.'

School age child: Between the ages of 6 and 11, the child must master diabetes care regimen, modify the diet while completing common developmental tasks. Children with normal psychosocial development adequately cope with diabetes.

Eating disorders in type 1 diabetes

In western countries, eating disorders are being increasingly recognized in subjects with type 1 diabetes⁶⁸⁻⁷². They may be associated with insulin

misuse for weight control, hyperglycaemia and resultant metabolic complications. In a small study where 36 subjects with eating disorder were reassessed after two years, 13.9 per cent showed full remission for at least 12 wk, 61.6 per cent showed no change and the remaining shifted from subclinical to clinical eating disorder⁷³. An increasing body mass index may be associated with greater dietary restraint, especially among girls⁷⁴.

Eating disorders should be suspected when, despite efforts to prevent, recurrent diabetic ketoacidosis or poor glycaemic control occur⁷⁵, particularly among those with family dysfunction⁷¹. However, eating disorder may not be specific to diabetes, but may result from living with chronic diseases (*e.g.*, phenylketonuria) where dietary management/restriction may increase the susceptibility to eating disorders⁷⁶.

Intervention should be seriously attempted, for the risk of death may be increased⁷⁷. Psychoeducation programme in a group of young women with type 1 diabetes and disordered attitude reduced eating disturbance, but did not improve metabolic control⁷⁸.

Coping with stress in diabetes

Coping with stress can be approached either by focussing on the emotional effects of stress or solving the problems of stress, or both²⁶. In emotion focused coping, stressful situations are viewed as being less stressful; *i.e.* the situations are unchanged, only the emotional response to stress is changed. In problem focused coping, one learns skills to remove the cause of stress. A variety of resources can be used to cope with stress, *viz.*, positive beliefs, social skills, social support and finally material resources²⁶.

Conclusion

Both diabetes and psychiatric disorders are frequent; the two may worsen one other. It is important that they are first identified, and the causative factors eliminated. A biopsychosocial

approach to diabetes and psychiatric diseases⁷⁹ can leverage the social strengths in India. Application of drugs to the broad and deep social networks of developing countries is both feasible and effective^{80,81}.

References

- Mohan V, Sandeep S, Deepa R, Shah B, Varghere C. Epidemiology of type 2 diabetes: Indian scenario. *Indian J Med Res* 2007; 125 : 217-30.
- Sridhar GR, Rao PV, Ahuja MMS. Epidemiology of diabetes and its complications. In: Ahuja MMS, Tripathy BB, Moses SGP, Chandalia HB, Das AK, Rao PV, editors. *RSSDI textbook of diabetes*. Hyderabad: Reseach Society for the Study of Diabetes in India; 2002 p. 95-112.
- Ramachandran A, Snehalatha C, Kapur A, Vijay V, Mohan V, Das AK, *et al*. Diabetes Epidemiology Study Group in India (DESI). High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey. *Diabetologia* 2001; 44 : 1094-101.
- Huizinga MM, Rothman RL. Addressing the diabetes pandemic: A comprehensive approach. *Indian J Med Res* 2006; 124 : 481-4.
- Sadikot SM, Nigam A, Das S, Bajaj S, Zargar AH, Prasannakumar KM, *et al*. The burden of diabetes and impaired glucose tolerance in India using the WHO 1999 criteria: prevalence of diabetes in India study (PODIS). *Diabetes Res Clin Pract* 2004; 66 : 301-7.
- Weiss MG, Isaac M, Parkar SR, Chowdhury AN, Raguram R. Global, national, and local approaches to mental health: examples from India. *Trop Med Int Health* 2001; 6 : 4-23.
- Kessler RC, Demler O, Frank RG, Olfson M, Pincus HA, Walters EE, *et al*. Prevalence and treatment of mental disorders, 1990-2003. *N Engl J Med* 2005; 352 : 2515-23.
- McVeigh KH, Mostashari F, Thorpe LE. Serious psychological distress among persons with diabetes - New York City, 2003. *MMWR Morb Mortal Wkly Rep* 2004; 53 : 1089-92.
- Khandelwal SK, Jhingan HP, Ramesh S, Gupta RK, Srivastava VK. India mental health country profile. *Int Rev Psychiatry* 2004; 16 : 126-41.
- Tiwari SC. Geriatric psychiatric morbidity in rural northern India: implications for the future. *Int Psychogeriatr* 2000; 12 : 35-48.
- Nandi DN, Banerjee G, Mukherjee SP, Ghosh A, Nandi PS, Nandi S. Psychiatric morbidity of a rural Indian community. Change over a 20-year interval. *Br J Psychiatry* 2000; 176 : 351-6.
- Dey AB, Soneja S, Nagarkar KM, Jhingan HP. Evaluation of the health and functional status of older Indians as a prelude to the development of a health programme. *Natl Med J India* 2001; 14 : 135-8.
- Patel V, Andrade C. Pharmacological treatment of severe psychiatric disorders in the developing world: lessons from India. *CNS Drugs* 2003; 17 : 1071-80.
- Jacob KS, Bhugra D, Lloyd KR, Mann AH. Common mental disorders, explanatory models and consultation behaviour among Indian women living in the UK. *J R Soc Med* 1998; 91 : 66-71.
- Ananth A, Kolli S, Gunatilake S, Brown S. Atypical antipsychotic drugs, diabetes and ethnicity. *Expert Opin Drug Safety* 2005; 4 : 1111-24.
- Begum A, Mahtab H, Khan AKA. Psychiatric morbidity in recently diagnosed diabetic subjects. *J Diab Assoc Bangladesh* 1991; 19 : 16-21.
- Desai MM, Rosenheck RA, Druss B, Perlin JB. Mental disorders and quality of diabetes care in the Veterans Health Administration. *Am J Psychiatry* 2002; 159 : 1584-90.
- Frayne SM, Halanych JH, Miller DR, Wang F, Lin H, Pogach L, *et al*. Disparities in diabetes care: impact of mental illness. *Arch Intern Med* 2005; 165 : 2631-8.
- Ramachandran A. Experiences of the WHO Collaborating Centre for Diabetes in India in managing tsunami victims with diabetes. *Pract Diabetes Int* 2005; 22 : 98-9.
- Sridhar GR, Madhu K. Psychosocial and cultural issues in diabetes mellitus. *Curr Sci* 2002; 83 : 1556-64.
- Sridhar GR, Madhu K, Veena S. Gender differences in well-being among persons with diabetes in India. *Diabetes Res Clin Pract* 2000; 50 : 981.
- Katon W, Cantrell CR, Sokol MC, Chiao E, Gdovin JM. Impact of antidepressant drug adherence on comorbid medication use and resource utilization. *Arch Intern Med* 2005; 165 : 2497-503.
- Rahman A, Iqbal Z, Bunn J, Lovel H, Harrington R. Impact of maternal depression on infant nutritional status and illness: a cohort study. *Arch Gen Psychiatry* 2004; 61 : 946-52.
- Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. *Br J Psychiatry* 2000; 177 : 212-7.

25. Marteau TM. Understanding and avoiding the adverse psychological effects of screening: a commentary. In: Williams R, Herman W, Kinmonth L, Wareham NJ, editors. *The evidence base for diabetes care*. West Sussex, John Wiley & Sons; 2002 p. 235-41.
26. Madhu K, Sridhar GR. Stress management in diabetes mellitus. *Int J Diab Dev Countries* 2005; 25 : 7-11.
27. Patel V, Pereira J, Mann AH. Somatic and psychological models of common mental disorder in primary care in India. *Psychol Med* 1998; 28 : 135-43.
28. Chadda RK. Psychiatry in non-psychiatric setting - a comparative study of physicians and surgeons. *J Indian Med Assoc* 2001; 99 : 24, 26-7, 62.
29. Farooq S, Akhter J, Anwar E, Hussain I, Khan SA, Inam-ul Haq Jadoon. The attitude and perception of hospital doctors about the management of psychiatric disorders. *J Coll Physicians Surg Pak* 2005; 15 : 552-5.
30. Miller G. A spoonful of medicine - and a steady diet of normality. *Science* 2006; 311 : 464-5.
31. Sridhar GR, Madhu K. Stress in the cause and course of diabetes. *Int J Diab Dev Countries* 2001; 21 : 112-20.
32. Bjorntorp P, Rosmond R. The metabolic syndrome - a neuroendocrine disorder? *Br J Nutr* 2000; 83 (Suppl 1) : S49-57.
33. Katz JR, Mohammed-Ali V, Wood PJ, Yudkin JS, Coppack SW. An *in vivo* study of cortisol-cortisone shuttle in subcutaneous abdominal adipose tissue. *Clin Endocrinol (Oxf)* 1999; 50 : 63-8.
34. Eaton WW, Armenian H, Gallo J, Pratt L, Ford DE. Depression and risk for onset of type II diabetes. A prospective population-based study. *Diabetes Care* 1996; 19 : 1097-102.
35. Freedland KE. Depression is a risk factor for the development of type 2 diabetes. *Diabetes Spectr* 2004; 17 : 150-2.
36. Mooy JM, de Vries H, Grootenhuys PA, Bouter LM, Heine RJ. Major stressful life events in relation to prevalence of undetected type 2 diabetes: the Hoorn study. *Diabetes Care* 2000; 23 : 197-201.
37. Haupt D, Newcomer J. Depression is associated with hyperglycemia and other metabolic abnormalities. *Diabetes Spectr* 2004; 17 : 154-5.
38. Lu XY, Kim CS, Frazer A, Zhang W. Leptin: a potential novel antidepressant. *Proc Natl Acad Sci USA* 2006; 103 : 1593-8.
39. Anderson RJ, Freedland KE, Clouse RE, Listman PJ. The prevalence of comorbid depression in adults with diabetes. *Diabetes Care* 2001; 24 : 1069-78.
40. Sridhar GR, Madhu K. Depression and psychosocial stress in diabetes mellitus. In: Kapur A, Joshi JK, editors. *Novo nordisk diabetes update proc*. Mumbai: Business Network Inc; 2002 p. 87-92.
41. Lustman PJ, Clouse RE. Practical considerations in the management of depression in diabetes. *Diabetes Spectr* 2004; 17 : 160-6.
42. Kohen D. Diabetes mellitus and schizophrenia: historical perspective. *Br J Psychiatry* 2004; 47 (Suppl) : S64-6.
43. Fadel J, Bubser M, Deutch A. Differential activation of orexin neurons by antipsychotic drugs associated with weight gain. *J Neurosci* 2002; 22 : 137-41.
44. Arranz B, Rosel P, Ramirez N, Duenas R, Fernandez P, Sanchez JM, *et al*. Insulin resistance and increased leptin concentrations in noncompliant schizophrenia patients but not in antipsychotic-naïve first-episode schizophrenia patients. *J Clin Psychiatry* 2004; 65 : 1335-42.
45. Toalson P, Ahmed S, Hardy T, Kabinoff G. The metabolic syndrome in patients with severe mental illness. *Prim Care Companion J Clin Psychiatry* 2004; 6 : 152-8.
46. Beyer J, Kuchibhatla M, Gersing K, Krishnan KR. Medical comorbidity in a bipolar outpatient clinical population. *Neuropsychopharmacology* 2005; 30 : 40-104.
47. Frankenburg FR, Zanarini MC. The association between borderline personality disorder and chronic medical illness, poor health-related lifestyle choices, and costly forms of health care utilization. *J Clin Psychiatry* 2004; 65 : 1660-5.
48. Sridhar GR, Thota H, Allam AR, Suresh Babu C, Silva Prasad A, Divakar C. Alzheimer's disease and type 2 diabetes mellitus: the cholinesterase connection? *Lipids Health Dis* 2006; 5 : 28.
49. Baptista T, De Mendoza S, Beaulieu S, Bermudez A, Martinez M. The metabolic syndrome during atypical antipsychotic drug treatment: mechanisms and management. *Metabolic Syndrome Rel Dis* 2004; 2 : 290-307.
50. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004; 27 : 596-601.

51. Guha P, Roy K, Sanyal D, Dasgupta T, Bhattacharya K. Olanzapine-induced obesity and diabetes in Indian patients: a prospective trial comparing olanzapine with typical antipsychotics. *J Indian Med Assoc* 2005; 103 : 660-4.
52. Tighe S, Dinan T. An overview of the central control of weight regulation and the effect of antipsychotic medication. *J Psychopharmacology* 2005; 19 (Suppl) : 36-46.
53. Best L, Yates AP, Reynolds GP. Actions of antipsychotic drugs on pancreatic beta cell function: contrasting effects of clozapine and haloperidol. *J Psychopharmacology* 2005; 19 : 597-601.
54. Melkersson K. Clozapine and olanzapine, but not conventional antipsychotics, increase insulin release *in vitro*. *Eur Neuropsychopharmacol* 2004; 14 : 115-9.
55. Melkersson KI, Dahl ML. Relationship between levels of insulin or triglycerides and serum concentrations of the atypical antipsychotics clozapine and olanzapine in patients on treatment with therapeutic doses. *Psychopharmacology (Berl)* 2003; 170 : 157-66.
56. Ader M, Kim SP, Catalano KJ, Ionut V, Hucking K, Richey JM, *et al*. Metabolic dysregulation with atypical antipsychotics occurs in the absence of underlying disease. A placebo-controlled study of olanzapine and risperidone in dogs. *Diabetes* 2005; 54 : 862-71.
57. Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, *et al*. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999; 156 : 1686-96.
58. Davis JM. The choice of drugs for schizophrenia. *N Engl J Med* 2006; 354 : 518-20.
59. Citrome LL, Jaffe AB. Relationship of atypical antipsychotics with development of diabetes mellitus. *Ann Pharmacotherap* 2003; 37 : 1849-57.
60. Lambert TJR, Chapman LH, Consensus Working Group. Diabetes, psychotic disorders and antipsychotic therapy: a consensus statement. *Med J Aust* 2004; 181 : 544-8.
61. Schwartz TL, Nihalani N, Virk S, Jindal S, Chilton M. Psychiatric medication-induced obesity: treatment options. *Obesity Rev* 2004; 5 : 233-8.
62. Sridhar GR. Gender differences in childhood diabetes. *Intl J Diab Dev Countries* 1996; 16 : 108-13.
63. Sridhar GR. Diabetes mellitus in children below the age of five. *Indian J Endocrinol Metab* 1997; 1 : 13-5.
64. Ryan CM. Neurobehavioral complications of type I diabetes. Examination of possible risk factors. *Diabetes Care* 1998; 11 : 86-93.
65. Jyothi K, Susheela S, Kodali VR, Balakrishnan S, Seshaiiah V. Poor cognitive task performance of insulin-dependent diabetic children (6-12 years) in India. *Diabetes Res Clin Pract* 1993; 20 : 209-13.
66. Sridhar GR, Madhu K. Psycho-social aspects of diabetes. In: Ahuja MMS, Tripathy BB, Moses SGP, Chandalia HB, Das AK, Rao PV, *et al*, editors. *RSSDI textbook of diabetes*. Hyderabad: Research Society for the Study of Diabetes in India; 2002 p. 737-55.
67. Ryan C, Longstreet C, Morrow L. The effects of diabetes mellitus on the school attendance and school achievements of adolescents. *Child Care Health Dev* 1985; 11 : 229-40.
68. Peveler RC, Bryden KS, Neil HA, Fairburn CG, Mayou RA, Dunger DB, *et al*. The relationship of disordered eating habits and attitudes to clinical outcomes in young adult females with type 1 diabetes. *Diabetes Care* 2005; 28 : 84-8.
69. Colton P, Olmsted M, Daneman D, Rydall A, Rodin G. Disturbed eating behavior and eating disorders in preteen and early teenage girls with type 1 diabetes: a case-controlled study. *Diabetes Care* 2004; 27 : 1654-9.
70. Maharaj SI, Rodin GM, Olmsted MP, Connolly JA, Daneman D. Eating disturbances in girls with diabetes: the contribution of adolescent self-concept, maternal weight and shape concerns and mother-daughter relationships. *Psychol Med* 2003; 33 : 525-39.
71. Rodin G, Olmsted MP, Rydall AC, Maharaj SI, Colton PA, Jones JM, *et al*. Eating disorders in young women with type 1 diabetes mellitus. *J Psychosom Res* 2002; 53 : 943-9.
72. Affenito SG, Adams CH. Are eating disorders more prevalent in females with type 1 diabetes mellitus when impact of insulin omission is considered? *Nutr Rev* 2001; 59 : 179-82.
73. Herpertz S, Albus C, Kielmann R, Hagemann-Patt H, Lichtblau K, Kohle K, *et al*. Comorbidity of diabetes mellitus and eating disorders: a follow-up study. *J Psychosom Res* 2001; 51 : 673-8.
74. Bryden KS, Neil A, Mayou RA, Peveler RC, Fairburn CG, Dunger DB. Eating habits, body weight, and insulin misuse. A longitudinal study of teenagers and young adults with type 1 diabetes. *Diabetes Care* 1999; 22 : 1956-60.

75. Hoffman RP. Eating disorders in adolescents with type 1 diabetes. A closer look at a complicated condition. *Postgrad Med* 2001; 109 : 67-9, 73-4.
76. Antisdel JE, Chrisler JC. Comparison of eating attitudes and behaviors among adolescent and young women with type 1 diabetes mellitus and phenylketonuria. *J Dev Behav Pediatr* 2000; 21 : 81-6.
77. Nielsen S, Emborg C, Molbak AG. Mortality in concurrent type 1 diabetes and anorexia nervosa. *Diabetes Care* 2002; 25 : 309-12.
78. Olmsted MP, Daneman D, Rydall AC, Lawson ML, Rodin G. The effects of psychoeducation on disturbed eating attitudes and behavior in young women with type 1 diabetes mellitus. *Int J Eat Disord* 2002; 32 : 230-9.
79. Madhu K, Sridhar GR. Model for coping with diabetes. *Intl J Diab Dev Countries* 2001; 21 : 103-11.
80. Bolton P, Bass J, Neugebauer R, Verdelli H, Clougherty KF, Wickramaratne P, *et al.* Group Interpersonal Psychotherapy for Depression in Rural Uganda: A randomized controlled trial. *JAMA* 2003; 289 : 3117-24.
81. Sridhar GR. Containing the diabetes epidemic. *Natl Med J India* 2003; 16 : 57-60.

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