Psychiatric co-morbidity & diabetes

G.R. Sridhar

Endocrine & Diabetes Centre, Visakhapatnam, India

Received November 8, 2007

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 boundaries. Neuropsychiatric disorders account for 12.7 per cent of the global burden of disease. Psychiatric problems are common; a recent population based study of 4319 individuals in US 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).

In India, morbidity due to mental disorders is comparable to global rates. 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 60. Another survey in a rural community, when repeated after 20 yr, 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 illness. Despite comparable prevalence of
psychiatric diseases, attitudes and concepts may vary across cultures. 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 consultation. Given that both diabetes and psychiatric morbidity are common, they are likely to co-exist, or one may worsen the other. 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 Depression. Diabetes is difficult to manage as such, but patients with mental health disorders receive even less intensive medical care for diabetes. Self care behaviour in diabetes was adversely affected by the occurrence of natural calamities. Lesser degree of psychological distress not amounting to psychiatric morbidity is more common. 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 illness. Counselling for psychological distress and treatment of depressive disorder would improve the well-being and/ or metabolic control in diabetes mellitus.

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 action. Similarly one must not falsely assume that lifestyle changes can minimize the risk of developing type 1 diabetes mellitus.

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 these, 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 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 practice. 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’. A redeeming feature is that in developing countries, people with schizophrenia fare better due to the ‘healing power of social interventions’.

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

Cortisol and obesity are closely associated and may be linked by stress. 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 Rosmond 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 secretory 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 obesity.

Depression and diabetes

Depression in the cause of diabetes: A meta-analysis of studies on the prevalence of co-morbid depression in adults with diabetes was published recently. 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 depression; 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 abnormalities.

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’\textsuperscript{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 complaint\textsuperscript{41}.

**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 thinking\textsuperscript{41}. 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 diabetes\textsuperscript{40}.

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 retention\textsuperscript{40}.

**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 disease\textsuperscript{42}. 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 cortex\textsuperscript{43}. A recent study showed that even after antipsychotic drugs were stopped, insulin resistance and hyperleptinaemia may persist\textsuperscript{44}. Patients with severe mental illness had higher prevalence of metabolic syndrome\textsuperscript{45}; similarly outpatients with bipolar disorder had greater severity of illness with increasing number of co-morbid conditions including diabetes mellitus\textsuperscript{46}. Remission from borderline personality disorder was poor when associated with chronic physical conditions such as obesity or diabetes mellitus\textsuperscript{47}. There is evidence for type 2 diabetes and Alzheimer’s to occur together, because of common underlying pathogenetic mechanisms\textsuperscript{48}.

**Antipsychotic drugs and metabolic changes**

Antipsychotic drugs are used in the management of schizophrenia, bipolar disorders, dementia and delirium, and other conditions\textsuperscript{49}. Earlier agents (chlorpromazine, thioridazine, haloperidol) were called ‘typical or conventional’; though they were effective, and they commonly induced neurological adverse effects and hyperprolactinemia. 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 syndromes\textsuperscript{50}. 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 > ziprasidone\textsuperscript{49}. 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 mellitus\textsuperscript{50}. 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 drugs\textsuperscript{51}.

**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 hypercortisolism\textsuperscript{49}. Environmental factors also contribute\textsuperscript{52}.

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 gain\textsuperscript{52}. 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 evaluated\textsuperscript{52}.

**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 membranes\textsuperscript{50}.

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 concentrations\textsuperscript{53}. Similarly clozapine and olanzapine were shown to increase basal insulin release, in contrast to conventional antipsychotics\textsuperscript{54}. These two drugs also led to hyperinsulinaemia, hyperglycaemia, hyperlipidaemia and hyperleptinaemia\textsuperscript{55}. Studies in dogs showed that olanzapine caused weight gain, trunkal obesity and insulin resistance\textsuperscript{56}. 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 basis\textsuperscript{57}. 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 months\textsuperscript{58}. Other risk factors to consider are activity level, family history of obesity/diabetes and ethnicity\textsuperscript{59}.

A flow chart for screening is available from the consensus statement published on ‘Diabetes, psychotic disorders and antipsychotic therapy’\textsuperscript{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 blockers\textsuperscript{61}).

**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\textsuperscript{62,63}.

**Cognitive dysfunction**

Diabetes mellitus can affect learning, memory, mental speed and eye-hand co-ordination\textsuperscript{64}. 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\textsuperscript{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 factors\textsuperscript{65}. It was shown that cognitive function was poorer, reaction time longer, memory scale poorer, although intelligence quotient was comparable with control children\textsuperscript{66}. 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 scores\textsuperscript{67}. 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 advice\textsuperscript{66}. 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 diabetes\textsuperscript{68-72}. 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 disorder\textsuperscript{73}. An increasing body mass index may be associated with greater dietary restraint, especially among girls\textsuperscript{74}.

Eating disorders should be suspected when, despite efforts to prevent, recurrent diabetic ketoacidosis or poor glycaemic control occur\textsuperscript{75}, particularly among those with family dysfunction\textsuperscript{71}. 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 disorders\textsuperscript{76}.

Intervention should be seriously attempted, for the risk of death may be increased\textsuperscript{77}. Psychoeducation programme in a group of young women with type 1 diabetes and disordered attitude reduced eating disturbance, but did not improve metabolic control\textsuperscript{78}.

**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 both\textsuperscript{26}. 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, \textit{viz.}, positive beliefs, social skills, social support and finally material resources\textsuperscript{26}.

**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 diseases\textsuperscript{79} 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\textsuperscript{80,81}.

References


*Reprint requests:* Dr G.R. Sridhar, Endocrine & Diabetes Centre, 15-12-16 Krishnanagar Visakhapatnam 530002, India
e-mail: grsridhar@hotmail.com