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Review Article

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How Diabetes and Depression are Linked

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Abstract

The current study aimed at evaluation of depression and its associated factor among type 2 diabetic patients in Tertiary health care centers of Govt. Medical College, Amritsar. One hundred and fifty type 2 DM patients following in the primary health care center were included in the study; the results showed that 63% of patients had depression. It was noticed that depression was more prevalent among patients between 40 and 60 years old. Also it was found that family history of psychiatric illness and use of insulin were significantly increasing the occurrence of depression. Another significant results were that taking more than 3 drugs or having more than 4 follow-ups per year will increase the odds of having depression which was explained that by the presence of complications in those patients, which was found to be a significant factor in increasing cases of depression among our sample. Also uncontrolled type 2 DM patients (FBG>130) were having more depression than controlled patients.

Conclusion: Depression among type 2 DM patients in our area was high and it is affecting the outcome of our care. Our recommendations were to screen every Type 2 DM patients for depression using Beck depression inventory or any validated tool.

Keywords: Diabetes, Depression, Pathophysiological, Pharmacotherapy, Psychotherapy, Collaborative care

Introduction

There are two principle forms of diabetes: Type 1 diabetes (formerly known as insulin-dependent) and Type 2 diabetes (formerly named non-insulin-dependent), that results from the body's inability to respond properly to the action of insulin produced by the pancreas. Type 2 diabetes is much more common and accounts for around 90% of all diabetes cases worldwide. It occurs most frequently in adults, but is being noted increasingly in adolescents as well. Psychological effect of diabetes on the patient's life especially depression which is preventable and treatable exists. Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration. The similarity in the hypothalamic-pituitary axis changes found in depression and poorly controlled diabetes mellitus indicates that diabetic patients are more susceptible to neurochemical and behavioral changes similar to those found in depression, and mood shifts often associated with glycemic changes. Previous studies have suggested that the extent of the difference in glycemic control between depressed and nondepressed patients is

equivalent to that of the glycemic differences between the intensive and conventional treatment groups of the Diabetes Control and Complications Trial [5, 6]. This suggests that if it persists over time, hyperglycaemia associated depression may have substantial medical consequences [7]. It also underscores the importance of recognition and proper treatment of depression in diabetic patients. Recent developments in the fields of health outcome research and health technology assessment have also fueled the tremendous increase in the use of quality of life evaluation as a technique for clinical research[5, 6]. Greater attention is now being devoted to evaluating the quality of health care and the economic value associated with new interventions. Moreover, chronic stress induces immune dysfunction directly or through the HPA axis or SNS, increasing the production of inflammatory cytokines. High amounts of inflammatory cytokines interact with the normal functioning of the pancreatic β-cells, induce insulin resistance, and thus, promote the appearance of DM2 [**6**,**7**]. Many new studies suggest that inflammatory responses are also involved in the pathophysiology of depression. Proinflammatory cytokines have been found to interact with many of the pathophysiological domains that characterize depression, including neurotransmitter metabolism, neuroendocrine function, synaptic plasticity, and behavior.50% of the patients treated with interferon Alfa develop depression and patients with depression had statistically higher blood levels of cytokines like tumor necrosis factor and interleukin 6 than those without depression.

Pathophysiological mechanism

We chose quality of life to be a multidimensional construct comprising the individual's subjective perception of physical, emotional and social well-being, including both a cognitive component (e.g. satisfaction) and an emotional component (e.g. happiness) The evidence base for the interrelationship of diabetes with mental illness has increased over the past 13 years. In 2001, Anderson *et al*[2] conducted a meta-analysis which indicated that the presence of diabetes doubled the risk of comorbid depression. A systematic review of more recent literature, published in 2012 by Roy and Lloyd,[3] found rates of depression in people with type 1 and type 2 diabetes three times and twice those in the general population, respectively. An understanding of the bi-directional pathophysiological relationship between diabetes and depression has been elucidated by Rustad *et al*,[4] but key posited aetiologies are activation of the innate immune system and increased activity of the hypothalamic – pituitary – axis, in addition to the psychological burden of the illness. The significance of a double diagnosis of diabetes with depression is illustrated by the associations with non-adherence to treatment, poor glycaemic control and increased numbers of complications (including diabetic retinopathy, nephropathy, neuropathy, macrovascular problems and sexual dysfunction).[5–7] In addition, Park *et al*[8] found a hazard ratio of 1.5 (1.35–1.66) for all-cause mortality in depressed patients with diabetes.Eating disorders are also associated with diabetes. In a meta-analysis published in 2005, Mannucci *et al*[9] found that bulimia nervosa is more prevalent in females with type 1 diabetes in comparison to the normal (ie non type 1) female population (1.73 vs. 0.69). Evidence for eating disorders in type 2 diabetes is less established, although this form of diabetes is associated with an increased prevalence of binge eating disorder.[10, 11] Although anorexia nervosa is not at increased prevalence in the diabetes population, patients with either anorexia or bulimia nervosa are significantly at risk of complications (retinopathy and nephropathy) and mortality if using insulin omission as a method of weight loss. In a meta-analysis by Smith *et al* in 2012, the odds ratio (OR) for anxiety disorder was 1.20 (1.10–1.31) and for anxiety symptoms 1.48 (1.02–1.93), whereas the pooled OR was 1.25 (1.10–1.39).[14] Anxiety disorders diagnosed by diagnostic interview have also been shown to be significantly associated with poor glycaemic control. However, different environmental factors (epigenetic factors) may activate common pathways that promote DM2 and depression in the end. One important factor is a low socioeconomic status that increases the odds for DM2 [9], but also appears to be a cause for depression [9]. The other common causes for DM2 and depression are

poor sleep, lack of physical exercises and diet. Taking into consideration these factors, a key candidate for a common pathway could be the activation and disturbance of the stress system. Chronic stress activates the hypothalamus – pituitary – adrenal axis (HPA-axis) and the sympathetic nervous system (SNS), increasing the production of cortisol in the adrenal cortex and the production of adrenalin and noradrenalin in the adrenal medulla [2]. Chronic hypercortisolemia and prolonged SNS activation promote insulin resistance, visceral obesity and lead to metabolic syndrome and DM2 [10]. On the other hand, chronic stress has behavioral consequences: noradrenalin, cortisol and other hormones activate the fear system determining anxiety, anorexia or hyperphagia; the same mediators cause tachyphylaxis of the reward system, which produces depression and cravings for food, other substances or stress [3,5]. Excess cortisol disturbs neurogenesis in the hippocampus [4,5], a region involved in depression as well as in DM2 [**8,9**].

Discussion

Pharmacotherapy

Selective serotonin re-uptake inhibitors (SSRIs) are the preferred antidepressants for older people with depression and diabetes due to their efficacy in treating depression and their lesser effect on blood glucose levels.[2,7] Treatment should be continued for at least six months or until complete remission of depression, and then stopped gradually. Long-term treatment is recommended in patients with recurrent depression. No single SSRI antidepressant has been found to be more effective than another and selection should be based on patient tolerability.[25] Those that have been found to be particularly well tolerated in older patients due to their lesser side effect profile are: citalopram, sertraline and escitalopram.[3,5] Tricyclic antidepressants are a less appropriate choice for older patients due to their anti-cholinergic side-effects—confusion, hyperglycaemia, orthostatic hypotension and cardiac arrhythmias.[2,6] In severe cases of depression, electroconvulsive therapy is another safe treatment option, even in frail older patients.[3,6]

Psychotherapy

In older people with comorbid diabetes and depression there are two main forms of psychotherapy that have found to be effective in reducing depressive symptoms—cognitive behavioural therapy (CBT) and interpersonal psychotherapy (IPT). CBT can be delivered individually by a trained medical professional and it aims to promote self-care and medication adherence through the reduction of the patient's own negative attitudes towards their health. IPT, on the other hand, focuses on helping patients to improve their interpersonal relationships; using this to help them overcome and deal with their depressive symptoms. A combination of pharmacological and psychological therapies is likely to be the most effective way of maintaining remission and/or reducing the number of relapses compared to either approach alone.[2,7]

Collaborative care

Collaborative care, which involves psychotherapy in conjunction with medical care can reduce depression and improve the management of self-care in patients with diabetes. In a cluster-randomised controlled trial of 387 patients with a record of diabetes associated with depressive symptoms, mean depressive scores were 0.23 points lower on the checklist-13 depression scale (95% CI -0.41 to -0.05) for patients on the collaborative care plan approach compared to conventional care after four months of follow-up. Patients receiving the collaborative care intervention also reported being able to manage their own health more effectively, rated their care as more patient-centred and were more satisfied overall.[2,8] Another study in Canada showed that collaborative care resulted in greater 12-month improvements in the patient health questionnaire (PHQ) score {7.3 (SD 5.6)} when compared with control subjects [5.2 (SD 5.7), P=0.015]. Recovery of depressive symptoms (PHQ reduced by 50%) was greater among intervention patients (61% versus 44%, P=0.03).[29,30]

Suggestions

These correlations suggested that stress (through the chronic impairment of HPA axis and SNS) and inflammation both promote depression and DM2, giving a feasible common link between them. Patients with DM1 need a different and more complicated management of their disease compared with DM2: they need a frequent monitoring of their glycemia, adjusting insulin doses accordingly, diet and physical activity. The age of onset of DM1 is much earlier than for DM2; the close chronological relation between DM1 and onset of depression is striking, diagnosis of DM1 and its treatment burden occur in a period when the individual has an increased vulnerability to depression [1,4]. Children and adolescents with diabetes have a two to three times greater prevalence of depression than youth without diabetes [2,9]. A poor glycemic control in pediatric DM1 is related with both depression and lower socioeconomic status and the chances of depression in these patients increase as glycemic control worsens [8]. There are not so many studies on DM1 and depression, but one important review on the subject evidences a biological link: increased circulating cytokines associated with autoimmune diabetes, the lack of insulin affecting neurogenesis and neurotransmitter metabolism, the effects of chronic hyperglycaemia and those of iatrogenic hypoglycaemia and a hyperactivity in the HPA axis [8]. Similarly to DM2, it seems that DM1 and depression have common pathophysiological pathways, contrary to what it was traditionally thought, that the burden of diabetes increases the prevalence of depression [8,9].

Diabetes risk in depressed patients

Several studies admitted that patients with depression have an increased risk of developing DM2 [3,4]. However, apart from the mechanisms explained earlier, other causes have been proposed. A recent study regarding the association between the antidepressant use and the glycemic control showed that in adults with diabetes, the use of multiple antidepressant subclasses increased significantly the levels of Hb A1C, suggesting that anti-depressive treatment may be a risk factor for suboptimal glycemic control [2]. Prior studies suggested that short-term anti-depressive treatment of nondiabetic depressed patients has a beneficial effect and improve insulin sensitivity together with improving depression, but on the long run, the effects might be opposite [3]. Noradrenergic antidepressants are an exception and may lead to impaired insulin sensitivity even in nondiabetic patients. Selective serotonin reuptake inhibitor treatment may improve the glycemic control in depressed DM2 patients and is the only class of antidepressants with confirmed favorable effects on glycemic control on both short and long term use.

Depression risk in diabetes patients

Diabetes produces structural changes in the brain: cerebral atrophy and lacunar infarcts, blood flow changes of both hypo- and hyperperfusion [5, 7]. Reductions in brain volumes restricted to the hippocampus were found in patients with diabetes, while an inverse relationship between glycemic control and hippocampal volume was present. HbA1C was described as the only significant predictor of hippocampal volume [**13**]. Similarly, depression is associated with neurodegenerative processes, especially at the level of the prefrontal cortex and hippocampus [**3,4**]. The enhancement of indoleamine 2, 3-dioxygenase enzyme activity with the kynurenine pathway activation and increased synthesis of interferon-stimulated gene products involved in the apoptotic process (Tumor necrosis factor-α-related apoptosis-inducing ligand, caspase-4, caspase-8, and death activating protein kinases) seems to be the principal mechanisms involved in the neurodegeneration-depression process induced by chronic inflammation [5,7].

Consequences of diabetes and depression patients

Due to the negative effects on health, the rise in complications, both diseases should be recognized in an individual and treated simultaneously, in order to reduce depression and better control the diabetes. However, depression remains under-diagnosed and untreated in diabetic patients [**10**].

Increased awareness for depression in diabetes might improve the outcomes and a first step would be a simple method for screening depression to be used on regular diabetic follow-ups. When depression is diagnosed in a diabetic patient, the common sense would be to treat both diseases at the same time. Petrak et al. recommended treating depression as a priority, as the response to medication is usually seen within 2-4 weeks for antidepressants, while the improvement in the glycemic control and levels of HbA1C needs several months to settle [**8**]. Moreover, Petrak et al. suggested that patients having a better mood might follow their diabetic treatment better [**7**]. They also proposed a model for treating depression and diabetes, stepped according to the degree of depression [**6**]. A new approach would be to identify the common triggers for diabetes and depression, and try to address them, but further studies should be done in this direction – controlling or preventing stress and inflammatory responses. Lifestyle changes such as increased physical activity or exercise, dietary modification, adequate relaxation/ sleep and social interaction, use of mindfulness-based meditation techniques, and the reduction of recreational substances such as nicotine, drugs, and alcohol already proved their benefits in the improvement of depression as well as diabetes [**5**].

Conclusion

Depression tends to co-exist with diabetes in older people and appears to have a bi-directional relationship, acting as a risk factor and as a consequence of diabetes. Early diagnosis and treatment of depression is vital in order to break this vicious cycle. Healthcare professionals involved in the care of older people with diabetes need to be aware of this relationship and of the benefits that a collaborative care approach can bring to that patient's physical and mental health.

For a healthy society, it is important to prevent, identify, and treat the health problems. However, the World Health Organization warns us that there is "a substantial gap between the burden caused by mental disorders and the resources available to prevent and treat them. It is estimated that four out of five people with serious mental disorders living in low and middle income countries do not receive the mental health services that they need"[7]. In diabetic patients, depression remains underdiagnosed and an important aspect for the diabetic specialist would be the awareness of this quite common co-morbidity. A multidisciplinary approach of the diabetic patient would help improve the outcomes of disease, decrease the number of DALYs and even mortality.

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