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Conference paper

THE COMORBIDITY OF DIABETES MELLITUS AND PSYCHIATRIC DISORDERS

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SUMMARY

Diabetes mellitus is a chronic disease affecting approximately 6% of the general population. Depression and schizophrenia are often comorbid with diabetes. There are two main ways to explain this phenomenon. Firstly, patients with diabetes mellitus have higher incidence of psychiatric disorders and secondly, antidepressants and antipsychotics may cause metabolic abnormalities. Antidepressants with noradrenergic activity have the highest potential to cause metabolic abnormalities. In schizophrenia, the risk is highest with clozapine and olanzapine pose the highest risk, moderate for risperidone and quetiapine, while ziprasidone and sertindole have not been associated with diabetes. American Diabetes Association and American Psychiatric Association suggested that optimal management of patients with schizophrenia should include baseline assessment on their weight, waist circumference, blood pressure, blood glucose level and lipidogram and family history on obesity, diabetes, dyslipidemia, hypertension and cardiovascular illness. During the first three months, weight gain should be monitored on monthly basis, while biochemical analysis should be performed after the first three months, and then once a year. In patients with significant weight gain, increase of blood glucose level or dyslipidemia, the first intervention should be switch to another antipsychotic. If necessary, a patient should be referred to an endocrinologist and advised on changing their life style.

Key words: *diabetes mellitus – depression - schizophrenia*

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DIABETES MELLITUS AND DEPRESSION

Diabetes mellitus is a chronic disease affecting 6.2% of the population of the Unites States or approximately 17 million people (ADA 2003). The prevalence of depression and anxiety among patients with diabetes is higher than in the general population (Anderson et al. 2001, Grigsby et al. 2002). Results from a meta-analysis based on 39 studies showed that 11% of patients with diabetes met the criteria for comorbid major depressive disorder (MDD), while 31% experienced different depressive symptoms (Anderson et al. 2001). The prevalence of depression was much higher in women than in men (Anderson et al. 2001). Today we are witnessing the growing evidence from clinical studies that suggest interaction between diabetes and depression. For example, a longitudinal study by Golden and colleagues showed the bidirectional adverse interaction between depression and diabetes. They followed-up patients with diabetes over a 3-year period and found that depressive symptoms at baseline were associated with an increased incidence of type 2 diabetes at follow-up, and an increased risk for developing depressive symptoms over his period was associated with treated type 2 diabetes. Conversely, baseline impaired fasting glucose and untreated type 2 diabetes were associated with reduced risk for depression (Golden et al. 2008). These patients have a poor therapeutic and diet compliance which contributes to glucose dysregulation and diabetic complications such as retinopathy, neuropathy, nephropathy, sexual dysfunction and macrovascular disease. A review of the literature performed by de Groot and colleagues reported that the number and the level of diabetic symptoms are in linear proportion to the number of depressive symptoms (De Groot et al. 2001).

Depression in diabetes contributes to neurohormonal and neurotransmitter changes that

might affect the metabolism of glucose. Activation of sympathoadrenal and hypothalamus-pituarity-adrenal axes leads to increased release of contraregular hormones and cortisol which strengthens the insulin resistance and decreases glucose uptake. Moreover, antidepressants may influence glucose homeostasis. Therefore, in a way, depression in patients with diabetes may "use" both here mentioned pathways to interfere with blood glucose metabolism.

THE USE OF ANTIDEPRESSANTS IN DIABETES MELLITUS

The patients with diabetes frequently use antidepressants. These psychotropic agents may impair glycemic control, paradoxically increasing the risk of both hyper- and hypoglycaemia (Goodnick et al. 1995). However, literature on this association is scarce and mainly originates from case-reports or short-term studies of small groups of patients. If antidepressants interfere with glucose homeostasis, then this means that they should be taken into account when assessing risk factors for microvascular complications.

The largest epidemiological study on association between antidepressants and glucose homeostasis was performed on the database from the World health Organisation's center for adverse drug interactions in Uppsala, Sweden (Derijks et al. 2008). Antidepressants were classified in four categories, based on their pharmacological binding properties of six common transporter and receptor sites: 5-HT (serotonin) reuptake transporter, norepinephrine reuptake transporter, M3 receptor, H1 receptor, alfa 1 receptor and 5-HT 2c receptor. Results of this study indicate that the use of antidepressants from cluster 1 (sertraline, fluvoxamine, paroxetine, venlafaxine, fluoxetine, citalopram and clomipramine), cluster 2 (amitriptyline, doxepin and imipramine), cluster 3 (maprotiline, nortriptylin, mianserin and mirtazapine) antidepressants was associated with hyperglycaemia. It was most pronounced for antidepressants with affinity for the 5-HT 2c receptor, H1 receptor and norepinephrine reuptake transporter, whereas the association with hypoglycaemia was most pronounced for antidepressants with affinity for serotonin reuptake transporter (sertraline, fluoxamine, paroxetine, venlafaxine, fluoxetine, citalopram and clomipramine). Only trazodone was not associated with hyperglycaemia. The report also stated that hyperglycaemia usually appears one year after the start of using antidepressants. It was found that the use of benzodiazepines do not contribute to either hyper- or hypoglycaemia.

How to explain the influence of antidepressants' pharmacodynamic characteristics on glucose homeostasis? It has been suggested that inhibition of the NE reuptake transporter increases synaptic NE disposal directly by stimulating glycogenolysis and gluconeogenesis, resulting in raised blood glucose levels (Larsen et al. 2003). Moreover, the central blockade of the H1 receptor and 5-HT2C receptor stimulates energy intake by increasing appetite with a resultant positive energy balance, thus causing a weight gain. Weight gain may lead to insulin resistance and increased risk of hyperglycaemia. Antidepressants that have affinity for M3 and alfa-1 adrenergic receptors cause side-effects such as dry mouth, leading to drinking large quantities of (high-calorie) drinks. Peripheral blockade of M3 receptors in beta cells results in suppression of insulin secretion and raises leptin levels (Gilon & Henquin 2001).

It has been showed that tricyclics lead to up to 25% of weight gain (Derijks et al. 2008). Moreover, they might cause arrhythmias in patients with coronary disease, a condition that may already exist in diabetes. Interestingly, a study on bupropion showed that it does not lead to the weight gain, hyper- or hypoglycaemia or sexual dysfunctions. Furthermore, bupropion was proven beneficial considering neuropathic pain.

All this strongly indicates that patients with depression should be monitored for development of diabetes.

DIABETES MELLITUS AND SCHIZOPHRENIA

Metabolic abnormalities in patients with schizophrenia have been described even before the antipsychotic era. Thonnard-Neumann in 1945 reported a high incidence of diabetes in schizophrenia (4.2%) (Thonnard-Neumann 1945). However, after introducing antipsychotics in the treatment of these patients, the incidence of diabetes mellitus has increased four times (Lindenmayer et al. 2003).

The second generation antipsychotics have different potentials for causing metabolic syndrome (Medved et al. 2008, Newcomer 2005). The pathophysiological mechanism through which

they cause the weight gain is almost completely unknown. Weight gain found in antipsychotic-treated patients has frequently been attributed to an antihistaminic activity since many of these drugs are potent antagonists at histamine H1 receptors (Goudie et al. 2003). Another possible receptor related mechanism is antagonism at 5-HT2C receptors since it has been suggested that genetic variants for 5-HT2C receptors might be associated with weight gain (Kuzman et al. 2008).

The treatment with clozapine induces a significant weight gain which may be up to 12 kg after the first year (Newcomer 2005). If there is a predisposition for developing diabetes, in half of these patients symptoms will be noticeable after the first three months of treatment. However, if the treatment is stopped in this early phase, glycemia can be normalized.

During the first year of olanzapine treatment, weight gain can be increased from 6 to 12 kg. This has been recorded in 12% patients who were using olanzapine, but also in 12% patients on haloperidol treatment. Diabetes might be more often during the olanzapine treatment and it usually occurs within the first six months (Newcomer 2005). Risperidon treatment is more likely to worsen glycemia, than cause diabetes mellitus. Weight gain in the first year of treatment is usually around 4 kg. This kind of moderate weight gain occurs with another quetiapine as well. The latter might worsen both glycemia and existing diabetes mellitus (Newcomer 2005). Number of papers exploring metabolic effects of ziprasidone and sertindole is limited. However, some of them analyzed blood glucose levels during short and long-term treatment with these drugs and found no positive associations (Newcomer 2005).

There is no doubt that second generation antipsychotics differ in their metabolic effects. Being aware of this risk, American Diabetes Association and American Psychiatric Association have given several suggestions for optimal management of patients with schizophrenia (ADA 2004). Before starting an antipsychotic treatment, each patient should be assessed on their weight, waist circumference, blood pressure, blood glucose level and lipidogram and family history on obesity, diabetes, dyslipidemia, hypertension and cardiovascular illness. Moreover, during the first three months the weight gain should be monitored on monthly basis, but later on this should be obtained every three months. Biochemical analysis should be performed after the first three months, and then once a year. In patients with significant weight gain, increase of blood glucose level or dyslipidemia, the first intervention should be switch to another antipsychotic. If necessary, a patient should be referred to an endocrinologist and advised on changing their life style.

CONCLUSION

Depression and schizophrenia are often in comorbidity with diabetes. There are two main ways to explain this phenomenon. Firstly, patients with diabetes mellitus have higher incidence of psychiatric disorders and secondly, antidepressants and antipsychotics may cause metabolic abnormalities. The latter is less known when it comes to antidepressants. Those with noradrenergic activity have highest potential to cause metabolic abnormalities. The second generation antipsychotics have different potentials for causing metabolic syndrome – it is highest for clozapine and olanzapine, moderate for risperidone and quetiapine, while ziprasidone and sertindole have not been associated with diabetes.

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