Chapter 2

Depression and Glucose Metabolism (Diabetes Mellitus)

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Additional information is available at the end of the chapter

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1. Introduction

The occurrence of depression with diabetes mellitus has been intensively researched for a number of decades now. It was Thomas Willis (1621 – 1675) who introduced the phrase diabetes mellitus (before then called Willis's disease) and associated it with what had already been known for decades – that patients with diabetes have glycosuria (sweet urine). He also noted that "sadness or excessive melancholy, similar to fits or other depressions and breakdowns of the animal spirit, give rise to or instigate this diseased condition (diabetes)". His follower J. C. Brunner (1653 – 1727) is known because of several studies with the pancreas. The large number of epidemiological studies documents the increasing interest in this problem.

Evidence of a bidirectional relationship between depression and diabetes has also been recently documented in large prospective studies. Comorbid depression is associated with an increased risk of poor glycaemic control, diabetes complications have also been found to be risk factors for subsequent development of depressive episodes

The importance of the research on depression and diabetes has been emphasized in recent years because of the modern-day epidemic of obesity and diabetes that is emerging in both high and low income countries. The direct medical and indirect personal and familial costs of this epidemic are starting to get international attention.

2. The epidemiology, risk factors and clinical features of depression and diabetes

2.1. The epidemiology of depression and diabetes

From the meta-analysis Petrak (2009) it follows that 9% of patients with DM have at the same time some form of affective spectrum disorder. If we also take the subclinical form of

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depression into consideration, then the number of patients with depression increases to 26%. diabetes mellitus (DM) doubles the risk of the occurrence of depression independently of the study design, the sample of patients and the methods of evaluating depression. Contemporary knowledge related to type 2 diabetes points out the worsening of depressive displays in individuals treated (but not those untreated) for type 2 diabetes. These findings could reflect stress or an association with management of diabetes and a large number of diabetic complications and co-morbidities in adults undergoing diabetic treatment in comparison with the untreated. Depressive displays occur in approximately 43 million people with diabetes, keeping in mind the overall prevalence of diabetes in the year 2000 (Wild et al., 2004). From the results of the study Sequenced Treatment Alternatives to relieve Depression (STAR-D), the largest study relating to depression carried out in the USA, the most common occurrence of the co-morbidity of depression and diabetes occurs in the elderly and in minorities (Hispanics and black African-Americans).

Clinically significant depressive symptoms occur in approximately 31% of patients with diabetes, more often in women (in a ratio of 1:1.8); the picture of severe depression (according to strict diagnostic criteria) occurs in 11% of patients with diabetes. With diabetes the risk of a depressive disorder arising is approximately 2 times higher than in the common population (OR = 2.0, 95% CI 1.7 – 2.2), independently of the type of diabetes or on the method of evaluating depressive symptoms (Katon et al., 2004). Approximately 30% of those ill with diabetes have a depressive disorder (28% of women with diabetes and 18% of men with diabetes – the preponderance of women with depression is similar as in the non-diabetic population). The risk of depression arising in patients with diabetes, whether insulin dependent or not, is higher by 15 – 20%. Depressive displays in the common population occur approximately in the age range from 27 to 35 years, but in patients with diabetes this already begins around the 22nd year. The relationship between demographic parameters, lifestyle and behaviour, anti-depressive treatment, BMI, diagnosis of diabetes, its duration and treatment and depressive symptoms were tested in 70,000 patients. Diabetes was identified in 21.7% and had a link with depressive symptoms (AOR, 1.24; 95% CI, 1.14-1.34). Demographic parameters, lifestyle and behaviour, BMI and anti-depressive treatment were more strongly linked with serious depression than a diagnosis of diabetes (Osborn et al., 2011). In a report, Gendelman et al. (2009) showed that prevalence rates were even higher if reports of elevated symptoms were combined with the use of antidepressant medication. This suggests that the available evidence should be considered with particular methodological differences in case ascertainment kept in mind.

In people diagnosed with type 1 or type 2 diabetes, depression increased the risk of lingering hyperglycemia, microvascular and macrovascular complications and overall mortality (Barnard et al., 2006; Ismail et al., 2007). It is interesting that complications and mortality in connection with diabetes are also observed even with less serious depressive displays. Older patients appear as a high-risk group, which is also reported by the result of a 7-year longitudinal study, which shows a five-fold growth in mortality without any significant differences of the impact of the seriousness between moderate and heavy displays of depression (Black et al., 2003).

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2.2. Clinical symptoms

Depression is usually defined by the number of symptoms present, usually within the past two weeks. In order to diagnose major depression using DSM-IV or ICD-10 criteria, a clinical interview is conducted and a number of symptoms have to be present (table 1). Most epidemiological research on the prevalence of depression uses self-report instruments (for example Patient Health Questionnaire-9- PHQ-9) for detecting depression or depressive symptomatology, and most instruments that are used measure symptoms that approximate clinical levels of disorder (table 1). The specific symptoms for depression and diabetes are little difference as only for depression alone (table 2), (Lloyd et al., 2010).

DSM-IV criteria(at least five symptoms present nearly every day for 2 wk and causing significant distress or functional impairment
Depressed mood
Markedly diminished interest or pleasure in all or almost all activities
Significant weight loss/gain or decreased/increased appetite
Insomnia or hypersomnia
Psychomotor agitation or retardation
Fatigue or loss energy
Feelings of worthlessness/guilt
Diminished ability to concentrate/make decisions
Recurrent thoughts of death or suicide
Symptoms of depression measured using self-report instruments
Feeling sad/depressed mood
Inability to sleep
Early waking
Lack of interest/enjoyment
Tiredness/lack of energy
Loss of apetite
Feelings of guilt/worthlessness
Recurrent thoughts about death/suicide
DSM-IV criteria extracted from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, Copyright 2000. American Psychiatric Association

Table 1. Symptoms listed in the DSM-IV criteria for major depressive disorder and symptoms of depression measured using self-report instruments

Fatigue
Loss of weight, poor apetite
Psychomotor retardation
Insomnia
Pain
Gastrointestinal problems

Table 2. Common symptoms for depression and diabetes (free by Montano, 2004)

Salomé et al. (2011) evaluated the seriousness of depressive symptoms in patients with a diabetic ulcer of the shin area and determined that in 41 patients out of 50 depressive symptoms were present and in 32 of them found displays of moderate-severe depression with reduced self-evaluation, anorexia, disfigured body-image and a worse libido.

2.3. Risk factors associated with depression and with diabetes

Quality of life is worsened in regard to psychological, physical and social functioning (e.g. ability to work). Complications caused by diabetes are considered as the most serious, and treatment of diabetes is significantly more complicated and worse if depression is present at the same time. In a recent study patients with depression and diabetes were physically less active, smoked more, had fewer healthy dietary habits and were less inclined to diabetic treatment (Gonzales et al., 2008). Depression during diabetes, despite everything, often goes undiagnosed and untreated. In an American study, in which more than 9000 patients with diabetes took part – 51% of which had identified depression – only 43%of them used one or more antidepressants and only 7% took part in four or more psychotherapeutic meetings during a 12-month period (Katon et al., 2004).

2.3.1. Risk factors for depression in patients with diabetes

Through a number of epidemiological studies, aside from the prevalence of depression in patients with diabetes, it was also possible to identify a number of risk factors which are more or less associated with depression. These are the risk factors – demographic (female sex, younger age, lower education, poverty), clinical (seriousness of diabetes, duration of illness, complication of diabetes, high values of glycosylated HbA1c) and behavioral (smoking, obesity) (table 3). Their importance in relation to depression, however, is continuously being verified (Egede & Zheng, 2003). In connection with the presented results it was shown that the most significant association exists between depression, obesity and smoking. Obesity positively correlates with the growing prevalence of type 2 diabetes. It has been shown that smoking associates with increased insulin resistance and represents a risk factor for macrovascular complications in patients with diabetes mellitus. But we know that depression also increases the risk of smoking, which has been documented in several longitudinal studies in which it was confirmed that there are notably more smokers in the group of patients with depression than in the control group (Katon et al., 2004). In the study of Fisher et

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al., 2011, in a group of more than 480 patients it was compared whether patients educated about regular observation of glucose monitoring, treatment and regimen also have better results in association with HbA1c and with glucose, which also confirmed at the same time the fact that improved depressive symptoms were not dependent on improved metabolic parameters or glucose. In a pilot randomized controlled study integrated treatment of type 2 diabetes and depression was more successful versus common treatment in improved HbA1c results and depression in older, perhaps 60 Afro-Americans. It follows from this that integrated treatment could be available and effective in real conditions taking into consideration certain limitations.

Although depression is not a part of normal ageing, prevalence rates of severe depressive episodes/major depressive disorder are higher amongst certain groups of older people, in particular, individuals with a co-morbid medical illness (Kovacs et al., 1997). However, to date, little epidemiological data has been available with which to examine rates of depression in older people with diabetes (Collins et al., 2009). To further complicate the picture, several studies have reported that depressive symptoms are more common in younger individuals, in both type 1 and type 2 diabetes (Fisher et al., 2008). Collins et al. (2009) also reported lower rates of depression in older individuals with type 1 diabetes, suggesting that age might have a protective effect. In a cohort of patients aged 70 -79 years followed for about six years, those with diabetes had an increased level of depression with attenuated after adjustment for diabetes-related co-morbidities, although this still represented a significantly increased risk compared to controls. In this study, HbA1c was a predictor of recurrent depression (Maraldi et al., 2007). The specific factors associated with recurrence of depression remain unclear. Gender has not been found to be associated with the number of episodes or the severity of recurrence or chronicity of depression, and the association between stress and depressive episodes appears to be less pronounced over time (Stroud et al., 2008). There is some evidence of a link between depression and the occurrence of diabetic complications and poorer glycaemic control. Painful neuropathy may be another trigger for depression. Diabetes can cause small vessel pathology in the brain that leads to subcortical encephalopathy, not unlike that seen in vascular depression. This may lead to both cognitive impairment and depressed mood (Baldwin, 2010).

Non-diabetic specific risk factors	Diabetes specific risk factors
Female gender	Manifestation of diabetes
Lack of social support	Occurrence of late complications
Low socioeconomic status	Persistent poor glycaemic control
Younger age; older age and physical health problems	Need for insulin therapy in type 2 diabetes
Occurrence of critical life events	Hypoglycaemia problems

Table 3. Risk factors for depression in diabetes

2.3.2. Depression - a risk factor for diabetes?

The link between depression and diabetes was made as early as the seventeenth century, when the famous English physician T. Willis (1621 -1675) noted that diabetes often appeared among patients who had experienced significant life stresses, sadness or long sorrow (Rubin & Peyrot, 2002). Whether depression increases the risk of type 1 diabetes is currently unknown. However, recent studies have suggested that people with depression are more vulnerable to the development of type 2 diabetes (Mezuk et al., 2008), thereby confirming Willis´ hypothesis. It is important to recognize that depression is not only associated with an increased risk for the development of type 2 diabetes, but is also an established risk factor for cardiovascular disease and several features of the metabolic syndrome, particularly hypertension, abdominal obesity and low HDL cholesterol (Vogelzangs et al., 2008). Several hypotheses have been put forward regarding the pathophysiological mechanisms that could explain the increased risk of type 2 diabetes in depressed subjects. For example, increased activity of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system might play a role; there are examined elsewhere in this volume (Lloyd et al., 2010).

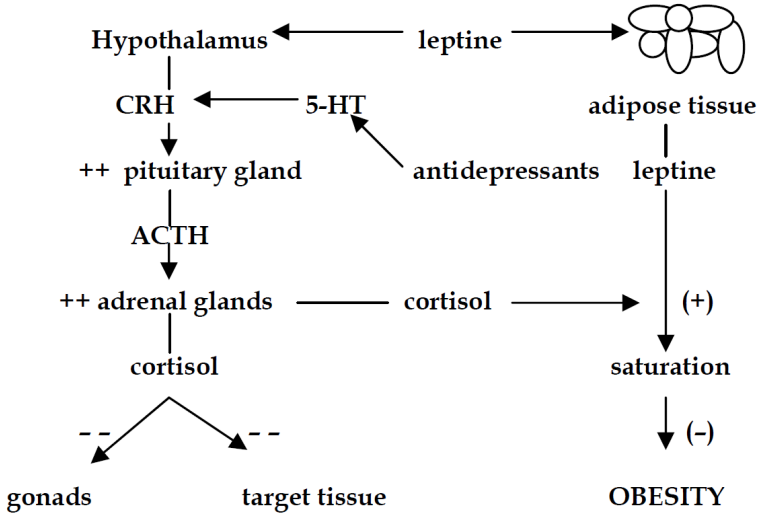

Figure 1. Pathophysiological abnormalities in HPA axis hyperactivity, which in response to elevated levels of CRH, ACTH production and secretion is increased, it stimulates the adrenal cortex to secrete cortisol, and cortisol concentrations inhibit secretion only other hormons, but it is also a signal for the (no) supersaturation

Depression may also increase the risk for type 2 diabetes via behavioural mechanisms. It is well known that the most important risk factor for type 2 diabetes is obesity, and that physical inactivity further increases this risk (Manson et al., 1991). Finally, the evidence to date suggests that depression may indeed increase the risk of developing type 2 diabetes. However, the mechanisms via which this may occur still require investigation. The link between depression and the development of type 1 diabetes remains unclear.

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Anxiety is common in diabetes populations and is frequently associated with depression (Katon et al., 2007). A recent systematic review found that around 14% of people with diabetes have generalized anxiety disorder, but subclinical anxiety and symptoms were more common and affected 27% and 40% respectively (Grigsby et al., 2002). The presence of comorbid depression or anxiety has been associated with increased somatic symptoms of disease, which has important implications for treatment (Katon et al., 2007). Diabetic-specific psychological problems, such as fear of self-injecting insulin or self-testing blood glucose (which may or may not be full-blown needle phobia) and fear of complications, are all associated with anxiety and depression (Mollema et al., 2001). Fears regarding hypoglycaemia and psychological insulin resistance are also common, but their relationship with depression is less clear (Petrak et al., 2007).

3. The common pathophysiological mechanisms of depression and diabetes

Many etiological factors play a role in the pathophysiology of depression. Among them are the depletion of serotonin and other monoamines in areas of the brain which are connected with the managing of emotions, sleep and the taste for food. Another factor is the chronic activation of the hypothalamic-pituitary-adrenal axis with subsequent increased production of a corticotropic hormone (CRF). Depression can also originate as a consequence of insufficient plasticity of neurons as a response to different burdens, e. g. chronic stress (Wayne et al., 2004). Genetic influences also apply with depression and metabolic syndrome as well as unfavorable factors from the external environment. Among these, for example, are disorders of equilibrium in the autonomic nervous system with an inclination toward more rapid heart activity, reduced variability of heart frequency and increased level of catecholamines in peripheral blood. According to one of the theories of development of metabolic syndrome, an improper daily regimen (especially low physical activity during the day and intake of food in the late night hours) leads to disorders of equilibrium in the autonomic nervous system, with a preponderance of the sympathetic system in the area of the thorax and in the skeletal muscles, with a subsequent increase in blood pressure, insulin resistance in the muscles and, in contrast, to increased activity of the parasympathetic system in the stomach area, which leads to hyper secretion of insulin and the accumulation of visceral fatty tissues, which can lead further to increased risk of origin of metabolic syndrome, type 2 diabetes, dyslipidemia, hypertension and visceral obesity (Zeman & Jirák, 2008). In patients with a metabolic syndrome, as well as in patients with depression, oxidation stress is shown to be increased with subsequent destruction of neurons in the hippocampus, whose smaller volume we find also in patients with depression (Sapolsky, 2000). An association between symptoms of depression and metabolic syndrome was shown in a study tracking pairs of male twins (McCaffery et al., 2003). In the population tracked in NHANES III (Third National Health and Nutrition Examination Survey) the prevalence of metabolic syndrome among women with depression was double that of women without depression (Kinder et al. 2004).

In the study of Poulsen et al. (2001) 303 older twins were tracked, and significantly higher glucose intolerance was found along with obesity and low HDL-cholesterol among monozygotic versus dizygotic twins, which shows the genetic impact on the development of these phenotypes. They observed a higher genetic influence on glucose intolerance and systolic pressure and a lower genetic influence on low HDL-cholesterol and diastolic pressure in male twins versus female twins. Pouwer & Snoek (2001) observed in more than 1500 patients for the first time significant associations between depression and HbA1c in women with type 2 diabetes. The values of estrogen and the daily regimen could play a significant role in these associations.

With type 1 diabetes the development of an endocrine disorder precedes the first episode of depression. Anderson et al. (2001) in a meta-analysis of 27 clinical studies (a total of 5370 patients) found a statistically significant relationship between depression and diabetic complications (diabetic retinopathia, nephropathia, neuropathia, macrovascular complications and sexual dysfunction) ($p<0,0001$, $z=5,94$). Pro-inflammatory cytokines also show a clear association of both disorders (Tůma, 2005). Cytokines, interleukins and TNF alpha are increased with both disorders and can associate with some depressive displays (Tůma & Hubeňák, 2007).

From a biological point of view depression and diabetes overlap on a number of levels. Among endocrine and neurotransmitter changes are a lower concentration of catecholamines, primary serotonin (Kuzmiaková et al., 1998), stimulation of the production of glucocorticoides, growth hormone and glucagon, which work counter-regulationally against the hypoglycaemic effect of insulin. Increased levels of cortisol are observed equally in patients with diabetes and depression, similarly glucose intolerance disorder and the origin of insulin resistance (Lustman et al., 2000). In many patients with depression, glucose intolerance linked with hyperinsulinemia and insulin resistance develops (Okamura et al., 2000). According to Zimmet et al. (1991) metabolic changes with depression evoke the destabilization of a preexisting metabolic imbalance in individuals with a risk of developing type 2 diabetes. An abnormality of serotonergic neurotransmission localized in pre-synaptic and post-synaptic areas plays an important (thought not the only one) role in the pathogenesis of depression (the so-called serotonin hypothesis of depression). Substances which have a serotonergic effect (serotonin precursors, fenfluramine, SSRIs) conditioned a clinically significant improvement in depressive symptoms. In this association the results of human studies are known: 6 weeks of issuing certain SSRIs (paroxetine, fluoxetine and sertraline) to patients with both depression and diabetes led to a drop in weight, a fall in triglycerides and cholesterol in the blood, a drop in HbA1c and improved compliance (Talbot & Nouwen, 2000; Rubin & Peyrot, 2002).The positive effect of serotonergic substances on depressive mood as well as on a number of disease parameters of diabetes points to a possible etiological relationship.

The conjoined occurrence of depression and diabetes is not a chance phenomenon which evokes consideration about their possible relationship. Scientific authorities present several hypothetical interpretations: 1. Depression arises as a primary consequence of neurochemical – biochemical changes which associate with diabetes; 2. Depression is a consequence of

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psychosocial factors which associate with the disease or its treatment; 3. Depression is an independent risk factor for the origin of diabetes.

3.1. Depression with diabetes: result of biochemical factors

Current knowledge supports the presence of a relationship between depression, depressive symptoms and possible growth of the risk for the development of type 2 diabetes. In contrast, type 1 diabetes leads to the later development of depression. Kovacs et al. (1997) determined that the first year from the origin of type 1 diabetes was the most risky for the origin of depression. Lustman et al. (1988) observed that the values of glycaemia in individuals with DM improve simultaneously with improvements in remission of depression. In double-blind randomized studies the hypoglycemic effect of antidepressant treatment was confirmed. The origin of depression is a later result of type 2 diabetes, but depression can increase the risk of its development. Results are similar for type 1 diabetes. Control of DM improves simultaneously with the remission of depression, but also without a clear explanation of the mechanism for this assumption.

Depressive phases are more common in individuals with diabetes (Fava & McGratth, 2003, Berken et al., 1984) and have longer duration (Bogner et al., 2007). In a 5-year monitoring Lustman et al. (1988) found that in 22 of 28 patients with diabetes the occurrence of some kind of depressive disorder was found, while depression was not manifested in only 2 of 20 individuals with diabetes. No differences between type 1 diabetes and type 2 diabetes in this regard were observed. According to all, a longer duration of the depressive phase is more associated with type 1 diabetes, although the differences between type 1 diabetes and type 2 diabetes were not observed in relation to inducing remission after the first depressive episode. Peyrot & Rubbin (1989) also observed a longer duration of depressive symptoms in 245 individuals with type 1 diabetes and type 2 diabetes during a 6-month study, and 73% were identified as having depressive symptoms. On the other hand Lustman et al. (1988) did not find any differences in relation to the course and length of duration of depression between both types of diabetes. They found a higher risk for longer duration of depression only in patients with type 2 diabetes who were not treated with insulin. Wellset al. (1993) did not find any significant differences between the course and the duration of the depressive phase in patients with or without a case history of type 1 diabetes or hypertension. It's possible to say that depression and depressive symptoms have a higher recurrence and duration in patients with diabetes.

3.2. Depression with diabetes: the result of psychosocial factors in relation to DM

With an increasing number of complications in diabetes, the probability of depressive symptoms is also higher (Peyrot & Rubbin, 1997). In a study carried out by Davis et al. (1988) it was shown that the social consequence of existence with DM (e.g. on traveling, active leisure time, relationships) is connected with an increased risk of mortality, although no causal association was demonstrated. A significant relationship was shown between overall and specific social support and depressive symptoms with diabetes (Littelfield et al., 1990).

The presence of positive family history of depression occurs more often in patients with depression in comparison with individuals with diabetes without depression *(27 vs. 3%).* Depression in mothers was found as a specific risk factor for the origin of depression in their children type 1 diabetes at a low age with (Downey & Coyne, 1990). Kovacs et al. (1997) did not find any significant differences in relation to sex and the origin of depression, but young women with diabetes had a 9-times higher risk for the recurrence of depression compared with young men with diabetes.

3.3. Depression with diabetes: a risk factor for the origin and worsening course of the result of DM

Brande & Egede (2008) followed the long-term impact of depression on the control of glycaemia in more than 11,000 people with type 2 diabetes with an average age of 66 years with relatively well controlled diabetes (HbA1c = 7.3%), while depression was identified in 6% of the them. A significant relationship was consequently found between depression and control of glycaemia by measuring the HbA1c values, which were persistently higher (on average by 0.13, 95%CI, 0.03-0.22, p=0.008) with each measurement at 3 months during a 4-year study of patients with diabetes and concurrent depression.

Akbaralya et al. (in Barclay, 2008) monitored more than 5000 patients age 41-61 years with depressive symptoms from 1991 to 1993 and then again 6 years later by using the 30-item subscale General Health Questionnaire; metabolic syndrome was determined on the basis of criteria from the National Cholesterol Education Program. They found that the presence of metabolic syndrome was linked with the increased risk of possible depressive symptoms (OR, 1.38, 95%CI, 1.02-1.96). Central obesity, increased triglycerides and HDL (but not other components of metabolic syndrome) were predictors of manifestation of depressive symptoms. These findings are thus consistent with the hypothesis that depressive symptoms could be a consequence as well as the reason for metabolic syndrome.

In a study by Backes et al. (2007) of more than 11,000 women with gestation diabetes, depression was retrospectively found in up to 15.2% of women in the period of the last 6 months of gravidity up to a year after giving birth, versus only 8.5% of women without diabetes. These findings support the existence of a relationship between the two diseases – diabetes and depression – namely, that both are frequent during gravidity and after birth, and it is relevant, that post-partum depression is treatable but often goes unrecognized. It is known that women with diabetes (keeping in mind the (non)use of insulin) have during gravidity approximately two-times the risk of depression arising versus women without diabetes (OR 1.85 (95%CI)).This is similar with the occurrence of depression in women with diabetes in the post-partum period (OR 1.69 (95%CI)).

We can say that particularly late rising of depression could be the result of micro or macrovascular changes, and the origin of depression often precedes predominately type 2 diabetes by a number of years. The newest findings support the consideration regarding the reciprocal interaction among depression and diabetes, because depressive symp-

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toms could increase the risk of origin of type 2 diabetes and the diabetic complications associated with it.

4. The treatment of comorbidity depression and diabetes

Referring to some evidence that depression has an adverse psychological impact than the "well being" as a diabetes, we can say that the treatment of depression in diabetes can directly improve the psychological as well as medical parameters. Improving depressive symptoms and induce remission, the main objectives related to psychological parameters. The treatment of diabetes involves improving glycaemic control and reducing the risk for the occurrence of either short or long-term complications of diabetes and premature mortality.

Based on mainly anecdotal evidence and a handful of randomized controlled trials, monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) are considered to have a hyperglycaemic effect, which is in keeping with their noradrenergic and(or appetitogenic effects, while selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and sertraline, are more likely to be anorectic, improve insulin sensitivity and reduce glucose levels, probably because the central serotoninergic pathways are important in the regulation of food intake and food preferences (Ismail, 2010).

The common mechanisms etiopathogenetic diabetes and depression to some extent highlights the fact that intensive treatment of depression leads to improved disease manifestations diabetes (eg. decrease glucose) and vice versa, effective treatment for diabetes determines retreat depressive symptoms. Selective serotonin reuptake inhibitors (SSRIs - sertraline, paroxetine, fluoxetine, fluvoxamine, citalopram) due to a beneficial effect on a number of pathological parameters diabetes - decrease glucose levels, weight loss, decreased serum cholesterol and triglycerides - and given the antidepressant effect comparable with TCAs and MAOIs are in the treatment of depression in diabetes first-line drugs.

The use of TCAs in patients with diabetes is mainly limited to their cardiotoxicity. TCAs may increase serum concentrations of glucose and increased craving for sweets. Considerably better is to use antidepressants - SSRIs or SNRIs later, while in patients with diabetes on this treatment was demonstrated the hypoglycaemic effect. From the observation of about 2% of 40 000 patients (Derijks, Heerdink et al., 2008) that the use of antidepressants is associated with an increased risk of hypoglycaemia, but if they are used in patients with diabetes for more than 3 years, the risk of hypoglycaemia is almost three times, it is important to monitor the symptoms of hypoglycaemia and blood glucose. The use of antidepressants was associated with hyperglycaemia (ROR 1.52 (95% CI: 1.20 to 1.93) and hypoglycaemia (ROR 1.884 (95% CI: 1.4 to 2.42). Connection with hyperglycaemia was risky for antidepressants with affinity for serotonergic reuptake transporter (Derijks, Meyboom et al., 2008), the published data show that in terms of impact on the metabolic parameters between SSRIs differences. Paroxetine abdominal obesity leads to more frequent administration than other SSRI antidepressants (Reader, Bjelland et al., 2006).

The other antidepressants should mention bupropion, venlafaxine and nefazodone, which are favorable for their pharmacological properties in terms of comorbid conditions also convenient - to have a neutral effect on body weight and glucose metabolism. Among the nine antidepressants especially in pursuit of their effects on the gastrointestinal, central nervous system and sexual life come out with the best profile of bupropion and soon fluvoxamine (Dewan, Ananad, 1999). Weight gain is a common adverse side effect of acute and long-term treatment with antidepressants. TCAs and MAOIs are probably more common cause of weight gain than SSRIs and newer antidepressants, except mirtazapine, which is in this respect between SSRIs and TCAs. Also, paroxetine causes higher weight gain compared to other SSRIs preparation for longer-term therapy and bupropion or nefazodone cause less weight gain over the longer-term treatment (Fava, 2000).

According to several studies being less effective in patients with depression and diabetes mirtazapine, in view of a higher risk of gaining weight. The case study series of patients receiving doses of mirtazapine and 15 mg were observed gain weight during 5 months 16 kg, with obesity and by all important risk factor for glucose dysregulation (Fisfalen, Hsiung et al., 2003).

TCAs (Carney, 1998) and MAOIs should be administered only as a last option (Nickelson, Box, 1999) for the treatment of depression in patients with diabetes. TCAs are associated with weight gain (Nakra, Rutland et al., 1977, Berken, Weinsthein et al., 1984) and taste the sweet and carbohydrate (Paykel, Mueller et al., 1973, Harris, Young et al., 1984), which can be problematic for patients with increased consumption of calories (Goodnick, Henry et al., 1995, Carney 1998). TCAs can worsen hyperglycaemia and glycaemic control during longer treatment (Nickelson, Box 1999, Carney, 1998) and their anticholinergic, cardiovascular and musculoskeletal adverse side effects may worsen symptoms in relation to diabetes (constipation associated with diabetic gastroparesis) (Carney, 1998, Lane, 1993). MAOIs can aggravate hypoglycaemia and delay the restoration of normal glucose concentrations when taken with insulin or sulfonylurea (Cooper & Ashrocft., 1966). In addition, treatment with MAOIs is associated with weight gain and the need for strict dietary restrictions, which certainly complicates the diet such as in patients with diabetes (Carney, 1998).

In 80 patients with depression Kopf, Westpal et al. (2004) observed values of lipoproteins, insulin sensitivity and cortisol in saliva before and after 35 days of treatment with amitriptyline or paroxetine. The main findings were that patients with depression and weight in the standard have insulin resistance corresponding to the HPA axis, overweight patients had total and LDL cholesterol out of standard antidepressant treatment led to an improvement in lipoprotein and cholesterol levels, changes in triglyceride metabolism affected by the treatment and weight three important factors control lipid parameters depending on the presence of the metabolic state: weight, hypercorticolism and insulin resistance. This study first examined the detailed lipid profile in patients with diabetes and depression.

Bupropion contrast in patients with diabetes suited to the fact that side does not sexual reactions and decreases body weight in obese patients had more than placebo (Jain, Kaplan et al. 2002). Lustman, Williams et al. (2007) in a group of 90 patients with type 2 diabetes and depression and taking over 16 months bupropion found decrease BMI, total fat, and HbA1c (p

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≤ 0.01 for all parameters). Reduction of BMI and severity of depression independently predicted lower HbA1c after treatment of the acute phase of depression, while only reducing the severity of depression (p≤0.001) affected on HbA1c with the passage of time. Sawhney et al. (2007) observed the good effect of TCAs administered in low doses in depressed patients suffering from chronic vomiting, did not respond to prokinetic therapy. Antidepressant duloxetine is recommended for the treatment of diabetic neuropathy (Švestka, 2005).

Data from a large study of over 4800 patients with diabetes enrolled in a health maintenance organization (HMO) found that approximately 70% of those with comorbid depression (based on scoring ≥ 10 on the PHQ-9) had experienced affective symptoms for two years or longer(Katon et al., 2004). Patients with diabetes tend to be older, and recent primary care data have shown that the average length of an episode of depression in older primary care patients is approximately 18 months, whereas in mixed-aged populations the mean length of an episode is approximately 4 - 6 months (Vuorilehto et al, 2009).

The tendency for depressive symptoms to be chronic in patients with diabetes is also shown by recent data from a five-year follow-up study of approximately 2700 patients with diabetes. Approximately 82% of patients who met DSM-IV criteria for major depression at five-year follow-up had minor or major depression at baseline (Katon et al., 2009). Finally, the recurrent course of depression was shown in a longitudinal study, which found that 79% of patients with diabetes who had major depression relapsed over a five-year follow-up period, with a mean of four episodes per patients (Katon, von Korff et al. 2004).

Several systematic reviews have been completed exploring effect sizes of psychotherapeutic as well as pharmacological treatments of patients with comorbid depression and diabetes (Petrak 2009; van der Feltz-Cornelis et al. 2010). Efficacy trials generally evaluate intensive treatment of a carefully selected patient group by highly trained staff. Patients with clinically significant psychiatric comorbidities, such as panic disorder of medical comorbidities, are often excluded from these trials. An important question for researchers and clinicians is whether evidence-based pharmacotherapies and psychotherapies that have proven effective in populations of patients with depression with minimal medical illness would be as efficacious in patients with diabetes.

A systematic review of efficacy trials performed in 2009 yielded 11 randomized clinical trials, five on psychotherapeutic interventions and six on pharmacological treatments. Most trials were small, with only one recruiting more than 100 patients and the others including 60 or fewer patients. Most trials were completed on patients with type 2 diabetes with serious depressive symptoms or major depressive disorder, and effect sizes were specified for depressive symptom severity as well as for glycaemic control.

4.1. Pharmacological studies

As shown Table 4, the pharmacotherapeutic interventions had moderate effects on depressive symptoms, and small effects on glycaemic control. The effect on depressive outcomes was very similar, but the effect on glycaemic control was smaller than that of the psychotherapeutic studies, many of which had explicit interventions aimed at improving glycaemic

control. The pharmacologic trials were also small, mostly under 100 patients enrolled. The small numbers of patients enrolled in both psychotherapy and pharmacologic efficacy trials limits the generalizability of the findings.

Study	N (completers), diabetes type, mean age	Intervention conditions, follow-up (FU)	Outcome assessment (depression, diabetes	Effect size
Lustman et al., 1997b	N=28, type 2-50% 49-49,2ys	nortriptyline vs placebo,FU- 9 ws	Depression: BDI (p=0.03), DM: HbA1c, n.s., no outcome reported	Depression: Δ -0.868, DM: Δ 0
Lustman et al., 2000	N=54,type 2- 56% 45-47ys	fluoxetine vs placebo, FU- 8 ws	Depression: HAMD (p<0.04), DM: HbA1c (p=0.13, n.s.)	Depression: Δ -0.573, DM: Δ 0.419
Paile-Hyvärinen et al., 2003	N=13, type 2-100%, 61-62ys	paroxetine vs placebo, FU- 4ws	Depression: MADRS (p=0.25,ns.), DM:GHbA1c (p=0,08, n.s.)	Depression: Δ -0.68, DM: Δ 1.07
Xue et al., 2004	N=48, type 2-85%, 21-65ys	paroxetine vs placebo	Depression: HAMD-17 (p<0.01), DM: HbA1c (p=0.25, ns.)	Depression: Δ -0.78, DM: Δ 0.34
Gülseren et al., 2005	N=23, type 2-100%, 58ys	fluoxetine vs paroxetine	Both groups improved –HDRS (p=0.003, s.f.), HbA1c – n.s. both	No significant difference between the two conditions
Lustman et al., 2006	N=152, type 2-65%, N/A	sertraline (flexible doses) vs placebo	n. s. between groups	
Paile-Hyvärinen et al., 2007	N=49, type 2-100%, 59ys	paroxetine vs placebo	Depression: HADS (p=0.45, n.s.), DM: HbA1c (p=0.7, n.s.)	Depression: Δ -0.26, DM: Δ 0.14

Table 4. Overview of the most important trials with antidepressant treatment under: BDI-Beck Depression Inventory, HAMD-Hamilton Asberg Montgomery Depression Scale, ns- no significant

Due to the lack of data in our conditions in relation to the comorbidity of depression and disorders related to glucose and lipid metabolism and at the same time of the presented high prevalence independently existing of these disorders, we decided to work-up a pilot study on the impact of antidepressants primarily on glucose and lipid metabolism in patients with depression. We found changes in lipid – HDL, LDL, triglycerides, glucose, HbA1c and BMI parameters in patients with depression during antidepressive treatment without diabetes. The assess changes of treatment with two groups of antidepressants – SSRI´s and SNRI´s in flexible doses. It was prospective study of outpatients and in-patient's file hospitalized at the 1st Dept. of Psychiatry University Hospital and University of P. J. Šafárik, Košice (2010 – 2011). Hypothesis was that SSRI´s and SNRI´s do not deteriorate theese metabolic parameters, HbA1c will be decrease, HDL will be increase and compare the differences between groups. After six months 74 patients completed follow-up (65% women with MDD, DSM-IV). We used scales: MADRS, Beck Anxiety Inventory, Zung Depression Scale, statistical program IBM SPSS (version 20. 0). The consent to research granted Ethics committee of School of Medicine of University of P. J. Šafárik in Košice.

Scale	Groups SSRI´s/SNRI´s	N	Mean
Beck Anxiety Inventory - baseline	SSRI/SNRI	38/36	23,29/ 24,14
Beck Anxiety Inventory - final	SSRI/SNRI	38/36	15,18*/16,50*
Zung Depression Inventory- SDS-baseline	SSRI/ SNRI	38/36	67,26/ 66,83
Zung Depression inventory – final	SSRI/SNRI	38/36	49,39*/ 52,44*
MADRS baseline	SSRI/SNRI	38/36	37,21/ 36,89
MADRS final	SSRI/SNRI	38/ 36	16,95*/ 17,89*
BMI baseline	SSRI/SNRI	38/ 36	25,54/ 26,76
BMI final	SSRI/SNRI	38/ 36	26,22/ 27,1

* the mean difference is significant at the,05 level

Table 5. Score in some scales

In both groups dominated by women (three times) – 27/9 (SSRI´s group); 28/10 (SNRI´s group) and on the other hand, less presumptive SNRI medication type were deployed globally in patients with a higher mean age (SNRI´s = 52,7/28-73/; SSRI´s = 41,7 /20-64/). There was an improvement in the scales in both groups: MADRS, Beck Anxiety Inventory, Zung Depression Scale (s. f., table 5). Similar, the results in study Songar et al. (1993) indicate that some relations exist between anxiety and the worsening of metabolic control (mainly in HbA1c). The HDL cholesterol values have improved after six months antidepressive treatment in both groups (1.31 vs 1.4 /SNRI´s/ 1.38 vs 1.5 /SSRI´s/), which corresponds to the data Svačina et al. (2006) and Hardy et al. (2007). These findings are particularly important because from this one that is most closely connected with cardiovascular risks play mainly LDL and HDL components. The triglycerides values have improved statistical significant after six months SSRI treatment vs SNRI treatment (Mann-Whitney U=496,000 Asymp. Sig. (2-tailed)=0.042 = p≤0.05), which correlates with the monitoring Flechtner-Mors (2008) also in SSRI preparations, which is important from the point of view that higher levels of triglycerides are considered primary in the aetiology of disorders that are related to oxidative stress and increased levels of LDL. As we expected, HbA1c improved in the SNRI´s (5.55 vs 5.24, n. s.) and SSRI´s group (5.23 vs 5.18, n. s.) which corresponds with the results of several pharmacological studies (Lustman et al., 1997b, 2006; Gülseren et al., 2005). On the other hand can not draw definite causal conclusions regarding the limitations on file size and especially the length of the monitoring itself. We confirmed the hypothesis that SSRI´s and SNRI´s do not deteriorate metabolic parameters – HDL, LDL, triglycerides, HbA1c, BMI, even HbA1c will be decrease (n. s.), HDL will be increase (n. s.), triglycerides were im-

proved in SSRI´s group (s. f.), but in addition the differences between groups we didn´t find similar as Gülseren et al. (2005).

4.2. Psychotherapeutic interventions

The effect size of the psychotherapeutic interventions were moderate to large for improvement of depressive symptoms, and moderate to large for improvement of glycaemic control. Three of the five psychotherapy trials compared an evidence-based depression psychotherapy and diabetes education to diabetes education alone. Therefore, it is unclear whether improvements in glycaemic control were due to the beneficial effect of the depression-focused psychotherapy or the combination of both depression therapy and diabetes education.

Study	N (completers), diabetes type, mean age	Intervention conditions, follow-up (FU)	Outcome assessment (depression, diabetes	Effect size
Lustman et al., 1998	N=41, type 2-100%, 53-56,4ys	CBT+ diabetes education vs diabetes education alone, FU- 11ws	Depression: BDI ($p<0.001$)in CBT group, DM: HbA1c in CBT group ($p<0.03$)	Depression: Δ -1.112, DM: Δ -0.704
Huang et al., 2002	N=59,type 2-100%, N/A	Antidiabetics + diabetic education + psychological +relaxation vs antidiabetics only, FU- 3mo	Depression: SDS ($p<0.05$), DM: HbA1c ($p<0.05$)	Depression: Δ -0.521, DM: Δ -0.521
Li et al., 2003	N=120, N/A, 50,5-52,3ys	Antidiabetics + diabetic education + psychological treatment vs antidiabetics only, FU- 4ws	Depression: SDS ($p<0.01$), DM: FBG($p<0.05$)	Depression: Δ -0.478, DM: Δ -0.362
Lu et al., 2005	N=60, type 2-100%, 65ys	Diabetes and CVA education + electromyographic treatment + psychological treatment vs usual care, FU- 4ws	Depression: HAMD-17 ($p<0.01$), DM: FBG ($p<0.05$)	Depression: Δ -0.688, DM: Δ -0.517
Simson et al., 2008	N=30, type 2-80%, 60,5ys	Individual supportive psychotherapy vs usual care, FU- discharge (3-20ws)	Depression: HADS ($p=0.018$), DM: PAID mean ($p=0.008$)	Depression: Δ -0.918, DM: Δ -1.043

Table 6. Overview of the most important trials with psychotherapeutic interventions under table: CBT - Cognitive-behavioral therapy, BDI- Beck Depression Inventory

5. Discussion

The probability of the occurrence of depression in patients with diabetes is higher, because depression in patients with diabetes is often unrecognized and therefore also untreatable and the association between depression and glycaemic control is small in cross-sectional

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studies and almost disappears in most of the handful of prospective studies (Lustman et al., 2000a). It is interesting that complications associated with diabetes and mortality are already observed with less serious depressive displays (Black et al., 2003). The comorbidity of depression and obesity worsens the course of diabetes, and furthermore, depression worsens the adherence to a diabetic diet and treatment and predicts low compliance in diabetological programs (McKellar et al., 2004). From the results of several studies (Katon et al., 2004) it follows that the relationship between depression and obesity runs in both directions. From several studies it follows that the course of depression in individuals with diabetes is not causally dependent on diabetes. Depression in individuals with diabetes represents a more complex phenomena following from interactions between genetic, biological and psychosocial factors, which could significantly influence the recurrence and longer duration of depression. In the case of type 2 diabetes it is unlikely that the first episode of depression would be as a consequence of diabetes. The development of depression often precedes the manifestation of type 2 diabetes by many years. Depressive symptoms could increase the risk of development of type 2 diabetes and its complications. It is shown that depression ranks among the most important risk factors for the development of type 2 diabetes and is not merely a secondary emotional response to a chronic and complicated bodily illness, but that an independent risk factor for the origin of type 2 diabetes is involved (Lustman et al., 2006). Despite all, we today still do not have sufficient proof about confirmation of the hypothesis relating to the occurrence of depression as a consequence of biochemical changes following directly from diabetes or its treatment or from psychological factors. But these factors can influence the increasing of insulin resistance and the reduction of glucose as a result of changes during depression.

6. Conclusion

The occurrence of depression with bodily diseases represents an unfavorable prognostic indicator. It worsens the therapeutic response and the course of the bodily disease, makes regaining health and rehabilitation more difficult, prolongs hospitalization, weakens the ability of the ill individual to care for his or her own needs, represents a risk of suicidal behaviour and as a final consequence increases the costs for treatment and demands on the health care system. Its timely recognition and adequate treatment are exceptionally important. Depression in patients with diabetes mellitus represents a complex phenomenon which is the result of complicated interactions between biological, genetic and psycho-social factors. There has been the hypothetical assumption that depression originates as a direct consequence of neurochemical changes with diabetes mellitus. More proof, however, supports the so-called inverse hypothesis, according to which depression represents a risk for the origin of type 2 diabetes mellitus as well as its complications.

The fact that intensive treatment of depression leads to improved disease displays of diabetes (e.g. a drop in glucose levels) and the reverse, that effective treatment of diabetes conditions the regression of depressive symptoms, points to common etiopathogenic mechanisms to a certain measure point. There is high prevalence of depressive and anxiety disorders in

patients with diabetes, and these disorders adversely affect diabetes self-care, disease control and clinical outcomes. Complications of diabetes resulting in functional impairment can also precipitate a depressive episode. Efficacy data have demonstrated that both evidence-based psychotherapies and pharmacotherapies are effective treatment modalities for depression in patients not only with diabetes. The choice of antidepressant medication for the patient with diabetes and depression remains one in which the clinician needs to individualize therapy to the specific needs of the patient. There are strong data showing that the specific initial choice of antidepressant, with the aforementioned exceptions, may be less crucial than the duration of appropriate therapy, the coordination of psychiatric and medical care, and the input of the clinician in modification of dose or choice of medication dependent upon the response to therapy. The patient´s tolerance to a specific antidepressant is not predictable, in part due to genetic variations in the metabolism of specific medications, as well as other less well studied aspects of biologic variability.

To what measure treatment of comorbid depression reduces morbidity and mortality of diabetes mellitus and to what measure treatment influences the unfavorable consequences of depression still remain an open question.

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