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Diabetes, Diet and Mental illness

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Abstract: *A review of data on interactions between Mental illness and Diabetes taking into account the multifactorial causation, sustanence of illness and outcome variables together makes absolutely confusing reading. An attempt has been made to mention only that material where the controversies regarding the stated facts are relatively less.*

Keywords: *Schizophrenia, Depression, Bipolar Disorder, Fasting glucose*
Abbreviations*: **DM** – Diabetes Mellitus, **APA** – Antipsychotic agents.*

I. Introduction

The close association between Diabetes mellitus and Schizophrenia and other mental disorders have been known for a long time. Maudsley in 1879 noted that "Diabetes is a disease which often shows itself in families in which insanity prevails". However it wasn't until relatively recently that the issue was investigated with renewed vigour following the detection of an increased incidence of Type II DM in patients receiving atypical antipsychotics. However it may be noted that similar concerns were and are often raised during the beginning of many forms of treatment modalities, e.g Lithium as well as typical APA.

Prior to the onset of treatment with APAs, studies on the relationship between DM and Psychotic illnesses reported a 3 – 4 times higher risk of DM in patients with psychiatric illness. Subsequent analysis of these studies reveals a lot of methodological limitations in these studies. Between 1919 to 1946, several studies were conducted to study the correlation between these two illnesses. These studies assessed blood glucose in a variety of ways such as Fasting Blood Glucose estimation; Oral Glucose tolerance tests; or intravenous glucose tolerance tests. Test subjects included patients with psychotic as well as mood disorders. A 2 – 4 times increased risk of DM was reported from these studies. However these studies were plagued by notable methodological limitations. For example, a few of these studies included healthy control subjects but were not matched for anthropometric or demographic variables. No data regarding independent risk factors for DM such as BMI, familial loading, ethnicity etc was collected. Obesity was not an exclusion criteria in any save one study. Subjects in a majority of studies were acutely ill and elevation of glucose secondary to the stress of acute illness was not taken into account. Furthermore diagnostic nomenclature confusions prevailed so much so that some studies refrained from diagnostic classification and simply divided the study subjects into inpatients categories only The limitations notwithstanding, elevation of blood glucose was consistently reportedly from patients diagnosed as acutely catatonic and melancholic, and in a majority of studies with bipolar patients (Keck et al, 2007).

Post 1949, several studies began controlling for the confounding factor of the previous studies, and this along with the emerging diagnostic and nomenclature consensus yielded more reliable data.

Schizophrenia and Diabetes

Tabata et al. (1987) examined the prevalence of diabetes in 248 patients with schizophrenia and 239 sedentary office workers and reported a significantly higher rate of diabetes in the schizophrenia group (9%) compared with the sedentary group (5%). Both groups might have been expected to have higher rates of diabetes compared with the general population. Unfortunately, the Tabata et al. study did not include data regarding other risk factors for diabetes or examined the potential influence of antipsychotic or other pharmacological treatments.

Ryan et al. (2003) conducted the only controlled, prospective study of glucose tolerance in treatment-naive patients with schizophrenia reported to date. In this cross-sectional study, fasting plasma concentrations of glucose, insulin, lipids, and cortisol were measured in 26 patients with DSM-IV diagnosis of schizophrenia who had never been treated with antipsychotic agents and 26 age- and sex-matched healthy control subjects. Subjects were also matched on several lifestyle variables (e.g., habitual amount of exercise and diet) and anthropometric measures. The results of this study indicated significantly higher fasting glucose, insulin, and cortisol levels in the Schizophrenic group. As much as 15% of the Schizophrenia group satisfied ADA criteria for impaired glucose tolerance as opposed to none in the control group. This provides some of the clearest evidence that

schizophrenia itself may be an independent risk factor for impaired glucose tolerance, which is a known risk factor for the development of type 2 diabetes.

A number of surveys examined the prevalence rate of diabetes in large cohorts of patients with schizophrenia (McKee et al. 1986; Mukherjee et al. 1996; Schwarz and Munoz 1968; Thonnard-Neumann 1968). Schwarz and Munoz (1968) reported that only 0.6% of 859 patients developed new-onset diabetes following chlorpromazine initiation. Risk factors for developing diabetes were age, body weight, and ethnicity.

Thonnard-Neumann (1968) compared the prevalence of diabetes in 450 female patients hospitalized in 1954 with a second group of 528women with schizophrenia hospitalized in 1966 in order to examine the potential impact of treatment with typical antipsychotics on diabetes. The prevalence rate of diabetes increased from 4% in 1954 to 17% in 1966, and risk factors associated with diabetes in the 1966 cohort included age, obesity, and treatment with a typical antipsychotic.

McKee et al. (1986) reported that 2.5% of 1,960 patients with schizophrenia had diabetes—a rate within the range of the general population in the mid-1960s, but at the upper end. Although most patients developed diabetes after treatment with typical antipsychotics, the drugs' potential role as a risk factor could not be determined without a control group.

Finally, Mukherjee et al. (1996) specifically examined the role of antipsychotic treatment in the development of diabetes and found a higher prevalence of diabetes in patients not receiving treatment with typical antipsychotics compared with those who were. Age was the only risk factor identified with developing diabetes in this study. Interestingly, in a separate study, Mukherjee et al. (1989) also found an increased prevalence of T2DM in the first-degree relatives of patients with schizophrenia compared with the general population. Overall, the results of these surveys are inconclusive regarding the magnitude of risk of diabetes posed by psychotic disorders alone, apart from treatment.

Bipolar Disorder and Diabetes

Studies relating to the relationship between Bipolar disorders and DM are inconclusive as the effect of the use of APA was not taken into account in most studies. Lilliker (1980) and Cassidy et al (1999), reported the prevalence DM at 10% and 9.9% respectively. This figure is nearly three times higher than the general population. Regenold et al (2002) assessed the medical records of 243 in-patients, aged 50–74 years, with a diagnosis of major depression, bipolar I disorder, schizoaffective disorder, schizophrenia or dementia, and compared their rates of diabetes with rates in the US general population matched for age, gender and race. The prevalence of diabetes was found to be significantly higher than national norms in patients with bipolar I disorder (26%) and schizoaffective disorder (50%), and was independent of psychotropic drug use. This study, and the work of others (Lilliker, 1980; Cassidy et al, 1999), indicates that the prevalence of diabetes in patients with bipolar disorder may be two to three times higher than that found in the general population. In contrast, a 2 year follow-up study by Vestergaard and Schou (1987) in a sample of 226 patients failed to detect any higher prevalence of Diabetes in Bipolar disorder patients. Thus, as with surveys of the prevalence of diabetes in patients with schizophrenia, the results of these studies in patients with bipolar disorder are mixed and inconclusive.

Major Depressive Disorder and Depressive symptoms and Diabetes

In 1684 the British physician Thomas Willis observed that diabetes resulted from "sadness or long sorrow and other depressions and disorders". Epidemiological studies indicate that individuals with T2DM have elevated rates of depression compared with the general population and with patients with most other chronic medical illnesses (Musselman et al. 2003). In other words, individuals with T2DM are at increased risk of developing major depressive disorder. This observation has been borne out in most, but not all, recent epidemiological studies. A number of studies also strongly suggest that the converse is true—namely, that patients with major depressive disorder are at increased risk for developing T2DM (Arroyo et al. 2004; L.C. Brown et al. 2005; Carnethon et al. 2003; Eaton et al. 1996; Kawakami et al. 1999; Kessing et al. 2004; Palinkas et al. 2004;)

Majority of studies support the notion that depressive symptoms bear a strong association with the risk of developing diabetes, although they do not distinguish between patients with Major depression, Bipolar or psychotic disorders, given that all these conditions are associated with a higher lifetime prevalence of depressive symptoms.

One of the first studies that correlated T2DM to Major depression was a community based survey by Eaton et al (1996). The authors, using the Diagnostic Interview Schedule to ascertain a diagnosis of Major Depression found a two-fold higher risk of lifetime prevalence of DM at 13 years follow up. Similar findings were reported by Kawakami et al (1999) in a eight year follow up study done on employed Japanese men, reporting moderate to severe baseline depressive symptoms on the Zung Self Rating Depression Scale. The risk of developing DM was higher in individuals reporting more severe depressive symptoms and is not so well demarcated in individuals with mild or even moderate symptomatology. This was borne out by Cornethon et al

(2003) in follow up and analysis of data from participants of First National Health and Nutrition Examination Survey (NHANES I) conducted between 1971 – 1975, who were followed as part of the NHANES I Epidemiological Follow- up Survey (NHEFS).

Palinkas et al. (2004) in a 8 year follow-up study study using Beck Depression Inventory, on a sample of 971 individuals found that elevated scores on the Beck Depression Inventory at baseline predicted development of T2DM. Importantly this study indicated that the risk of developing T2DM was independent of sex, age, exercise, and BMI when assessed by the presence of baseline depressive symptoms.

Diabetes Mellitus has been linked to significantly higher rates of a rapid-cycling bipolar disorder, chronic course of illness and greater rates of disability when compared to patients of Bipolar Disorder without co-occurring diabetes (Ruzickova et al., 2003). Other studies have suggested that patients with major depressive disorder and co-occurring diabetes have a higher recurrence rate of depression and longer duration of depressive episodes compared with patients without co-occurring diabetes (Talbot and Nouwen 2000).

Although, in summery these epidemiological data suggest a strong relationship between depressive symptoms and the risk for T2DM, they are limited by heavy reliance on self-report instruments and lack of clinician-administered diagnostic instruments and hence are a measure of the relationship of the illness to depressive symptoms only and not a diagnosis of depression per se, given that patients with major depressive disorder, bipolar disorder, and psychotic disorders, are all of likely to share a higher lifetime prevalence of depressive symptoms.

The possible links

The available evidence indicates a reasonably strong relationship between DM and psychotic and mood disorders. Keck et al postulates several possible mechanisms for this strong association. First, both DM and Psychotic/mood disorders may be the result of the influence of a third independent factor such as a shared or genetically inherited vulnerability to stress diathesis. Second, Blood glucose elevation may be the result of metabolic changes due to the primary psychiatric illness itself. Third, behavioural and lifestyle associations of psychiatric illnesses act as a risk factor for the development of DM. Psychiatric illnesses may behave as a additive risk for the genesis of Diabetes in combination with independent DM vulnerability factors. Lastly, elevated blood glucose may result from the adverse iatrogenic metabolic changes.

Heredity

Bushe and Holt (2004) reported tentative overlap in gene regions associated with susceptibility to Mental illness and T2DM. This overlap may provide evidence of a common genetic factor increasing susceptibility to both illnesses. Pooling data from family studies in patients with Schizophrenia, Bushe and Holt reported a 50% prevalence of DM in the families with a history of Schizophrenia compared to only 5% in families of control group subjects – indicating the possibility of a common genetic loading. Data relating to DM and Mood disorder in terms of common genetic loading are however lacking.

Several studies have related the poor fetal growth (low birth weight) to impaired glucose tolerance. The published literature shows that, generally, people having a low birth weight have an adverse profile of later glucose and insulin metabolism. This is related to higher insulin resistance, but the relationship to insulin secretion in adults is less clear. (Newsome et al, 2003). The works of Jones (1997) and Smith et al (2001) throw light on the association of poor fetal growth to psychotic and mood disturbances (Jones, 1997; Smith et al, 2001).

Neurobiological factors

Psychosis, mania, melancholic depression, and mixed states all activate the sympathetic nervous system and the hypothalamic-pituitary- adrenal (HPA) stress hormone axis, resulting in elevation of catecholamines and hypercortisolemia (Dinan 2004; McElroy et al. 1992; Ryan et al. 2003; Shiloah et al. 2003; Talbot and Nouwen 2000).

These effects have implications on glucose metabolism that are not trivial. Glucocorticoids interfere with insulin function in a number of ways. Cortisol decreases glucose utilization in muscle, reduces the binding affinity of insulin receptors, and antagonizes the insulin's inhibiting effects on hepatic glucose release (Meyer and Badenhoop 2003). Hypercortisolemia also suppresses growth hormone and gonadal hormone axes (Bjorntorp and Rosmond 2000), and decreased levels of insulin-like growth factor and testosterone in men are associated with obesity and insulin resistance (Marin et al. 1993; Rosmond and Bjorntorp 1998; Seidell et al. 1990).

Cortisol elevations may also be expected to interfere with leptin-mediated satiety signaling (Rosmond and Bjorntorp 1998; Zahrzewska et al. 1997).

25% of patients receiving long-term glucocorticoid therapy develop impaired glucose metabolism (Dinan 2004). Repeated endogenous hypercortisolemia from recurrent and/or protracted psychotic and mood episodes may have a similar effect.

Data from various sources on the use of atypical antipsychotics indicate that some drugs in this class notably Olanzepine and Clozapine are associated with a significant risk for weight gain and disordered glucose metabolism. Both Olanzepine and Clozapine are believed to induce Insuline resistance, although the mechanism remains unclear. A range of evidence suggests clozapine and olanzapine have a higher propensity to cause these changes compared with quetiapine, risperidone, ziprasidone, and aripiprazole (American Diabetes Association et al. 2004). Iterestingly, short term or long-term weight gain due to ziprasidone and aripiprazole treatment bear little or no evidence of adverse effects on metabolic outcomes in terms of glycemic control.(American Diabetes Association et al. 2004; Casey et al. 2004; Haupt and Newcomer 2001b; Yang and McNeely 2002). The diabetogenic potential of antipsychotic medications referred to in literature is open to review, and as Bushe and Leonard (2004) comments may be "incorrect" or exaggerated.

In general, an increase in insulin resistance is an expected outcome of increase in adiposity (Ebenbichler et al. 2003; Eder et al. 2001)- leading to compensatory insulin secretion in persons with pancreatic β-cell reserve and to hyperglycemia in individuals with relative β-cell failure. The caveat that increasing adiposity is associated with increasing insulin resistance is based on the association between these variables consistently observed in many studies in humans and other mammals.

But notably, weight gain is not an absolute prerequisite for the development of insulin resistance, impaired glucose tolerance, or T2DM during antipsychotic treatment. Additional research is needed to examine the pharmacological factors that contribute to these adverse effects in vulnerable individuals.

Behavioral Factors

The lifetime prevalence rates of alcohol and substance use disorders, smoking, and obesity—all of which are risk factors for T2DM—are all significantly elevated in patients with psychotic and mood disorders (McElroy et al. 2004; Meyer and Nasrallah, 2003).

Binge eating disorder, a common cause of obesity, is highly comorbid with mood disorders (McElroy et al. 2005). Fagiolini et al. (2002) reported that in patients with Bipolar disorders, the number of previous depressive episodes bear a direct relationship to the prevalence of obesity. These findings seem to suggest that repetitive/sustained changes – both neurobiological (e.g., HPA hyperactivity) and/or behavioural (anergia, hyperphagia, reduced physical activity) associated with depressive episodes and/or negative symptoms may contribute to overweight and obesity and indirectly to the risk of T2DM.

Thakore et al. (2002) found that central adiposity—strongly correlated with risk for the metabolic syndrome, of which impaired glucose tolerance is one component— was evident in drug-naïve patients with schizophrenia compared with age and sex-matched healthy control subjects, again suggesting that risk factors for T2DM were apparent at least in patients with Schizophrenia even prior to the onset of illness and treatment.

Of late, among behavioural factors, the role of diet in the precipitation or increasing vulnerability to illness has gathered a lot of interest. Although not all of what is mentioned in the following lines may be relevant to diabetes per se, it certainly is relevant to mental illness and the dietary restriction in the management of diabetes needs to be borne in mind. It is in this context that some elaboration on diet and mental disorders appears to be in order.

Diet, diabetes and schizophrenia:

The influence of diet and other lifestyle factors in patients with Schizophrenia as risk factor for the development of DM has been evaluated by Peet (2004). People with schizophrenia consume a type of diet that is known to promote diseases of the metabolic syndrome (i.e. high in saturated fat, low in fibre, with a high glycaemic load). This is an inference from two ecological studies of diet in relation to schizophrenia. These have investigated the association between schizophrenia outcomes and diet, using data from World Health Organization (WHO) reports (World Health Organization, 1979; Jablensky et al, 1992) and national dietary data published annually by the Food and Agriculture Organization of the United Nations (Food and Agriculture Organization, 2003). The first of these studies (Christensen & Christensen, 1988) showed that a poor outcome of schizophrenia was associated with a high ratio of saturated fatty acid to polyunsaturated fatty acids (PUFA) in the national diet. A subsequent ecological analysis, which looked at all individual foodstuffs rather than specific nutrients, found that refined sugar consumption was a robust and independent predictor of poor outcome of schizophrenia (Peet, 2004). Although associations of this nature cannot be assumed to be causal, these findings nevertheless allow the hypothesis that a diet high in saturated fat, low in polyunsaturated fat and high in sugar is detrimental to the outcome of schizophrenia.

McCreadie et al (1998) found that patients with schizophrenia consumed substantially less dietary fibre and antioxidant vitamins (C and E) than a matched control group. The patients also consumed fewer portions of fruit and vegetables. Brown et al (1999) found that patients with schizophrenia consumed significantly less fibre and more fat than a matched control group. Ryan et al (2003) reported that drug naive patients with first-episode schizophrenia consumed substantially more saturated fat than carefully matched, healthy comparison individuals.

Stokes, 2003 found an empirical increase in the amount of sugar consumption in patients with long drawn out Schizophrenia although it is not clear whether the increased sugar intake found in this study was related to treatment resistance or to clozapine treatment.

There is substantial evidence that schizophrenia is associated with abnormalities of phospholipid metabolism and cell membrane PUFA levels (Peet, 2002). Two studies have shown that levels of PUFA in the normal daily diet correlate with the severity of schizophrenia symptoms. Mellor et al (1996) showed significant negative correlations between dietary intake of omega-3 fatty acids and symptoms of schizophrenia and of tardive dyskinesia. In a separate study, Stokes (2003) found that total PUFA in the normal daily diet correlated negatively with severity of schizophrenia symptoms and that this was independent of the dietary intake of other nutrients.

Depression and diet

Barring a certain amount of associative data linking omega3 fatty acid and tryptophan containing food to mood disorders, the evidence on diet and Mood disorders in largely anecdotal only.

is increasing evidence that diet may play a causative role in some cases of depression. Omega 3 fatty acid deficiencies has been linked to depression, anxiety, aggressiveness and even insomnia. In some studies it was observed that patients suffering from depression have lower levels of omega-3 fatty acids in their cell membranes. Research has shown that patients with bipolar depression who increased their consumption of foods containing omega 3 showed remarkable improvement in mood, which supports the role of omega 3 fatty acids in the treatment of depression.

Amino acids are also not produced within the human body. Tryptophan is an amino acid which is converted into serotonin in the body and is a natural relaxant. This can be used in the treatment of depression to assist with a good night's sleep, treat migraines and even boost the immune system. Deficiency in the essential amino acid Lysine may cause fatigue, irritability and a lack of concentration. Good sources of lysine include meat, chicken, and eggs and legumes.

Carbohydrate in the diet is one of the factors that modulate the release of serotonine in the brain Depression seems to stem from reduced serotonin in the brain. It has been suggested that an increase in complex carbohydrates that are absorbed slowly such as brown rice, whole grain wheat, bran, fruits and vegetables may be important in the treatment of depression, as this will help ensure a steady supply of serotonin. Depression can also be intensified or even caused by deficiencies of folate, B12 and vitamin C and magnesium. In a major study, a direct link between low folate levels and neuropsychiatry disorder was established. It has also been suggested that an increased intake of folate can help reduce the high levels of homocysteine often present during depression. Foods rich in folate

Other lifestyle issues

A sedentary lifestyle and the number of pack years of cigarettes smoked are independent predictors of the central metabolic syndrome (Jakes et al, 2003; Rimm et al, 1995). These are also lifestyle patterns in people with mental illness, and not in all cases can such behaviour be attributed to the sedative effect of medications.

Effects of antipsychotic medication on food intake

The mechanism by which antipsychotic medications increase food intake is probably related to their effect upon dopamine and serotonin receptors (Kaur & Kulkarni, 2003). There is no good evidence to suggest that antipsychotic medications have a primary effect on resistance to leptin mediated satiety signalling. Neither do they have a primary effect on pancreatic ß-cell function (Sowell et al, 2002). Thus, it appears that glucose dysregulation following antipsychotic treatment might be due to an increased dietary intake of unhealthy food, rather than a direct effect of the antipsychotic drug on glucose regulation.

Diet, diabetes and schizophrenia - a HYPOTHESIS: BDNF and Glycemic control

The most parsimonious explanation for the increased prevalence of diabetes in patients with schizophrenia is that a genetic predisposition to insulin resistance is compounded by an unhealthy lifestyle and the effect of antipsychotic medication on food intake. The genetic influence is suggested by the increased frequency of diabetes in the relatives of patients with schizophrenia.

However, evidence of a significant association between diet and the outcome and severity of schizophrenia raises the possibility that both diabetes and schizophrenia share a common pathology which is influenced by lifestyle factors such as diet and exercise.

One physiological factor that could partly explain the link between diabetes, schizophrenia and diet is brain derived neurotrophic factor (BDNF). This protein is required to maintain dendrites, and its expression in the prefrontal cortex shows a significant increase during young adulthood at a time when the frontal cortex matures both structurally and functionally. The peak requirement for BDNF to preserve dendritic outgrowth thus occurs at the time of life when schizophrenia has its peak age of onset. Apart from influences on neuronal

architecture, BDNF is also a neurotransmitter modulator and facilitates long-term potentiation in the hippocampus. It has recently been shown that BDNF expression is reduced in the prefrontal cortex of patients with schizophrenia, and it is being suggested that this might be a central component of the disease process. Polymorphism of the BDNF gene has been associated with the susceptibility to schizophrenia.

It is known that brain expression of BDNF is reduced by a high-fat, high-sugar diet and increased by exercise. In BDNF knockout mice, neuronal soma size and dendrite density in the prefrontal cortex are reduced (Gorski et al, 2003), and the same structural abnormalities have been reported in the brains of people with schizophrenia (Broadbelt et al, 2002). Brain-derived neurotrophic factor is also involved in the control of insulin resistance. Heterozygous BDNF knockout mice show a 50% reduction in brain levels of BDNF, and they also show hyperphagia and features of the metabolic syndrome (Duan et al, 2003). Administration of BDNF into the cerebral ventricles of obese/diabetic rodent models reduces obesity and improves glucose tolerance (Nakagawa et al, 2000), suggesting that the effect of BDNF on the metabolic syndrome is centrally mediated.

On the basis of the findings discussed so far, Peet (2004) proposes a hypothesis wherein it is proposed that a high-fat, high-sugar diet of patients with schizophrenia leads to reduced expression of BDNF in the brain. This would exacerbate any genetically determined abnormalities of BDNF expression. Although very speculative, this provides a possible explanatory model for the observed epidemiological association between a high-fat, high-sugar diet and poor long-term outcome of schizophrenia. Such a diet would also lead to an increased risk of diabetes, through both peripheral and central mechanisms.

There is evidence that typical and atypical antipsychotic medications have differential effects upon BDNF. Haloperidol has been found to reduce hippocampal expression of BDNF, whereas BDNF expression is increased by olanzapine and clozapine (Bai et al, 2003). However, since there is no clear correlation between these effects and the efficacy and side-effect profiles of these drugs, at least in the short term, it is unlikely that these agents are acting through an effect on BDNF.

Further Readings

[1]. Arroyo C, Hu FB, Ryan LM, et al: Depressive symptoms and risk of type 2 diabetes in women. Diabetes Care 27:129–133, 2004.
[2]. Brown S, Birtwistle J, Roe L, et al: The unhealthy lifestyle of people with schizophrenia. Psychol Med 29:697–701, 1999.
[3]. Bushe C, Holt R: Prevalence of diabetes and impaired glucose tolerance in patients with schizophrenia. Br J Psychiatry 47(suppl):S67–S71, 2004.
[4]. Bushe C., Leonard B.,. Association between atypical antipsychotic agents and Type 2 Diabetes: Review and prospective clinical data. Br J Psychiatry 184 (suppl 47):s87–s93, 2004.
[5]. Bjorntorp P, Rosmond R: Obesity and cortisol. Nutrition 16:924–936, 2000.
[6]. Carnethon MR, Kinder LS, Fair JM, et al: Symptoms of depression as a risk factor for incident diabetes: findings from the National Health and Nutrition Examination Epidemiologic Follow-up Study. Am J Epidemiol 158:416–423, 2003.
[7]. Cassidy F, Ahearn E, Carroll BJ: Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. Am J Psychiatry 156:1417–1420, 1999.
[8]. Christiansen, O., Christiansen, E. Fat Consumption and Schizophrenia. Acta Psychiatrica Scandinavica; 78, 587-591, 1988.
[9]. Dinan TG: Stress and the genesis of diabetes mellitus in schizophrenia. Br J Psychiatry 47(suppl):S72–S75, 2004.
[10]. Duan, W., Guo, Z., Jiang, H., et al (2003). Reversal of behavioural and metabolic abnormalities, and insulin resistance syndrome, by dietary restriction in mice deficient in brain-derived neurotrophic factor. Endocrinology, 144, 2446 -2453
[11]. Eaton WW, Armenian H, Gallo J, et al: Depression and risk for onset of type II diabetes: a prospective population-based study. Diabetes Care 19:1097–1102, 1996.
[12]. Fagiolini A, Frank E, Houck PR, et al: Prevalence of obesity and weight change during treatment in patients with bipolar I disorder. J Clin Psychiatry 63:528–533, 2002.
[13]. Jablensky, A., Sartorius, N., Ernberg, G., et al. Schizophrenia: Manifestations, Incidence and course in different Cultures. A World Health Organization Ten-country study. Psychological Medicine Monograph Supplement 20. Ew York: Cambridge, 1992.
[14]. Kawakami N, Takatsuka N, Shimizu H, et al: Depressive symptoms and occurrence of type 2 diabetes among Japanese men. Diabetes Care 22:1071–1076, 1999.
[15]. Keck PE Jr, Buse JB, Dagogo-Jack S, et al: Managing Metabolic Concerns in Patients with Severe Mental Illness. Minneapolis, MN, Postgraduate Medicine, McGraw-Hill, 2003.
[16]. Kessing LV, Nilsson FM, Siersma V, et al: Increased risk of developing diabetes in depressive and bipolar disorders? J Psychiatr Res 38:395–402, 2004.
[17]. Lilliker SL: Prevalence of diabetes in a manic-depressive population. Compr. Psychiatry 21:270–275, 1980.
[18]. McCreadie R, Macdonald E, Blacklock C, et al: Dietary intake of schizophrenic patients in Nithsdale, Scotland: case-control study. BMJ 317:784–785, 1998.
[19]. McElroy SL, Kotwal R, Keck PE Jr, et al: Comorbidity of bipolar and eating disorders: distinct or related disorders with shared dysregulations? J Affect Disord 86:107–127, 2005.
[20]. McKee HA, D'Arcy PF, Wilson PJ: Diabetes and schizophrenia: a preliminary study. J Clin Hosp Pharm 11:297–299, 1986.
[21]. Meyer G, Badenhoop K: Glucocorticoid-induced insulin resistance and diabetes mellitus: receptor-, postreceptor mechanisms, local cortisol action, and new aspects of antidiabetic therapy. Med Klin 98:266–270, 2003.
[22]. Mukherjee S, Decina P, Bocola V, et al: Diabetes mellitus in schizophrenic patients. Comp Psychiatry 37:68–73, 1996.
[23]. Newsome CA, Shiell AW, Fall CH, et al: Is birth weight related to later glucose and insulin metabolism? A systematic review. Diabet Med 20:339–348, 2003.
[24]. Palinkas LA, Lee PP, Barrett-Connor E: A prospective study of type 2 diabetes and depressive symptoms in the elderly: the Rancho Bernardo Study. Diabet Med 21:1185–1191, 2004.
[25]. Peet M: Diet, diabetes and schizophrenia: review and hypothesis. British Journal of Psychiatry 184 (suppl), s102-s105 (2004).

[26]. Paul E. Keck Jr., M.D, Susan L. McElroy, M.D. and Rakesh Kaneria, M.D. Severe Mental illness and Diabetes Mellitus. In Eds. Richard A Bermudes, M.D. and Paul E Keck Jr., M.D. Susan L McElroy, M.D.: Managing Metabolic Abnormalities in the Psychiatrically ill – A Clinical guide for Psychiatrists. American Psychiatric Publishing Inc. Washington DC, 2007.
[27]. Ruzickova M, Slaney C, Garnham J, et al: Clinical features of bipolar disorder with and without comorbid diabetes mellitus. Can J Psychiatry 48:458–461, 2003.
[28]. Schwarz L, Munoz R: Blood sugar levels in patients treated with chlorpromazine. Am J Psychiatry 125:253–255, 1968
[29]. Shiloah E, Witz S, Abramovitch Y, et al: Effect of acute psychotic stress in nondiabetic subjects on beta-cell function and insulin sensitivity. Diabetes Care 26:1462–1467, 2003
[30]. Smith GN, Flynn SW, McCarthy N, et al: Low birthweight in schizophrenia: prematurity or poor fetal growth? Schizophr Res 47:177–184, 2001
[31]. Tabata H, Kikuoka M, Kikuoka H, et al: Characteristics of diabetes mellitus in schizophrenic patients. J Med Assoc Thai 70(suppl):90–93, 1987
[32]. Tod H: Studies on carbohydrate metabolism in nervous and mental disorders, I: glucose tolerance tests in manic-depressive insanity and other depression. Edinburgh Med J 43:524–527, 1934.
[33]. World Health Organization: Schizophrenia: An International Follow-Up Study. New York, John Wiley, 1979.
[34]. World Health Organization: Diet, Nutrition and the Prevention of Chronic Diseases. WHO Technical Report Series 916. Geneva, Switzerland, World Health Organization, 2003.
[35]. Zahrzewska KE, Cusin I, Sainsbury A, et al: Glucocorticoids as counterregulatory hormones of leptin: toward an understanding of leptin resistance. Diabetes 46:717–719, 1997.