Depression and diabetes: from epidemiology to neurobiology

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Introduction. Worldwide, diabetes mellitus and depression are among the most prevalent diseases in their respective fields, metabolism and psychiatry. However, there is evidence that patients with diabetes are at increased risk of developing depression, although a bidirectional relationship might also exist.

Aim. To present a comprehensive review of the clinical, epidemiological, psychosocial, emotional, and neurobiological basis of the relation between diabetes and depression.

Development. Epidemiological studies indicate that there is not only an augmented risk of developing depression in diabetic patients, but that this association increases the morbidity and mortality of these patients. While there is a considerable number of clinical studies that support this relation, little is known about the neurochemical mechanisms that would constitute its biological basis.

Conclusion. Alterations in monoamines (serotonin and noradrenaline), the increases in cortisol by the hypothalamus-pituitary-adrenal axis, and trophic agents such as the brain-derived neurotrophic factor, through glycogen synthase kinase-3, constitute some of the abnormalities documented in diabetic patients and in animal models that could explain the association between depression and diabetes. Additionally, we briefly consider the psychoemotional factors that might underlie the depression-diabetes relation. The effects (most of them deleterious) of the antidepressive therapy in glucometabolic control are also discussed.

Key words. BDNF. Cortisol. Depression. Diabetes. GSK-3. Insulin. Psychological distress. Serotonin.

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Introduction

Diabetes mellitus (DM) has been associated with a variety of neuropsychiatric disorders, including major depressive disorder (MDD), schizophrenia, Parkinson's disease, mild cognitive impairment and Alzheimer's disease [1-3]. Several epidemiological and clinical reports and even neuroimaging studies support the connection between these neuropsychiatric entities and DM [1,2,4]. Case-control and cohort studies have documented the increased prevalence and incidence of depression in DM [5,6]. The presence of depression coupled with diabetes has been associated with poor metabolic control, increased complications and even increased mortality [5,7]. Although the impact of diabetes has been extensively studied in animal models, the neurobiological and neurochemical bases of this neuro-psycho-endocrinologic interaction are not yet fully understood, although various cellular and molecular alterations have been reported [1-2,8]. In the last part of this review possible psychosocial and emotional factors that may underlie the diabetes-depression relationship are considered, and the glucometabolic deleterious effects of antidepressant therapy are also briefly discussed.

Epidemiology of depression

Depression is classified as a mood disorder, and is among the most prevalent mental illnesses, affecting twice as many women as men [9,10]. Since 1960, depression has been diagnosed as major depressive disorder (MDD) based on symptomatic criteria established in the *Diagnostic and Statistical Manual* (DSM IV-TR), while mild cases are classified as dysthymia, although a clear distinction between the two does not exist [10,11]. Its diagnosis requires a change in mood characterized by sadness or irritability accompanied by several psychophysiological changes including sleep, appetite or sexual desire disturbances, constipation, loss of or inability to feel pleasure at work or with friends (anhedonia), crying, suicidal ideation, slowness of speech, and bradykinesia. These changes should last a minimum of two weeks and interfere significantly with interpersonal relationships and occupa-

tional functioning [11,12]. According to epidemiological data from the World Health Organization (WHO) collected in 14 countries in America, Europe, Middle East, Africa, and Asia, from studies involving 60,463 adults, it was determined that the prevalence of mental disorders varies from 4.3 to 26.4%, the most prevalent being anxiety and mood disorders. The prevalence of mood disorders during 2001-2003 in these 14 countries ranged between 0.8 and 9.6%. The United States was the country with the highest prevalence of mood disorders with 9.6%; Mexico and Spain reported values near the mean, of 4.8 and 4.9%, respectively, while the country with the lowest prevalence of mood disorders was Nigeria (0.8%) [13]. A study on mental disorders carried out in six European countries, which included a sample of 21,425 non-institutionalized adults, found that one in four people have presented some mental disorder (according to DSM-IV) during their lifetime, and 12.8% reported having suffered major depression at some point in their lives [14]. The World Health Report 2001 shows that the point prevalence of depression in the world was 1.9% in men and 3.2% in women [15]. However, these point prevalence figures may be too conservative, since other reports indicate values of 3-5% for males and 8-10% for women (6-9% combined) [9,15-17]. WHO ranks depression as the fourth leading cause of disability worldwide and by 2020, if not before, it will be in second place. And in 2001 it estimated that the prevalence of depression in the world was 5-10%, and the lifetime risk of developing the disease was 10 to 20% for women, and only slightly lower in men. People under 45 years are most likely to develop depression, in contrast to what happens with the elderly. That is, depression is most likely to affect people during the years of productive working life. Typically the age of onset for depression is between 20 and 40 [10,18]. Other socio-demographic factors that have been associated with the development of depression are: divorce, widowhood, low or unfavorable socioeconomic status, and low educational level [18]. It is the most frequent consultation reason for psychiatrists and one of the most common in general [15,19]. In addition, according to WHO, only 30% of cases are diagnosed and treated appropriately [18].

Diabetes mellitus and neuropsychiatric disorders

DM is a chronic degenerative disorder characterized by metabolic defects in the secretion and action of insulin, resulting in hyperglycemia. The number of diabetic patients has increased disproportionately in recent decades. In addition to genetic components, environmental factors have played a decisive role in what has been called the epidemic of the 21st century [20]. DM is classified as type 1 (DM1) and type 2 (DM2). In the first case the absence of serum insulin, due to immune destruction of β-pancreatic cells, causes hypoinsulinemia and, consequently, leads to hyperglycemia. In the case of DM2, its origin is polygenic and multi-factorial, and its origins have been identified both in the lack of insulin secretion by β cells and in the resistance at the insulin receptor (IR), and in most cases it is associated with hyperinsulinemia [2,20].

For many years the relationship between DM and some psychosocial disorders has been the target of countless investigations relating biochemical alterations in serum with their effects on emotional disorders. Likewise, whether the latter participate in the perpetuation of the metabolic disturbances of DM has been studied. Cognitive defects have recently caught the attention of both biomedical researchers and clinicians [1-3]. It is proposed that the psycho-emotional disorders in patients with DM are the result of a mental or perceptual state due to the emotional burden associated with this chronic degenerative disease, rather than a neurochemical and biological alteration. This has led many to consider that depression and memory disturbances in DM share the same psychological mechanisms of grief, fear, guilt, and uncertainty that accompany degenerative diseases such as rheumatoid arthritis or terminal cancer. As a result, the interest of the researcher and the clinician has shifted from the biological and neurochemical fields to a more psychological approach. However, in the last 50 years advances have been reported in the study of the effects of DM in the central nervous system (CNS), suggesting the existence of significant cellular and molecular alterations, as well as clinical manifestations, that contribute to the risk of having a broad spectrum of neuropsychiatric diseases [2,21,22].

Prevalence of depression in diabetes mellitus

Since the 1980s, controlled studies were conducted to assess the prevalence of MDD in patients with DM. Kovacs and colleagues conducted the first study that prospectively evaluated the incidence of psychiatric disorders in children and adolescents aged 8-13 (n = 92) with DM1, who were followed from their initial diagnosis. They found that 20 years after

the diagnosis of DM, 47.6% had developed a psychiatric condition, and of these patients 26.1% (n = 24) were diagnosed with MDD or dysthymic disorder. However, this study did not have a control group, so this percentage could be much smaller [23,24]. A recent study concluded that although a significant percentage of patients with diabetes have depressive symptoms (22%), most of them do not have clinical depression, although these signs of illness are associated with high levels of glycosylated hemoglobin (HbA_{1c}), saturated fat consumption, and physical inactivity [5]. Similarly, depression has been associated with lipid abnormalities, lack of control of blood pressure, and chronic complications of the disease itself (diabetic retinopathy, nephropathy, neuropathy, macrovascular complications, and sexual dysfunction) [7,25]. Gonzalez and colleagues conducted a meta-analysis of existing studies up to 2007 about adherence to treatment in patients with diabetes and depression. Forty seven studies with independent samples (n = 17 000 patients) were included and they found that patients with DM associated with depression showed decreased treatment adherence [6]. The lack of adherence to treatment is three times higher in patients with diabetes and depression than in those without the latter [26]. It has also been documented that patients with DM2 and depression have lower self-care (dietary control, carbohydrate counting, checking their feet, exercising) than those who do not have associated depression [27]. Moreover, the cost of treating patients with associated depression rises compared with the one for those who do not have it, and intervention measures are beneficial not only to lessen the depressive symptoms but also by dramatically reducing the costs associated with the disease as shown when cost-benefit studies are performed [24,28].

There have been efforts to try to improve the mood of diabetic patients in order to assess the effects on blood glucose and other metabolic measures. Lustman et al found that diabetic patients treated with fluoxetine showed regression not only in depressive symptoms, but also showed trends for improvement in their glucose levels [29]. In a study in which symptoms of depression and anxiety were assessed in patients who were subsequently treated with paroxetine or fluoxetine, it was found that both were useful in the DM2 group and the severity of symptoms was reduced from the second week in both groups, although improvement for the treatment of depressive symptoms was more significant with fluoxetine. Furthermore, following 12 weeks of antidepressant treatment, fluoxetine showed a greater tendency to improve glycemic control [30]. Recently, Lustman et al treated patients with both DM2 and MDD and found that in the short term (10 weeks) body mass index (BMI), total body fat, HbA_{1c}, and self-care all showed improvements, although they did not find a correlation between the decrease in blood glucose and the improvement in mood or BMI. Those who received chronic treatment (24 weeks) maintained good performance in BMI, HbA_{1c}, and self-care. The improvement in blood glucose levels was anticipated by the mood reversal although through mechanisms independent of anthropometric values and self-control [31]. Additionally, the use of antidepressants has been linked to improved peripheral insulin sensitivity, so that patients with DM2 who present with hyperinsulinemia as a compensatory mechanism could benefit from this effect of antidepressants [32]. Another point that argues in favor of treatment of depression in DM is that the coexistence of these diseases increases cardiovascular risk and mortality. A 36-38% elevation in mortality with a risk increase of 2.3 times compared to the general population has been documented [33].

This brief overview illustrates the fact that both in DM1 and in DM2, the lack of gluco-metabolic control is associated with increased prevalence of depressive symptoms, and that with drug treatment not only are there psychological improvements, but these translate into a better gluco-metabolic profile and, thus, in a decrease in morbidity and mortality associated with both diseases.

Neurobiology and neurochemistry of depression

Biogenic amine hypothesis

There are several theories about the neurobiological basis of depression. However, the biogenic amine hypothesis is the one which has prevailed because its central tenet is solved by the mechanism of action of antidepressants [12,34]. This hypothesis suggests that depression represents a lower availability of noradrenaline (NA), serotonin (5-HT), or both [12,35]. Originally the idea comes from the observation made by serendipity (in 1950) that reserpine, an alkaloid of rauwolfia, widely used as antihypertensive, triggered depressive symptoms in 15% of patients [10,35].

Postmortem studies have identified an increase in the density of binding sites of the $5\text{-}HT_2$ receptor and a decrease in 5-HT transporter binding sites in

brain tissue of patients with MDD and suicide victims. An increase in 5-HT_{1A} autoreceptors in the dorsal raphe nuclei of suicide victims who suffered from MDD has also been reported. These results were supported by findings from positron emission tomography neuroimaging [10,34-35].

It has been suggested that there is a reduced release of NA in patients with MDD. The α_2 presynaptic noradrenergic receptor modulates the release of NA by negative feedback, and an increase in the sensitivity of this receptor has been documented [12].

Alteration of the hypothalamic-pituitary-adrenal axis: hypercortisolemia

Depressive illness has been associated with chronic stress in which there is overactivation of the hypothalamic-pituitary-adrenal (HPA) axis as this is a system that responds to physical or psychological stressful stimuli or stressors [36]. There is significant evidence indicating that in severe cases of MDD there is an increased activity of the HPA axis, as can be verified by serum, urine, and cerebrospinal fluid analyses [37]. This increased activity is related to periodic elevations of cortisol [10,12,36]. Indeed, it has been reported that 20-40% of depressed patients treated in outpatient departments have hypercortisolemia, as well as 60-80% of those hospitalized for depression in psychiatric institutions. Patients with MDD may have increased serum levels of cortisol, elevations in levels of corticotropin-releasing hormone –CRH, secreted by the hypothalamus and responsible for giving the signal for the release of adrenocorticotropic hormone (ACTH) from the pituitary which, in turn, is responsible for directing the adrenal glands to release cortisol–, reduced efficiency of glucocorticoid receptors in the CNS responsible for negative feedback, as well as mRNA increases in the corticotropin-releasing hormone in limbic regions [36-38]. So far there are no fully satisfactory explanations for these changes. However, the most likely theory involves the interaction of genetic susceptibility and environmental factors. The model suggests that repeated and chronic exposure to stressors results in prolonged or extreme elevations of glucocorticoids, which over time contribute to a downregulation of glucocorticoid receptors in the negative feedback loop [38]. This is more likely in people with genetic susceptibility to a hypofunction of receptors for glucocorticoids [36,38], so this could lead to a phenotype susceptible to hyperactivation of the HPA axis and, consequently, to depression. Interventions with antidepressants have shown some effects on these pathogenic mechanisms. For example, Calfa et al reported that the glucocorticoid receptor is decreased in mononuclear cells of patients with depression and that various antidepressants could increase its expression, which could even be taken as an indicator of therapeutic value [39].

It has been observed that hypercortisolemia can damage the structure and physiology of the hippocampus [37,38]. Neuroimaging studies have documented hippocampal atrophy in patients with MDD, with predominantly right-sided involvement [10,12]. On the other hand, overactivation of the HPA axis, together with the activation of the amygdala, leads to an increase in sympathetic tone that promotes the release of proinflammatory cytokines by macrophages. An increase in circulating cytokines has been associated with loss of sensitivity to insulin and glucocorticoids. Cytokines may also decrease the contribution of neurotrophic factors and the availability of monoamine neurotransmitters [36]. On the other hand, cytokines such as IL-1 and IL-6 can stimulate the release of CRH by the hypothalamus which, in turn, would perpetuate the overactivation of the HPA axis [38,40]. Additionally, it is known that these cytokines (IL-1β and IL-6) are associated with insulin resistance, which is present in patients with DM2 [41]. Overall, this implies a neuroimmuno-endocrinologic dysfunction of MDD.

Trophic factors in depression

Although in the past 50 years the biogenic amine hypothesis has been the dominant theory to explain the pathophysiology of depressive illness, lack of universality and the delay of two to three weeks to document the therapeutic effects of antidepressants have led to the assumption that the deficit of monoamines is not the center of the pathological explanation, but merely a reflection of neuronal dysfunction. As a result, trophic factors have received increased attention, in particular, the brain derived neurotrophic factor (BDNF), which is critical for the regulation of neuronal structure and plasticity in the adult brain. The neurotrophic hypothesis postulates that there is a loss of BDNF, which is an extremely important element in the pathogenesis of depression [34,42]. In fact, the serum level of the neurotrophin BDNF has been evaluated in depression and has been found to be significantly decreased in untreated MDD patients compared with control subjects and patients with MDD who received antidepressants [12,42] .

BDNF acts on the TrkB (tyrosine kinase) receptor activating various signaling pathways involved

in diverse cellular processes that not only regulate neurogenesis by promoting growth and proliferation through the activation of the mitogen-activated protein kinase (MAPK), but also have an influence on neuronal apoptosis and survival by regulating the inositol triphosphate/protein kinase B (PI3-K/PKB) pathway. Thus, its absence is deleterious to normal brain physiology, particularly for the hippocampus, and results in depressive symptoms [12,42]. It has been suggested that the delay in the effect of antidepressants is due to the need to up-regulate the transcription of trophic factors such as BDNF [42]. Although the absence of BDNF or lack of signaling through its receptor do not induce depressive behavior in animal models, it does seem to be important in the response to antidepressants and it is possible that this depends on the area of the hippocampus involved, since the absence of BDNF signaling in the dentate gyrus (DG) of the hippocampus attenuates the antidepressant response, whereas in the CA1 region the response is normal [43].

Moreover, in animal models of chronic immobilization a reduction of BDNF expression (mRNA) has been reported [42]. As already mentioned, BDNF signaling is required for neurogenesis in the hippocampus, and protocols involving stress reduce it as BDNF levels decrease. Furthermore, antidepressants induce neurogenesis in the DG [2,12], perhaps by restoring BDNF, since various antidepressants (monoamine oxidase inhibitors [MAOIs], serotonin reuptake inhibitors [SSRIs], norepinephrine inhibitors, and tricyclics) increase mRNA and BDNF protein levels in several brain areas. However, it is important to note that these changes are time dependent so chronic use is required [42]. The dynamics of BDNF have been assessed by biochemical methods in which the activation of the TrkB receptor and of some signaling pathways have been corroborated [12,44]. But the conclusive evidence came from animal experiments in which direct infusion of BDNF into the hippocampus reduced depressive behavior, and this effect was blocked in knock-out mice inducible for the *BDNF* gene [12,35,42].

The reduction of trophic factors such as BDNF has a negative impact on the morphology and physiology of limbic structures like the hippocampus. BDNF is important for processes of survival, maturation, and synaptic plasticity, so its absence is detrimental to proper neuronal, hippocampal, and, in general, cerebral performance [12,34]. For example, in the raphe nuclei (of the brain stem) BDNF regulates the expression of genes involved in serotonin functioning, such as the serotonin transporter and tyrosine hydroxylase (the limiting enzyme in the synthesis of 5-HT). By contrast, activation of 5-HT receptors by serotonin released from terminals of raphe neurons stimulates BDNF gene expression [12,35,42].

However, there are also basic and clinical studies that refute the neurotrophic hypothesis of depression [42].

Depressive behavior in models of diabetes

The protocol of the forced swimming test (FST) was developed by Porsolt in 1977. It is an acute behavioral model that induces learned helplessness [44,45]. In this phenomenon, after the application of repeated stimuli that cause aversion and do not allow an escape, some major and quantifiable pathognomonic signs of depressive illness occur. The FST has been used as an exemplary protocol for the study of depression as it responds to antidepressants and predicts the usefulness of candidate substances to have this effect [44]. It consists in immersing a rodent in a cylinder with water from which it can not escape. The results of this protocol are translated into periods of immobility, ie, the time during which the experimental animal remains motionless. The longer the time, the less useful a potential antidepressant drug is or the greater the depressive behavior. Drugs and other non-pharmacological measures that have proved useful clinically decrease the immobility time as well (the animal fights for a longer period) [44,45].

Hilakivi-Clarke et al evaluated by various protocols the behavior of mice with streptozoticin (STZ, a toxin that induces apoptosis of β-pancreatic cells when administered systemically) -induced diabetes and found a statistically significant difference only in the immobility time, reporting higher values for diabetic mice after 11 days of induction. Additionally, they studied the reversal of the STZ-induced hyperglycemia due to insulin administration and found that the periods of immobility decreased with respect to those of untreated diabetic mice and were not significantly different from those of controls [46]. Gómez and colleagues tested the learned helplessness model in diabetic rodents and found longer immobility times in the FST, which indicates depressive behavior [47].

Neurochemical changes in diabetes mellitus

Monoamines in diabetes mellitus

Studies in animal models have shown a reduction in the synthesis of 5-HT in rats with diabetes induced

by STZ and in type 1 diabetic BB rats (a strain that spontaneously develops DM1 due to immune destruction of pancreatic β-cells). Altered levels of tryptophan, 5-HT, and 5-HIAA in the striatum and decreased metabolism of 5-HT in the mesolimbic system have been reported [48]. Other authors have reported that despite the altered levels of tryptophan, the content of 5-HT and 5-HIAA in diabetic rats is normal, although some have suggested that the defects are functional and that the abnormality is in a decline in sensitivity to agonists of 5-HT in the behavioral effects [49]. Bellush and colleagues showed a reduction in 5-HT metabolism and in dopamine (DA) levels. By subjecting the animals to immobilization there were equivalent increases in DA in animals with DM and controls, but the increase in 5-HT was attenuated in diabetic rats [50]. Manjarrez-Gutiérrez and others observed that in the cerebral cortex of rats with induced diabetes concentrations of L-tryptophan, 5-HT, and their enzymes were significantly lower, while increases in the last two were found in the brain stem. When animals were treated with insulin, they regained normal levels of L-tryptophan in their brains; the activity of tryptophan 5-hydroxylase remained high during treatment with insulin, and synthesis of the neurotransmitter in both the stem and the cortex was persistently increased [51]. The results of Sandrini and colleagues support the idea that STZ-induced diabetes results in chronic hyperglycemia, which is associated with a decreased concentration of 5-HT (at 30 days), with a parallel increase in serotonergic 5-HT_{1A} and 5-HT_2 receptors in the studied areas: cortex and brainstem [52].

The synthesis of NA and DA has been reported to be reduced in models of DM. It has been suggested that basal levels of tyrosine and other large neutral amino acids (LNAA) do not alter the cerebral environment, but when a subject is exposed to stressful situations, which is when higher rates of synthesis and release are necessary, precursor reduction limits the availability of neurotransmitters [48]. It has been proposed that insulin is a physiological regulator of the synthesis and reuptake of NA and DA in the CNS. In parallel, and as in this study, it has been observed that diabetes causes a decrease in the activity of tyrosine hydroxylase in the cell bodies of dopaminergic and noradrenergic neurons. More generally, it has been postulated that insulin modulates catecholamine concentrations at synapses [53].

The HPA axis and cortisol in diabetes mellitus

Recent studies have documented a subset of patients with DM in which one can find an alteration of the HPA axis. Chiodini et al reported such alterations and they determined that there is a subclinical hypercortisolemia –elevated cortisol, with no specific data that would be expected of this increase, such as uncontrolled systemic arterial hypertension (SAH) or osteoporosis, among others– that is 4.8 times more common in patients with DM (regardless of the presence of obesity or SAH) than in control subjects. Additionally, they found that patients with hypercortisolemia presented a more aggressive form of DM (with associated comorbidities and complications) [54]. Later this same group reported that hypercortisolemia was only present in the group of patients with chronic complications and that the degree of hypercortisolemia in patients with DM2 is directly related to the presence and number of complications [55].

These abnormalities have also been studied in animal models of DM and have probably revealed the mechanism of this lack of control of the HPA axis. Chan et al conducted a study of the HPA axis in rats with diabetes induced by STZ. This model represents DM1 since hypoinsulinemia occurs when β-pancreatic cells are destroyed. They found that these animals had markedly elevated ACTH and corticosterone levels, as well as of CRH mRNA in the hypothalamic paraventricular nucleus and of mineralocorticoid receptor mRNA in all regions of the hippocampus (DG and CA1-4). By treating diabetic animals with insulin, the HPA axis activity was under control as the ACTH and corticosterone levels were normal [56]. Further, it has also been shown that hyperinsulinemia disrupts the HPA axis. The first reported study that evaluated the effect of hyperinsulinemia in the context of a euglycemic hyperinsulinemic clamp was performed by Fruehwald-Schultes et al, and significant increases in serum ACTH and cortisol were documented in healthy men [57].

Taking into account the finding of Chiodini [55] and Fruehwald-Schultes [57] we have proposed that patients with DM2 and compensatory hyperinsulinemia could present hypercortisolemia [58] and because the latter has been linked to the complications of DM [55], we raised the possibility that the neuropsychiatric complications to which DM has been associated (depression, mild cognitive impairment and Alzheimer's disease) could be secondary to hypercortisolemia that per se occurs in patients with these diseases [21]. Thus, our hypothesis is that one of the possible mechanisms by which memory and mood alterations are increased is due to an interaction of insulin and cortisol, where the elevation of the former causes a malfunction of the HPA

axis, in turn producing hypercortisolemia, which can damage specific structures of the brain, especially those affecting critical functions in limbic areas [2, 22,58].

Chan et al showed, as mentioned previously, that ACTH and corticosterone were elevated in rats with STZ-induced diabetes, which points to a hyperactivation of the HPA axis [56]. Because this model induces hyperglycemia due to hypoinsulinemia, it is possible to speculate that one of these two abnormalities may be causing hyperactivation of the HPA axis. It is widely known that the hypothalamus has glucose sensors in the ventromedial nucleus and the parvocellular portion of the paraventricular nucleus that are distinguished by their characteristic firing patterns. Hence, due to its role as a regulator of food intake and metabolic balance, glucose would be the first candidate as the substance responsible for this phenomenon. However, in a study in which DM was induced under the same conditions it was found that by reducing serum glucose by glucosuria, HPA axis activity was not normalized [59]. And the study of Chan et al reported normalization when their animals were treated with insulin [56]. Therefore, we are able to speculate that insulin plays an essential role in regulating the HPA axis. Thus, we propose that, in addition to the hyperactivation of the axis being caused by hyperinsulinemia, it can also be adversely affected by hypoinsulinemia. However, since a euglycemic hypoinsulinemic clamp is difficult even under experimental conditions, other methods are needed to fully elucidate the interaction of insulin and cortisol.

Cushing's syndrome, an endocrine disease in which the pathognomonic abnormality is an increased cortisol level, has helped to understand the effects of excess cortisol in the brain. In these patients neuropsychological abnormalities that are associated with hippocampal atrophy have been documented [60]. Studies in patients with DM have also documented hippocampal atrophy [4] so it is very possible that the lack of control of the HPA axis in diabetic patients plays an important role in the high prevalence of depression.

Trophic factors: BDNF and insulin

The first reports about alterations of serum BDNF levels in DM have been published recently, and this has led to speculation about their role in glucometabolic regulation. Fujinami et al conducted a case-control study in which BDNF levels were measured in 112 subjects with DM2 and 80 controls matched for age and sex. They found that serum BDNF levels were reduced in patients with DM2. This finding was significantly higher in men and was found to be related to higher indices of insulin resistance [61]. Krabbe et al made a similar assessment in which they also performed dynamic measurements of insulin and glucose. Likewise, they reported that patients with DM2 had decreased serum levels of BDNF and that this was related to high levels of glucose. They suggested that these alterations may be a pathogenic factor in the increased risk of dementia or depression present in this subgroup of patients [62].

Moreover, animals fed high-calorie diets (high in fat and carbohydrates) that develop insulin resistance show reduced levels of BDNF in the hippocampus [63]. In turn, repeated systemic administration of BDNF improves glucose utilization by muscle [64], reduces serum glucose, improves insulin levels, and protects the microarchitecture of the pancreas and its β cells [65].

As has been evidenced, DM alters BDNF levels in both the periphery and in the CNS. And it relates not only to effects seen in neurons but also at the muscle and pancreas [65]. Perhaps this is surprising at first glance, but when analyzing the BDNF signaling pathway, one can notice the reason for its broad spectrum of action. Although insulin (associated with the insulin receptor, IR) and BDNF (through the TrkB receptor) do not exert their cellular action by a common receptor, they share a common signaling pathway: the PI3-K/PKB [66,67].

Upon a glucose load, insulin is released from β-pancreatic cells and it exerts its effect through the IR, which consists of a heterotetramer ($\alpha_2\beta_2$) with tyrosine kinase activity in its intracellular portion [66]. As insulin binds to the extracellular α subunits it induces a conformational change of β subunits, which initiates a series of phosphorylations, and activates the PI3-K/Akt pathway, among others. The activation of PKB or Akt inactivates glycogen synthase kinase-3 (GSK-3), which constitutively maintains the inactivation of glycogen synthase (GS), the enzyme that is responsible for glycogen synthesis [66,67]. Hence, one of the purposes of insulin signaling is the inhibition of GSK-3 in order to allow the action of GS [8,67]. BDNF also activates this signaling pathway, and this is essential [68] since GSK-3 apart from being a 'gatekeeper' of glycogen synthesis, is a key relay to the nucleus for the synthesis of various proteins and enzymes that are responsible for the growth and survival of neurons as well as for synaptic plasticity [2,69].

The insulin receptor is widely distributed in the brain [8,69], and although its signaling is not necessary for the use of glucose, it appears to fulfill im-

portant roles in neuronal physiology. So, like BDNF, insulin acts as a trophic factor in the brain [69]. In either DM1 or DM2 there is hypofunction of the insulin receptor. In DM1 there is hypoinsulinemia so the insulin receptor does not receive its substrate and, therefore, the intracellular signaling that is necessary for proper neuronal functioning is lacking [2]. Furthermore, in DM2 there is insulin resistance at the receptor site so that even with serum availability, the cell (or, more specifically, neurons) are unable to activate, for example, the PI3-K pathway, which is necessary for the inactivation of GSK-3 [2,8,69].

Animal studies have shown that overactivation of GSK-3 increases the period of immobility in the FST [70], and its pharmacological blockade reduces depressive behavior [71]. Since in DM there is a poor signaling through the insulin receptor [2], and given that BDNF levels are reduced [66,67], it is possible that the lack of inactivation of GSK-3 could play an important role in the pathogenesis of depression in DM [8]. Although there are selective GSK-3 pharmacological blockers, lithium, a widely used drug to treat bipolar disorder, has proven effective in blocking the GSK-3 in the CNS in vivo [72,73]. We recently conducted a behavioral evaluation of the effect of blocking GSK-3 in a model of DM, and found that drug therapy with lithium is able to reduce the immobility time in a model of DM [8].

Abnormalities in the trophic factors, insulin and BDNF, may contribute to the increased prevalence of depression found in DM in epidemiological studies [8].

Depression and psychiatric therapy in the risk of diabetes

Depression as a risk for developing diabetes mellitus

As in the case of studies that have established an increased prevalence and/or risk of depression in patients with DM, there are also reports that have associated an increased risk of developing DM and other metabolic and cardiovascular disorders in patients with a history of depression [74]. This is not difficult to conceive if some pathophysiological factors (increased serum cortisol, alterations in neurotrophic factors, immune imbalance that causes insulin resistance, etc.) are evaluated. Recently Mezuk et al conducted a meta-analysis that evaluated the studies available in Medline from 1950 to 2007. They only included those studies where the prevalence of comorbidity was not reported as such. Taking into account only those studies that met the inclusion criteria (incidence rather than prevalence) they reported that the relative risk (RR) of depression associated with DM as the underlying disease is 1.15, while the RR of developing DM-associated depression as the primary condition is 1.60. Therefore, this meta-analysis suggests that diabetes increases the risk of developing depression only moderately, while the risk of developing diabetes from depression is greater. However, further studies are needed to evaluate these relationships [75].

In any case, it is evident that the risk of having either disease is increased bidirectionally [31].

Antidepressants: do they increase the risk of diabetes mellitus and obesity?

Although the association of weight gain and alterations of serum glucose with the use of antipsychotic drugs has been widely studied, few investigations have addressed the relationship between antidepressants and the risk of diabetes mellitus and obesity [76,77]. Some recent reports have indicated a possible link between antidepressant use and development of DM. However, contradictory results have also been reported. Selective inhibitors of serotonin reuptake inhibitors may have a beneficial effect on DM, by reducing insulin resistance in these patients [78]. Further, this effect has also been reported for the tricyclic antidepressant (TCA) amitriptyline, for the tetracyclic mirtazapine, for the SSRI paroxetine, and for venlafaxine [79]. In addition, it has been found that blood glucose is better controlled in diabetic patients who are in remission for depression [78]. In this kind of research it is essential to confirm the presence of diabetes in the study subjects and to control potential confounding variables, such as exercising. Equally important is specifying the type of antidepressant therapy administered and the period of its use, since there is evidence that indicates that tricyclic drugs elevate blood sugar in diabetic patients [79] and also that the prolonged use of antidepressants, whether tricyclic or SSRIs, increases the risk of diabetes [80].

Moreover, it has been reported that patients who consume either TCAs, SSRIs or monoamine oxidase inhibitors (MAOIs) tend to increase their body weight. This is extremely important when considering that antidepressant therapy is one of the most commonly prescribed psychotropic treatments [81]. Recently, Patten et al reported the results of a 10-year follow-up study in which 6,498 Canadian individuals with BMI < 30 (not obese according to WHO standards) were evaluated and it was found that the use of SSRIs increases the risk of develop-

ing obesity by almost 2 times (HR = 1.9; 95% CI = 1.2-3.2; $p = 0.01$) while venlafaxine increases it fivefold (HR = 4.9, 95% CI = 1.8-13.0, $p < 0.001$) [76]. It is important to mention that there are also reports supporting the existence of a bidirectional association between depression and obesity [77], although some studies do not sustain the relationship in either direction. This is especially important because obesity and diabetes are presented as a highly prevalent comorbidity, in which it is generally considered that patients with obesity have a higher risk of DM, and it has been reported that those patients who are overweight or obese have poorer response to treatment with antidepressants [82].

According to these data and those presented previously, patients with diabetes who also have depression may benefit from antidepressant therapy. And since drugs are the most commonly used therapy, it is logical to consider them as a first-line resource, and even more so when considering that they have demonstrated clinical efficacy in controlled trials [29]. However, considering that many of them can modify the metabolic profile of the patient, not only by altering serum glucose but also by causing weight gain and lipid abnormalities, it would be wise to consider the profile of glucometabolic involvement of the antidepressant being prescribed, as well as taking into account other therapies, such as psycho-educational interventions.

Psycho-emotional factors in the diabetes-depression relationship

In this text the role of biochemical alterations due to DM, or arising as a result of it, and which act as triggers of changes in brain neurochemistry, has been discussed. This may be the reason for the large number of epidemiological and clinical reports linking DM with the risk of developing depression [24]. However, both disorders involve psycho-emotional and psychosocial factors that could contribute to an increased risk of DM in depression or vice versa. For example, DM imposes a series of psychosocial adjustments on patients that can likely lead them to decrease their enjoyment of life, and eventually to develop a mood illness. On the other hand, depression is related to changes in nutrition and exercise that might be the cause for the increased risk of developing DM [24]. DM is a chronic degenerative disease that has a large impact on the socio-cultural environment, which directly affects the perception of the patient's own health. Some studies have shown that patients with DM2 have a high perception of their condition as a chronic disease [83], in which adherence to a drug or non-drug treatment is important. However, even when patients know about their disease and its possible evolution over time, strategies are still perceived as useful, although they are not implemented [84]. This could be related to the high prevalence of non-compliance to treatment (of any kind) that has been seen in patients with DM. In turn, it has been reported that the coexistence of depression and diabetes is significantly related to lack of adherence to treatment, especially for oral hypoglycemic agents and diet, which have a direct impact on the patient's glycemic control [6,26].

Moreover, DM is associated with increased psychological distress [85], and it is generally accepted that this is an important factor for the development of depression and other neuropsychiatric disorders [86]. It has been reported that patients with chronic complications of DM (e.g., diabetic foot) also have high rates of psychological distress, as identified with specialized questionnaires. This is logical since chronic complications usually appear due to uncontrolled metabolism, and this has also been associated with psychological distress [87]. Our experience has recently led us to determine that in patients with diabetes and depression much of this association may be attributed to psychological distress, even though we have also found a relationship with certain metabolic alterations (manuscript in preparation).

Conclusions

Through this brief presentation of the data found in the biomedical literature we have shown that from an epidemiologic point of view there is an increased prevalence of depression in patients with DM. This change in mood is associated with a loss of metabolic control, lack of adherence to treatment and self-care, as well as complications and increased mortality. Besides, there are sufficient reports to argue that there are neurochemical changes in biogenic amines, the HPA axis, and neurotrophic factors. Taken together, these changes constitute a neurobiological factor behind the increase of depression in DM. However, the psycho-affective component of this pathology can not be ignored, as has also been evidenced, given that psychological distress and social and emotional adaptation of the disease may also play an important role in the bidirectional relationship of both diseases.

It is important to consider that, although it was not mentioned in the body of this review, genetic

(more specifically, genomic) factors could play an important role, especially when taking into account that many of the neurobiological mechanisms that cause neuropsychiatric disorders may also promote peripheral pathologies of metabolic nature.

With all that has been mentioned, it is clear that the increase in prevalence and/or risk of depression in DM, or vice versa, involves neurobiological factors related to brain neurochemistry factors (that are probably genomic as well), and psycho-emotional and social elements, which either separately or acting synergistically may worsen the health and welfare of patients.

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Depresión y diabetes: de la epidemiología a la neurobiología

Introducción. La diabetes mellitus y la depresión constituyen las enfermedades más prevalentes en el mundo, dentro de sus respectivas áreas de estudio, la metabólica y la psiquiátrica. Sin embargo, existe evidencia de que los pacientes con diabetes tienen mayor riesgo de padecer depresión.

Objetivo. Presentar una revisión actualizada acerca de los aspectos clinicoepidemiológicos, psicosociales, emocionales y neurobiológicos acerca de la relación de la diabetes y la depresión.

Desarrollo. Estudios epidemiológicos indican que no sólo existe mayor prevalencia de depresión en la diabetes, sino que su asociación incrementa la morbimortalidad de los pacientes. A pesar de que existe un considerable número de estudios clínicos que apoyan esta relación, poco se ha descrito acerca de los mecanismos neuroquímicos que constituirían sus bases neurobiológicas.

Conclusión. Alteraciones en el metabolismo de las aminas biógenas (serotonina y noradrenalina), del eje hipotálamo-pituitaria-adrenal (al aumentar el cortisol) y de agentes tróficos, como el factor de crecimiento derivado del cerebro, a través de la glucógeno sintasa cinasa-3, constituyen algunas de las anormalidades documentadas en modelos animales o en pacientes con diabetes que podrían explicar la asociación entre la depresión y la diabetes. Adicionalmente, se consideran de manera breve los factores psicoemocionales que pudieran subyacer a la relación entre la depresión y la diabetes, haciendo también un paréntesis en los efectos (en su mayoría deletéreos) de la terapia antidepresiva en el control glucometabólico.

Palabras clave. BDNF. Cortisol. Depresión. Diabetes. Distrés psicológico. GSK-3. Insulina. Serotonina.