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“Is bipolar disorder an endocrine condition?” Glucose abnormalities in bipolar disorder

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The World Health Organisation placed bipolar disorder at the top ten causes of disability worldwide, due not only to its functional impairment but also to its increased medical morbidity and mortality. An increased suicide rate, poor healthcare access, poor health habits, and medication side-effects contribute to the increased morbidity and mortality. However, the leading contributors to the excess of mortality are cardiovascular pathologies (1), a finding already highlighted by Derby in 1933 in a cohort of manic-depressive patients admitted to a general hospital. Cardiovascular risk factors, such as obesity, hypertension, type 2 diabetes mellitus (T2DM) (2), and lipid disturbances, are highly increased in bipolar disorder. In between those, glycemic abnormalities are the most repeated finding, taking into account that since the onset of the 20th century, several authors had raised the attention toward an unexpected relationship between manic-depressive illness and glucose metabolism (3). In addition, the prevalence of T2DM in bipolar disorders ranges from 8% to 17% a threefold increase compared with the general population and bipolar patients with comorbid T2DM may have a more severe course of the psychiatric illness (greater number of depressive and manic episodes, more hospitalizations, and suicidality) and refractoriness to treatment. In addition, studies regarding metabolic disturbances in relatives of bipolar disorder and non-affective psychosis have described an increased risk of developing glucose abnormalities, adding more scientific background to the unexpected relationship. However,

pharmacological treatment, including both antipsychotic agents, antidepressants and mood stabilizers, may have confounded this relationship.

The studies undergone in the pre-antipsychotic era, described a high prevalence of glucose abnormalities in patients diagnosed with manic-depressive illness (3), suggesting that even before the use of psychotropic medication, bipolar patients showed a disturbed regulation in the homeostasis of glucose metabolism, a key factor for developing T2DM over years and for increasing the risk of mortality through different cardiovascular pathologies (i.e., myocardial infarction, stroke). However, the lack of homogeneity of psychiatric and endocrinologic methodology might have biased those findings. In fact, as opposed to patients with schizophrenia and other severe mental illnesses, no study has been conducted in drug-naïve bipolar patients to test the hypothesis that glucose abnormalities can be found in those patients more frequently than in the general population.

Now, preliminary data concerning 7 drug-naïve DSMIV- TR bipolar I patients who underwent an oral glucose tolerance test suggest that bipolar disorder may be highly associated with abnormal glucose metabolism irrespective of pharmacotherapy. The patients were evaluated at the time of their first clinical contact for psychotic symptoms at a general academic hospital. The patients were initially classified as first episode of non-affective psychosis, but their diagnosis was changed over a year time for an affective diagnosis, namely bipolar disorder type I. All subjects gave informed consent for participation in the study, which was conducted under the supervision of the authors' respective hospital ethics committees, and came from a larger study of metabolic abnormalities and glucose dysregulation in neuropsychiatric disorders (4). The results after an overnight fast showed a high incidence of glucose metabolism abnormalities, including impaired fasting glucose in two of seven patients and impaired glucose tolerance in six of seven patients. Abnormal glucose metabolism, measured as an increased two-hour glucose load, reflects that bipolar I disorder is associated with an elevated risk of death from cardiovascular pathologies and all causes, independently of other known risk factors.

Our data and the actual state of knowledge suggest that glucose abnormalities are linked to the diagnosis of bipolar disorder before the effects of medications and other confounders had taken place. Indeed, glucose abnormalities are the basis for the reportedly high number of medical comorbidities found in patients with bipolar disorder. The concept of 'Allostatic Load' has received considerable attention as a theoretic explanation of its medical burden. Allostasis is a term that describes a multisystemic view of the physiologic toll that is required for adaptation to different situations; these processes are adaptative to internal or external circumstances and so maintain the homeostasis of the organism. However, when extra loads appear pointy or over time (the adaptative mechanisms are repeatedly activated), the allostatic response becomes excessive or inefficient and the organism develops an allostatic load (overload) that can direct to abnormal responses through insulin dysfunction such as T2DM, hypertension, or arteriosclerosis (5).

The pathophysiology that underlies the association of bipolar disorder and T2DM or glucose abnormalities is far from being understood, but several explanations have been developed

over time. These include possible common pathophysiological processes, genetic and epigenetic links, and environmental factors.

Dysregulation in the hypothalamic–pituitary–adrenal axis is a highly consistent finding that would explain through cortisol disturbances the abnormalities in glucose homeostasis, increased body fat deposition and atherosclerosis, although in our sample, cortisol value was in the normal range, and in another naïve bipolar I study, it was lower compared with matched controls. Dysfunction in the purinergic system has been associated with both bipolar naïve patients (6) and T2DM, as purines play a crucial role in energy homeostasis and neuroregulation. Indeed, Kraepelin already described in 1921 an association between uric acid and manic-depressive illness. Evidence implicates also mitochondrial dysfunction, impaired phospholipid metabolism and fatty acid-related signal transduction, and dysregulation of glycogen synthase kinase-3, in the common pathophysiological processes that underlie bipolar disorder and T2DM (2). Common genetic abnormalities and shared susceptibility loci have been described between T2DM and bipolar disorder; however, genetic-wide association studies have not yielded conclusive results.

However, we would like to highlight the physiology of early environmental processes (7) and its epigenetic programming in the development of metabolic disturbances. Bipolar disorder, from a gene-environment model, is associated not only with familial risk but also with a certain number of early environmental factors. Birth and gestational-related problems appear to be risk factors for both bipolar disorder and diabetes, low birth weight being the most notable example, suggesting neurobiological adaptative changes that might underlie both pathologies. Obstetric, prenatal disturbances, and early growth patterns predict an increased risk of developing T2DM (8) and other cardiovascular pathologies over time, through epigenetic pathways, a finding that could also partially explain part of the increased risk of morbidity and mortality found in patients affected with bipolar disorder.

Understanding the onset of a severe mental illness not only as psychiatric but also as a medical condition would imply a metabolic control independent of the type of treatment. Hence, all physicians should be aware of the need of implementing primary preventive strategies in an effort to reduce the overall medical burden and mortality of bipolar patients.

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