

Diabetes mellitus and schizophrenia: historical perspective

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Background Although recent research has focused on the possible role of antipsychotic medications in the development of diabetes mellitus, studies conducted in the pre-neuroleptic era suggest that schizophrenia itself might predispose individuals to diabetes.

Aims To test the hypothesis that diabetes mellitus is an integral part of schizophrenia.

Method Historical literature review.

Results Many people with severe mental illnesses, including dementia praecox, showed abnormal responses to insulin and diabetes-like glucose tolerance curves long before the advent of phenothiazines. Early studies with chlorpromazine suggested that a latent tendency towards diabetes in patients with schizophrenia could be unmasked by this treatment.

Conclusions Diabetes and disturbed carbohydrate metabolism may be an integral part of schizophrenia. Further research is required to explain how metabolic factors, medications and lifestyle factors might precipitate diabetes in patients with this mental disorder.

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In recent decades medicine – especially psychiatry – has taken significant steps forward in understanding the biology, physiology and genetics of mental illness, and researchers have gained a deeper understanding of the complexity of severe mental disorders and their possible association with medical conditions. Psychopharmacology has expanded, and this has contributed to more effective treatment of mental disorders and our understanding of their underlying pathology. For more than half a century large numbers of patients have received long courses of psychotropic treatment, and the effects and side-effects of these medications have gained prominence in both clinical practice and academic circles. Extrapyramidal side-effects, tardive dyskinesia, hyperprolactinaemia, weight gain, cardiotoxicity and sexual dysfunction have all been associated with different classes of psychotropic drugs, and although some of these effects (hyperprolactinaemia and cardiotoxicity) are clearly caused by the medication, other side-effects appear to be an integral part of schizophrenia itself, and are only unmasked by psychotropic medications.

Diabetes and schizophrenia have been linked since the beginning of the 20th century (Kooy, 1919; Raphael & Parsons, 1921; Lorenz, 1922), but the number of new reports of an association between diabetes and schizophrenia has alarmed clinicians in recent years. This has led to a revival of interest in this neglected area, and many new epidemiological studies and randomised controlled trials have been conducted in an effort to redefine and clarify this association.

Research publications from 1919 onwards were providing an insight into the association between diabetes and mental illness long before the advent of psychotropic medication. These publications do not have the properties or reliability of modern research, but they do draw attention to the association between schizophrenia and diabetes without the interference of

psychopharmacology. These publications help us to answer two questions: whether schizophrenia is naturally associated with diabetes without the precipitating effect of psychotropics, and whether conventional neuroleptics such as the phenothiazines have had an unmasking effect on diabetes in patients with a diagnosis of schizophrenia.

This paper provides a summary of case reports and publications on schizophrenia and diabetes dating from 1919 to the late 1960s. Most of these are naturalistic compilations of cases; they do not have the subtlety and refinement of modern statistical methodology, the reliability of complex research designs, the power of randomised controlled trials, or the breadth of 21st-century epidemiological surveys. Most of them cannot even boast clear diagnostic categories. Nevertheless, they are unique in the way they assist in eliminating the narrow psychopharmacological perspective that may cloud the judgement of clinicians today, and help to broaden the current reductionist perspective.

METHOD

I carried out a review of the literature before and at the time of introduction of the phenothiazine antipsychotic medications.

RESULTS

Schizophrenia and diabetes in the pre-neuroleptic era

As early as 1919, Kooy, in his long and detailed article, published the daily account and mental state of 10 patients with hebephrenic schizophrenia, and came to the conclusion that their constant hyperglycaemic curve meant that they had both dementia praecox and hyperglycaemia. Raphael & Parsons (1921) studied blood glucose levels in 11 cases of dementia praecox and 11 cases of manic-depressive insanity: they found pronounced initial hyperglycaemia in both groups, and noted that the glucose tolerance curves of both groups showed diabetic characteristics.

Drury & Farron-Ridge (1921) looked at the blood glucose curves of a large group of psychiatric in-patients and compared these with the curves of patients with dementia praecox and manic depression. They concluded that the curves in the dementia praecox patients varied greatly from the accepted norms and that, in many

cases, general metabolism is far more disordered in insanity than one would be led to believe by casual observations. They also noted many cases where 'the blood sugar metabolism would appear to be normal but it is in fact greatly upset' and that 'confusion and melancholia are associated with the greatest disturbance of sugar metabolism' (Drury & Farron-Ridge, 1921).

Lorenz (1922) reported that some of his patients with catatonic dementia praecox responded to glucose feeding with hyperglycaemic curves. He also noticed that his catatonic and stuporous patients fared even worse in their hyperglycaemic curves. Barrett & Serre (1924) found an excess of sugar intolerance related to psychosis and manic depression. Thirty of their patients with dementia praecox had glucose tolerance curves similar to patients with diabetes. These investigators also found fluctuations in repeated tests, but could not establish a curve typical for both psychiatric conditions. In 1925, Henry & Mangan studied nine patients in acute stages of dementia praecox, and noted that their glucose tolerance curves indicated a definite 'retardation' in glucose metabolism (Henry & Mangan, 1925). Kasanin (1926) studied the blood glucose curves in a group of patients with dementia praecox. In his cohort of 33 individuals, 22 had abnormal curves, and he concluded that these patients had a derangement of carbohydrate metabolism. He also collected from the literature accounts of 154 patients with dementia praecox and abnormal blood glucose curves, and concluded that abnormal blood glucose levels were seen more frequently in patients with dementia praecox than in normal populations.

Freeman *et al* (1944) studied the carbohydrate tolerance of 91 soldiers with psychiatric diagnoses and 20 normal controls. In this series, psychiatric patients had higher blood glucose levels 60 min following oral glucose ingestion than the normal group. Abnormal glucose tolerance curves were found in 31% of his psychiatric patients.

Schizophrenia and insulin coma therapy

In the first decades of the 20th century, insulin-induced hypoglycaemic coma therapy was thought to relieve patients from symptoms of schizophrenia. Insulin coma therapy units were set up in many hospitals

and asylums in the 1940s and 1950s. This brutal and ineffective treatment method, based on producing coma by injecting high doses of insulin repeatedly until convulsions occurred, was used widely for almost three decades. While this therapy was in use, it came to the attention of clinicians that there was an abnormal response to insulin in patients with schizophrenia compared with people without this illness (Appel & Farr, 1929). Freeman *et al* (1943) studied the effects of insulin on glycaemia in 32 male patients with schizophrenia and 20 normal controls. They noted that 41% of patients showed 'greater resistiveness' and 'less responsivity' to insulin than did normal individuals. One year later, these investigators also noted less pronounced reductions in blood glucose levels following the administration of insulin compared with a normal control group, and they concluded that these results suggested a need for further investigation into 'carbohydrate metabolism of the central nervous system in cases of this psychosis' (Freeman *et al*, 1944).

This resistance to a lowering of blood sugar following insulin injection was replicated by Braceland *et al* (1945), who noted diabetic-like glucose tolerance curves and the delayed response to insulin.

Phenothiazines and the emergence of diabetes mellitus

Following the introduction of chlorpromazine in 1952, a further series of diabetes case reports were published. The first report came from Courvoisier *et al* (1953).

Dobkin *et al* (1954) designed a study in which they injected chlorpromazine 1.5 mg/kg into seven normal volunteers, and found them to respond with increased blood glucose levels. Giacobini & Lassenius (1954) noted transient glycosuria in patients treated with chlorpromazine. Merivale & Hunter (1954) described patients who had abnormal glucose tolerance tests during treatment with large doses of chlorpromazine and other sedatives commonly used at the time.

Charatan & Bartlett (1955) studied the effects of chlorpromazine on glucose tolerance in 11 patients with schizophrenia (seven women and four men, mean age 30.3 years) who were all on a hospital diet. Before chlorpromazine treatment, it was established that they all had normal glucose tolerance curves. After treatment with intravenous chlorpromazine, patients were

given a single loading dose of 50 g glucose. Results indicated 'a pronounced delay in the removal of glucose from blood' (Charatan & Bartlett, 1955).

Hiles (1956) observed that among patients receiving chlorpromazine therapy, five patients developed transient hyperglycaemia, five patients with controlled diabetes became unstable, and two patients who had normal fasting blood glucose levels before drug therapy developed overt diabetes mellitus during treatment. Waitzkin (1966) surveyed 359 men under the age of 50 years with severe mental illness living in a mental hospital. He discovered that 11.7% of the men had previously unknown diabetes, and concluded that diabetes rates were higher in patients with schizophrenia than in the normal population. However, his reports do not make it clear how many of these patients had been treated with psychotropic medication. Winkelmayer (1962) surveyed 798 male in-patients in the New Jersey State Hospital in Marlboro for the presence of diabetes mellitus and chronic renal disease. He noted that the high percentage of people with diabetes in the group of patients with schizophrenia suggested that this group 'could have a greater predilection toward the development of diabetes mellitus than the average individuals'. He also noted that the average period of hospitalisation before detection of diabetes was 25 years, and stressed the importance of surveys for detecting patients with unknown diabetes among the long-term residents of large mental hospitals.

Korenyi & Lowenstein (1968) investigated two patients with altered glucose metabolism associated with chlorpromazine, and noted that upon withdrawal of the drug, one patient remained diabetic while the second patient returned to normal.

Dynes (1969) compared 22 patients with diabetes with 33 patients with both schizophrenia and diabetes, and concluded that phenothiazines might have precipitated a latent diabetic tendency into full-blown diabetes mellitus in the latter group. He commented that patients with schizophrenia were more likely to have a family history of diabetes, and that such patients were more likely to show signs of obesity due to their altered physiological response.

Keskiner *et al* (1973) studied 249 patients, the majority of whom had a diagnosis of schizophrenia, and found that a quarter (25.7%) also had diabetes. The mean age of the patients was 48.9 years

and the mean duration in hospital was 16.5 years. These investigators concluded that there was a higher incidence of diabetes mellitus in patients treated with psychotropic drugs. They also recognised that undiagnosed diabetes in psychiatric patients receiving chemotherapy presented a new challenge to clinicians.

DISCUSSION

Case studies and thoughtful naturalistic publications prior to the availability of phenothiazines, albeit poor in design, still help the modern clinician to ask valid questions and gain an insight into possible pathological conditions associated with schizophrenia. They raise the intriguing possibility that diabetes and disturbed carbohydrate metabolism could be an integral part of the schizophrenia disease process.

Even in historical publications, schizophrenia seems to be associated with higher rates of diabetes. Research today is focusing on trying to explain how psychotropic medications, lifestyle and other metabolic factors could possibly precipitate or unmask diabetes in people with schizophrenia.

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CLINICAL IMPLICATIONS

- People with schizophrenia are naturally predisposed to develop diabetes, even before they have been given antipsychotic medication.
- Phenothiazines appear to be associated with impaired glucose tolerance.
- Impaired glucose tolerance and diabetes are often 'hidden' in the population with schizophrenia, suggesting an imperative to screen.

LIMITATIONS

- Evidence from historical publications focuses on case reports and naturalistic studies.
- Diagnostic categories were poorly defined in early reports of an association between schizophrenia and diabetes.
- Studies conducted in the pre-neuroleptic era did not have statistical rigour or power.

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