

Diet, diabetes and schizophrenia: review and hypothesis

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Background Diabetes is more common in people with schizophrenia than in the general population.

Aims To explore the possible reasons for the association between diabetes and schizophrenia.

Method Diet and other lifestyle factors in patients with schizophrenia were reviewed as risk factors for diabetes.

Results People with schizophrenia show features of the metabolic syndrome at the onset of illness, before treatment. They also eat a poor diet, take little exercise and have high rates of smoking. Food intake may be increased further by antipsychotic medication. Nutritional factors appear to have a key role in the development of diabetes in patients with schizophrenia and may also affect the outcome and severity of schizophrenia. A common pathway through which diet might contribute to the development of both diabetes and schizophrenia is proposed.

Conclusions Lifestyle factors may influence outcomes in both diabetes and schizophrenia. Lifestyle interventions are the key to improving the long-term health of people with schizophrenia.

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It is well recognised that there is an increased incidence of type 2 diabetes in people with a diagnosis of schizophrenia (Brown *et al*, 2000). The evidence suggests that this is not only due to the effect of medication, but is associated independently with the schizophrenic illness itself. Insulin resistance was demonstrated in people with schizophrenia even before antipsychotic medication was available, and this has now been confirmed in drug-naïve patients (Ryan *et al*, 2003).

Insulin resistance and type 2 diabetes are manifestations of the metabolic syndrome, which is strongly influenced by diet. The risk of the metabolic syndrome being expressed as disease is much reduced by diets that are low in saturated fat, high in polyunsaturated fatty acids (especially omega-3), low in glycaemic load, high in fibre, and contain adequate amounts of fresh fruits, vegetables, nuts and pulses (Mann, 2002). Dietary factors are also important in reducing the risk of diabetes and coronary heart disease for people with schizophrenia, just as for the rest of society. However, the possibility that nutritional factors might also affect mental health has been neglected.

METHOD

The literature is reviewed, relating to diet and other lifestyle factors in schizophrenia patients as risk factors for diabetes. A hypothesis is developed that proposes a common pathway through which lifestyle factors might contribute to the development of both schizophrenia and diabetes.

RESULTS

Ecological studies of diet and schizophrenia

The long-term outcome of schizophrenia is better in developing countries such as India and Nigeria than in developed countries

such as the UK and USA (Hopper & Wanderling, 2000). At first sight this is counterintuitive, since Western developed nations have superior medical resources. As yet unidentified social factors have been postulated to account for this. Diet is largely determined by social, cultural and political factors and is therefore pertinent to investigate in this context. It is notable that the pattern of a better outcome of schizophrenia in developing countries mirrors the pattern shown by diseases of the metabolic syndrome, which are also less common in developing countries than in developed nations (Tucker & Buranapin, 2001).

Two ecological studies of diet in relation to schizophrenia have now been completed. 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.

Diet of people with schizophrenia

The diet of the general public falls far short of the WHO recommendations for a healthy diet (World Health Organization, 2003). Young people – who are at the age of greatest risk for schizophrenia – have a particularly poor diet, consuming large quantities of burgers, fries and full-sugar carbonated drinks (Henderson *et al*, 2002). Studies have suggested that people with schizophrenia have an even worse diet than the general population. 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-naïve patients with first-episode schizophrenia consumed substantially more saturated fat than carefully matched, healthy comparison individuals. Another recent study (Stokes, 2003) found that sugar consumption was high among a group of schizophrenia patients, and that most of this was due to excessive sugar consumption by patients with treatment-resistant disease taking clozapine. 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.

In summary, people with schizophrenia consume the 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). Furthermore, there is emerging evidence of an association between dietary factors and the severity and long-term outcome of schizophrenia.

Other lifestyle issues

A low level of exercise and the number of pack-years of cigarettes smoked are both independent predictors of the central metabolic syndrome (Parker *et al*, 2003). People who have a sedentary lifestyle, participating in no vigorous physical activity and watching more than 4 h of television a day, are more prone to obesity and cardiovascular disease risk factors (Jakes *et al*,

2003). Smoking has been proposed as an independent risk factor for the development of diabetes (Rimm *et al*, 1995).

Lack of exercise and high levels of smoking are also typical of people with schizophrenia. It has been suggested that the sedative effect of antipsychotic medication might contribute to the sedentary lifestyle of patients with schizophrenia, although a study of adolescents with schizophrenia showed that daily energy expenditure was very low even before treatment with antipsychotic agents (Gothelf *et al*, 2002). Smoking is much more prevalent among patients with schizophrenia than in the general population, and Kelly & McCreadie (1999) found that in 90% of cases the smoking preceded the onset of schizophrenia.

Nicotine can lead to temporary improvement in cognitive function, which may explain why people with schizophrenia like to smoke (Levin & Rezvani, 2002). Kelly & McCreadie (1999) suggested that smoking may be associated with the neurodevelopmental form of schizophrenia, as it occurs more frequently in patients with poor premorbid childhood adjustment (Kelly & McCreadie, 1999) as well as predominant negative symptoms (Patkar *et al*, 2002) and a tendency to develop tardive dyskinesia (Chong *et al*, 2003).

Effects of antipsychotic medication on food intake

Antipsychotic medication can cause people to eat more (Briffa & Meehan, 1998; Gothelf *et al*, 2002). People with schizophrenia make poor dietary choices, so that any increase in appetite is likely to lead to an increased intake of snack and convenience foods, which are high in fat and sugar. Increased food intake leading to obesity was recognised in the early days of treatment with chlorpromazine and depot antipsychotic medications (Silverstone *et al*, 1988), and the problem of weight gain and diabetes has been highlighted in relation to atypical antipsychotic medication (Sernyak *et al*, 2002). However, an increase in obesity in the population of people with schizophrenia must be assessed against a background increase of obesity in the general population (Homel *et al*, 2002).

The mechanism by which antipsychotic medications increase food intake is probably related to their effect upon dopamine and serotonin receptors (Kaur & Kulkarni, 2003). Increased levels of circulating leptin

have been found after treatment with both conventional and atypical antipsychotic agents (Hagg *et al*, 2001). Leptin is produced by adipose cells and acts on the hypothalamus to reduce appetite. Obese people are often resistant to this effect of leptin (Zabeau *et al*, 2003), but there is no good evidence to suggest that antipsychotic medications have a primary effect on leptin resistance. Neither do they have a primary effect on pancreatic β -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

Insulin resistance results from an interplay of genetic and lifestyle factors (Ukkola & Bouchard, 2001). Insulin resistance is not in itself necessarily harmful and indeed may confer an evolutionary advantage (Colagiuri & Miller, 2002). Australian aboriginals show evidence of increased insulin resistance but this does not manifest itself as pathological until they give up their traditional lifestyle and adopt Western dietary practices (O'Dea, 1991). People with schizophrenia who exhibit insulin resistance at the start of their illness will therefore have an increased susceptibility to the adverse effects of a poor diet.

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 (Mukherjee *et al*, 1989). 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 (Gorski *et al*, 2003), 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 (Webster *et al*, 2002). 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 (Lessman *et al*, 2003). It has recently been shown that BDNF expression is reduced in the prefrontal cortex of patients with schizophrenia, and it was suggested that this might be a central component of the disease process (Weickert *et al*, 2003). Polymorphism of the BDNF gene has been associated with the susceptibility to schizophrenia (Szekeres *et al*, 2003) and with clozapine responders (Hong *et al*, 2003). It is known that brain expression of BDNF is reduced by a high-fat, high-sugar diet (Molteni *et al*, 2002) and increased by exercise (Cotman & Berchtold, 2002). 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, it is possible to construct a hypothesis whereby the 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.

DISCUSSION

Clinical importance of lifestyle interventions in schizophrenia

In order to reduce the risk of obesity, diabetes and coronary heart disease in people with schizophrenia, the importance of a healthy lifestyle – including good dietary practices and sufficient exercise – cannot be overemphasised. Because insulin resistance is a feature associated with schizophrenia independently of any specific drug treatment, lifestyle advice should be given to all patients with a diagnosis of schizophrenia. This should start immediately as part of the package of care at the first onset of illness.

The evidence presented allows the hypothesis that a diet low in saturated fat, high in polyunsaturated fatty acids and low in glycaemic load might be beneficial also in alleviating the symptoms of schizophrenia. There are five placebo-controlled trials of omega-3 fatty acids in the treatment of schizophrenia, of which three showed significant benefit, one showed benefit of omega-3 fatty acids only in a subgroup of patients already receiving treatment with clozapine, and one showed no advantage of omega-3 fatty acids over placebo (Peet, 2004). The proposition that the symptoms and the outcome of schizophrenia might be improved by a diet low in saturated fat and low in sugar has not been systematically investigated, although there are anecdotal reports of the successful use of this approach (Meiers, 1973).

Unfortunately, there is a dearth of evidence concerning the best way to achieve lifestyle changes in patients with schizophrenia. Werneke *et al* (2003) reviewed all studies assessing the behavioural management of antipsychotic-induced weight gain, including both dietary and exercise interventions. They found that current studies were methodologically flawed, with none meeting the criteria for a randomised controlled trial. Approaches aimed at the

management of obesity in the general population (Glenny *et al*, 1997) are not necessarily transferable to people with schizophrenia.

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CLINICAL IMPLICATIONS

- The metabolic syndrome and diabetes are associated with schizophrenia independently of medication.
- There is evidence that dietary factors may affect not only diseases of the metabolic syndrome, but also the severity and outcome of schizophrenia.
- Diet and lifestyle advice should be an integral part of the management of schizophrenia.

LIMITATIONS

- The evidence for an effect of nutrition on schizophrenic symptoms is limited.
- The proposed mechanism linking diet, diabetes and schizophrenia is speculative.
- There is only limited evidence on how to alter the diet and lifestyle of people with schizophrenia.

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