Metabolic syndrome and schizophrenia

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Metabolic syndrome – a cluster of disorders comprising obesity (central and abdominal), dyslipidaemias, glucose intolerance, insulin resistance (or hyperinsulinaemia) and hypertension – is highly predictive of type 2 diabetes mellitus and cardiovascular disease. In order to improve detection of this syndrome and estimate its prevalence, both the World Health Organization (Alberti & Zimmet, 1998) and the National Cholesterol Education Program Adult Treatment Panel (National Cholesterol Education Program, 2001) have provided working criteria for its diagnosis (the World Health Organization criteria are reproduced in an appendix to this paper; copyright restrictions prevent the inclusion here of the National Cholesterol Education Program criteria). Using the latter criteria, Heiskanen *et al* (2003) found that the frequency of metabolic syndrome was 2–4 times higher in a group of people with schizophrenia, treated with both atypical and typical neuroleptics, than in an appropriate reference population.

NEUROLEPTICS AND WEIGHT GAIN

Neuroleptics as a class can induce weight gain, with some agents having a greater propensity to do so than others, which may explain why patients with schizophrenia are at a higher risk for developing certain features of the metabolic syndrome (American Diabetic Association, 2004). Yet, the metabolic potential of weight is location-dependent. Large amounts of intra-abdominal fat are typically associated with adverse metabolic consequences. One group of investigators found that people with schizophrenia (both those with first episodes and those chronically exposed to conventional medications) have more than three times as much intra-abdominal fat as controls matched for age, gender and lifestyle and that 6 months of treatment with either olanzapine or risperidone, although increasing body mass index, does not significantly increase visceral fat stores (Thakore *et al*, 2002; Ryan *et al*, 2004*a*). In contrast, Zhang *et al* (2004) have shown that intra-abdominal fat stores are similar in Chinese individuals with first-episode schizophrenia and controls, but that 10 weeks of treatment with either risperidone or chlorpromazine significantly increased this fat depot. A number of methodological differences between the three studies may explain the apparent discrepancy; for instance, Zhang *et al* (2004) used elderly men as their control group (intra-abdominal fat increases with age), diet and exercise were not systematically examined and standardised scanning protocols were not employed.

SCHIZOPHRENIA AND DIABETES

Following their Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes, the American Diabetic Association (2004) noted that the aetiology of the increased prevalence of type 2 diabetes mellitus in psychiatric disorders was uncertain, although it might be due to the weight gain associated with certain atypical antipsychotic agents. This conclusion was based on data obtained from observational epidemiology, case reports and non-randomised cross-sectional studies. However, the issue is not straightforward, and two prospective studies in drug-naïve individuals with first-episode schizophrenia found that fasting plasma glucose concentration does not significantly change following either 10 weeks of treatment with risperidone or 52 weeks of treatment with either clozapine or chlorpromazine (Lieberman *et al*, 2003; Zhang *et al*, 2004).

Another possibility to consider is that the higher rates of type 2 diabetes mellitus found in schizophrenia might be a function of the illness itself. For instance, unaffected first-degree relatives of people with schizophrenia have high rates of type 2 diabetes mellitus (19–30%), pointing to a genetic association between these two disorders (Mukherjee *et al*, 1989). Furthermore, glucose dysfunction was documented in the pre-antipsychotic era, and over 15% of drug-naïve individuals with first-episode schizophrenia have impaired fasting glucose levels, hyperinsulinaemia and high levels of the stress hormone, cortisol (Ryan *et al*, 2003).

CAN STRESS LEAD TO METABOLIC INSTABILITY?

Long-standing 'stress' may have a role in the pathogenesis of obesity-related illness. A biological correlate of such stress is chronic activation of the hypothalamic–pituitary–adrenal (HPA) axis, as a result of either excess feed-forward activity caused by increased secretion of corticotrophin-releasing hormone or cytokines (such as interleukin 6), or defective feedback activity due to glucocorticoid receptor resistance leading to hypercortisolaemia. Whether such changes occur in schizophrenia is in doubt, as evidence to support a dysfunctional HPA axis in this disorder is not universally found (Holsboer, 1998). In order to address the confounding variables of neuroleptic treatment (which can affect plasma levels of cortisol), drug-naïve individuals with first-episode schizophrenia were tested during the period 13.00 h to 16.00 h (a time frame that correlates well with 24 h cortisol oversecretion) (Hellewell, 1999; Ryan *et al*, 2004*b*). They were found to have higher levels of corticotrophin and cortisol than did normal controls, indicating that they have an overactive HPA axis (Ryan *et al*, 2004*b*). Indirect support for the hypothesis that chronic stress can lead to metabolic changes comes from the observation that melancholic depression and Cushing syndrome are associated with physical illnesses related to hypercortisolaemia (Thakore, 2001).

SCREENING FOR THE METABOLIC SYNDROME

In view of the evidence for an increased prevalence of metabolic syndrome in

schizophrenia, individuals presenting with a first episode of psychosis should be screened using one of the sets of diagnostic criteria (Alberti & Zimmet, 1998; National Cholesterol Education Program, 2001). Once they have been prescribed medication, patients should be monitored on a regular basis (American Diabetic Association, 2004). Apart from the blood tests mentioned in the Appendix, practical anthropometric measures of intra-abdominal fat are waist circumference (taken at the level of the umbilicus) and waist-to-hip ratio (measured standing; 'waist' is the minimum circumference measured at the navel and 'hip' is the widest circumference at the buttocks). Screening for diabetes is rather more complicated. The most reliable yet least practical test is the 2 h oral glucose tolerance test. Fasting or random plasma glucose levels are associated with high false negative rates (40–95%), resulting in the failure to detect a significant number of cases of type 2 diabetes mellitus. Psychiatrists should screen for such metabolic disturbances if patients have no access to primary care. Finally, simple lifestyle advice on the virtues of a balanced diet and regular exercise should be routinely given to all patients, as these are still the most effective ways of preventing diabetes and its related complications.

DECLARATION OF INTEREST

J.T. has received unrestricted educational grants from Bristol-Myers Squibb, Eli Lilly and Pfizer.

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(First received 5 January 2004, final revision 15 June 2004, accepted 9 August 2004)

APPENDIX

World Health Organization criteria for metabolic syndrome (from Alberti & Zimmet, 1998, with permission)

Insulin resistance and/or impaired fasting glucose and/or impaired glucose tolerance AND two or more of the following:

(a) waist–hip ratio >0.90 (men), >0.85 (women) OR body mass index $\geqslant 30\ kg/m^2$;

(b) triglyceride level $\geqslant$1.7 mmol/l OR high-density lipoprotein <0.9 mml/l (men), <1.0 mmol/l (women);

(c) blood pressure $\geqslant$140/90 mmHg (or treated hypertension);

(d) microalbuminuria.

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