

## METABOLIC SYNDROME IN PATIENTS WITH PSYCHOTIC DISORDERS: diagnostic issues, comorbidity and side effects of antipsychotics

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### SUMMARY

**Background:** Metabolic syndrome and other cardiovascular risk factors are highly prevalent in people with schizophrenia. Metabolic syndrome can contribute to significant morbidity and premature mortality and should be accounted for in the treatment of mental disorders. Along with results of numerous investigations regarding metabolic syndrome, different issues have occurred. The aim of this article is to review literature regarding diagnostic and treatment of metabolic syndrome and point at some issues regarding diagnostic and treatment of metabolic syndrome in patients with psychotic disorders and in general population.

**Content analysis of literature:** Literature research included structured searches of Medline and other publications on the subject of metabolic syndrome, particularly diagnostic and treatment of metabolic syndrome in patients with psychotic disorders and in general population.

**Conclusion:** Despite numerous investigations of metabolic syndrome, many issues remain unclear, becoming objectives for future research. The experts disagree in their opinions on particular issues, such as clustering risk factors, importance of particular diagnostic procedures for the early detection and monitoring of metabolic syndrome and the role of antipsychotics in occurrence of metabolic syndrome. There is, however, unique attitude about importance of early detection and treatment of metabolic syndrome as well as necessity of further investigations.

**Key words:** psychotic disorder – metabolic syndrome – side effects - antipsychotics

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### INTRODUCTION

Metabolic syndrome has been a target of many investigations in the past years. Results of investigations show that people with schizophrenia are at greater risk of obesity, diabetes type II, dyslipidaemia and hypertension than the general population. This results in an increased incidence of cardiovascular disease and reduced life expectancy (Barnett et al. 2007). Metabolic syndrome can contribute to significant morbidity and premature mortality and should be accounted for in the treatment of mental disorders (Jakovljević et al. 2007). Persons with major mental disorders lose 25 to 30 years of potential life in comparison with the general population, primarily due to premature cardiovascular mortality (Newcomer 2007). Metabolic syndrome and other cardiovascular risk factors are highly prevalent in people with schizophrenia. Patients are at risk for premature mortality and overall have limited access to physical health care. In part these cardio-metabolic risk factors are attributable to unhealthy lifestyle, including poor diet and sedentary behavior (DE Hert et al. 2009a). The results of previous investigations on the subjects of metabolic syndrome pointed at importance of early

detection and monitoring of metabolic risk factors, as well as treating patients with metabolic syndrome. Along with results of numerous investigations regarding metabolic syndrome, different issues have occurred, including even the name of this syndrome – metabolic syndrome, Syndrome X, etc. Reaven called the clustering of several risk factors (e.g. dyslipidemia, hypertension, hyperglycemia) Syndrome X (Reaven 1988). Other researchers use the term metabolic syndrome for the clustering of metabolic risk factors.

The aim of this article is to review literature regarding diagnostic and treatment of metabolic syndrome and point at some issues regarding diagnostic and treatment of metabolic syndrome in patients with psychotic disorders and in general population.

### CONTENT ANALYSIS OF LITERATURE

Literature research included structured searches of Medline and other publications on the subject of metabolic syndrome, particularly diagnostic and treatment of metabolic syndrome in patients with psychotic disorders and in general population.

## Diagnostic issues

There is no unique definition of metabolic syndrome. It depends on which group of experts is quoted. The differences include different disorders constituting metabolic syndrome, and sometimes different referent ranges for the same disorder (e.g. referent ranges for high blood pressure or impaired fasting glucose values). Although the differences may seem slight, in the same time the comparison of results of different investigations on this subject becomes more complicated.

Another issue is should we use the same referent ranges for metabolic risk factors (for instance regarding waist circumference or body mass index (BMI)) for every man / woman, anywhere in the World? In case of different standards, again, the problem of comparison of the results based on different referent ranges occurs. In the study that aimed to determine the sensitive cut-off values of waist circumference (WC) in relation to the BMI for detecting the clustering of cardiovascular risk factors in Japanese men and women it was concluded that for the early detection and management of clusters of cardiovascular risk factors a BMI-specific WC cutoff value of 80 cm for normal weight in both men and women and 89 cm for overweight men and 86 cm for overweight women should be discriminate cutoff values (Lee et al. 2010). In the study that aimed to determine the optimal cut-off points of WC and BMI at which cardiovascular risk factors can be identified with maximum sensitivity and specificity in a representative sample of the Tunisian adult population and to investigate any correlation between WC and BMI the results suggested a WC of 85 cm for both men and women as appropriate cut-off points to identify central obesity for the purposes of cardiovascular disease and diabetes-risk detection among Tunisians. WCs of 85 cm in men and 79 cm in women were the most sensitive and specific to identify most subjects with a BMI  $\geq 25$  kg/m<sup>2</sup> (Bouguerra 2007).

The question is, also, which parameters, for instance different anthropometric indices, are better predictors of the presence of cardiovascular disease risk factors. In the investigation performed in Korea, anthropometric indices, such as BMI, WC, and waist-to-height ratio (WHtR), were evaluated as predictors of the presence of cardiovascular disease risk factors in Korean adults. The WHtR cut-off value to predict diabetes mellitus, hypertension, and dyslipidemia was approximately 0.50 in men and 0.51 in women.

The WC cut-offs varied from 81.6 to 85.2 cm in men and from 78.1 to 81.9 cm in women. The optimal BMI cut-off point varied from 23.0 to 24.7 kg/m<sup>2</sup> in both men and women. It was concluded that WC or WHtR may be a better predictor of cardiovascular disease risk factors than BMI in Korean adults (Park et al. 2009). In a meta-analysis of published literature that aimed to determine which simple index of overweight and obesity is the best discriminator of cardiovascular risk factors, BMI was the poorest discriminator for cardiovascular risk factors. WHtR was the best discriminator for hypertension, diabetes, and dyslipidemia in both sexes. It was concluded that statistical evidence supports the superiority of measures of centralized obesity, especially WHtR, over BMI, for detecting cardiovascular risk factors in both men and women (Lee et al. 2008).

Many different investigations observed relation between disorders that constitute metabolic syndrome and cardiovascular disease and diabetes type II. The concept of a clustering of risks factors leading to cardiovascular disease and diabetes is well accepted, today. Previous investigations showed that patients with schizophrenia are at increased risk of developing diabetes mellitus (Blonde et al. 2008), and researchers are underlining the importance of early detection of diabetes. Researchers have different opinions on the value of performing oral glucose tolerance test (OGTT) in patients with schizophrenia. In the investigation that aimed to assess the diagnostic properties of 2 different screening guidelines for the detection of diabetes in patients diagnosed with schizophrenia, the sensitivity of 2 screening strategies was compared with the "gold standard": the OGTT. The 2 strategies were (1) assessing fasting glucose in all patients, as suggested by the American Psychiatric Association/ American Diabetes Association (APA/ADA), and (2) a screening strategy derived from the guidelines of the World Health Organization (WHO) of assessing fasting glucose in all patients (step 1) and subsequently performing an OGTT in patients with impaired fasting glucose (step 2). The guidelines to detect diabetes as proposed by the APA/ADA did not sufficiently detect diabetes in this specific high-risk group. The alternative 2-step strategy was able to detect the vast majority of diabetes cases and the authors concluded that it should therefore be considered in the clinical routine of screening and monitoring patients with schizophrenia (van Winkel et al 2006). Still, investigations point to necessity of

evaluation of confounding factors, such as medications known to affect plasma glucose (e.g. oral corticosteroids), that could cause misleading results (Ryan et al. 2009).

### **Treatment issues**

People with severe mental illnesses, such as schizophrenia, depression or bipolar disorder, have worse physical health and reduced life expectancy compared to the general population. Patients with schizophrenia are at risk of undetected somatic comorbidity. They present physical complaints at a late, more serious stage (Oud & Meyboom 2009). Patients may have limited access to general healthcare with less opportunity for cardiovascular risk screening and prevention than would be expected in a non-psychiatric population (DE Hert et al. 2009b).

Factors that are related to the mental illness (e.g., cognitive impairment, reduced ability to function, and a lack of communication skills) as well as factors such as the high cost of medical care may make accessing general health care a difficult task for patients. Even when medical care is received by patients, the quality is often poor, and dangerous illnesses may be undiagnosed and untreated (Fagiolini & Goracci 2009).

In the investigation that aimed to examine whether persons with severe mental disorder, defined as persons admitted to a psychiatric hospital with bipolar affective disorder, schizoaffective disorder, or schizophrenia, were in contact with hospitals and undergoing invasive procedures for heart disease to the same degree as the nonpsychiatric general population, and to determine whether they have higher mortality rates of heart disease, individuals with severe mental disorder had only negligible excess rates of contact for heart disease. The authors furthermore concluded that given their excess mortality from heart disease and lower rates of invasive procedures after first contact, it would seem that the treatment for heart disease offered to these individuals was neither sufficiently efficient nor sufficiently intensive, and that this undertreatment may explain part of their excess mortality (Laursen et al. 2009).

Evidence from data linkage analyses to clinical trials demonstrate that smoking, poor diet, reduced physical activity and alcohol or drug abuse are prevalent in people with schizophrenia and contribute to the overall cardiovascular disease risk (Barnett et al. 2007). The results of the study that examined the detailed body composition of people

with different psychotic disorders in a large population-based sample showed that individuals with schizophrenia have metabolically unfavorable body composition, comprising abdominal obesity, high fat percentage and low muscle mass. This leads to increased risk of metabolic and cardiovascular diseases (Saarni et al. 2009). Investigations are aiming to evaluate effectiveness of different nonpharmacological approaches, such as diet and exercise in the prevention and treatment of metabolic disorder. Results of previous investigations have confirmed usefulness of implementation of wellness programs during treatment of patients with schizophrenia with metabolic syndrome (Lindenmayer et al. 2009).

The question is what kind of exercise and what kind of diet produces best results? The results of a previous investigation showed that physical inactivity had profound negative effects on lipoprotein metabolism. Modest exercise prevented this. Moderate-intensity but not vigorous-intensity exercise resulted in sustained very-low-density lipoprotein (VLDL)-triglyceride lowering. Thirty minutes per day of vigorous exercise, like jogging, had sustained beneficial effects on high-density lipoprotein (HDL) metabolism (Slentz et al. 2007). The results of another investigation showed that weight loss induced by increased daily physical activity without caloric restriction substantially reduced obesity (particularly abdominal obesity) and insulin resistance in men, while exercise without weight loss reduced abdominal fat and prevented further weight gain (Nicklas et al. 2009). Another study showed that daily exercise without caloric restriction was associated with substantial reductions in total fat, abdominal fat, visceral fat, and insulin resistance in women. Exercise without weight loss was also associated with a substantial reduction in total and abdominal obesity (Ross et al. 2004). In the investigation that aimed to examine the relationship between dietary patterns and metabolic syndrome the results confirmed the deleterious effect of a very-low-fat, high-carbohydrate diet and also of high intakes of animal products. The consumption of a diet high in vegetal fats or rich in fruits and vegetables was associated with a healthier metabolic profile (Leite & Nicolosi 2009).

The issue of participation of patients with schizophrenia and other psychotic disorders in different diet and exercise programs, however, remains.

The contribution of treatment with antipsychotics to occurrence of metabolic

syndrome, diabetes and cardiovascular disease is also a target of investigations. Antipsychotic treatment, in particular with some second-generation antipsychotics, is associated with weight gain and other metabolic side effects (Birkenaes et al. 2008). Never the less, it is not clear in what extent side effects of antipsychotics contribute to such development, especially as a general conclusion.

In order to establish the side effects of treatment with antipsychotics, patients should be monitored from the beginning of treatment, enabling comparison of baseline values (e.g. body weight, fasting plasma glucose, A1c levels, lipid profile hemoglobin) and values of the same parameters during treatment. Guidelines for such monitoring are described in different guidelines for treatment of schizophrenia (American Psychiatric Association 2004; Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for the Treatment of Schizophrenia and Related Disorders 2005).

In the investigation that aimed to further define the metabolic profiles of second-generation antipsychotics during the treatment of young patients with early psychosis, the results showed that weight gain and metabolic syndrome occur commonly even in young patients receiving antipsychotic treatment for early psychosis. The authors concluded that targeted interventions are therefore warranted from the onset of antipsychotic therapy (Patel et al. 2009). Furthermore, the results of the investigation that aimed to determine whether the coprescribing of two or more antipsychotics is associated with an increased prevalence of metabolic syndrome showed that, compared with patients receiving antipsychotic monotherapy, patients on antipsychotic polytherapy had higher rates of metabolic syndrome and lipid markers of insulin resistance (triglycerides/high-density lipoprotein cholesterol ratio > 3.5 (TG/HDL), a sensitive marker of insulin resistance) (Correll et al. 2007).

Second generation antipsychotics induce substantial weight gain but the mechanisms responsible for this phenomenon remain speculative. In the investigation that aimed to explore eating behaviors among SGA-treated patients and compare them with nonschizophrenic healthy sedentary individuals (controls), the findings suggested that patients under SGA seem to develop disordered eating behaviors in response to altered appetite sensations and increased susceptibility to hunger, a factor which may

influence the extent of body weight gain triggered by these drugs (Blouin et al. 2008).

However, case reports tentatively suggest that substantial weight gain or obesity may not be a factor in up to one-quarter of cases of new-onset diabetes that occur during treatment (Newcomer 2005). There is evidence that schizophrenia itself is an independent risk factor for impaired glucose tolerance, which is a known risk factor for developing type 2 diabetes, regardless of whether patients receive antipsychotic medication (Ryan et al. 2003, Bushe & Holt 2004).

Side effects of antipsychotics may cause diagnostic problems in deciding regarding the origin of such symptoms (somatic illness vs. side effects) during treatment of psychotic disorders. Bearing in mind frequent comorbidity between of psychotic and somatic disorders, early recognition of such comorbidity is important, as well as the selection of antipsychotics. It is important to recognize psychotic symptoms in patients with somatic illnesses, as well as somatic illness in patients primarily treated because of psychotic disorder (Kozumplik et al. 2009). Guidelines recommend that side effects should be monitored regularly, and the side effect profile of the prescribed antipsychotic should be considered. In case of unacceptable side effects, changing to a different antipsychotic is recommended (Kozumplik & Uzun 2009).

## CONCLUSION

Despite numerous investigations of metabolic syndrome, many issues remain unclear, becoming objectives for future research. The experts disagree in their opinions on particular issues, such as clustering risk factors, importance of particular diagnostic procedures for the early detection and monitoring of metabolic syndrome and the role of antipsychotics in occurrence of metabolic syndrome. There is, however, unique attitude about importance of early detection and treatment of metabolic syndrome as well as necessity of further investigations.

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