



## RISK ASSESSMENT AND MANAGEMENT OF METABOLIC SYNDROME DUE TO ANTIPSYCHOTIC MEDICATION

Rucsandra Dănciulescu Miulescu<sup>1</sup>, Mădălina Mușat<sup>1</sup>, Suzana Dănoiu<sup>2</sup>,  
Cătălina Poiană<sup>1</sup>, C. Dumitrache<sup>1</sup>

1 Carol Davila University of Medicine and Pharmacy Bucharest,

2 University of Medicine and Pharmacy, Craiova

---

**Abstract.** The metabolic syndrome is comprised of several cardiovascular risk factors such as central obesity, hyperglycemia, hypertension and hyperlipidemia, most probably pathogenically correlated. Patients with schizophrenia have an increased risk of developing metabolic syndrome due to inappropriate physical activity, disorders of food intake or secondary to antipsychotic medication. Due to the increased prevalence of metabolic syndrome and diabetes mellitus in patients with schizophrenia, the American Association of Psychiatry recommends screening and follow-up for metabolic risk factors. Thus the recommendation is to assess fasting glycemia and glycated hemoglobin at 4 months from commencement of a new drug therapy, then annually. BMI has to be monitored every 3 to 6 months. Except for the patients with a BMI below 18.5, every increment of their BMI of 1kg/m<sup>2</sup> should be followed by either a change in antipsychotic medication or the admission of the patient in a weight control program.

**Keywords:** metabolic syndrome, schizophrenia, antipsychotic drugs

---

### Introduction

The metabolic syndrome is comprised of several cardiovascular risk factors such as: central obesity, hyperglycemia, hypertension, and hyperlipidemia, most probably pathogenically correlated. Several expert groups: World Health Organization (WHO) [1], European Group for the Study of Insulin Resistance (EGIR) – 1992 [2], The National Cholesterol Education Program (NCEP) – 2001 [3] have established and reviewed diagnostic criteria for the metabolic syndrome.

In 1999 the WHO has defined metabolic syndrome as the association of diabetes mellitus or impaired glucose tolerance with two of the following: hypertension, (BP >140/90 mmHg), hy-

perlipidemia (plasma triglycerides  $\geq$  150 mg/dl or HDL cholesterol  $\leq$  35 mg/dl in men and  $\geq$  39 mg/dl in women), albuminuria  $>$  20  $\mu$ g/min, obesity (BMI  $>$  30kg/m<sup>2</sup> or waist to hip ratio  $>$  0.90 in men, respectively  $>$ 0.85 in women). The EGIR definition of metabolic syndrome is slightly different from the WHO one: this uses hyperinsulinemia as marker for insulin resistance and abdominal circumference as measure of obesity.

In 2001 the NCEP ATP III revised the above criteria and defined metabolic syndrome as the association of 3 or more of the following:

- waist  $\geq$  102 cm in men and  $>$ 88cm in women
- plasma triglycerides  $\geq$  150 mg/dl or HDL cholesterol  $<$  40 mg/dl in men, respectively HDL  $<$  50 mg/dl in women,
- fasting glycemia  $\geq$ 110 mg/dl,
- blood pressure  $\geq$  130/85 mmHg.

In 2005 the International Diabetes Federation (IDF) revised the diagnostic criteria for metabolic syndrome [4] defined by central obesity plus at

least two of the following:

- plasma triglycerides  $\geq 150$  mg/dl or treatment for hyperlipidemia
- HDL cholesterol  $\leq 40$  mg/dl
- BP  $\geq 130/85$  mmHg or antihypertensive drugs
- fasting glycemia  $\geq 100$  mg/dl, or known diabetes mellitus

These obesity-focused criteria are easy to apply in clinical settings. They also have sharp cutoff values that are very close to the upper limit of what was previously considered normal.

This great variety of definitions renders difficult the comparison between various studies that have looked at the epidemiology of the syndrome. Thus in European population the incidence of metabolic syndrome as defined by WHO varies between 7 and 36% in men of 40-55 years of age and 5-22% in women of the same age [5].

+Epidemiological studies have demonstrated that the incidence of metabolic syndrome has increased overall in population, especially increasing with aging. Patients with schizophrenia have a higher risk of developing metabolic syndrome due to inappropriate physical activity, disorders of food intake or secondary to antipsychotic medication. De Hert et. al. have published a prospective study on the prevalence of metabolic syndrome in 415 patients with schizophrenia [6]. They used ATP III, slightly modifying fasting plasma glucose threshold to  $> 100$  mg/dl. The study has shown a higher prevalence of metabolic syndrome and diabetes mellitus in the schizophrenic patients compared to general population. Over time the prevalence of metabolic syndrome in schizophrenic patients increases with age as in general population and also with the duration of psychiatric disorder. In contrast, diabetes mellitus has a dramatic increase from 1.6% in age group 15-25 to 19.2% in age group 55-65. The prevalence of diabetes mellitus in age groups is 4-5 fold higher in schizophrenic patients as compared to general population.

The pathogeny of metabolic syndrome has not been completely elucidated. The suggested mechanisms involved are:

- insulin resistance
- increased release of free fatty acids from visceral fat that are subsequently used in VLDL synthesis and gluconeogenesis in the liver
- increased inflammatory cytokines and decreased adiponectin production in visceral fat [8].

#### Metabolic side effects of antipsychotic drugs:

- *Glucose homeostasis disorders.* Second generation antipsychotic drugs increase the risk of hyperglycemia and diabetes mellitus. Clozapine has been associated with ketoacidosis and hyperosmolar coma. However, the intimate mechanisms through which antipsychotic drugs cause hyperglycemia are not completely clear.
- *Hypertriglyceridemia*
- *Weight gain* can occur during antipsychotic therapy with 1<sup>st</sup> and 2<sup>nd</sup> generation drugs. This is encountered progressively during the first 6 months of treatment, but the process can continue in some patients beyond this period, too. The weight gain is presumably due to deregulation of various neurotransmitters [7].

#### Metabolic Syndrome- Associated conditions

**1. Endothelial dysfunction.** Disorders associated to metabolic syndrome alter endothelial auto- and paracrine function, thus impairing the vascular tonus. Endothelial cells release several vasoregulators, out of which the best-known is nitric oxide. Nitric oxide has vasodilating effects, but also exerts antiatherogenic actions by reducing proliferation of parietal smooth muscle cells, platelets aggregation, LDL oxidation, expression of adhesion molecules and monocyte adhesion. Metabolic syndrome components have a negative influence on nitric oxide production and its biological function, thus inducing oxidative stress and proinflammatory status. Endothelial dysfunction diminishes fibrinolysis, favoring platelets' aggregation and atherogenesis. Thus metabolic syndrome speeds up the atherogenic process.

**2. Hypertension.** Systolic hypertension in patients with metabolic syndrome is related to arterial stiffness. This is, at least partly, due to hyperinsulinemia in diabetic patients and in patients with impaired glucose tolerance. The two neurohormonal systems involved in hypertension and hyperinsulinemia are the sympathetic nervous system and the hypothalamus-pituitary-adrenal axis. Trigger factors involved in metabolic syndrome, such as excessive food intake, economic/social stress, anxiety, depression generate alteration in cortisol secretion, increase of leptin and sympathetic nervous system tonus, favoring hypertension, insulin resistance and central obesity.

**3. Hyperlipidemia.** Hypertriglyceridemia and low HDL-cholesterol are present in 40-50% of patients diagnosed with metabolic syndrome. However the condition is more complex involving

alterations in fatty acids degradation and triglycerides composition. Increase of LDL in triglycerides favors glycosilation and oxidation processes. Thus hyperlipidemia is a major risk factor in diabetes and atherosclerosis.

**4. Insulin resistance** plays a major role in metabolic syndrome pathogeny. It is involved in hyperlipidemia, hypertension, endothelial dysfunction, inflammatory and hypercoagulation status. Insulin also influences ions change, thermogenesis and cardiac function.

**5. Hepatic steatosis.** Several studies have suggested that non-alcoholic hepatic steatosis is associated with metabolic syndrome. The condition, characterized by excessive lipid storage in the liver and moderate hepatic cytolysis, is a major risk factor for type 2 diabetes and cardiovascular disease. The causes for non-alcoholic hepatic steatosis are insulin resistance and serum adipokines alteration [9].

**6. Endocrine disorders.**

In women, insulin resistance is associated with hyperandrogenism. Polycystic ovary syndrome is the most frequent endocrine disease in women of fertile age. Insulin resistance is involved in the etiopathogeny of the syndrome. There is a close correlation between hyperinsulinemia and hyperandrogenism in polycystic ovary syndrome:

- Increased levels of insulin bind to IGF1 (*insulin-like growth factor I*) receptors which resemble insulin receptors thus signaling through tyrosin kinase activation. In the ovary, IGF1 increases androgen production in theca cells in response to LH stimulation [10]. Insulin stimulates LH secretion from the pituitary, which in turn increases androgen production in the ovary [12].
- Hyperinsulinemia blocks SHBG (*sex hormone binding globulin*) synthesis in the liver, thus increasing free androgens and estrogens in plasma. Hyperinsulinemia also blocks the IGFBP-1 (*insulin-like growth factor binding protein*) level which releases free IGF1 and IGF2 which act in the ovary [11]
- Activation of IGF1 receptors in the endometrium increases proliferation and the risk of neoplasia.

In men, metabolic syndrome is frequently associated with low testosterone. Several studies have emphasized that low seric testosterone is an independent risk factor for metabolic syndrome. It is not clear what causes the decrease of testosterone in metabolic syndrome. One of the factors

involved is likely to be increased aromatization of androgens in the adipose tissue [13].

In psychiatric patients, various drugs can increase prolactin levels due to dopaminergic inhibition. Hyperprolactinemia in women gives rise to menstrual abnormalities, galactorrhea, infertility and osteoporosis. In men hyperprolactinemia gives rise to gynecomastia, erectile dysfunction and osteoporosis. In these patients with symptomatic drug-induced hyperprolactinemia, the American Association of Psychiatry recommends lowering of dosage or change in antipsychotic medication. If neither is possible, then bromocriptin 2-10 mg/day should be added to the psychiatric medication.

**Complications of metabolic syndrome**

**Cardiovascular disease.** Patients with metabolic syndrome have a double risk of cardiovascular disease compared to normal population and an increased mortality from cardiovascular causes (12% vs. 2% in normal population). Osby et al. studied mortality over 22 years (1973-1995) in 3928 men and 3855 women with schizophrenia. There was an increased overall mortality in schizophrenic patients. While suicide was the most frequently encountered cause of death in men, in women cardiovascular events were on the first place [14, 15].

**Diabetes mellitus.** Patients with metabolic syndrome have a fivefold risk of developing type 2 diabetes compared to general population. In schizophrenic patients the diabetes incidence is 4-5 fold higher compared to general population.

**IDF Recommendations for therapy in metabolic syndrome**

Once the diagnostic of metabolic syndrome has been established, the therapeutic goal is decreasing cardiovascular and diabetes risk.

First line intervention acts towards changes in lifestyle by:

- Reducing calory intake to obtain a weight loss of 5-10% within the first year
- Moderately increasing physical activity
- Optimizing nutrient composition of food intake with an increase of fibers
- Avoiding alcohol excess and ceasing smoke

Secondary intervention with drug therapy should be commenced in patients with a higher cardiovascular risk or in those in which the primary measures did not meet therapeutic goals. All the features of metabolic syndrome should be addressed.

**A. Goals in reducing hyperlipidemia:**

- Decrease of serum triglycerides
- Increase HDL

- Reduce LDL  
Means for tapering hyperlipidemia:
- Fibrates (alpha PPAR agonists) amend all components of hyperlipidemia in metabolic syndrome and seem to decrease cardiovascular risk in these patients. The VA-HIT trial (Veterans Affairs High Density Lipoprotein Intervention Trial) showed that fibrates increase HDL and reduce the incidence of acute coronarian events in patients with cardiovascular disease [16].
- Statins decrease ApoB- containing lipoproteins. There are several studies that emphasize the benefits of this therapy in metabolic syndrome [17,18].
- Fibrates-statins association if necessary should be closely monitored for an increased frequency of adverse events.

#### B. Hypertension therapy intervention:

- TA >140/90 mmHg should be treated according to the Seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure (JNC7) [19].
- TA > 130/80 mmHg should be addressed in all patients with diabetes mellitus.

Antihypertensive drug choice: ACE inhibitors or angiotensin receptor blockers. There are no recommendations for using a certain antihypertensive drug to control hypertension in association with metabolic syndrome.

#### C. Insulin resistance and hyperglycemia:

Diabetes Prevention Programme has stipulated that metformin therapy could prevent or delay diabetes onset in patients with prediabetes. Other studies suggest that *thiazolidinedione*, acarbose or orlistat could also delay diabetes onset in patients with impaired glucose tolerance [20, 21, 22, 23, 24].

Due to the increased prevalence of metabolic syndrome and diabetes in patients with schizophrenia, the American Association of Psychiatry recommends screening for monitoring metabolic risk factors in these patients.

At first visit the following should be noted:

- Family history
- Weight, height, BMI, waist measurement. A BMI 25-29.9kg/mp is considered a cut-off for the overweight threshold and a BMI over 30 for obesity.
- Blood pressure
- Fasting plasma glucose and diabetes risk factors (age over 45, low physical activity, first

grade relatives with diabetes mellitus, offsprings with an increased birth weight >4kg, history of gestational diabetes\* or impaired fasting glucose\* or glucose tolerance\*, obesity, polycystic ovary syndrome, hypertension, valvular disease, HDL < 35 mg/dl and/or triglycerides > 250 mg/dl). If one or two risk factors marked as \* is present, standard glucose tolerance test is recommended.

- Lipid level

D. The monitoring of metabolic risk factors is not standardized. There is a recommendation to monitor BMI at 3 to 6 months. An increase with 1 unit in BMI assessment indicates the necessity of introducing the patient in a program of weight maintenance or reduction (if BMI is not <18.5 kg/mp) or a change in antipsychotic therapy. Fasting plasma glucose or HbA1C should be reassessed at 4 months after starting a new drug, then annually.

Periodic assessment of metabolic risk factors is important in the prevention of metabolic syndrome and its complications in schizophrenic patients.

## References

1. **World Health Organization** - *Definition, diagnosis and classification of diabetes mellitus and its complications*. Geneva, 1999.
2. **Balkau B, Charles MA** - Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). *Diabet Med* 1999;16:442-443.
3. **Executive Summary of the third Report of The National Cholesterol Education Program (NCEP)**, Expert Panel on Detection Evaluation And Treatment of High Blood Cholesterol In Adults. *JAMA* 2001;285(19)2486-97.
4. **Alberti KG, Zimmet P, Show J** - IDF Epidemiology Task Force Consensus Group. The metabolic Syndrome-a new worldwide definition et al. *Lancet* 2005;366:1059-62.
5. **Lorenzo C, Serrano Rios M** - *Epidemiology of the Metabolic Syndrome in The Metabolic Syndrome at the Beginning of the XXI Century* 2005;7:110-123.
6. **De Hert et al.** *Clin Pract Epidemiol Mental Health* 2006;2:14
7. **American Psychiatric Association.** *Practice Guidelines for the Treatment of Schizophrenia (2nd Edn)* ( 2004).
8. **Standl E** - Aetiology and consequences of the metabolic syndrome *EHJ*, 2005 **Supplement D**, 7, D10-D13.
9. **Avogaro A, Natali A, Ferannini E, Hanefeld M, Scharper F et al** - *Related Diseases in the Metabolic Syndrome in The Metabolic Syndrome at the Beginning of the XXI Century* 2005;4:321-393.
10. **Bergh C, Carlsson B, Olsson JH, Selleskog U, Hillensjo T** - (1993), Regulation of androgen production in cultured human thecal cells by insulin - like growth factor I and insulin, *Fertil Steril* 59: 323.

11. **Buyalos RP** - (1995), The relationship between circulating androgens, obesity and hyperinsulinemia in serum insulin – like growth factor binding protein – 1 in the polycystic ovary syndrome. *Am J Obstet Gynecol* **172**: 932.
12. **Nestler JE** - (1997), Role of hyperinsulinemia in the pathogenesis of the polycystic ovary syndrome and its clinical implications. *Seminars reprod Endocrinol* **15**: 111.
13. **Jones TH** - *The role of testosterone in the metabolic syndrome the 1st congress on Controversies in Obesity, Diabetes and Hypertension, 2006, Berlin.*
14. **Osby, et al.** - *Schizophr Res* **2000**;45:21–28
15. **Brown, et al.** - *Br J Psychiatry* **1997**;171:502–508
16. **Robins SJ, Rubins HB, Faas FH et al.** - Insulin resistance and cardiovascular events with low HDL The Veterans Affairs High Density Lipoprotein Intervention Trial. *Diabetes Care* **2003**; **26** (5):1513-7.
17. **Heart Protection Study Collaborative Group** MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomized placebo-controlled trial. *Lancet* **2003**;361:2005-16.
18. **Haffner SM, Alexander CM, Cook TJ et al.** - Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes mellitus or impaired fasting glucose levels: subgroup analysis on the Scandinavian Simvastatin Survival Study. *Arch Intern Med* **1999**;159(22):2661-7.
19. **Cholbanian AV, Bakris GL, Black HR et al.** - Seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure. *Hypertension* **2003**;42(6):1206-52.
20. **Knowler Wc, Barrett-Connor E, Fowler SE et al.** - Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *NEJM* **2002**;346(6):393-403.
21. **Buchmanan TA, Xiang AH, Peters RK et al.** - Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* **2002**;51:2796-803.
22. **Durbin RJ** - Thiazolidinedione therapy in the prevention of type 2 diabetes in patients with impaired glucose tolerance and insulin resistance. *Diabetes, Obesity and Metabolism* **2004**;6:280-5.
23. **Chiasson JL, Josse RG, Gomis R et al.** - STOP-NIDDM Trial Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance. *JAMA* **2003** **23**;290(4):486-94.
24. **Torgerson JS, Hauptman J, Boldrin MN et al.** - XENICAL in the Prevention of Diabetes in Obese Subjects Study. *Diabetes Care* **2004**;27:155-61.