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THE PREVALENCE OF METABOLIC SYNDROME AND FRAMINGHAM CARDIOVASCULAR RISK SCORES IN ADULT INPATIENTS TAKING ANTIPSYCHOTICS - A RETROSPECTIVE MEDICAL RECORDS REVIEW

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SUMMARY

Background: *The objective of this retrospective records review was to evaluate the prevalence of metabolic syndrome (MetS) and Framingham cardiovascular risk scores in adult inpatients taking antipsychotics.*

Subjects and methods: *Hospital records of 62 patients (27 women and 35 men) taking antipsychotics were retrospectively reviewed for: body height and weight, waist circumference, cigarette smoking, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides (TGA), fasting plasma glucose (FPG), blood pressure, concomitant use of antidiabetic, antihypertensive and antihyperlipidemic medications.*

Results: *MetS was diagnosed in 29.0% (ATPIII), 35.5% (ATPIII A) and 41.9% (IDF) of patients. The prevalence of MetS components was: central obesity 50.0% (ATPIII and ATPIII A), 75.8% (IDF); hypertension 40.3% (ATPIII, ATPIII A and IDF); reduced HDL cholesterol 51.6% (ATPIII, ATPIII A and IDF); raised TGA 38.7% (ATPIII and ATPIII A), 41.9% (IDF); raised FPG 11.3% (ATPIII), 24.2% (ATPIII A) and 24.2% (IDF). Most of cardiovascular risk scores were higher in subjects with MetS. Mean BMI (28.4 kg/m2) and waist circumference (97.8 cm) were above cut-points for overweight and IDF-defined abdominal obesity. Mean total cholesterol (203.2 mg/dL) and TGA (159.1 mg/dL) levels were above upper limit of normal ranges. Overweight or obesity and abdominal obesity (more frequent in women: 88.9% vs. 65.7%; P=0.035) were found in 69.4% and 75.8% of the patients, respectively. Over 60% of subjects with hyperlipidemia (77.4% of the whole group) had no hypolipidemic therapy on discharge.*

Conclusions: *The prevalence of MetS in subjects taking antipsychotics exceeds the prevalence in general population. Its presence increases the risk of cardiovascular events. Increased body weight and metabolic abnormalities were frequent in our group of patients (particularly in women) taking antipsychotics. Most patients with hyperlipidemia had no antihyperlipidemic introduced.*

Key words: *antipsychotics - metabolic syndrome - cardiovascular risk*

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INTRODUCTION

Patients with psychiatric disorders have increased mortality resulting from, among others, increased risk of cardiovascular events (e.g. myocardial infarction, sudden cardiac death and stroke) (Correll et al. 2006). These events are closely related to metabolic abnormalities (raised lipids and glucose blood levels, central (abdominal) obesity, diabetes, hypertension). Metabolic syndrome (MetS) is a cluster of disorders comprising of abdominal obesity, hypercholesterolemia, hyperlipidemia, hypertension and abnormal blood glucose levels. Various criteria are used to diagnose MetS. International Diabetes Federation (IDF) criteria are the most widely used in European studies (Alberti et al. 2006). These are slightly more restrictive than American ATPIII criteria (Grundy et al. 2004). The presence of MetS increases the risk of death due to cardiovascular diseases. Comparing to general population, the prevalence of MetS is increased in patients taking psychotropic agents (De Hert et al. 2006, Kozumplik et al. 2010). This applies not only to antipsychotics, but also to mood stabilizers (Teixeira & Rocha 2007) and antidepressants (McIntyre et al. 2010). Treatment-induced metabolic disorders may account for up to 60% of premature deaths of people with serious mental illness (Parks et al. 2006).

Framingham cardiovascular (CVD) risk scores allow to estimate risk score profiles of various cardiovascular disease outcomes in different time horizons: coronary heart disease, type 2 diabetes, general cardiovascular disease and hypertension. Ten-year coronary heart disease risk is significantly elevated in schizophrenia patients (Goff et al. 2005). Jin et al. showed that middle-aged and older patients with psychotic symptoms (and thus taking antipsychotics) have increased 10-year risk of coronary heart disease (up to 79% in case of schizophrenia) (Jin et al. 2011).

The objective of this retrospective, chart review study was to evaluate the prevalence of metabolic syndrome and its components in in-hospital patients treated with antipsychotics. On the basis of metabolic data Framingham risk scores were calculated in order to assess the risk of various cardiovascular events. Our hypothesis is that the presence of metabolic syndrome increases risk scores for various cardiovascular events, at different time points.

SUBJECTS AND METHODS

Medical records of 62 European Caucasian patients (males, n=35; females, n=27) hospitalized in our unit of psychotic disorders were reviewed in a retrospective manner. The only inclusion criterion was current in-hospital antipsychotic treatment with at least one antipsychotic, irrespective of treatment type, previous treatment duration and diagnosis. The following data were acquired: body height and weight, waist circumference, cigarette smoking, lipid panel and glucose blood levels, blood pressure. Treatment of comorbidities (diabetes, arterial hypertension and hyperlipidemia) was also recorded. The study protocol was approved by the local Bioethics Committee. There was no financial involvement from the industry.

The blood for the chemistry panel that included fasting plasma glucose and lipid panel (total, HDL, and LDL cholesterol as well as triglycerides) was collected between 7 and 8 am, after ensuring at least 8 h of overnight fasting. The samples were immediately transferred to the central laboratory where they were analyzed. Plasma glucose and serum lipids were estimated using a Dirui CS-400 Auto-Chemistry Analyzer (Dirui, China).

Height was measured with a wall-mounted height measure to the nearest 1 cm. Weight was measured with a spring balance that was kept on a firm horizontal surface. Subjects wore light clothing, stood upright without shoes and weight was recorded to the nearest 1.0 kg. Body mass index (BMI) was calculated as body weight in kilogram divided by the height in meter (kg/m^2). Waist circumference was measured using a non-stretchable fiber measuring tape. Waist circumference was measured at a level midway between the lowest rib and the iliac crest.

MetS and its components were defined according to the National Cholesterol Education Program criteria (NCEP, Adult Treatment Protocol, ATPIII) (2001), adapted ATP-III criteria (ATPIII A) (Grundy et al. 2004) and International Diabetes Federation (IDF) criteria. These criteria are defined in Table 1. For IDF criteria, if body-mass index (BMI) was over 30 kg/m^2, central obesity was assumed irrespective of waist circumference (Alberti et al. 2005).

Impaired fasting glucose was defined as fasting plasma glucose level 110-125 mg/dL based on ADA guidelines (2004b), new onset of type 2 diabetes was defined as fasting plasma glucose level ≥125 mg/dL. Normal weight, overweight and obesity were defined as BMI <25 kg/m^2, 25-30 kg/m^2 and ≥30 kg/m^2, respectively. Raised triglycerides (TGA) level ≥150 mg/dL and/or total cholesterol (TC) ≥200 mg/dL and/or reduced HDL cholesterol level <40 mg/dL for men and <50 mg/dL for women and/or raised LDL cholesterol level ≥135 mg/dL were interpreted as hyperlipidemia. Castelli atherogenic indices (AI) allow to evaluate atherosclerosis risk (Castelli et al. 1983). $AI_{LDL/HDL}$ is the ratio of LDL cholesterol to HDL cholesterol and $AI_{TC/HDL}$ is the ratio of TC to HDL cholesterol. Low risk values are: $AI_{LDL/HDL} \leq 3.3$ for men and ≤2.9 for women; $AI_{TC/HDL} \leq 5.1$ for men and <4.4 for women.

Framingham cardiovascular risk scores were calculated using current Framingham Heart Study algorithms (http://www.framinghamheartstudy.org/risk/index.html) using variables including LDL level, HDL level, blood pressure, diabetes and smoking status. The following scores were calculated: coronary heart disease, 2-year risk (D'Agostino et al. 2000); coronary heart disease, 10-year risk (Wilson et al. 1998); type 2 diabetes, 8-year risk (Wilson et al. 2007); general cardiovascular disease (coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, heart failure), 10-year risk (D'Agostino et al. 2008); hard coronary heart disease (myocardial infarction or coronary death), 10-year risk (2001); recurring coronary heart disease (mostly hospitalized events consisting of myocardial infarction, coronary insufficiency, angina pectoris, and sudden and non-sudden coronary death), 2-year risk (D'Agostino et al. 2000); stroke, 10-year risk (D'Agostino et al. 1994); and arterial hypertension, 4-year risk. Next, the risk points were converted to corresponding percentage of risk (Parikh et al. 2008).

Table 1. Definitions of the metabolic syndrome

Criteria	ATP-III*	ATP-III A*	IDF†
Central obesity (waist circumference)	men >102 cm women >88 cm	men >102 cm women >88 cm	men ≥94 cm women ≥80 cm
Raised blood pressure or specific treatment	≥130/≥85 mm Hg	≥130/≥85 mm Hg	≥130/≥85 mm Hg
Reduced HDL level	men <40 mg/dL women <50 mg/dL	men <40 mg/dL women <50 mg/dL	men <40 mg/dL women <50 mg/dL
Raised TGA level	≥150 mg/dL	≥150 mg/dL	≥150 mg/dL or specific treatment
Raised FPG level or specific treatment	≥110 mg/dL	≥100 mg/dL	≥100 mg/dL

* MetS if 3 of 5 criteria are met; † MetS if central obesity (obligatory) and additional 2 criteria are met;
HDL = high density lipoproteins; TGA = triglycerides; FPG = fasting plasma glucose

Statistical Analysis

Statistical procedures were conducted with STATA 12.0 for OS X (StataCorp, Texas, USA). Simple descriptive statistics (means, standard deviations and 95% confidence interval) were generated for all continuous variables. For discrete variables number of patients and percentages are given. The difference between two group means was analyzed by Student's t-test. The difference between two group proportions was analyzed by chi-squared test. The significant level was set at $P<0.05$.

RESULTS

Detailed subject characteristics are shown in Table 2. For the majority of patients (74.2%) clinical diagnosis at discharge from the unit was schizophrenia. There were three subjects (4.8%) with a first episode of psychosis, other patients were taking antipsychotics for at least 4 months. During current hospital stay 93.5% of patients were taking second generation antipsychotics and 40 patients (64.5%) were taking more than one antipsychotic agent. Olanzapine, quetiapine, risperidone and aripiprazole were the most common. Five patients were also taking valproate (mean daily dose 1180±389.9 mg), 2 were taking lithium carbonate, another two - carbamazepine and 8 patients were taking selective serotonin reuptake inhibitors (SSRI). Women were significantly older, no other differences between men and women were found for subject characteristics.

Table 3 shows detailed anthropometric data and results of laboratory tests. Analysis of these data revealed that mean body height and weight were significantly lower in women. Both in men and women mean BMI was above 25 kg/m^2, the WHO overweight cut-point. Similarly, mean waist circumference was above IDF-defined abdominal obesity cut-points for men and women. Laboratory tests revealed no differences between men and women. There were no differences in anthropometric variables or laboratory result between smokers and non-smokers.

High rate of various metabolic abnormalities was found in the study group. Table 4 describes these in details with respect to body weight, hyperlipidemia, abnormal glucose levels and specific treatment of these abnormalities. Raised body weight (overweight or obesity) was found in 69.4% of the patients. Female patients were significantly more likely to meet the increased waist criterion according to IDF. What was particularly interesting is that while any type of hyperlipidemia was found in 77.4% of patients, only 16.7% of

Table 2. Subject characteristics

	All (N=62)	Men (N=35)	Women (N=27)	P
Age (years)	38.0±12.35 (34.85-41.12)	34.6±11.1 (30.80-38.46)	42.3±12.7 (37.32-47.35)	0.01† t=2.5
Diagnosis on discharge:				NS
schizophrenia (F20)	46 (74.2%)	25 (71.4%)	21 (77.8%)	
delusional disorders (F22)	4 (6.4%)	3 (8.6%)	1 (3.7%)	
brief psychotic disorder (F23)	1 (1.6%)	1 (2.9%)	0	
schizoaffective disorders (F25)	6 (9.7%)	3 (8.6%)	3 (11.1%)	
bipolar disorder (F31)	1 (1.6%)	1 (2.9%)	0	
major depressive disorder (F33)	3 (4.8%)	1 (2.9%)	2 (7.4%)	
somatoform disorders (F45)	1 (1.6%)	1 (2.9%)	0	
Tobacco smoking	31 (50.0%)	16 (45.7%)	15 (55.6%)	NS
Treatment duration (months)	113.9±109.3 (86.15-141.75)	105.6±105.9 (69.22-141.98)	124.8±115.1 (79.26-170.29)	NS
Patients taking FGAs	15 (24.2%)	10 (28.6%)	5 (18.5%)	NS
Patients taking SGAs	58 (93.5%)	33 (94.3%)	25 (92.6%)	NS
Number of APs				NS
1	22 (35.5%)	14 (40.0%)	8 (29.6%)	
>1	40 (64.5%)	21 (60.0%)	19 (70.4%)	
APs, dose (mg/day) (no. of subjects)				
Quetiapine	494.2±211.5 (408.82-579.64) (26)	445.8±215.8 (308.72-582.95) (12)	535.7±206.3 (416.59-654.84) (14)	NS
Olanzapine	12.7±6.5 (9.89-15.50) (23)	12.5±7.0 (8.58-16.35) (15)	13.1±5.8 (8.29-17.96) (8)	NS
Risperidone*	4.0±2.2 (2.79-5.28) (15)	3.9±2.0 (2.41-5.46) (9)	4.2±2.8 (1.24-7.11) (6)	NS
Aripiprazole	24.0±9.0 (18.99-29.01) (15)	24.6±9.4 (15.95-33.34) (7)	23.5±9.3 (15.62-31.25) (8)	NS

Data shown as mean ± standard deviation (95% Confidence Interval) for continuous variables or n (%) for discrete variables;
APs = antipsychotics; FGAs = first generation antipsychotics; SGAs = second generation antipsychotics;
NS = not significant; † Men vs. Women; Including depot risperidone

Table 3. Anthropometric data and results of laboratory tests

	All (N=62)	Men (N=35)	Women (N=27)	P
Body height (cm)	170.6±9.8 (168.06-173.06)	174.9±8.4 (172.06-177.83)	164.9±8.7 (161.44-168.33)	<0.001† t=4.6
Body weight (kg)	82.6±17.6 (78.19-87.11)	87.5±16.3 (81.85-93.06)	76.4±17.3 (69.52-83.33)	0.01† t=2.6
BMI (kg/m^2)	28.4±5.6 (26.97-29.81)	28.6±5.0 (26.86-30.28)	28.2±6.3 (15.2-40.8)	NS
Waist circumference (cm)	97.8±14.8 (94.06-101.58)	100.5±14.1 (95.70-105.39)	94.3±15.2 (88.29-100.30)	NS
TC (mg/dL)	203.2±46.2 (191.44-214.88)	198.3±39.0 (184.88-211.63)	209.5±54.2 (188.06-230.97	NS
HDL cholesterol (mg/dL)	44.6±11.4 (41.69-47.50)	42.4±10.5 (38.80-46.00)	47.4±12.2 (42.61-52.27)	NS
LDL cholesterol (mg/dL)	126.7±41.6 (116.09-137.39)	120.7±33.9 (108.84-132.51)	134.4±49.2 (114.91-153.83)	NS
TGA (mg/dL)	159.1±92.9 (135.52-182.71)	170.5±93.4 (138.36-202.55)	144.4±91.9 (108.06-180.75)	NS
$AI_{LDL/HDL}$	3.0±1.4 (2.65-3.36)	2.9±1.2 (2.52-3.39)	3.1±1.6 (2.46-3.70)	NS
$AI^{TC/HDL}$	4.9±1.9 (4.42-5.36)	5.0±1.7 (4.38-5.57)	4.8±2.0 (3.97-5.59)	NS
FPG (mg/dL)	95.4±18.5 (90.76-100.15)	93.1±11.1 (89.30-96.92)	98.5±25.0 (88.60-108.36)	NS

Data shown as mean ± standard deviation (95% Confidence Interval); BMI = body mass index; TC = total cholesterol; HDL = high density lipoproteins; LDL = low density lipoproteins; TGA = triglycerides; AI = atherogenic index; FPG = fasting plasma glucose; NS = not significant; † Men vs. women

Table 4. Prevalence of metabolic abnormalities.

	All (N=62)	Men (N=35)	Women (N=27)	P
Normal weight	19 (30.6%)	10 (28.6%)	9 (33.3%)	NS
Overweight	20 (32.6%)	13 (37.1%)	7 (25.9%)	NS
Obesity	23 (37.1%)	12 (34.3%)	11 (40.7%)	NS
Abdominal obesity (European IDF criteria)	47 (75.8%)	23 (65.7%)	24 (88.9%)	0.035†
Hyperlipidemia*	48 (77.4%)	27 (77.1%)	21 (77.8%)	NS
Hyperlipidemia treatment	8 (12.9%)	4 (11.4%)	4 (14.8%)	NS
FPG ≥100 mg/dL	15 (24.2%)	6 (17.1%)	9 (33.3%)	NS
Impaired FPG	4 (6.4%)	2 (5.7%)	2 (7.4%)	NS
New onset DM type 2	2 (3.2%)	1 (2.9%)	1 (3.7%)	NS
Antidiabetic treatment	3 (4.8%)	1 (2.9%)	2 (7.4%)	NS
HA or antihypertensive treatment	25 (40.3%)	13 (37.1%)	12 (44.4%)	NS

Data shown as number of patients (percentage); FPG = fasting plasma glucose; DM = diabetes mellitus; HA = hypertension; NS = not significant; † Men vs. women, X2 =4.46, df=1; TGA ≥150 mg/dL or total cholesterol ≥200 mg/dL or HDL cholesterol <40 mg/dL for men and <50 mg/dL for women or LDL cholesterol ≥135 mg/dL

them were receiving specific treatment for these lipid abnormalities on discharge. That leaves 83.3% of patients with hyperlipidemia without any hypolipidemic therapy. More than 40% of the subjects had hypertension or had antihypertensive treatment of previously diagnosed hypertension. Raised FPG, impaired FPG and new onset of type 2 diabetes were the least frequent abnormalities.

Table 5 shows detailed data on the prevalence of MetS and its individual components. The prevalence of MetS was insignificantly higher in women comparing to men. There was a significant effect of age on the prevalence of MetS (ATPIII: t=2.1; P=0.04, ATPIII A: t=2.2; P=0.03, IDF: t=2.5; P=0.02). Patients with the MetS were, on average, 7 to 8 years older than patients without the MetS. Median treatment duration in patients with MetS (IDF) was 54 months and 96 months in those without MetS. The difference was not significant. The majority of patients had more than one component of MetS (ATPIII: 54.9%; ATPIII A: 62.9%; IDF: 67.7%),

Table 5. Metabolic syndrome and its components

	All (N=62)	Men (N=35)	Women (N=27)	P
MetS (ATPIII)	18 (29.0%)	10 (28.6%)	8 (29.6%)	NS
MetS (ATPIII A)	22 (35.5%)	10 (28.6%)	12 (44.4%)	NS
MetS (IDF)	26 (41.9%)	12 (34.3%)	14 (51.8%)	NS
MetS (ATPIII) criteria met:				NS
0	9 (14.5%)	6 (17.1%)	3 (11.1%)	
1	19 (30.6%)	12 (34.3%)	7 (25.9%)	
2	16 (25.8%)	7 (20.0%)	9 (33.3%)	
3	7 (11.3%)	4 (11.4%)	3 (11.1%)	
4	8 (12.9%)	5 (14.3%)	3 (11.1%)	
5	3 (4.8%)	1 (2.9%)	2 (7.4%)	
MetS (ATPIII A) criteria met:				NS
0	8 (12.9%)	6 (17.1%)	2 (7.4%)	
1	18 (29.0%)	10 (28.6%)	8 (29.6%)	
2	14 (22.6%)	9 (25.7%)	5 (18.5%)	
3	11 (17.7%)	4 (11.4%)	7 (25.9%)	
4	7 (11.3%)	4 (11.4%)	3 (11.1%)	
5	4 (6.4%)	2 (5.7%)	2 (7.4%)	
MetS (IDF) criteria met:				NS
0	5 (8.1%)	4 (11.4%)	1 (3.7%)	
1	15 (24.2%)	10 (28.6%)	5 (18.5%)	
2	15 (24.2%)	8 (22.9%)	7 (25.9%)	
3	13 (21.0%)	7 (20.0%)	6 (22.2%)	
4	10 (16.3%)	4 (11.4%)	6 (22.2%)	
5	4 (6.4%)	2 (5.7%)	2 (7.4%)	
Central obesity				
ATPIII	31 (50.0%)	16 (45.7%)	15 (55.6%)	NS
ATPIII A	31 (50.0%)	16 (45.7%)	15 (55.6%)	NS
IDF	47 (75.8%)	23 (65.7%)	24 (88.9%)	0.035†
Raised blood pressure				NS
ATPIII	25 (40.3%)	13 (37.1%)	12 (44.4%)	
ATPIII A	25 (40.3%)	13 (37.1%)	12 (44.4%)	
IDF	25 (40.3%)	13 (37.1%)	12 (44.4%)	
Reduced HDL cholesterol				NS
ATPIII	32 (51.6%)	15 (42.9%)	17 (63.0%)	
ATPIII A	32 (51.6%)	15 (42.9%)	17 (63.0%)	
IDF	32 (51.6%)	15 (42.9%)	17 (63.0%)	
Raised TGA				NS
ATPIII	24 (38.7%)	16 (45.7%)	8 (29.6%)	
ATPIII A	24 (38.7%)	16 (45.7%)	8 (29.6%)	
IDF	26 (41.9%)	17 (48.6%)	9 (33.3%)	
Raised FPG				NS
ATPIII	7 (11.3%)	3 (8.6%)	4 (14.8%)	
ATPIII A	15 (24.2%)	6 (17.1%)	9 (33.3%)	
IDF	15 (24.2%)	6 (17.1%)	9 (33.3%)	

Data shown as number of patients (percentage); MetS = metabolic syndrome; TGA = triglycerides; FPG = fasting plasma glucose; NS = not significant; † Men vs. women, X2 = 4.46, df=1

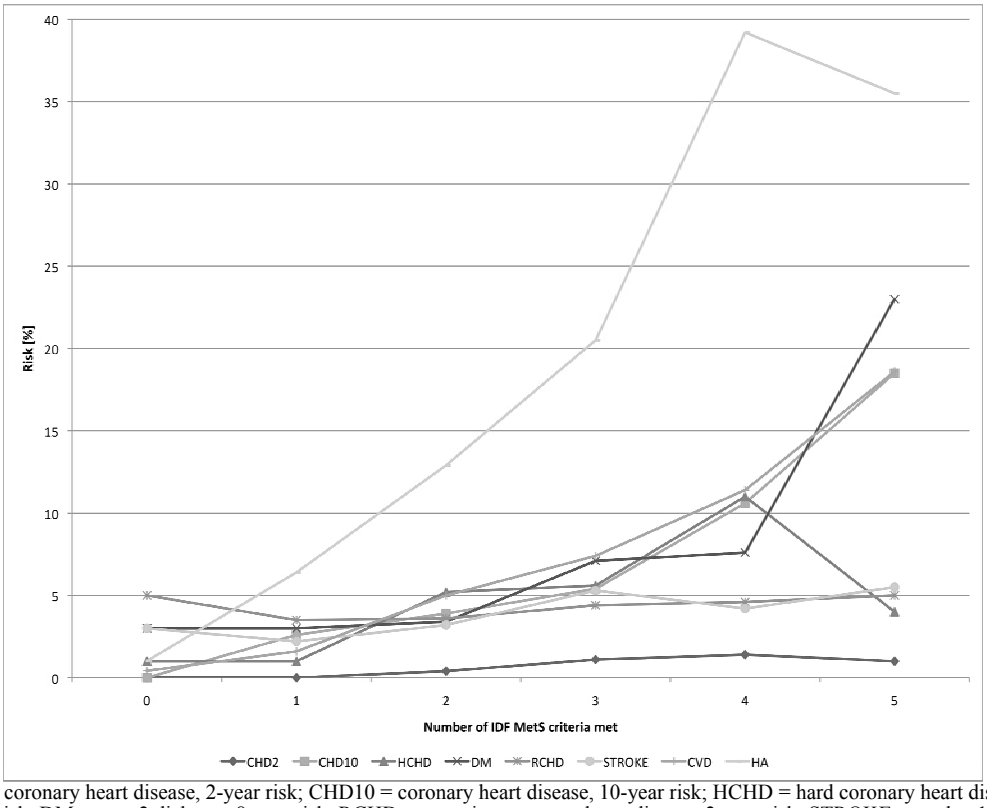
among which abdominal obesity and reduced HDL cholesterol were the most common. In comparison to patients without the metabolic syndrome, subjects with MetS (IDF) had significantly higher TGA levels (208.7±106.3 vs. 123.8±61.8 mg/dL; t=4.0; P<0.001) and FPG levels (103.3±25.1 vs. 89.7±8.0 mg/dL; t=3.0; P=0.003) and significantly lower HDL levels (39.8±11.6 vs. 48.0±10.2 mg/dL; t=2.9; P=0.004).

Results of Framingham CVD risk scores are shown in Table 6. Analysis of these scores revealed that with the exception of hard coronary heart disease and recurring coronary heart disease, all other risk scores were significantly higher in subjects who met IDF MetS criteria. The 2-year risk of recurring coronary heart disease was significantly higher in men than in women (6.4% vs. 2.4%; t=8.6; P<0.001). There were no other differences between men and women. Figure 1 illustrates a non-linear relation between increasing average risk of cardiovascular outcomes and the number of IDF MetS criteria met. For hypertension, type 2 diabetes, coronary heart disease (10-year risk) and general cardiovascular disease there is an increase of risk above 3 MetS components. Since this is a minimum number of criteria required for diagnosing MetS, this clearly shows that the presence of MetS rapidly increases the risk of cardiovascular events.

Table 6. Framingham cardiovascular risk scores

	All (N=62)	Men (N=35)	Women (N=27)	MetS (+) (N=26)	MetS (-) (N=36)	P*
Coronary heart disease, 2-year risk (%)	0.6±1.1 (0.25-1.04)	0.7±0.8 (0.18-1.21)	0.6±1.2 (0.01-1.23)	1.2±1.4 (0.37-2.09)	0.2±0.4 (0.01-0.43)	0.008 t=2.8
Coronary heart disease, 10-year risk (%)	5.8±6.1 (3.57-8.04)	5.8±4.8 (2.97-8.72)	5.8±7.0 (2.28-9.28)	9.1±7.6 (4.46-13.69)	3.4±3.2 (1.86-5.03)	0.009 t=2.8
Type 2 diabetes, 8-year risk (%)	6.1±6.5 (3.69-8.44)	6.0±8.8 (0.69-11.31)	6.1±4.4 (3.91-8.31)	10.1±8.6 (4.87-15.28)	3.2±0.7 (2.81-3.52)	0.002 T=3.4
General cardiovascular disease, 10-year risk (%)	6.4±7.2 (3.75-9.06)	5.2±5.3 (1.97-8.37)	7.3±8.4 (3.13-11.48)	10.4±9.0 (4.93-15.84)	3.5±3.7 (1.67-5.41)	0.007 t=2.9
Hard coronary heart disease, 10-year risk (%)	4.9±6.1 (2.69-7.18)	4.7±5.0 (1.68-7.71)	5.1±7.0 (1.65-8.57)	7.2±7.9 (2.44-12.02)	3.3±3.8 (1.36-5.19)	NS
Recurring coronary heart disease, 2-year risk (%)	4.1±2.4 (3.20-4.93)	6.4±1.6 (5.44-7.32)	2.4±1.0 (1.87-2.90)	4.2±2.4 (2.79-5.67)	3.9±2.4 (2.74-5.14)	<0.001† t=8.6
Stroke, 10-year risk (%)	3.7±2.8 (2.72-4.76)	4.3±1.3 (3.51-5.10)	3.3±3.5 (1.61-5.05)	5.0±3.7 (2.74-7.26)	2.8±1.3 (2.19-3.48)	0.03 t=2.3
Hypertension, 4-year risk (%)	18.2±17.0 (12.03-24.48)	17.9±14.6 (9.05-26.74)	18.5±18.9 (9.11-27.91)	30.3±17.5 (19.73-40.85)	9.6±10.1 (4.53-14.59)	<0.001 t=4.2

Data shown as mean ± standard deviation (95% Confidence Interval); MetS (+) = subjects with IDF-defined metabolic syndrome; MetS (-) = subjects without IDF-defined metabolic syndrome; NS = not significant; * MetS (+) vs. MetS (-). † Men vs. women, not significant for MetS (+) vs. MetS (-).



CHD2 = coronary heart disease, 2-year risk; CHD10 = coronary heart disease, 10-year risk; HCHD = hard coronary heart disease, 10-year risk; DM = type 2 diabetes, 8-year risk; RCHD = recurring coronary heart disease, 2-year risk; STROKE = stroke, 10-year risk; CVD = general cardiovascular disease, 10-year risk; HA = hypertension, 4-year risk

Figure 1. Risk of cardiovascular outcomes by the number of IDF MetS criteria met

DISCUSSION

Studies of general population demonstrated that the overall prevalence of MetS in European countries varies from 5.9% in men and 2.1% in women (France) (Maumus et al. 2005), through 15.7% in men and 14.2% in women (Finland) (Hu et al. 2004) and 16.2% in men and 20.9% in women (Poland) (Szurkowska et al. 2006) to 11.0% in men and 23.1% in women (Russia) (Sidorenkov et al. 2010). American study found that MetS was present in 23.4% of women and 24% of men (Ford et al. 2002). The prevalence of MetS increases

with age and can reach up to 47.2% in the 80-89 years of age group in men and 64.4% for women in the corresponding age groups (Hildrum et al. 2007).

Meta-analysis of 126 analyses in 77 publications (n=25,692) revealed that the overall rate of MetS in schizophrenia and related disorders is 32.5% (Mitchell et al. 2011). European study by De Hert et al. (2006) showed a prevalence of the metabolic syndrome in patients with schizophrenia treated with antipsychotics of 28.4% (ATP-III), 32.3% (ATP-III A) and 36% (IDF). Yumru et al. (2007) found that the prevalence of MetS (ATP-III) in bipolar patients taking antipsychotics was 32%. Therefore, the rate of MetS in our study is slightly higher than reported in earlier European studies (particularly in women). On the other hand, our results are considerably lower to those obtained in Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Study (ATPIII: 40.9%; ATPIII A: 42.7%) (McEvoy et al. 2005). Krane-Gartiser et al. (2011) also reported higher prevalence of MetS (IDF: 48.2%) in psychiatric outpatients. Nevertheless, our study on the prevalence of MetS in patients taking antipsychotics confirms high prevalence of MetS in this population, reaching as much as twice the prevalence of the general population. We observed higher prevalence in women, which is consistent with other observations, but the difference did not quite reach significance and was mainly explained by more frequent central obesity, which in turn may result from the fact that women in this study were older than men.

We have also shown that the prevalence of individual MetS components to be higher than in other studies. De Hert et al. (2006) found abdominal obesity, raised blood pressure, reduced HDL, raised TGA and raised FPG in 62.1%, 48.8%, 29.8%, 42.3% and 25.3% of patients, respectively. The corresponding rates (IDF criteria) in our study are: 75.8%, 40.3%, 51.6%, 41.9% and 24.2%. We are unsure why reduced HDL level was a lot more frequent in our group. Our results are also higher than reported by Sicras-Mainar et al. (ATPIII A): abdominal obesity (defined as BMI >28.8 kg/m^2) 17.8%, raised blood pressure 24.3%, reduced HDL 29.3%, raised TGA 11.2% and raised FPG 9.7% (Sicras-Mainar et al. 2008).

The risk of cardiovascular events was significantly higher in patients with MetS comparing to those without, even if there are no significant differences for variables such as age, sex, tobacco smoking, total cholesterol, LDL cholesterol and HDL cholesterol levels, which are used to calculate most of the risk scores. In subjects with MetS Framingham risk scores were increased by up to 6 times (for 2-year risk of coronary heart disease). A very high risk (30.3%) for the 4-year hypertension risk was found in that group. Although we have found no significant differences for one score (hard coronary heart disease, 10-year risk), there was a relative difference of more than 200% between patients with and without MetS for that score. Moreover, since the outcomes of this risk score (myocardial infarction or coronary death) overlaps with other scores, we may assume that the risk of all cardiovascular outcomes evaluated here is higher in individuals with MetS. Our observation confirms other results indicating that the presence of MetS is associated with increased cardiovascular risk (Arango et al. 2008) and cardiovascular mortality (Fontaine et al. 2001). This also emphasizes that patients should be monitored on a regular basis using available algorithms (2004a).

In our study population mean values of BMI and waist circumference exceeded upper normal limits (as defined by WHO and IDF). We also found that mean total cholesterol levels were above 200 mg/dL (upper limit of normal range, ULN) in women and for the whole group. Mean HDL cholesterol levels were below lower normal limit in women (50 mg/dL), while mean TGA levels were above 150 mg/dL (ULN) in men and for the whole group. Mean value of atherogenic index AILDL/HDL was above 3.0 (ULN) for women. Moreover, a very high (up to 89%) prevalence of increased body weight, abdominal obesity (which was signifycantly more frequent in women) and hyperlipidemia was found in patients taking antipsychotics. This confirms that physical health condition of people taking antipsychotics (regardless they have metabolic syndrome or not) is poor (Brown et al. 2000). Since increased mortality and morbidity is potentially preventable by improving medical treatment, our finding that the majority (more than 80%) of patients with hyperlipidemia did not receive specific treatment is alarming.

Another two worrisome issues are the widespread use of antipsychotic polypharmacy and high percentage of subjects who confirm tobacco use. Although there is no clear connection between antipsychotic polypharmacy and metabolic syndrome, Misawa et al. (2011) suggest that antipsychotic polypharmacy may be associated with an increased risk of pre-metabolic syndrome, even after adjusting for patients' lifestyle characteristics. With respect to smoking, although other studies report that the prevalence of cigarette smoking among patients with schizophrenia can be up to 90% (Dervaux & Laqueille 2008), our result (50%) is twice as high as in the general population (Smith and Fiore 1999). This is particularly important in the light of adverse effects of smoking on low-density and high-density lipoprotein-cholesterol, and triglycerides in a hypercholesterolemic population of men and women, regardless of age (Schuitemaker et al. 2002).

Every research has its limitations, and so has this one. First of all, this is a preliminary report, so sample size is relatively small. Therefore, detailed analysis of some factors (e.g. individual antipsychotics) was not possible. We are continuously collecting data and updated results will be published in the future. Second, due to a naturalistic study design, a sufficient control for the effect of different pharmacological treatments is limited. Moreover, it results in heterogeneity of the

study group (e.g. in terms of diagnosis, treatment duration, types and doses of antipsychotics). Since patients were recruited only in one site, this could have also affected our results. Retrospective medical records review limits data available for analysis (e.g. on physical activity and diet). Last but not least, being a retrospective review, the study is limited to data included in medical records. We had to exclude the majority of patients hospitalized in the unit due to missing data, mainly waist circumference and height. This also shows that monitoring of metabolic parameters is far from a daily routine, but hopefully will become so in the near future.

CONCLUSIONS

High rate of MetS in patients treated with antipsychotics that we found in this study (41.9%) exceeds MetS prevalence in general population. Most patients had at least one component of MetS. Abdominal obesity and reduced HDL cholesterol levels were the most frequent MetS components, while raised blood pressure and FPG levels - the least frequent ones. The risk of various cardiovascular events is significantly increased in patients with metabolic syndrome and thus may contribute to increased mortality. The majority of our subjects were overweight or obese, had abdominal obesity and had lipid abnormalities. A very important clinical finding was that the majority of patients with hyperlipidemia had no antihyperlipidemic introduced. The prevalence of tobacco use is still too high. Antipsychotic polypharmacy is widespread in our unit. This sheds light on where improvements are required. Regular monitoring of metabolic parameters is highly recommended.

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