Endokrynologia Polska
DOI: 10.5603/EP.a2021.0037
Volume/Tom 72; Number/Numer 3/2021
ISSN 0423–104X, e-ISSN 2299–8306

Insulin resistance in metabolic syndrome depending on the occurrence of its components

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Abstract

Introduction: Metabolic syndrome (MetS) is described as a cluster of several commonly occurring disorders including abdominal obesity, hypertension (HT) (≥ 130/85 mm Hg), carbohydrate disorders: impaired fasting glucose or type 2 diabetes mellitus and lipids disorders such as hypertriglyceridaemia (TG), and low levels of high-density-lipoprotein cholesterol (HDL-C). Insulin resistance (IR) is defined as a glucose homoeostasis disorder involving a decreased sensitivity of muscles, adipose tissue, liver, and other body tissues to insulin, despite its normal or increased concentration in blood.

Material and methods: The study group included 424 subjects with MetS (260 females, 164 males). All patients were recruited for 24 months from the Internal Ward of the District Hospital in Wąbrzeźno, Poland and the Department of Endocrinology and Diabetology Collegium Medicum in Bydgoszcz, Poland. The diagnosis of the MetS was made on the basis of International Diabetes Federation (IDF) criteria. MetS diagnosis was established when three or more criteria were met. To evaluate and measure IR, a hyperinsulinaemic-euglycaemic clamp was performed in each patient. IR was also determined through HOMA-IR.

Results: All patients of the study group were diagnosed with obesity, 73.5% with high fasting glucose levels, 66.9% with HT, 48.3% with lower level of HDL-C, and 38.2% with TG. It did not have an influence on the IR results. The study group was divided into 6 subgroups according to the constellation of 3 particular components of MetS (O + DM2T + ↑TG; O + HT + DM2T; O + DM2T + ↓HDL-C; O + HT + IFG; O + HT + ↑TG and O + HT + ↓HDL-C). IR of different degree was diagnosed in all patients of the study group. The results of our study showed that the highest IR was observed in patients with central obesity accompanied by DM2T and ↑TG. Also in subgroups with DM2T and HT or DM2T and ↓HDL-C, a high index of IR was noticed.

Conclusions: The occurrence of IR in patients with MetS is obvious. However, despite the fact that they are high or very high cardiovascular risk patients, they are not a homogeneous group. Such patients differ from each other depending on the presence and constellation of particular disorders that make up the diagnosis of the MetS. Patients with MetS are a heterogeneous group differing in degree of IR and the risk of CVD. **(Endokrynol Pol 2021; 72 (3): 243–248)**

Key words: *metabolic syndrome; insulin resistance; diabetes mellitus; obesity*

Introduction

Metabolic syndrome (MetS) is described as a cluster of several commonly occurring disorders including abdominal obesity, hypertension (HT) (≥ 130/85 mmHg), carbohydrates disorders such as impaired fasting glucose or type 2 diabetes mellitus (DM2T), and lipids disorders such as hypertriglyceridaemia (↑TG) and low level of high-density-lipoprotein cholesterol (↓HDL-C) [1]. Insulin resistance (IR) is defined as a glucose homoeostasis disorder involving a decreased sensitivity of muscles, adipose tissue, liver, and other body tissues to insulin, despite its normal or increased concentration in blood [2]. The gold-standard method in the diagnosis of IR is the metabolic clamp, but it is mainly used in clinical trials, so we often assess the IR using various indicators, for example HOmeostasis Model Assessment — Insulin Resistance (HOMA-IR). IR is common in people with central obesity and is an additional risk factor for atherosclerotic and nonatherosclerotic cardiovascular disease (CVD).

The aim of our study was to assess the level of IR in patients with metabolic syndrome, depending on its components, measured with the HOMA-IR index and hyperinsulinaemic-euglycaemic clamp.

Material and methods

The study group included 424 subjects with MetS (260 females, 164 males). All patients were recruited for 24 months (for September 2016 to August 2018) from the Internal Ward of the District Hospital in Wąbrzeźno, Poland and the Department of Endocrinology and Diabetology Collegium Medicum in Bydgoszcz, Poland. The diagnosis of the MetS was made on the basis of the International Diabetes Federation (IDF) criteria (Tab. 1). MetS diagnosis was established when three or more criteria were met.

All procedures were performed after 12 h of fasting. Anthropometric measurements including height, weight, and waist

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Table 1. *International Diabetes Federation (IDF) criteria of metabolic syndrome*

Abdominal obesity [cm]	F ≥ 80 or M ≥ 94
Arterial hypertension [mm Hg]	≥ 130/85 or treated for arterial hypertension
Triglycerides [mg/dL]	≥ 150 [1.7 mmol/L] or treated for dyslipidaemia
HDL-C [mg/dL]	< 50 [1.3 mmol/L] in women and < 40 [1.0 mmol/L] in men
Fasting glycaemia [mg/dL]	≥ 100 [5.6 mmol/L] or treated for diabetes

HDL-C — high-density lipoprotein cholesterol

circumference (WC) were obtained from all participants. BMI was calculated as body weight (in kilograms) divided by the square of body height (in metres). WC was measured by placing a measuring tape around the waist at the upper point of the iliac crest. Systolic and diastolic blood pressure were measured in the sitting position after 15 min of rest using an appropriately sized cuff on both upper extremities. Patients were seated quietly with their feet on the floor, and the blood pressure readings were taken at 1-min intervals. An average of both measurements was calculated and used for data analysis. Arterial hypertension was diagnosed according to the IDF definition. Levels of fasting total plasma cholesterol (TC), triglycerides (TG), high-density-lipoprotein cholesterol (HDL-C), and fasting blood glucose (FBG) were evaluated in all patients. Low-density-lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula. Non-high-density-lipoprotein cholesterol (non-HDL-C) was figured on the base of the following formula:

$$TC - HDL\text{-}C.$$

In patients with abnormal fasting glycaemia values and waist circumference > 80 cm in women or > 94 cm in men, an oral glucose tolerance test (OGTT) was performed to determine glycaemia in the fasting state and 2 hours after the administration of 75 g of glucose, to diagnose DM2T or pre-diabetes. All tests were performed at the Department of Laboratory Medicine, Nicolaus Copernicus University, Collegium Medicum, Bydgoszcz, Poland using a Horiba ABX Pentra 400 analyser (Horiba ABX, Montpelier, France).

Exclusion criteria were as follows: a history of heart surgery or other cardiovascular interventions, congenital defects of the heart, cardiac rhythm disorders, pregnancy, electrolyte disorders, inflammation, anaemia, prostate disease, and Cushing's syndrome. A self-reported history of medical and psychiatric problems, including a list of all currently prescribed medications, was obtained from each participant. Also subjects after stroke or with dementia were excluded, as were those presenting other conditions that compromised cognition, such as depression, anxiety, taking psychotropic drugs, psychiatric diseases, and history of alcohol or chemical addiction or uncorrected visual or hearing disorder.

To evaluate and measure IR, a hyperinsulinaemic-euglycaemic clamp was performed in each patient. The method involves quantification of 20% glucose solution administered to the patient to maintain a constant glycaemia (90–100 md/dL) during a 120-minute insulin infusion. Plasma glucose was analysed with a Yellow Springs Instruments 2300STAT Glucose Analyzer. Plasma insulin was measured by chemiluminescent immuno-assays on an Immulite 2000 Analyzer.

Insulin resistance was also determined through HOMA-IR. It was calculated using the following equation:

$$(Fasting\ glucose\ level\ [mg/dL]) \times (Fasting\ insulin\ level\ [\mu U/mL]/405).$$

The physiological value of the index is 1.0. Higher values are indicative of IR.

Statistical analysis was performed using the Statistica 8.0 software (StatSoft Poland, Bydgoszcz). The results were expressed as mean ± standard deviation (SD). The normality test of the distribution (Shapiro-Wilk test) was performed, followed by the ANOVA test. The results were considered statistically significant when $p < 0.05$.

The study was approved by the Bioethics Committee of the clinical hospital in Bydgoszcz (KB 219/2016), before its commencement.

Results

The characteristics of the study group are described in Table 2. We noted some differences between the female and male groups. The difference between sexes (260 *vs.* 164; $p < 0.05$), the level of TG (133.6 *vs.* 159.7; $p < 0.05$), and the occurrence of ↑TG [84/260 (32.3%) *vs.* 78/164 (48.2%); $p < 0.05$) were statistically significant. It did not have an influence on the IR results.

All patients of the study group were diagnosed with obesity, 73.5% with high fasting glucose levels, 66.9% with HT, 48.3% with lower level of HDL-C, and 38.2% with increased concentration of TG. Then the study group was divided into 6 subgroups according to the constellation of 3 particular components of MetS (Tab. 3). IR of different degree was diagnosed in all patients, both males and females. Figures 1 and 2 show the level of IR in particular subgroups depending on the type of measure. The highest level of IR was observed in patients with central obesity accompanied by DM2T and ↑TG.

Discussion

Insulin resistance may be asymptomatic or present a variety of disorders, such as impairment of glucose tolerance, DM2T, as well as hypercholesterolaemia, hypertriglyceridaemia, obesity, and arterial hypertension. Bonora et al. [3] in their study showed that the prevalence of IR was 58% in hypertension subjects, 84.2% in ↑TG subjects, 88.1% in subjects with ↓HDL-C, and 83.9% in DM2T subjects.

The results of available studies indicate a relationship between IR and the risk of developing CVD. Gast et al. [4] in their meta-analysis of 65 studies showed a strong correlation between IR, evaluated by HOMA index, and risk of CVD. IR can promote the development of atherosclerosis through elevated glucose and insulin concentrations, but also through mechanisms

Table 2. *The characteristics of the study group*

Parameters	Total	Female	Male	p < 0.05
N (%)	424	260 (61.32%)	164 (38.67%)	p < 0.05
Age [y] ± SD	61.3 ± 4.8	60.8 ± 5.1	62.1 ± 4.3	NS
BMI [kg/m^2] ± SD	31.64 ± 1,3	31.48 ± 1.2	31.91 ± 1.5	NS
WC [cm] ± SD	109.1 ± 3.7	107.1 ± 3.4	112.5 ± 4.3	NS
SBP [mm Hg] ± SD	144.6 ± 11.2	144.1 ± 10.6	145.8 ± 11.5	NS
DBP [mm Hg] ± SD	92.1 ± 6.3	91.3 ± 6.2	93.5 ± 6.5	NS
LDL-C [mg/dL] ± SD	103.1 ± 22.7	102.1 ± 22.1	104.8 ± 23.0	NS
HDL-C [mg/dL] ± SD	43.9 ± 6.4	47.2 ± 6.9	38.8 ± 5.3	NS
TG [mg/dL] ± SD	143.7 ± 32.1	133.6 ± 26.5	159.7 ± 40.1	p < 0.05
Non-HDL-C [mg/dL] ± SD	129.3 ± 26.4	125.9 ± 24.2	134.8 ± 29.1	NS
IFG (n;%)	140/424(33%)	76/260(29.2%)	64/164(39%)	NS
DM2T (n;%)	172/424(40.5%)	110/260(42.3%)	62/164(37.8%)	NS
HT (n;%)	284/424 (66.9%)	172/260 (66.1%)	112/164 (68.3%)	NS
↓HDL-C (n;%)	205/424 (48.3%)	126/260 (48.4%)	79/164 (48.2%)	NS
↑TG (n;%)	162/424(38.2%)	84/260 (32.3%)	78/164 (48.2%)	p < 0.05

BMI — body mass index; WC — waist circumference; SBP — systolic blood pressure; DBP — diastolic blood pressure; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; TG — triglycerides; IFG — impaired fasting glycaemia; DM2T — diabetes mellitus type 2; HT — hypertension; SD — standard deviation; NS — non significant

Table 3. *The characteristics of the metabolic syndrome (MetS) subgroups according to the constellation of 3 particular components of MetS*

Parameters	O + HT + ↑TG		O + HT + ↓HDL-C		O + HT + IFG		O + HT + DM2T		O + DM2T + ↑TG		O + DM2T + ↓HDL-C	
n	94		71		66		110		68		114	
Sex	F	M	F	M	F	M	F	M	F	M	F	M
	48	46	42	29	34	32	74	36	36	32	64	50
Age ± SD [y]	59.8 ± 5.0	61.7 ± 4.1	59.4 ± 5.2	60.9 ± 3.9	58.3 ± 4.8	60.4 ± 3.8	61.1 ± 5.2	63.4 ± 4.8	62.4 ± 5.4	62.6 ± 4.6	63.2 ± 5.8	62.0 ± 4.3
BMI ± SD [kg/m^2]	31.62 ± 1.3	31.42 ± 1.3	30.86 ± 0.9	31.11 ± 1.2	30.83 ± 1.0	31.68 ± 1.5	31.21 ± 1.2	32.61 ± 1.7	32.82 ± 1.4	32.52 ± 1.6	32.94 ± 1.4	32.34 ± 1.6
WC ± SD [cm]	107.3 ± 3.5	112.1 ± 4.0	106.2 ± 3.1	111.7 ± 3.8	106.4 ± 3.2	111.8 ± 4.0	108.3 ± 3.7	113.4 ± 4.7	107.1 ± 3.4	112.9 ± 4.5	108.2 ± 3.6	112.6 ± 4.3
HEC [mg/min/kg bw]	3.44	3.40	4.14	4.09	3.79	3.76	2.69	2.59	2.47	2.42	2.99	2.94
HOMA-IR	3.40	3.42	2.79	2.84	3.96	4.01	5.23	5.38	5.73	5.82	4.27	4.35

O — obesity; HT — hypertension; ↑TG — hypertriglyceridaemia; IFG — impaired fasting glucose; DM2T — type 2 diabetes mellitus; ↓HDL-C — low level of high-density-lipoprotein cholesterol; HEC — hyperinsulinaemic-euglycaemic clamp; HOMA-IR — HOmeostasis Model Assessment — Insulin Resistance

that involve dyslipidaemia, hypertension, and inflammation.

In patients with MetS, where multiple metabolic disorders are present, the IR can be found in the vast majority of subjects [3]. Its severity depends on a constellation of individual components of MetS that occur in a given patient. In our study, IR of different degree was diagnosed in all patients. All patients were diagnosed with obesity. In the study subgroup with obesity, DM2T, and ↑TG the highest IR, measured by hyperinsulinaemic-euglycaemic clamp, was found. Also, Juarez-Lopez et al. [5] revealed that the highest IR is found in patients with increased WC, DMt2, and ↑TG. Abbasi et al. [6] showed in their study including 587 apparently healthy individuals with normal FBG or prediabetes that hypertriglyceridaemia (fasting

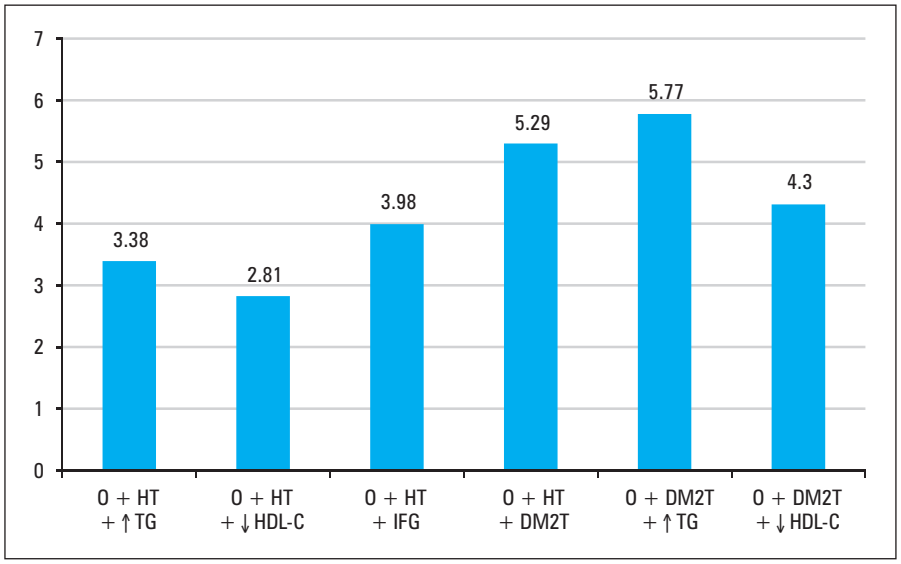

Figure 1. *Insulin resistance in separate subgroups depending on constellation of particular components of metabolic syndrome (MetS) measured by HOMA-IR. O — obesity; HT — hypertension; ↑TG — hypertriglyceridemia; IFG — impaired fasting glucose; DM2T — type 2 diabetes mellitus; ↓HDL-C — low level of high-density-lipoprotein cholesterol*

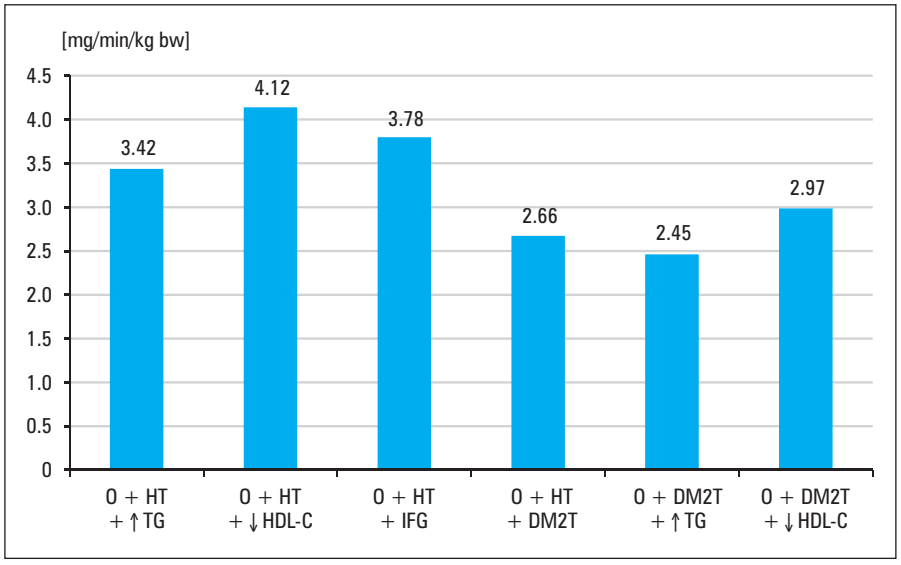

Figure 2. *Insulin resistance in separate subgroups depending on the constellation of particular components of MetS measured by hyperinsulinaemic-euglycaemic clamp. O — obesity; HT — hypertension; ↑TG — hypertriglyceridaemia; IFG — impaired fasting glucose; DM2T — type 2 diabetes mellitus; ↓HDL-C — low level of high-density-lipoprotein cholesterol*

TG concentration ≥ 1.7 mmol/L) identified a subset of individuals with prediabetes, who had a higher mean steady-state plasma glucose concentration during the insulin suppression test (11.3 ± 3.5 mmol/L *vs.* 9.3 ± 3.9 mmol/L, $p < 0.001$) and were more likely to be IR (66% *vs.* 39%, $p < 0.001$), and had a more adverse coronary heart disease (CHD) risk factor profile. Many other authors in their studies show a relationship between IR and MetS components, such as hyperlipidaemia [5, 7]. IR may be an underlying mechanism leading to dyslipidaemia featuring increased TG, reduced high-density lipoprotein, and the presence of small, dense LDL [7]. The key pathological mechanism underlying the dyslipidaemia commonly observed in IR states is dysregulation of VLDL production, particularly increased hepatic secretion of large amounts of very low-density lipoprotein (VLDL1). There are a large number of them in the blood, and changes in lipase activity and lipid transfer proteins, accompanying obesity and IR, modulate plasma lipoprotein metabolism, lead-

ing to the formation of lipoproteins with an increased atherogenic potential. Under physiological conditions, insulin reduces the production of VLDL1 as a result of inhibition of the mobilization of free fatty acids (FFA) from peripheral tissues, as well as by stimulating apo B degradation and inhibition of the synthesis of the microsomal triglyceride transport protein in the liver. In the state of IR, the supply of TG in the liver increases, and at the same time the inhibitory effect of insulin on the synthesis of VLDL1 disappears. As a result, the liver produces more particles of this type. TGs incorporated into VLDL particles arise primarily as a result of the esterification of FFAs, which are absorbed by the liver from blood in proportion to their concentration. The main source of FFA is adipose tissue. In the state of IR, the inflow of FFAs from adipose tissue to the liver increases. This is due to a decrease in lipogenesis in adipose tissue. Its efficiency depends to a large extent on glucose uptake, the α-glycerophosphate precursor necessary for the synthesis of TG in adipose tissue. Thus, reduction of insulin sensitivity reduces not only glucose uptake, but also uptake of FFA by adipose tissue. In addition, insulin is a factor that inhibits intracellular hormone-sensitive lipase, which plays a major role in the process of TG hydrolysis in adipose tissue. In IR, therefore, there is also an increased release of FFA from adipose tissue. The inflow of FFA to the liver inhibits insulin-stimulated apo B degradation and stimulates the increase of VLDL synthesis [8].

The second subgroup with the highest IR comprised those with obesity, diabetes, and hypertension. IR is common in patients with HT. The results of the available studies show that the prevalence of IR in HT patients was 58% [3]. It has been shown that high blood pressure and high insulin levels are associated, independently of weight or BMI. However, the association between IR and HT is not as strong as between IR and dyslipidaemia. Approximately 50% of hypertensive patients are IR [7]. In the pathogenesis of HT associated with abdominal obesity, IR and hyperinsulinaemia, as a compensatory response to IR, are particularly important [9, 10]. Hyperinsulinaemia activating numerous tubular sodium transport systems in the kidneys increases sodium and water retention by about 30–40%. This can be associated with a volume-dependent HT [11–13]. However, it is not known how often volume-dependent HT is present in IR individuals and patients with DM2T. Hyperinsulinaemia also stimulates the sympathetic nervous system [12, 14]. There is evidence suggesting that overaction of the sympathetic system is present in obese and IR individuals. However, it has not been proven that this is a primary defect in these patients [9]. Another possible link between HT and IR can be abnormalities in vasodilatation and blood flow. Insulin affects the transmembrane transport of ions and causes vasodilatation when administered intravenously in normal subjects. This reaction is deficient in patients with obesity and IR and in DM2T patients. IR and hyperinsulinaemia can lead to ionic disturbances inside the vascular wall cells, leading to their remodelling (muscle hypertrophy) and increased contractility, narrowing of the lumen of resistance vessels, and the development of HT. Insulin also induces oxidative stress, leading to free-radical damage that impairs the function of endothelial cells and induces a mitogenic effect on the myocardium [15].

There were some limitations to our study. Antidiabetic drugs and insulin were used in some patients, which may have had some impact on the assessment of IR.

Conclusions

The occurrence of IR in patients with MetS is obvious. However, despite the fact that they are high or very high cardiovascular risk patients, they are not a homogeneous group. Such patients differ from each other depending on the presence and constellation of particular disorders that make up the diagnosis of the MetS. Patients with MetS are a heterogeneous group differing in degree of IR and the risk of CVD. The results of our study show that the highest IR is observed in patients with central obesity accompanied by DM2T and ↑TG.

Conflict of interest

The authors declare no conflict of interest.

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