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Original Research Article

Cardiometabolic risk factors in type 2 diabetic patients according to the definition for metabolic syndrome of International Diabetes Federation

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Abstract

Identifying type 2 diabetic patients (T2D pts) with metabolic syndrome (MS) enables physicians for early and active treatment of cardiometabolic risk factors. The aim of the study was to assess characteristics of cardiometabolic risk factors in T2D pts according to the definition for MS of International Diabetes Federation (IDF) and to test the hypothesis whether IDF definition for MS could identify T2D pts with insulin resistance. Three hundred and eighty three (194 females, 189 males) T2D pts (mean±SD; age 62.2±10.4 yrs; body mass index 30.8±4.8 kg/m^2) took part in the study. A manual hyperinsulinaemic euglycaemic clamp technique was used for a measurement of insulin sensitivity (IS), expressed as a glucose disposal rate (M), and homeostasis model assessment of insulin resistance (HOMA-IR). According to the definition of IDF, MS was diagnosed in 76.5% of the T2D pts (82% females, 70.9% males).The most common cardiometabolic risk factor in females was raised blood pressure (84.9%) and in males-reduced HDL cholesterol (76.9%). IS of the MS pts M 3.238±1.673 was significantly lower compared to that of non MS pts M 6.893±3.846 (mg/kg/min), p=0.007. HOMA-IR of the MS pts 6.02±1.69 was significantly higher compared to that of non MS pts 3.07±1.27, p<0.001. In conclusion, T2D pts, included in our study, were presented with multiple cardiometabolic risk factors. According to our data, IDF definition for MS could identify T2D pts with insulin resistance. Multiple risk factor treatment strategy is required for reduction of global cardiometabolic risk.

Keywords: Cardiometabolic Risk Factors, Insulin Resistance, Insulin Sensitivity, International Diabetes Federation, Metabolic Syndrome, Type 2 Diabetes Mellitus

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is becoming one of the most challenging health burdens in the 21st century, leading to impaired quality of life, increased disability and enormous health cost. Concerning its effect on cardiovascular disease (CVD), T2DM is a leading cause of death. Actually, 50 % to 80% of people with T2DM die of CVD. The potential impact of CVD is alarming, bearing in mind the epidemic proportions of people suffering from T2 DM and undiagnosed cases worldwide (Wild et al., 2004). In fact, CVD risk is significantly increased beginning as early, as 15 years before the diagnosis of diabetes, and it is becoming higher in the years closer to the actual time of clinical diagnosis (Hu et al., 2002). According to the International Diabetes Federation (IDF) Atlas, the prevalence of diabetes in adults aged 18-99 years is estimated of 8.4% in 2017 and predicted to rise to 9.9% in 2045. In 2017, 424.9 million people aged 20-79 years or 451 million people aged 18-99 years are lived with diabetes. It is estimated that almost half of all people living with diabetes are undiagnosed (Cho et al., 2018).

While we once diagnose T2DM, obesity, hypertension and dyslipidaemia are also occurred. They are simply

Table 1. Characteristics of type 2 diabetic patients (mean±SD); HDL= high density lipoprotein

Variables	Mean ± SD
Number	383
Sex (females / males)	194 /189
Age (yr)	62.2 ± 10.4
Body Mass Index (kg/m^2)	30.8 ± 4.8
Waist circumference (cm)	99.8 ± 15.4
Systolic blood pressure (mm Hg)	144 ± 25
Diastolic blood pressure (mmHg)	91 ± 15
Total cholesterol (mmol/l)	5.55 ± 1.30
HDL cholesterol (mmol/l)	1.12 ± 0.39
Triglycerides (mmol/l)	2.14 ±1.46

different faces of the same disorder. It has been recognized for over 130 years, that these conditions tend to cluster each other in the same individual. Specifically, this risk factor clustering, and its association with CVD, has led investigators to discover the existence of a unique pathophysiological condition, named a "metabolic syndrome" (Kahn et al., 2005). The metabolic syndrome (MS) is defined as a constellation of cardiometabolic risk factors that have been associated with an increased risk of CVD, as well as with T2DM (Wilson and Meigs, 2008). The links between MS and T2DM are even stronger than those with CVD. Many people who have the MS, already have T2DM. For those who have the MS, but do not have T2DM, the risk of developing T2DM is particularly high (Grundy et al., 2004). T2DM is considered as a prerequisite for MS in the first official definition of World Health Organization (WHO). It requires impaired glucose regulation (impaired fasting plasma glucose and/or impaired glucose tolerance or T2DM and/or insulin resistance together with two other CVD risk factors for the MS to be diagnosed (WHO Consultation, 1999). The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) state, that MS may be diagnosed when a person has three or more of five risk factors amongst which is elevated fasting plasma glucose level (NCEP Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, 2001). The 2001 NCEP ATP III guidelines give of T2DM status of "cardiovascular disease risk equivalent". That means that patients with T2DM have the same CVD risk as individuals with established CVD. The WHO and European Group for the Study of Insulin Resistance (EGIR) definitions address the fact that insulin resistance may be the pathophysiological risk factor underlying the MS. Insulin resistance is accepted a priori for T2DM patients and it is defined as the lowest quartile of a glucose disposal rate during hyperinsulinaemic euglycaemic clamp technique or the highest quartile of homeostasis model assessment of insulin resistance (HOMA-IR) in people with normal glucose tolerance in WHO definition and as hyperinsulinaemia, defined as the highest quartile of fasting insulin in EGIR definition (WHO Consultation, 1999; Balkau and Charles, 1999). However, the WHO and EGIR definitions have limitations to their clinical application. Hyperinsulinaemic euglycaemic clamp technique is the "gold standard" for measurement of insulin sensitivity, but it requires special equipment, expertise and skills, which limit its use to small sample size studies. Fasting insulin and HOMA are surrogate measures of clamp technique derived insulin sensitivity, applicable in large epidemiological studies (Fortson et al, 2008; Olufadi and Byrne, 2008).

The IDF created a consensus definition with simple and easily measurable in routine clinical practice diagnostic criteria. It made central obesity a necessary requirement and for the first time provided different cutoff points of waist circumference for different ethnic groups (Alberti et al., 2005).

Considering a significance of the MS as a state of increased cardiovascular risk, the assessment of cardiometabolic risk factors has become a crucial part of CVD risk management in patients with T2DM. The aim of the study was to assess characteristics of cardiometabolic risk factors in type 2 diabetic patients (T2D pts) according to the definition for MS of IDF and to test the hypothesis whether IDF definition for MS could identify T2D pts with insulin resistance.

SUBJECTS AND METHODS

Subjects

Three hundred and eighty three T2D pts from different regions of the country, attended department of Diabetology of the Clinical Center of Endocrinology and Gerontology, Sofia, Bulgaria with mean age 62.2 yr (ranged from 35 to 83), mean duration of diabetes 7.6 yr (from one month to 30 yr) and mean glycated hemoglobin (HbA_1c) value 7.5% (from 5% to 14.4%) participated in a cross-sectional study. Characteristics of T2D pts is presented in Table 1. Written informed consent for participation in the study was obtained from all subjects. The study protocol was approved by the local Ethical Committee of the Clinical Center of Endorinology and Gerontology.

Methods

Clinical methods

Case history and physical examination were performed in all participants. Waist circumference was measured in the middle between lowest rib and the iliac crest in inspiration and expiration position and the mean value was taken. Body mass index (BMI) was calculated as body weight (kg) divided by squared height (m^2). Blood pressure was measured on the left arm in a sitting position after at least 10 min of rest. Mean value was determined from two independent measurements.

Laboratory methods

Blood samples for glucose, insulin and lipids were taken after a 12-hour overnight fast. Plasma glucose concentration was measured by a glucose oxidase method (Glucose analyzer Beckman, USA). The concentration of HbA_1c (%) was measured by immunoturbidimetric method with a commercial kit (Roche Diagnostics, Germany) on Cobas Integra System using monoclonal antibodies attached to latex particles. Plasma insulin concentration was determined by a Microparticle-Enzyme Immunoassay (MEIA Insulin, IMX System, Abbott, USA), reference range-2-25 mIU/l. Serum level of total cholesterol, high density lipoprotein (HDL) cholesterol and triglycerides were measured by enzymatic method with a commercial kit (Roche Diagnostics) on biochemical analyzer (Cobas Mira Plus, Switzerland).

Definition of metabolic syndrome

As T2DM is a component of the MS according to the IDF definition, T2D pts were considered as having a MS by the presence of necessary requirement waist circumference≥80 cm in females and ≥94 cm in males plus at least one more of the following: raised triglycerides ≥1.7 mmol/l or specific treatment for this lipid abnormality, reduced HDL cholesterol < 1.03 mmol/l in males and <1.29 mmol/l in females or specific treatment for this lipid abnormality, and raised blood pressure: systolic≥130 mmHg or diastolic≥85 mmHg or treatment for previously diagnosed hypertension. If BMI was >30 kg/m^2, central obesity was assumed independently of the waist circumference measurement (Alberti et al., 2005).

Measurement of insulin sensitivity

Insulin sensitivity was measured with a “gold standard”-a manual hyperinsulinaemic euglycaemic clamp technique, as described previously (De Fronzo et al., 1979; Heine et al., 1985; Kamenova, 2017). In brief, it was performed at 8.0 AM after a 12-hour overnight fast. After obtaining the baseline samples for glucose and insulin, a priming insulin infusion (Actrapid HM, 100 U/ml) in saline (0.9% NaCL, at a concentration of 1U/ml) was started to decline plasma glucose concentration to 5 mmol/l, followed by a constant infusion of 40 mU/ m^2 body surface area/min for 120 min. Plasma glucose concentration was kept constant at a level of 5 mmol/l by 20 % glucose infusion (B. Braun infusion pump, Germany) added after decrease of blood glucose to 5 mmol/l. The adjustment of glucose infusion rate was done manually according to the plasma glucose level measured at 5 min intervals. Blood samples for determining plasma insulin concentration were drawn at 100, 110 and 120 minutes of the clamp. Steady state plasma glucose and plasma insulin concentrations were calculated as the mean of the values obtained between 90 and 120 minutes of the clamp study. Under steady state conditions of hyperinsulinaemia and euglycaemia, endogenous insulin secretion and hepatic glucose production are suppressed and glucose infusion rate equals glucose disposal mainly in muscles. Insulin sensitivity was calculated from the amount of glucose infused during the last 30 min of the clamp, when the plasma glucose concentration and glucose infusion rate were stable (steady state) and expressed as a glucose disposal rate per kg body weight per min (M; mg/kg/min) (Ponchner et al., 1984; Kamenova, 2017).

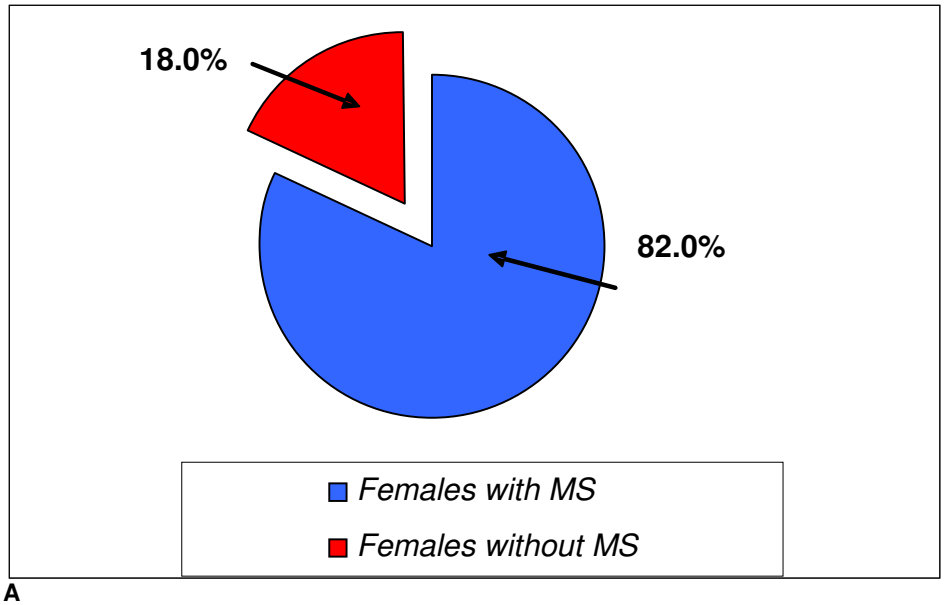
Homeostasis model assessment of insulin resistance (HOMA-IR) was used for estimation of insulin sensitivity, as well. HOMA was calculated by formula: Fasting glucose (mmol/l) x Fasting insulin (mIU/l) /22.5 (Matthews et al., 1985).

Statistical analysis

Statistical analysis was performed using a statistical package for social science (SPSS, version 14 for Windows, Chicago, IL, USA). Data are presented as means ± SD. The prevalence of the metabolic syndrome and its individual components is presented as a percent distribution. Analysis of variance (ANOVA) or Friedman test according to a normal or a nonparametric distribution of the tested variable was used to determine statistically significant differences between the study parameters of two groups. Shapiro-Wilk test was used for normality. A significant level of $p<0.05$ was considered.

RESULTS

According to the definition of IDF, MS was diagnosed in 293 (159 females, 134 males) T2D pts (76.5%). The prevalence of the MS in T2D females and T2D males is presented in Figure 1 (A,B). The highest percent of T2D pts (37.5%) were having all 5 components of the MS,



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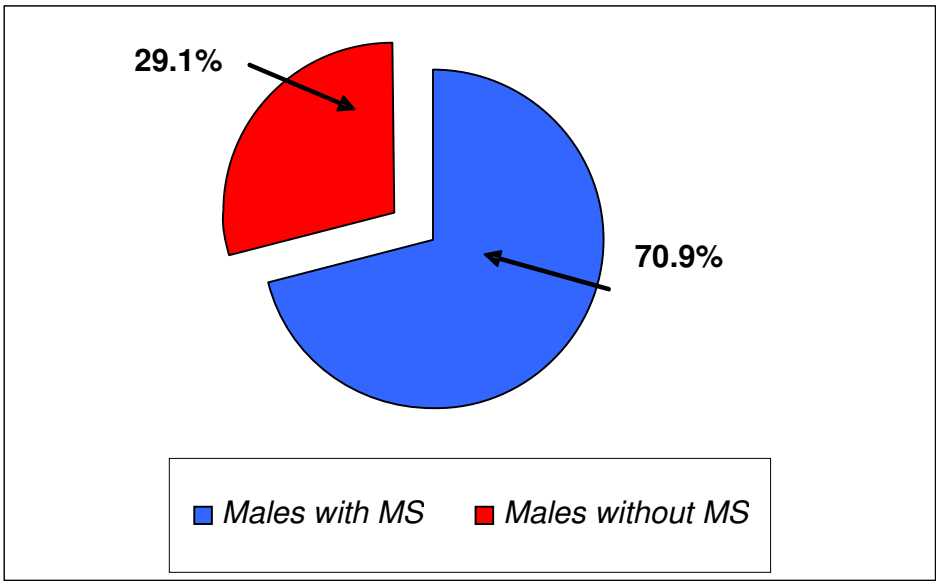

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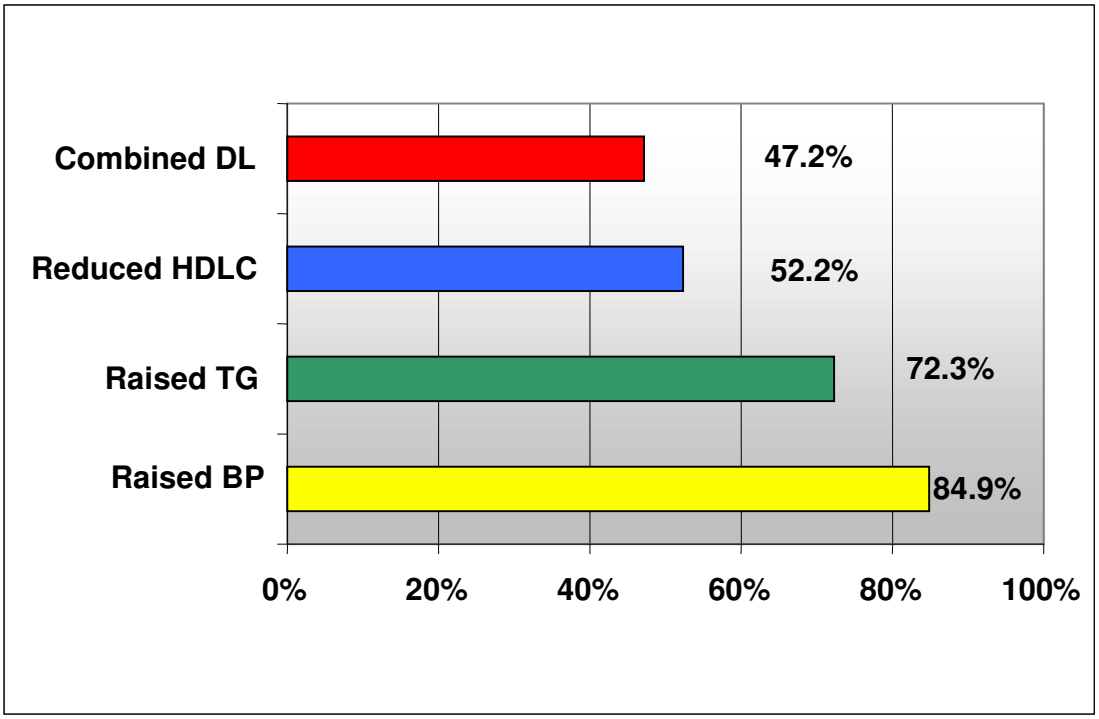
Figure 1. Prevalence of the MS in A) Type 2 diabetic females, B) Type 2 diabetic males; MS=metabolic syndrome

followed by those with 3 components (33.5%) and 4 components of the MS (28.7%). The most common component of the MS in T2D pts was raised blood pressure (75.1%), followed by reduced HDL cholesterol (63.5%) and raised triglycerides (62.5%). Combined dyslipidaemia (raised triglycerides and reduced HDL cholesterol) was established in 42.3% of the MS patients. Characteristics of the MS in diabetic females and diabetic males is presented in Figure 2 (A,B). Among 135 T2D females with raised blood pressure, 12 were with isolated systolic hypertension. All 85 hypertensive T2D males were with raised systolic and diastolic blood pressure. Table 2 shows the comparison of cardiometabolic risk factors in T2D pts with MS (MS pts) and T2D pts without MS (non MS pts) according to the sex.

According to the definition of IDF, MS was not diagnosed in 90 (35 females, 55 males) T2 D pts (23.5%). The prevalence of the cardiometabolic risk factors in T2D patients without MS is presented in Table 3.

Fasting glucose of MS pts 7.62±1.86 was significantly higher in comparison to that of non MS pts 6.65±1.69



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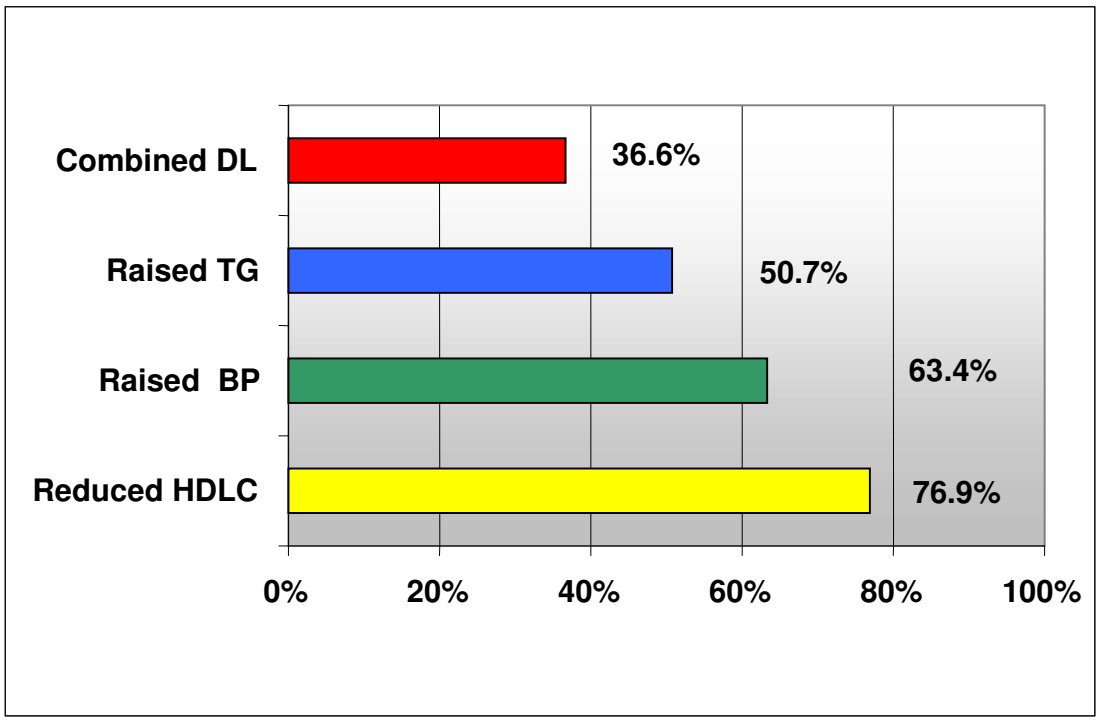

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Figure 2. Characteristics of the metabolic syndrome according to the IDF definition in: A) Type 2 diabetic females, B) Type 2 diabetic males; DL=Dyslipidaemia, HDLC=High density lipoprotein cholesterol, TG=Triglycerides, BP=Blood pressure

Table 2. Comparison of selected cardiometabolic risk factors between: A. T2D females with MS and T2D males with MS; B. T2D females with MS and T2D females without MS; C. T2D males with MS and T2D males without MS (mean±SD); T2D=Type 2 diabetic, MS=metabolic syndrome, T2DM=Type 2 diabetes mellitus, HbA_1c=glycated hemoglobin, BMI=body mass index, HDL=high density lipoprotein

A. **Risk factor**	**T2D females with MS (n=159)**	**T2D males with MS (n=134)**	**p value**
Age (yr)	61.8±10.4	61.5±9.7	0.808
Duration of T2DM (yr)	9.3±7.1	4.7±4.0	<0.001*
HbA_1c (%)	7.5±1.6	7.5±1.2	0.960
Waist circumference (cm)	102.7±14.3	107.4±10.4	0.002 *
BMI (kg/m^2l)	32.3±4.3	32.8±2.8	0.200
Total cholesterol (mmol/l)	5.93±1.51	5.38±1.06	<0.001*
HDL cholesterol (mmol/l)	1.16±0.40	0.96±0.32	<0.001*
Triglycerides (mmol/l)	2.46±1.70	2.28±1.37	0.324
Systolic blood pressure (mmHg)	152±21	145±29	0.017*
Diastolic blood pressure (mmHg)	94±13	94±15	0.972

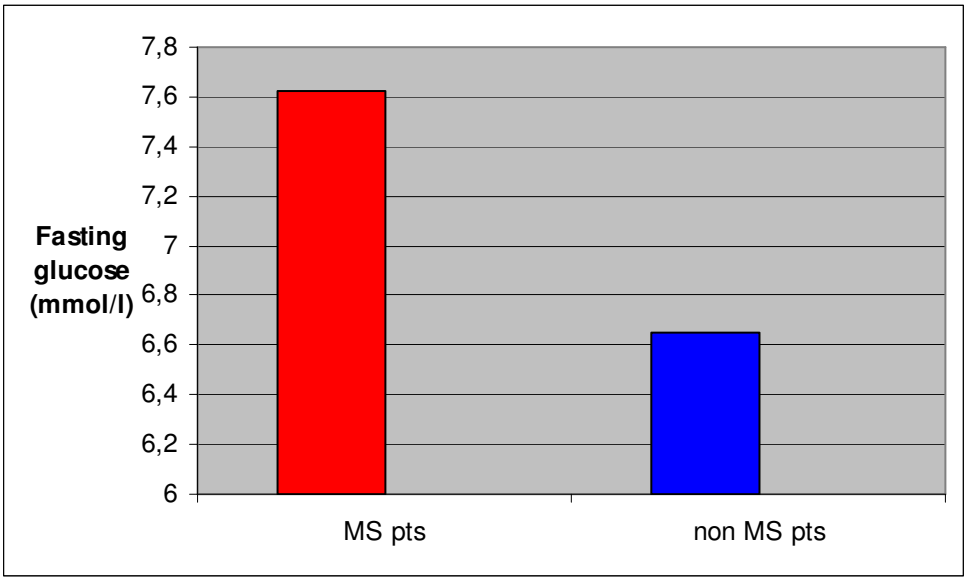
B. **Risk factor**	**T2D females with MS (n=159)**	**T2D females without MS (n=35)**	**p value**
Age (yr)	61.8±10.4	67.2±8.6	0.005*
Duration of T2DM (yr)	9.3±7.1	10.7±9.2	0.329
HbA_1c (%l)	7.5±1.6	7.1±1.0	0.120
Waist circumference (cm)	102.7±14.3	76.8±7.9	<0.001*
BMI (kg/m^2)	32.3±4.3	24.7±2.6	<0.001*
Total cholesterol (mmol/l)	5.93±1.51	5.11±0.78	0.003*
HDL cholesterol (mmol/l)	1.16±0.40	1.44±0.27	<0.001*
Triglycerides (mmol/l)	2.46±1.70	0.99±0.41	<0.001*
Systolic blood pressure (mmHg)	152±21	125±12	<0.001*
Diastolic blood pressure (mmHg)	94±13	77±10	<0.001*

C. **Risk factor**	**T2D males with MS (n=134)**	**T2D males without MS (n=55)**	**p value**
Age (yr)	61.5±9.7	61.8±12.2	0.893
Duration of T2DM (yr)	4.7±4.0	7.2±6.0	0.001*
HbA_1c (%)	7.5±1.2	7.3±0.9	0.240
Waist circumference (cm)	107.4±10.4	87.3±10.6	<0.001*
BMI (kg/m^2)	32.8±2.8	25.3±4.2	<0.001*
Total cholesterol (mmol/l)	5.38 ±1.06	5.03±0.97	0.036 *
HDL cholesterol (mmol/l)	0.96±0.32	1.20±0.44	<0.001*
Triglycerides (mmol/l)	2.28±1.37	1.55±0.57	<0.001*
Systolic blood pressure (mmHg)	145±29	129±16	<0.001*
Diastolic blood pressure (mmHg)	94±15	84±15	<0.001*

* statistically significant

Table 3. Prevalence of the cardiometabolic risk factors according to the definition of IDF in T2D pts without MS (non MS T2D pts), T2D females without metabolic syndrome (non MS T2D females) and T2D males without MS (non MS T2D males). Data are presented as number/percent; T2D pts=T2 diabetic patients, MS=metabolic syndrome

Risk factor	**Non MS T2D pts Number/Percent**	**Non MS T2D females Number/Percent**	**Non MS T2D males Number/Percent**
Central obesity	11/12.2%	5/14.3%	6/10.9%
Raised triglycerides	23/25.6%	0/0%	23/41.8%
Reduced HDL cholesterol	26/28.9%	7/20%	19/34.5%
Combined dyslipidaemia	6/6.7%	0/0%	6/10.9%
Raised systolic blood pressure	34/37.8%	12/34.3%	22/40%
Raised diastolic blood pressure	18/20%	6/17.1%	12/21.8%



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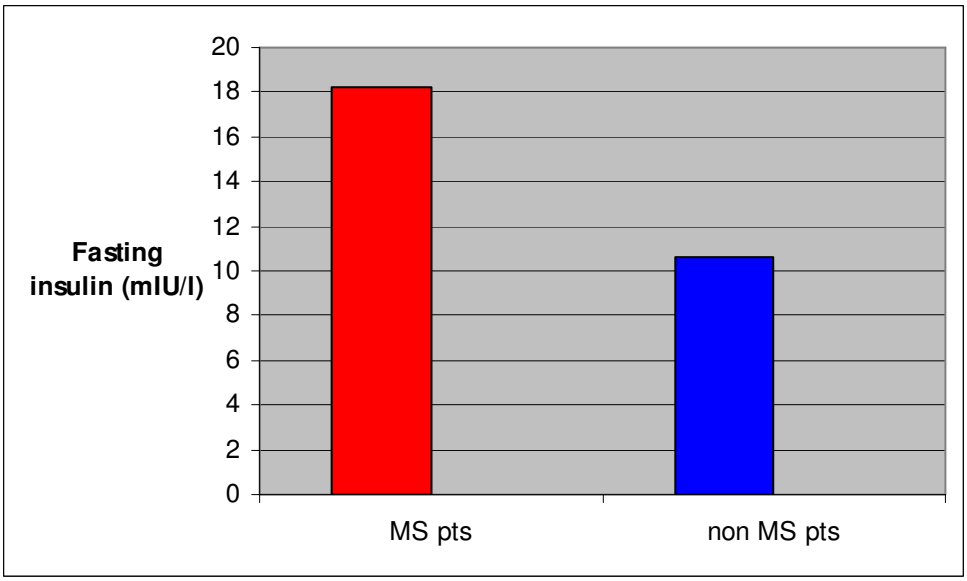

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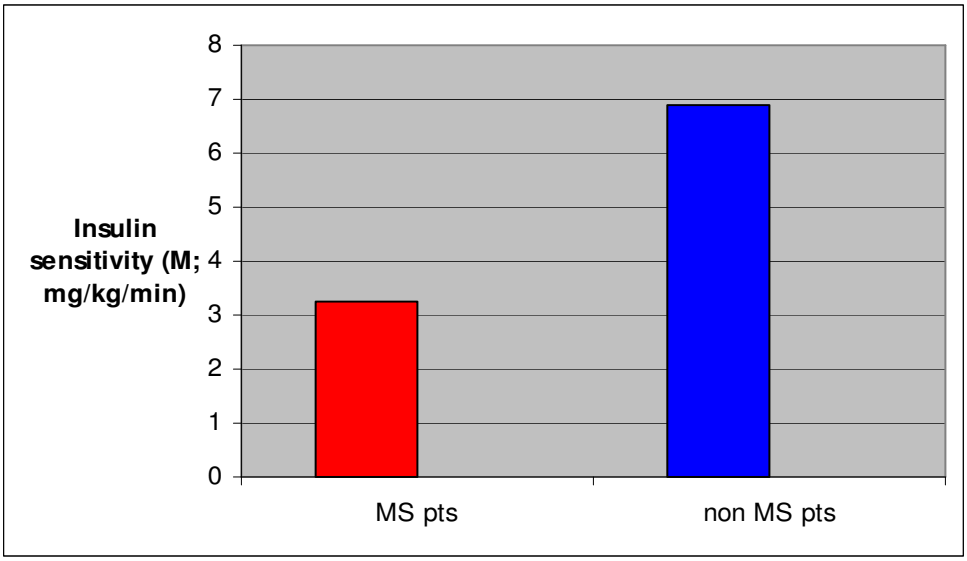
Figure 3. A) Fasting glucose (mmol/l) of MS pts and non MS pts, B) Fasting insulin (mIU/l) of MS pts and non MS pts; MS pts=Metabolic syndrome patients

(mmol/l), p= 0.02. Fasting insulin of MS pts 18.21±8.17 was significantly higher in comparison to that of non MS pts 10.62±3.56 (mIU/l), p<0.001 (Figure 3 A,B).

Determination of insulin sensitivity with a manual hyperinsulinaemic euglycaemic clamp and HOMA-IR was performed in a sample of 63 T2D pts (MS pts, n=51 and non MS pts, n=12). During the all clamp tests an euglycaemic level of 5 mmol/l of mean (0-120 min) and steady state (90-120 min) plasma glucose was kept. There was no a statistically significant difference in the level of a steady state plasma insulin concentration between MS pts 85.56±32.92 and non MS pts 83.79±33.68 (mIU/l). The mean steady state insulin level, obtained during the clamps has been reported to suppress hepatic glucose production, therefore glucose infusion rate reflects glucose disposal rate in all tissues but primarily skeletal muscles (Heine et al., 1985). The median level of insulin sensitivity, expressed as a glucose disposal rate (M, mg/kg/min) in all T2D pts was 3.934. M of MS pts 3.238±1.673 was significantly lower compared to that of non MS pts 6.893±3.846, p= 0.007. The median level of HOMA-IR in all T2D pts was 5.18. HOMA IR of MS pts 6.02±1.69 was significantly higher compared to that of non MS pts 3.07±1.27, p<0.001 (Figure 4 A,B).



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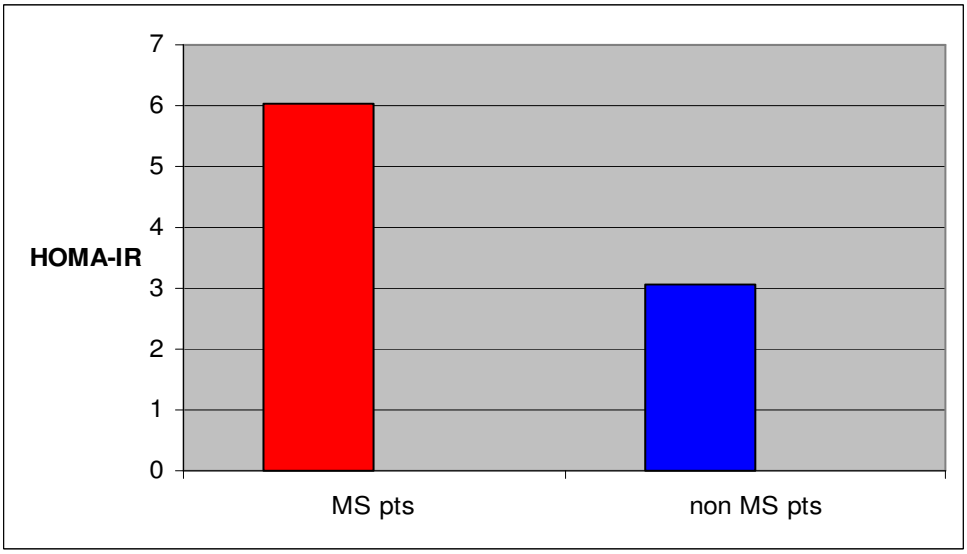

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Figure 4. A) Insulin sensitivity (M; mg/kg/min) of MS pts and non MS pts, B) HOMA-IR of MS pts and non MS pts; HOMA-IR= Homeostasis Model Assessment of Insulin Resistance, MS pts=Metabolic syndrome patients

DISCUSSION

Data about the prevalence of the MS are controversial and depend on many factors like a definition applied, cutoff values of the components, ethnicity, age and gender of the study population. There is no doubt, however, that the syndrome of increased cardiometabolic risk is affecting more and more people worldwide. Most studies suggest a prevalence of the MS in T2D pts of 70-95% (Bruno et al., 2004; Gimeno et al., 2004; Bonora et al., 2004; Song and Hardisty, 2008; Kengne et al., 2012). Lower incidence of the MS in T2D pts has been reported in studies from India 57.7 % according to the IDF definition and 54.8% in T2D men according to the ATP-III guidelines and it is of 58% in a study from Ghana (Yadav D et al., 2013; Kumar SV et al., 2013; Nsiah et al., 2015). The prevalence of the MS is of 12-45% in a general non diabetic population (Jia et al., 2002; Meigs et al., 2003; Ozsahin et al., 2004; Henneman et al., 2008; Scuteri et al., 2015). A large body of evidence emphasize the contribution of the MS to the development of CVD and T2DM (Grundy et al., 2004; Wilson and Meigs, 2008; Cho et al., 2018).

T2DM is a disorder of high cardiovascular risk. MS is an independent predictor of CVD in T2D pts. Consequently, it is of a great importance to identify T2D

pts with MS for cardiovascular risk assessment and active multiple risk factor treatment (Bonora et al., 2004; Barnett, 2008; Dragsbaek et al., 2016; Cho et al., 2018). There is an increasingly urgent need for governments to implement policies to decrease the risk factors for T2DM, and ensure appropriate access to treatment for all people living with DM (Cho et al., 2018).

The IDF definition is a health message to all clinicians that central obesity, defined by a simple measurement of waist circumference, is an useful start point to assessment of risk for development of T2 DM and CVD. We used the IDF criteria for diagnosing of MS because they are easily applicable not only in routine clinical practice, but in large scale studies, as well. According to the IDF definition, the prevalence of the MS in T2D pts was 75.6 %. Studies performed in countries from Europe, at similar climatic, geographic and dietary lifestyle conditions to Bulgaria, like Italy and Spain, including T2DM pts at a similar mean age as patients in our study, have established the similar prevalence of the MS of 75.6% and 77% (Bruno et al., 2004; Gimeno at al., 2004). That confirms the important role of environmental factors to development of the MS. The prevalence of the MS was 82% in diabetic females and 70.9% in diabetic males. As central obesity is a necessary requirement in the IDF definition of MS and T2 DM is one of its components, it might be expected that the predomination of these risk factors in one of both sexes, would have the major contribution to the prevalence of the MS, as well. Studies from different continents of the world Europe, Africa and Asia show the higher prevalence of the MS in T2D women than in T2D men (Song and Hardisty, 2008; Kengne et al., 2012; Yadav et al., 2013; Nsiah et al., 2015). Applying the IDF criteria of MS at the same sample size of T2D pts like this in our study, the study from United Kingdom has shown the higher prevalence of 94.8% in diabetic females vs 91.7% in diabetic males (Song and Hardisty, 2008). The prevalence of MS has been significantly higher in T2D women 72. 1% vs 55.7% in T2D men from the National Obesity Center of the Yaounde Central Hospital of Cameroon. In Ghanaian population, T2 D women have shown a higher incidence of the MS 77.1% vs 22.99% of T2D men. In a study including T2D pts from Central India, women have had a higher incidence of the MS 70.4 % vs 52.7% in men (Yadah et al, 2013). Among non diabetic Dutch population, however, a higher prevalence of MS in males in comparison to the females according to the IDF definition has been reported (Henneman et al., 2008).

Taking into account all T2D pts, the prevalence of central obesity was 76.8%, like that of the MS, while as an individual risk factor in non MS T2D pts, it was presented just in 11 of 90 patients. Comparing MS T2D males and MS T2D females, we did not find a statistically significant difference in BMI between both groups, whereas it was found in waist circumference. This finding confirms the important role of waist circumference, but not body mass index, as a measure of central obesity. The most common cardiometabolic risk factor, excepting central obesity as a necessary requirement, was raised blood pressure. It was at the first position in MS diabetic females and at the second position in MS diabetic males. Hypertension was the most prevalent cardiometabolic risk factor in T2D pts without MS. Considering all T2D pts, the prevalence of hypertension was 66.3%, of which isolated systolic hypertension was 11%. Hypertension and T2DM in coexistence, have a particularly potent effect on the risk of CVD. In the Systolic Hypertension in the Elderly Program (SHEP) study, T2D pts with hypertension receiving antihypertensive treatment with low dose diuretics, have shown twice the absolute risk reduction in cardiovascular events compared to hypertensive patients without diabetes (Curb et al., 1996). In the Systolic Hypertension in Europe Trial, the same degree of blood pressure lowering has been associated with a 76% risk reduction in cardiovascular mortality among diabetic patients receiving blood pressure lowering treatment compared with a 13% reduction among non diabetic patients (Tuomilehto et al., 1999). Patients with MS had significantly higher fasting plasma glucose in comparison to that of patients without MS. The published data in older adults with MS from USA, have been shown a higher risk of total, cardiovascular and non-cardiovascular mortality to persons having elevated fasting glucose≥6.1 mmol/l or treated diabetes, or hypertension, as one of the criteria. Persons without elevated fasting glucose, or diabetes, or hypertension have not shown a higher risk. This study pointed out the predictive power of elevated blood glucose, or diabetes, or hypertension to all cause mortality. Persons with both hypertension and elevated fasting glucose, are having 82% higher mortality (Mozzafarian et al., 2008). Bearing in mind our data about the prevalence of hypertension among T2D pts, we should aggressively treat these patients, even at the stage of prehypertension.

Reduced HDL cholesterol was following hypertension being the major cardiovascular risk factor in MS T2D males. It was on the second position in non MS T2D pts, as well. Given all T2D pts, its prevalence was 55.4%. Low HDL cholesterol and high waist circumference have been the main contributors to the MS among 3000 individuals from Dutch genetic isolate (Henneman et al., 2008). In 1548 subjects from the Hong Kong Cardiovascular Risk Factor Prevalence Study, waist circumference and low HDL cholesterol have predicted the MS as well, as all five components of the MS according to NCEP and IDF definition. The prevalence of a low HDL cholesterol in that population has been lower in comparison to that in MS T2D pts included in our study. HDL cholesterol has been shown to have the highest positive predictive value for NCEP MS and central obesity for IDF MS (Cheung et al., 2008).

Raised triglycerides were on the third position in both

groups-MS and non MS T2D pts. The prevalence of hypertriglyceridaemia in all T2D pts was 53.7%. We should point out, that none of non MS T2D females were having raised triglycerides, which mean that this cardiometabolic risk factor is more usual to cluster with others. As the "so-called hypertriglyceridaemic waist" is well established cardiometabolic risk factors, it has been suggested, a measurement of plasma triglycerides along with waist circumference for better quantification of visceral obesity than waist circumference alone (Despres et al., 2008). The prevalence of combined dyslipidaemia among all T2D pts was 33.9%.

As could be expected, both MS T2D females and MS T2D males, were having a significantly higher waist circumference, body mass index, total cholesterol, triglycerides, systolic and diastolic blood pressure and significantly lower HDL cholesterol compared with non MS pts. T2D females with MS were younger than those without MS. We noted, that MS T2D males were having a significantly shorter duration of diabetes compared with MS T2D females and non MS T2D males. On the other hand, there was no a significant difference in the duration of diabetes between MS T2D females and non MS T2D females. We might conclude, that this finding confirms the hypothesis that cardiovascular risk factors appear early before the clinical diagnosis of diabetes to be made and the duration of T2DM is not a factor influencing the presence of the MS (Hu et al., 2002). It means, that screening for MS should be done in all subjects at increased risk to development of T2DM.

Insulin resistance is an important cardiovascular risk factor and a key pathogenic defect of T2DM. Insulin resistance, like CVD, precedes diagnosis of T2DM approximately 10 years (Kahn, 2003; Fortson et al., 2008). The close relationship between T2DM and CVD has created the "common soil hypothesis" postulating the common antecedents of T2DM and CVD (Stern, 1995). Insulin resistance is considered to be one of the most important of these possible antecedents (Stern, 1995). Early identification of insulin resistant individuals could improve cardiovascular prognosis of these individuals, allowing physicians more time for preventive measures (Fortson et al., 2008). The two major cardiometabolic risk factors are considering being the underlying pathophysiology of the MS-central obesity and insulin resistance (Jiamsripong et al., 2008). Central obesity, defined by waist circumference, is a necessary requirement in the IDF definition. Insulin resistance, defined by HOMA and glucose clamp, is a necessary requirement in WHO definition in NGT persons and it is accepted a priori in T2D pts (WHO Consultation, 1999). There is a positive correlation between waist circumference and insulin resistance (Barnett, 2008). Consequently, we tested the hypothesis whether IDF definition could identify T2D pts with insulin resistance. HOMA is a mathematical model used to the estimation of a steady state insulin and glucose concentration, widely used in epidemiological studies, because it is easily applicable. Hyperinsulinaemic euglycaemic clamp technique is the "gold standard" for quantification of in-vivo insulin sensitivity. The clamp test, however, is invasive, technically demanding and expensive, that limited its use in clinical practice (Olufadi and Byrne, 2008; Jiamsripong et al., 2008). HOMA-IR estimated insulin resistance has been shown to be an independent predictor of CVD in T2D pts (Bonora et al., 2002). We found, applying both methods, that MS T2D pts, compared with non MS T2D pts are significantly less insulin sensitive.

In conclusion, T2D pts included in our study were presented with multiple cardiometabolic risk factors and their cardiovascular prognosis is driven by combinations of these factors which are more potent that suggested by their sums. Screening of MS should be done in all T2D pts and in all subjects at risk for development of T2DM. According to our data, using IDF definition as a diagnostic MS tool, we could identify T2D pts with insulin resistance, as well. Multiple risk factor treatment strategy is required for reduction of global cardiometabolic risk.

Conflict of Interest

There is no conflict of interest to declare.

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