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Original article

Impact of metabolic syndrome and its severity on microvascular complications in type 2 diabetes

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ABSTRACT

Aims: It is much debated whether metabolic syndrome (MetS) is a predictor for microvascular disease in hyperglycemic states. Whether present scoring systems for MetS provide additional risk assessment knowledge related to the severity of the score (from 1/5 to 5/5) remains to be determined for macro- and microangiopathy. Moreover, atherogenic dyslipidemia (low HDL-C and high triglycerides), which provides 2 out of 5 identifying MetS components, is increasingly considered as an emerging risk factor for residual vascular risk.

Material and Methods: We therefore analyzed a T2DM cohort (M:F ratio 63:37) with comparable age and diabetes duration with (MetS (+); $n = 593$) or without MetS (MetS (−); $n = 145$) regarding both macro- and microangiopathy prevalence and risk factors of both types of complications. MetS was defined according to AHA/NHLBI criteria. Blood pressure, glycemic control, insulin resistance (IR), hyperbolic product (B × S) and B × S loss rate, atherogenic dyslipidemia and low-grade systemic inflammatory markers were compared. We also determined whether there was a gradient for microangiopathy alongside MetS scores.

Results: Mean MetS score was 1.8 in MetS (−) *vs.* 4.0 in MetS (+), with hypertension as paramount non-glycemic contributor in MetS (−). BMI, waist, relative/absolute fat mass, visceral fat, conicity and IR were all significantly increased in MetS (+). Current triglycerides levels were almost twice as high in MetS (+) than in MetS (−), while HDL-C was lower by 20%. Mean HbA_{1c} was higher by 0.54% in MetS (+). Hypertension prevalence was twice higher in MetS (+) patients, who had increased systolic blood pressure by +7 mm Hg. Albuminuria was markedly elevated in MetS (+). Inflammatory markers ($_{hs}$CRP, leucocytes and urate) were significantly higher in MetS (+). Retinopathy was diagnosed in 14% of MetS (−) *vs.* 27% of MetS (+), polyneuropathy in 21% of MetS (−) *vs.* 31% of MetS (+) and macroangiopathy in 17% of MetS (−) *vs.* 36% of MetS (+), either as peripheral artery disease (PAD), coronary artery disease (CAD) and/or TIA (transient ischaemic attack)/stroke: 7, 10, and 5% (PAD, CAD, TIA/stroke) in MetS (−) *vs.* 11, 26, and 8% in MetS (+) (NS, $p < 0.0001$, and NS, respectively). Significant trends for increasing prevalence of all three types of microvascular complications were observed according to MetS scores severity from 1/5 to 5/5.

Conclusion: Further to macroangiopathy, there was a marked association between MetS and the presence of all types of microvascular complications in T2DM patients. Microangiopathy prevalence was also associated with MetS score severity in a gradient-type relationship.

1. Introduction

Current definitions of the metabolic syndrome (MetS) reckon that it both identifies a cardiometabolic phenotype associated with insulin resistance (IR)/hyperinsulinemia and predicts incident cardiovascular (CV) disease and/or type 2 diabetes (T2DM) [1]. Since the vast majority (80–90%) of T2DM patients qualify for MetS, the usefulness of determining its presence in such a population with overwhelming MetS prevalence is debated. Establishing the presence of MetS may nevertheless further inform on residual vascular risk in cardiometabolic patients currently receiving standards of care [2]. It is much debated whether MetS is a predictor for microvascular disease in hyperglycemic states. In the Metascreen Study, MetS predicted incident microangiopathy in

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both T1DM and T2DM, being defined with IDF or AHA/NHLBI criteria [3]. In the DCCT study, IR also predicted microangiopathy [4]. By contrast, in the large UKPDS prospective trial in newly-diagnosed T2DM, MetS, whatever the definition used, was not an independent predictor for microvascular disease [5]. Lack of predictive value for microangiopathy of IDF-defined MetS was also reported in T2DM by Iwasaki et al. [6]. In order to better characterize the impact of MetS on microvascular disease, we analyzed a well-phenotyped T2DM cohort with (MetS (+)) or without MetS (MetS (−)) regarding both macro and microvascular disease prevalence, in the prospect of standard or emerging risk factors for both vascular complications, including IR, HOMA hyperbolic product (B × S) and B × S loss rate, glycemic control, atherogenic dyslipidemia and low-grade systemic inflammatory markers. We also determined whether there was a gradient for microangiopathy alongside MetS scores.

2. Patients and methods

The study design was cross-sectional and included 738 consecutive adult, >90% white Caucasian patients with T2DM defined according to the *Expert Committee on the Diagnosis and Classification of Diabetes* [7]. The presence of a metabolic syndrome (MetS) was defined according to *AHA/NHLBI* definition: presence (≥3/5 criteria) or absence (1-2/5 criteria) [1]. Two groups were analyzed: a MetS (−) group (n = 145) *vs*. a MetS (+) group (n = 593) of comparable age and with similar diabetes duration. The following sociodemographic and clinical variables were recorded: age, gender, educational level (dichotomized as [*low vs. high*], based on higher achieved education degree [no education, primary or secondary *vs*. higher education and university]), age at diabetes diagnosis, known diabetes duration, family history (cardiovascular disease, T2DM), current medications (oral anti-diabetic drugs (OAD)), insulin, blood-pressure (BP)-lowering drugs, aspirin, lipid-lowering drugs (LLD), weight, height, body mass index (BMI), body fat (four-limbs electrical bioimpedancemetry, BodyFat Analyser, Omron BF 500). Surrogates for estimating central adiposity were waist circumference and conicity index (waist circumference (m)/ $0.109\sqrt{}$ [weight (kg)/height (m)] [8]).

Each subject underwent non-invasive combined assessment of insulin sensitivity and β-cell function using the Homeostasis Model Assessment (HOMA-2; http://www.dtu.ox.ac.uk), from triplicates means of fasting glucose and specific insulin levels obtained after an overnight fast and discontinuation of glucose-lowering or glucose-sentitizing therapies for 24 h (48 h in case of glargine or long-acting sulfonylureas). Values of HOMA-B (%) were plotted as a function of HOMA-S (%), defining a HOMA-product area (B × S) [unit: $\%^2$; normal value: 100%, corresponding to $10^4\%^2$], which represents the true, underlying β-cell function adjusted for individual insulin sensitivity. (B × S) loss over a subject's lifetime span was obtained by dividing 100 − (B × S) by subjects' age at the time of HOMA-modeling, providing an estimate of annual (B × S) loss rate (B × S LR; unit: % $year^{-1}$) [9–11]. Hypertension prevalence was defined as systolic BP ≥ 140 mm Hg and/or diastolic BP ≥ 90 mm Hg and/or current treatment with BP-lowering drug(s) prescribed for treating high BP. The presence of a peripheral neuropathy was based on clinical examination (knee and ankle reflexes, Semmes-Weinstein 5.07 monofilament test) and/or electromyography. Eye visual examinations by an experienced ophthalmologist and/or fluorescein angiography were performed to diagnose retinopathy. Regarding macroangiopathy, coronary artery disease (CAD) was defined by a well-documented medical history of myocardial infarction, angioplasty, stenting, revascularization surgery and/or significant coronary stenosis confirmed by angiography. Peripheral artery disease (PAD) was defined by a well-documented medical history of lower-limb(s) claudication and/or ischaemic diabetic foot, angioplasty, stenting, revascularization surgery and/or significant lower-limb artery stenosis confirmed by Doppler ultrasonography and/or angiography. Stroke was defined according to UK Prospective Diabetes Study (UKPDS) criteria, i.e. any neurological deficit with symptoms or signs lasting ≥1 month, with no distinction made between ischaemic, embolic and haemorrhagic strokes. In patients with multiple strokes, only the first event was considered for prevalence recording [12].

The following biological variables were measured: current HbA_{1c}, fasting lipids (total cholesterol (C), HDL-C, triglycerides; LDL-C was computed using Friedewald's formula, and non-HDL-C by subtracting HDL-C from total C), normo, microalbuminuria and proteinuria were defined as urinary albumin excretion <30 (normo-), 30–299 (microalbuminuria) and ≥300 μg mg $creatinine^{-1}$ (proteinuria) from first-morning urine sample. Glomerular filtration rate (eGFR) was estimated using Cockcroft and Gault's formula [13].

3. Statistical methods

Results are presented as means (±1 SD) or as median [percentiles 25–75]. The significance of differences between means was assessed by Student's t-test or by alternate Welch's test for data sets with significant differences in SDs, and by Fisher's Exact test for differences in proportions. Chi^2 test for trend was also used to estimate the significancy of complication prevalence across MetS scores categories. Results were considered significant or non-significant (NS) for $p<$ or ≥0.05, respectively.

Table 1
Patients' characteristics.

		MetS (−)	MetS (+)	p
n		145	593	
Age	years	66 (14)	66 (10)	–
Diabetes duration	years	13 (9)	13 (8)	–
Sex ratio (M:F)	%	77:23	63:37	0.0018
BMI	$kg\,m^{-2}$	24.5 (3.6)	30.8 (5.3)	<0.0001
Waist	cm	91 (10)	107 (13)	<0.0001
Fat mass	%	26 (7)	34 (8)	<0.0001
Liver steatosis	%	31	75	<0.0001
HOMA-S	%	75 (42)	46 (30)	<0.0001
HOMA product (B × S)	%	33.3 (18.5)	24.5 (16.1)	<0.0001
HbA_{1c}	%	7.26 (1.39)	7.80 (1.52)	<0.0001
Systolic blood pressure	mm Hg	135 (18)	142 (22)	<0.0001
Hypertension	%	46	83	<0.0001
eGFR	$ml\,min^{-1}\,1.73\,m^2$	81 (30)	89 (38)	0.0069
Albuminuria	μg mg $creatinine^{-1}$	28 (58)	107 (303)	<0.0001

Results are expressed as means (1 SD) or proportions (%). B: beta-cell function (HOMA); BMI: body mass (Quetelet's) index; eGFR: estimated glomerular filtration rate; F: female; HOMA: homeostatic model assessment; HOMA-S: insulin sensitivity; M: male; MetS: metabolic syndrome (AHA/NHLBI criteria).