Diabetes & Metabolism 43 (2017) 217–222

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Original article

Predictors of cardiovascular risk among patients with type 1 diabetes: A critical analysis of the metabolic syndrome and its components

V. Gingras [a,b], C. Leroux [a], A. Fortin [a,b], L. Legault [a,c], R. Rabasa-Lhoret [a,b,d,e,*]

[a] Institut de Recherches Cliniques de Montréal, Montreal, Quebec, Canada
[b] Department of nutrition, Université de Montréal, Montreal, Quebec, Canada
[c] Montreal Children's Hospital, McGill University Health Center, Montreal, Quebec, Canada
[d] Montreal Diabetes Research Center (MDRC), Montreal, Quebec, Canada
[e] Division of Endocrinology, Department of Medicine, Université de Montréal Hospital Center (CHUM), Montreal, Quebec, Canada

ARTICLE INFO

Article history:
Received 25 August 2016
Received in revised form 17 October 2016
Accepted 25 October 2016
Available online 27 January 2017

Keywords:
Cardiovascular risk
Definition
Insulin resistance
Metabolic syndrome
Type 1 diabetes

ABSTRACT

Patients with type 1 diabetes (T1D) are at increased risk for cardiovascular diseases. The metabolic syndrome (MetS), a complex disorder defined by a cluster of interconnected factors including abdominal obesity, hypertension, dyslipidaemia and insulin resistance, has been proposed to identify patients with T1D at high cardiovascular risk. The MetS has been identified in 8–45% of patients with T1D, depending on the definition and cohort studied. However, clinicians and researchers face several issues with the criteria for MetS in patients with T1D, therefore questioning its value in routine care. For example, three criteria can lead to overestimation of MetS prevalence; the impaired fasting glucose criterion is irrelevant as it is automatically fulfilled; and the widespread use of antihypertensive and lipid-lowering medications for cardiac and renal preventative purposes can contribute to overestimations of the prevalence of raised blood pressure and elevated triglycerides. In cross-sectional studies, the MetS has been associated mostly with an increased risk of microvascular complications whereas, in prospective cohorts, the predictive value of MetS for micro- and macrovascular outcomes has been inconsistent. While identifying diabetes patients at increased risk for cardiovascular complications and early mortality is crucial from a prevention standpoint, for patients with T1D, the current definition of MetS may not be the most suitable tool. The aims of the present report are to review the applicability and limitations of the MetS in patients with T1D, and to discuss alternative avenues to identify high-risk patients.

The metabolic syndrome

Definition

In the general population, the metabolic syndrome (MetS) is defined by a cluster of interconnected factors that confer a twofold increase in the risk of cardiovascular atherosclerotic diseases and a fivefold increase in the risk of type 2 diabetes (T2D) [1]. The MetS has been studied for several decades with the objective of identifying patients who would most benefit from specific preventative or therapeutic interventions (lifestyle and pharmacotherapy). Yet, the pathophysiology and definition of MetS have been widely debated, and various definitions and criteria proposed (Table 1) [1–4]. Recently, International Diabetes Federation (IDF) and American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) representatives agreed on criteria for a clinical diagnosis of MetS, including a large waist circumference, elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol, raised blood pressure and elevated fasting glucose (Table 1) [1].

Ongoing issues with the MetS

The MetS has been widely debated over its definition, its underlying mechanisms and its association with cardiovascular risk. In a critical appraisal of the MetS, Kahn et al. [5] identified several concerns, including ambiguity of the criteria and thresholds, and the unclear value of the 'syndrome' compared with each component alone for risk identification and treatment. For example, the dysglycaemia criterion has been considerably modified throughout multiple definitions. In the World Health

* Corresponding author at: Institut de recherches cliniques de Montréal (IRCM), 110, avenue des Pins Ouest, Montréal, Québec H2W 1R7, Canada.
Tel.: +15149875666; fax: +15149875670.
E-mail address: remi.rabasa-lhoret@ircm.qc.ca (R. Rabasa-Lhoret).

http://dx.doi.org/10.1016/j.diabet.2016.10.007
1262-3636/

Table 1
Definitions of the metabolic syndrome.

	WHO 1999 [2]	NCEP-ATP III 2001 [4]	IDF 2005 [3]	Consensus (IDF and AHA/NHLBI) 2009 [1]
General	Hyperglycaemia +2 components	≥3 components	Abdominal obesity +2 components	≥3 components
Abdominal obesity	BMI > 30 kg/m^2 and/or WHR: M > 0.90, F > 0.85	Waist circumference: M > 102 cm, F > 88 cm	Waist circumference (ethnic-dependent): M ≥ 94 cm, F ≥ 80 cm	Waist circumference (ethnic-dependent): M ≥ 102 cm, F ≥ 88 cm
Hypertension	≥140/≥90 mmHg	≥130/≥85 mmHg	≥130/≥85 mmHg or treatment	≥130/≥85 mmHg or treatment
HDL cholesterol	M < 0.9 mmol/L, F < 1.0 mmol/L	M < 1.0 mmol/L, F < 1.3 mmol/L	M < 1.03 mmol/L, F < 1.29 mmol/L, or treatment	M < 1.0 mmol/L, F < 1.3 mmol/L, or treatment
Triglycerides	≥1.7 mmol/L	≥1.7 mmol/L	>1.7 mmol/L or treatment	>1.7 mmol/L or treatment
Hyperglycaemia	Diabetes diagnosis or FBG ≥6.1 mmol/L or hyperinsulinaemia	FBG ≥6.1 mmol/L	Diabetes diagnosis or FBG ≥5.6 mmol/L	Diabetes diagnosis or FBG ≥5.6 mmol/L
Microalbuminuria	UAE rate ≥20 μg/min or ACR 30 mg/g	–	–	–

WHO: World Health Organization, NCEP-ATP III: Third National Cholesterol Education Program Adult Treatment Panel; IDF: International Diabetes Federation; AHA/NHLBI: American Heart Association/National Heart, Lung, and Blood Institute; BMI: body mass index; WHR: waist-to-hip ratio; M: male; F: female; HDL: high-density lipoprotein; FBG: fasting blood glucose; UAE: urinary albumin excretion; ACR: albumin-to-creatine ratio.

Organization (WHO) definition, insulin resistance was the central component for diagnosis and defined as either T2D, impaired fasting glucose, impaired glucose tolerance or hyperinsulinaemia. In subsequent definitions, increased fasting blood glucose (with various thresholds) or a diabetes diagnosis was used as a more realistic assessment in larger populations. Also, there is no agreement on the method of measurement for certain criteria, which makes it difficult to compare studies: the WHO suggests measuring waist circumference at the midpoint between the lowest point of the last rib and top of the iliac crest [6], while the US National Institutes of Health (NIH) suggest measuring it at the top of the iliac crest [7]. However, both measures appear to be good clinical markers of cardiometabolic risk [8].

Nevertheless, to avoid differences in measurement from one professional to another, a rigorous and consistent technique is necessary. Moreover, gender-specific thresholds have been identified for waist circumference and HDL cholesterol, but it has also been suggested that ethnic-specific thresholds may be required for certain criteria; indeed, in the most recent definition of MetS, waist circumference cut-offs based on ethnicity have been proposed [1]. It is also debated whether MetS as a whole is more important than the sum of its components. Still, a meta-analysis has suggested that the MetS is a strong risk factor of morbidity and mortality [9].

Thus, despite general concerns associated with the MetS, its diagnosis in the general population has been widely used as a simple and practical tool for identifying patients who deserve greater attention in terms of cardiovascular disease and diabetes prevention [10]. However, additional issues arise with the MetS definition and usefulness in patients with type 1 diabetes (T1D), a population characterized by insulin deficiency. The present report aims to review the applicability and limitations of the MetS (definition and threshold values) in patients with T1D, and to discuss other potential avenues of identifying patients at increased cardiovascular disease risk.

A critical analysis of MetS criteria for T1D

Elevated fasting glucose

All the current definitions of MetS present limitations for studies in T1D, as the hyperglycaemia criterion is automatically fulfilled and therefore likely to lead to an overestimation of prevalence. Although the first MetS definition by the WHO [2] included several markers of impaired glucose metabolism, such as hyperinsulinaemia, subsequent definitions simplified this criterion by including only elevated fasting blood glucose. Yet, for patients with T1D, replacing elevated fasting blood glucose with an estimation of insulin resistance suitable for T1D may be more appropriate. Insulin sensitivity estimation formulas and their potential application in T1D are discussed below and presented in Table 2.

Elevated triglycerides (or its treatment)

Patients with T1D are often treated with lipid-lowering medications for preventative rather than curative purposes, at least initially. According to the 2013 Canadian Diabetes Association Clinical Practice Guidelines for vascular protection in people with diabetes, patients aged > 40 years or having a diabetes duration of ≥ 15 years, as well as those with micro- or macrovascular complications, should be using antihypertensive drugs that target the renin–angiotensin system, and statins for cardiac and renal preventative purposes [11]. In most patients, however, it is virtually impossible to determine whether the treatment was implemented exclusively for primary prevention reasons, which should probably not be considered a criterion for MetS, or because the patient had reached the threshold for treatment, which does indeed fulfil the criterion for MetS.

Table 2
Insulin sensitivity estimation formulas in type 1 diabetes (T1D).

Study	Formula	Sample from which formula was derived
Pittsburgh Epidemiology of Diabetes Complications (EDC) Study, 2000 [15]	eGDR = 24.31 – 12.22 (WHR) – 3.29 (hypertension; 1 = yes, 0 = no) – 0.57 (HbA_{1c}, %)	24 adults (age: 20–49 years) with T1D
SEARCH for Diabetes in Youth Study, 2011 [43]	Log eIS = 4.64725 – 0.02032 (waist, cm) – 0.09779 (HbA_{1c}, %) – 0.00235 (triglycerides, mg/dL)	53 youths (age: 12–19 years) with T1D or type 2 diabetes
Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study, 2016 [44]	ISe = exp 4.1075 – 0.1299 (waist, cm) – 1.05819 (daily insulin dose, U/kg) – 0.00354 (triglycerides, mg/dL) – 0.00802 (DBP, mmHg)	36 adults with T1D and 41 non-diabetic adults

eGDR: estimated glucose disposal rate; eIS: estimated insulin sensitivity; ISe: insulin sensitivity estimation; WHR: waist-to-hip ratio; DBP: diastolic blood pressure.