

Metabolic Syndrome, Insulin Resistance and Cardiovascular Disease in Type-1 Diabetes Mellitus

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Abstract

Metabolic syndrome (MS) is a complex disorder represented by a cluster of cardiovascular risk factors related to central fat distribution and insulin resistance (IR), and is associated with early mortality in non-diabetic individuals and in patients with type-2 diabetes mellitus (DM).

The presence of MS and its components has also been described in patients with type-1 DM and may contribute to the increased risk of cardiovascular disease seen in this patient population.

The objective of this study was to review the available evidences of the role of MS and IR in the development of cardiovascular disease in patients with type-1 DM.

Introduction

Metabolic syndrome (MS) is a complex disorder represented by a cluster of cardiovascular risk factors related to central fat distribution and insulin resistance (IR)¹. These risk factors include dyslipidemia, central obesity, changes in blood glucose homeostasis and hypertension. The prevalence of MS in the overall population is of approximately 24%², reaching more than 80% among patients with type-2 diabetes mellitus (DM)³. MS is an important risk factor for early mortality in non-diabetic individuals^{4,5} and in patients with type-2 DM⁴. However, the role of MS as an independent entity, associated with a higher risk for the development of cardiovascular events has been recently questioned⁶.

The presence of MS and its components has also been described in patients with type-1 DM and may be associated with the presence of diabetic nephropathy (DN) and worse glycemic control⁷.

Although the absolute risk of cardiovascular disease (CVD) in patients with type-1 DM is lower than that in patients with type-2 DM, it is dramatically increased when compared to that of non-diabetic individuals of a similar age⁸. The conventional risk factors and the presence of DN only partially

explain this finding⁹. The hypothesis that the presence of MS in patients with type-1 DM could be a risk factor for CVD has a theoretical background. The presence of IR has been described in patients with type-1 DM⁹⁻¹¹ and may contribute to the elevated risk of CVD seen in this patient population. Studies analyzing the role of MS as a risk factor for micro and macrovascular complications are scarce and were conducted in selected populations.

The objective of this study was to review the available evidences of the role of MS and IR in the development of CVD in patients with type-1 DM.

Diagnostic Criteria of Metabolic Syndrome

Several clinical definitions of MS have been proposed. The three most frequently used are those of the World Health Organization (WHO)¹², National Cholesterol Education Program's Adults Treatment Panel III (NCEP-ATP III)¹³ and, more recently, the International Diabetes Federation (IDF)¹⁴. The WHO definition was proposed in 1998 and recommends the assessment of IR or of glucose metabolism disorders as the starting point; it includes measurement of albuminuria and is thus more complex to evaluate. The NCEP-ATP III definition was developed for clinical use and does not require confirmation of IR. Because it is simple and easy to use, this is the definition recommended by the I Brazilian Guideline on the Diagnosis and Treatment of Metabolic Syndrome¹⁵. During the congress on MS and prediabetes held in Berlin in 2005, another definition was presented that puts central adiposity as a major component. Also, the cut-off points of waist circumference are lower than those used in the NCEP definition, and there are specific values for the different ethnic groups^{14,16}. The criteria of the three recommendations are described in Table 1.

Methods of Assessment of Insulin Resistance

IR is believed to be the main pathogenic factor of MS¹⁷. IR is classically defined as a defect in insulin action that results in compensatory hyperinsulinemia to keep glucose levels within normal limits. An important contributing factor for IR is the presence of high serum levels of free fatty acids, resulting from increased mobilization of fat tissue tryglicerides¹⁷.

The gold standard for the assessment of IR is the euglycemic hyperinsulinemic clamp technique¹⁸. In summary, this is performed via a venous access and insulin is administered with the purpose of suppressing the endogenous glucose production and increasing its physiological uptake. In order to keep blood glucose levels between 90 and 140mg dL, glucose

Key Words

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is intravenously infused. Insulin sensitivity is quantified by the rate of glucose infusion required to keep blood glucose levels within the goals established¹⁸. Due to the difficulties in performing clamp studies, other forms of IR assessment were developed. For more than two decades, fasting insulin was

Table 1 - Diagnostic criteria of MS according to the three most frequently used definitions: WHO, NCEP-ATP III and IDF.

The WHO requires the presence of insulin resistance or hyperglycemia plus two other components:		Levels
Presence of hypertension*		≥ 140/90 mmHg
BMI ≥ 30 kg/ m ² and/or waist/hip ratio	Men	> 0.90
	Women	> 0.85
Presence of micro- or macroalbuminuria		≥ 20 µg/min
Triglycerides*		≥ 150 mg/dl
HDL cholesterol*	Men	< 35 mg/dl
	Women	< 39 mg/dl
Glycemia*		≥ 110 mg/dl
The NCEP-ATP III requires the presence of at least three of the following components:		Levels
Blood pressure*		≥ 130 mmHg SBP or ≥ 85 mmHg DBP
Abdominal circumference	Men	≥ 102 cm
	Women	≥ 88 cm
Triglycerides*		≥ 150 mg/dl
HDL cholesterol*	Men	< 40mg/dl
	Women	< 50 mg/dl
Blood glucose*		≥ 100 mg/dl
The IDF requires the presence of abdominal obesity and at least three additional components:		Levels
Obligatory presence of abdominal obesity		
For Europeans and Arabs	Men	≥ 94 cm
	Women	≥ 80 cm
For Asians, Central and South Latin Americans	Men	≥ 90cm
	Women	≥ 80 cm
Blood pressure*		≥ 130 mmHg SBP or ≥ 85 mmHg DBP
Triglycerides*		≥ 150 mg/dl
HDL cholesterol*	Men	< 40mg/dl
	Women	< 50 mg/dl
Blood glucose*		≥ 100 mg/dl
Glicemia*		≥ 100 mg/dl

* Or use of specific medication is considered as having this component in the criteria of the metabolic syndrome

used as a marker of insulin sensitivity in several epidemiological studies, it being assumed that fasting insulin was an IR equivalent^{18,19}. However, fasting insulin is not able to explain more than 30% to 40% of the variation of insulin sensitivity found in the clamp technique²⁰. A better, yet still not optimal way to estimate IR is the Homeostasis Model Assessment (HOMA-IR) developed by Matthews et al, who used a mathematical model that takes into consideration the serum glucose and insulin levels²¹. HOMA-IR correlates closely with the results of clamp in relation to IR^{21,22}. However, in patients using insulin, such as type-1 DM patients, both the dosage of serum insulin and the use of HOMA are invalid, thus making another form of IR assessment necessary.

Clinical markers may identify patients with IR²³. In addition to the conventional clinical characteristics of hypertension, waist/hip ratio, family history of type-2 diabetes mellitus, and triglyceride and HDL cholesterol levels, poor glycemic control and total insulin dose are also associated with IR²⁴. Based on this information, an IR assessment score named glucose disposal rate (GDR) was developed and validated, using the euglycemic hyperinsulinemic clamp technique (60 mU. m⁻².min⁻¹)²⁴ in a group of patients with type-1 DM. This assessment gave rise to the following equation:

$$GDR (mg.kg^{-1}.min^{-1}) = 24.31 - 12.22 \times (\text{waist/hip ratio}) - 3.29 \times (\text{presence of hypertension}) - 0.57 \times (\text{HbA1c}),$$

where presence of hypertension = 1 and absence of hypertension = 0.

This equation was modified for the use of Hb_{A1c} in place of HbA1 (7), and is currently described as follows:

$$GDR (mg.kg^{-1}.min^{-1}) = 24.4 - 12.97 \times (\text{waist/hip ratio}) - 3.39 \times (\text{presence of hypertension}) - 0.60 \times (\text{Hb}_{A1c}).$$

Several studies have used this equation as a method of IR assessment in patients with type-1 DM^{7,9,25,26}.

Cardiovascular Disease in Patients with Type-1 Diabetes Mellitus

Atherosclerotic CVD, especially coronary artery disease (CAD), is the major cause of mortality and morbidity in patients with DM²⁷. A higher occurrence of mortality from CAD in patients with type-1 DM has already been reported since the 1970's²⁸. Krolewski et al demonstrated that at 55 years of age the cumulative mortality rate in this population was 30%-40% in comparison with a 4%-8% mortality rate in non-diabetic patients described in the Framingham study²⁹. Data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) show a risk of CAD mortality of 9.1 for men and 13.5 for women, in patients diagnosed with diabetes before the age of 30 years in relation to the general population in an 8-year follow-up period³⁰. Recently, a prospective study that followed-up a cohort of more than seven thousand patients with type-1 DM for seven years demonstrated that the relative risk of cardiovascular events was 3.6 (95% CI 2.9-4.5) for men and 7.7 (95% CI 5.5-10.7) for women in comparison with non-diabetic individuals³¹. That study also estimated at 5%

the risk of fatal CVD in the next 10 years for a 50-year-old diabetic individual, which corresponds to 10 to 15 years before the same risk is present in the non-diabetic population. The follow-up of 23,751 patients with DM diagnosed before 30 years of age and treated with insulin showed mortality rates similar to those previously described, and demonstrated that other CVD forms such as hypertension, heart valve disease, cardiomyopathy, heart failure and stroke are also frequent among this population of patients³². Pathological studies and intravascular ultrasonography demonstrated atheromatosis and abnormalities in the coronary wall consistent with early CAD in patients with type-1 DM^{33,34}.

Although the association of early CVD in patients with type-1 DM has been known for a long time, the underlying pathogenesis is still not fully understood. Hyperglycemia is, a priori, the most important factor accounting for the high incidence of CVD³⁵. However, despite recent evidence that a better glycemic control has been associated with reduction of CVD³⁶, the literature is conflicting as to the association of CVD and glycemia in patients with type-1 DM. While some studies state that the glycemic control after adjustment for the conventional risk factors for CVD is not significantly associated with cardiovascular events^{9,37-39}, others point to a positive association^{36,40-42}. A recent meta-analysis of clinical trials showed that an improved glycemic control reduced the incidence of CVD in patients with type-1 and 2 diabetes⁴¹. The beneficial effect of the intensive glycemic control for six years on cardiovascular endpoints was confirmed after an 11-year follow-up of patients with type-1 DM⁴². More recently, an analysis after a 16-year follow-up showed that the positive variation of glycosylated hemoglobin was strongly associated with CVD and CAD, and that the discrepancies found in the results of previous studies may in part be the result of different prevalence rates of renal disease³⁶.

European guidelines do not consider patients with type-1 DM as being at high risk, unless microalbuminuria is present⁴³. A recent study evaluating a group of patients with long-standing type-1 DM and without symptoms of cardiovascular disease showed an association of atherosclerotic disease in the coronary arteries, but not in the aorta, with diabetic nephropathy⁴⁴. Patients with type-1 DM and diminished renal function often develop extensive atherosclerosis⁴⁵.

The high risk of CVD observed in female patients with type-1 DM is not explained by the conventional risk factors for CVD⁴⁶, and the underlying mechanisms are still not fully understood.

A prospective study evaluating the risk factors associated with the development of CVD showed that nephropathy (especially in men), hypertension, smoking, dyslipidemia, depressive symptoms, and IR were all related to CV endpoints in patients with type-1 DM⁹. Glycemic control was not associated with cardiovascular events, but maintained a close relation to microvascular disease.

The presence of coronary artery calcification (CAC) has an excellent correlation ($r > 0.9$) with coronary atherosclerosis, and is useful as a measurement of extent of atherosclerosis⁴⁷. The presence of CAC predicts cardiovascular events, especially in asymptomatic individuals⁴⁸. Patients with type-1 DM have more CAC in comparison with non-diabetic individuals^{49,50},

which favors the hypothesis of accelerated atherosclerosis in these patients. The presence of CAC in this group of patients was associated with clinical disease and the presence of risk factors for CVD⁵¹. The evaluation of studies including patients with type-1 DM and CAC showed that the presence of any amount of calcium increases the risk of CVD³⁵. Previous studies have confirmed the higher risk of CAD in women with type-1 DM^{31,49}. The evaluation of a group of patients with type-1 DM showed that the presence of CAC in women may be due to the higher incidence of IR observed in this group of patients, especially associated with body fat distribution⁴⁹.

The Impact of the Metabolic Syndrome and Insulin Resistance on Type-1 Diabetes Mellitus

The first study that evaluated patients with type-1 DM and presence of MS showed a prevalence of 38% in men and 40% in women⁷. In patients without renal disease, in those with microalbuminuria, those with macroalbuminuria, and in patients with end-stage renal disease the prevalence of MS observed was 28%, 44%, 62%, and 68%, respectively⁷. Also, the worse the glycemic control of these patients, the higher the frequency of MS. All the components of the syndrome were individually associated with DN. More recently, the prevalence of MS in patients with type-1 DM has had a more wide variation, from 12.5% to 42%^{26,31,52}. These variations may be explained by different levels of IR and age range between the populations studied.

MS and IR are characteristic of type-2 DM. The presence of MS according to the WHO criteria is associated with the presence of micro and macrovascular complications in patients with type-2 DM^{3,53}. In patients with type-1 DM this association requires further understanding, but in relation to IR it seems to be similar, since IR was associated with the presence of diabetic retinopathy (DR)⁵⁴, DN^{53,55-57}, and CVD²⁵.

Patients with type-1 DM and microalbuminuria with mild reduction in the glomerular filtration rate (GFR) have a higher degree of IR in comparison with patients with microalbuminuria without reduction in GRF and patients without nephropathy⁵⁶. However, patients with nephropathy have high levels of blood pressure, dyslipidemia, low degree of inflammation and IR secondary to renal failure, which makes the distinction between nephropathy and MS difficult^{56,58}. IR as assessed by euglycemic hyperinsulinemic clamp is predictive of the development of microalbuminuria⁵⁷.

Data from prospective studies help us understand these relationships. An analysis of patients with type-1 and 2 diabetes demonstrated that in the first ones the presence of MS was associated with the development of nephropathy and neuropathy⁵³. An evaluation carried out after nine years of follow-up demonstrated that IR as estimated by the GDR equation enabled the identification of patients who developed nephropathy, retinopathy and CVD⁵⁹, differently from the presence of MS or the insulin dose initially administered. The patients who participated in the intensive treatment group and had greater weight gain had a higher incidence of MS⁵⁹. Another prospective analysis of an 11-year follow-up in a small group of patients with type-1 DM did not show association

between the presence of MS and development of CVD either, and MS did not add prognostic value to the conventional CVD risk factors⁵². Only one study showed that the presence of MS according to the three known criteria (WHO, NCEP and IDF) was predictive of the risk of CAD and renal disease in patients with type-1 DM; however, its individual components had a higher power, especially the presence of microalbuminuria in the WHO criterion²⁶.

Although insulin deficiency is the primary metabolic defect in patients with type-1 DM, the studies described above show that IR is a frequent finding and can partly contribute to the high rates of vascular events in this population.

Exogenous insulin administration enough to reach adequate levels in the portal circulation and keep euglycemia leads to systemic hyperinsulinemia. This hyperinsulinemia has been proposed to account for the abdominal fat accumulation in patients with type-1 DM⁶⁰. The mechanism proposed is that insulin increases the activity of 11 β -hydroxysteroid-dehydrogenase, especially in the omental adipocytes, thus favoring hypercortisolism and increasing the differentiation of stromal cells into adipocytes, and promoting abdominal obesity⁶¹⁻⁶³.

An analysis carried out four years after the conclusion of the Diabetes and Complications Trial (DCCT) demonstrated that patients that underwent intensive treatment and who presented greater weight gain had increased waist-hip ratio, higher blood pressure levels and higher insulin requirements for a better metabolic control when compared with patients who did not have an exaggerated weight gain. These patients also presented a more atherogenic lipid profile, as well as liver enzyme abnormalities, which could be explained as a consequence of MS in function of the weight gain in this group of patients with type-1 DM⁵⁹.

The evaluation of patients with type-1 DM classified according to their body weight demonstrated that overweight patients have a higher prevalence of diabetic retinopathy and neuropathy; however, after regression analysis, the major determinants were still glycemic control and duration of DM⁵⁴.

The use of insulin sensitizer (rosiglitazone) in overweight patients with type-1 DM results in improved glycemia and control of blood pressure levels without an increase in insulin requirements. This result was more pronounced in patients with IR markers, especially among those with BMI > 30 kg/m²⁶⁴. The use of another insulin sensitizer (metformin) in adults and adolescents with type-1 DM also improves the glycemic control and reduces insulin requirements in these patients⁶⁵⁻⁶⁸.

In a large cohort of patients with type-1 DM, lipid levels were associated with smoking and abdominal adiposity, thus characterizing the IR syndrome⁶⁹.

We conducted a cross-sectional study in 100 patients with type-1 DM to evaluate the association of MS and presence of CAC. We observed an association between the presence of CAC and MS, especially in female patients. Hypertension was the individual risk factor of MS associated with the presence of CAC. This finding underscores the role of IR in patients with type-1 DM. MS may have a clinical impact and more severe consequences on atherosclerosis of female patients with type-1 DM⁷⁰.

Conclusion

CVD is the major cause of mortality in patients with type-1 DM, as well as in patients with type-2 DM.

Markers of IR are associated with micro and macrovascular complications in patients with type-1 DM. IR is one of the landmarks of MS. In type-2 diabetic and non-diabetic individuals, MS is an important cardiovascular risk factor. In patients with type-1 DM, the association of MS and IR with nephropathy is quite evident, but MS alone does not seem to predict CVD. The presence of MS may have a greater impact on atherosclerosis of female patients with type-1 DM.

The benefits of the improvement in DM care seem not to have reduced CVD mortality in patients with type-1 DM yet. We should probably change the way we look at these patients: in addition to pursuing optimal goals of glycemic, pressure, and lipid control, we should also increase our efforts in the control of body weight, a modifiable risk factor that is associated with the presence of IR.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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