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Review

Type 1 diabetes, metabolic syndrome and cardiovascular risk

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ABSTRACT

Patients with type 1 diabetes mellitus (T1DM) traditionally had a low body mass index and microangiopathic complications were common, while macroangiopathy and the metabolic syndrome were exceptional. The Diabetes Control and Complications Trial, published in 1993, demonstrated that therapy aimed at maintaining HbA1c levels as close to normal as feasible reduced the incidence of microangiopathy. Since then, the use of intensive insulin therapy to optimize metabolic control became generalized. Improved glycemic control resulted in a lower incidence of microangiopathy; however, its side effects included a higher rate of severe hypoglycemia and increased weight gain. Approximately 50% of patients with T1DM are currently obese or overweight, and between 8% and 40% meet the metabolic syndrome criteria. The components of the metabolic syndrome and insulin resistance have been linked to chronic T1DM complications, and cardiovascular disease is now the leading cause of death in these patients. Therefore, new therapeutic strategies are required in T1DM subjects, not only to intensively lower glycemia, but to control all associated metabolic syndrome traits.

1. Introduction

Traditionally, patients with type 1 diabetes mellitus (T1DM) suffered microangiopathic complications, especially nephropathy, which had a negative impact on prognosis and quality of life [1]. In 1993, the Diabetes Control and Complications Trial (DCCT) demonstrated that intensive glucose lowering therapy could reduce by 50% the incidence of microangiopathy [2]. The Epidemiology of Diabetes Interventions and Complications trial (EDIC), an extension study of the DCCT, with a mean follow-up of 17 years, revealed a 57% reduction in the relative risk of non-fatal myocardial infarction, stroke or cardiovascular death in the group that had initially received intensive insulin therapy [3]. Ever since, most therapeutic efforts in T1DM have focused on reducing glycated hemoglobin levels. However, a growing body of evidence underlines the frequent coexistence of metabolic syndrome components in patients with T1DM [4–7], resulting in the so-called "double diabetes" [8] (Fig. 1). This fact, together with the decline in the incidence of microangiopathy, has led to cardiovascular disease now

Abbreviations: ADA, American Diabetes Association; Apo, apolipoprotein; DCCT, Diabetes Control and Complications Trial; EASD, European Association for the Study of Diabetes; EDIC, Epidemiology of Diabetes Interventions and Complications trial; eGDR, estimated glucose disposal rate; HDL, high-density lipoproteins; HOMA-IR, homeostasis model assessment-insulin resistance; LDL, low-density lipoproteins; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

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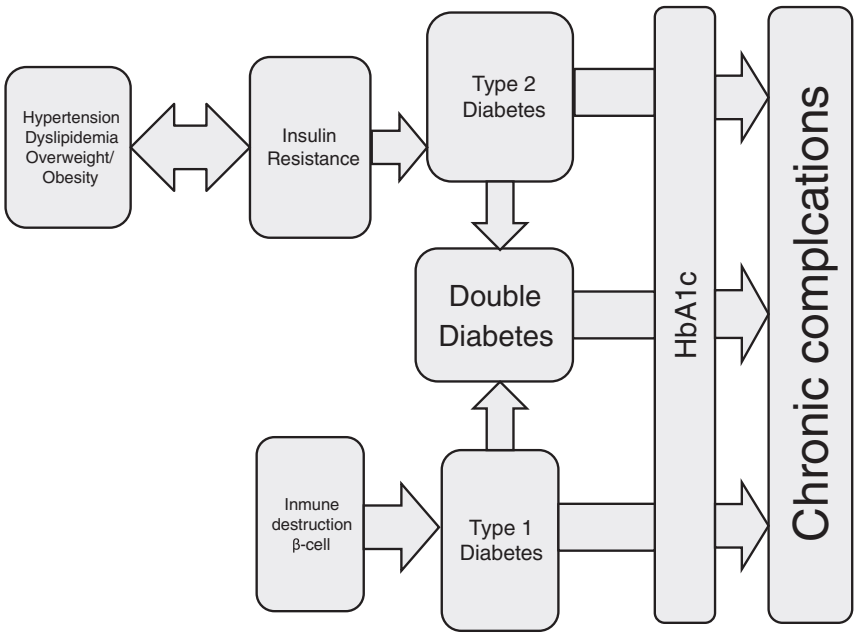

Fig. 1 – Physiopathologic aspects of type 1 and type 2 diabetes.

being the leading cause of death in T1DM patients over 30 years of age [9].

Although acceptance of the metabolic syndrome has been controversial in certain scientific forums [10], several studies have shown the classic phenotype of the metabolic syndrome to be associated with increased mortality, nearly 10 times higher in those meeting all components [11]. The prevalence of the metabolic syndrome in the general population ranges from 20% to 50% [5,12] but it can reach almost 80% in type 2 diabetes patients (T2DM) [5]. In T1DM patients its prevalence varies between 8% and 40% depending on the study population and the diagnostic criteria (Table 1) [4–7,13–20].

Since all these aspects must be taken into account for therapeutic management, we considered it appropriate to review the main factors associated with the metabolic syndrome in T1DM patients and its relationship with the development of chronic complications and mortality.

2. T1DM and insulin resistance

The metabolic syndrome can be considered a surrogate marker for insulin resistance. Therefore, quantification of insulin resistance in this group of patients seems particularly relevant. The reference method for its calculation is the hyperinsulinemic euglycemic clamp; however, being too invasive, time-consuming and expensive, this technique is limited to research purposes. Thus, various formulas for insulin resistance calculation have been devised for its use at population level, with the homeostasis model assessment-insulin resistance (HOMA-IR) being the most frequently used. However, since insulinemia is included in the formula, this index is not applicable in T1DM patients who receive insulin exogenously. In 2000, Williams et al. validated the estimated glucose disposal rate (eGDR) [21], which is easily applicable and its correlation with the hyperinsulinemic euglycemic clamp is excellent. It should be emphasized that higher eGDR levels indicate greater insulin sensitivity and lower levels greater resistance.

Several studies confirm the relationship between insulin resistance and the presence of chronic complications of diabetes, both type 1 and 2[22–28]. Insulin resistance, assessed by eGDR in T1DM patients has been linked to chronic complications, both micro and macrovascular, and increased mortality [6,7,23–28]. A study by our group showed that no patient with eGDR levels exceeding 8.16 mg kg^{-1} min^{-1} had diabetes-related chronic complications. Additionally, an eGDR value less than 8.77 mg kg^{-1} min^{-1} showed 100% sensitivity and 85.2% specificity for the diagnosis of the metabolic syndrome.

3. Adiponectin and insulin resistance

Recent studies reported that adiponectin, a fat-derived protein, plays an important role in the regulation of insulin action, glucose and lipid metabolism. In this regard, plasma concentrations of adiponectin are reduced in human obesity and negatively correlated with insulin resistance [29]. Hypoadiponectinemia is independently associated with the metabolic syndrome and with T2DM prevalence and incidence [30].

Paradoxically, adiponectin levels are elevated in T1DM and associated with the presence of microalbuminuria and diabetic nephropathy in cross-sectional data. Furthermore, elevated adiponectin levels predict all-cause mortality and end-stage renal disease in those with diabetic nephropathy [31]. Since levels decrease after renal transplantation, this association may be due to impaired renal clearance of the protein [32]. On the other hand, it could represent a