Physiopathology of Atherosclerosis in Type 1 Diabetes

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People with type 1 diabetes (T1D) have a high cardiovascular disease (CVD) risk, which remains the leading cause of death in this population. Despite the improved control of several classic risk factors, particularly better glycaemic control, cardiovascular morbidity and mortality continue to be significantly higher than in the general population.

Keywords: type 1 diabetes ; cardiovascular risk ; atherosclerosis

1. Introduction

Cardiovascular disease is the leading cause of mortality and morbidity worldwide. Although medical advances have reduced the incidence of death over the past decade, global prevalence and mortality have continued to rise [1]. Atherosclerotic cardiovascular disease (ASCVD), mainly coronary artery disease (CAD) and atherothrombotic stroke, represents the leading cause within this group, accounting for over 13 million deaths in 2021 [2].

Cardiovascular risk (CVR) is often assessed using various equations that estimate the 10-year probability of suffering an event. This strategy has several disadvantages: (1) most of them are not applicable in people aged <40 years, and age greatly influences the estimated risk, which makes it difficult to identify young people at high risk; (2) they are designed to use cross-sectional data, although the impact of the main risk factors occurs cumulatively; and (3) they consider only a few classical risk factors (e.g., sex, age, smoking habit, cholesterol levels or systolic blood pressure) and leave it to the clinician to decide how to weight the risk indicated by several other variables that modify CVR (e.g., social deprivation, the presence of obstetric factors or autoinflammatory diseases). Furthermore, there is no clear consensus between the different strategies. Several studies show heterogeneous recommendations depending on the equation used, and a lower than desired discriminatory power [3][4][5]. All this underlines the need for additional tools to better assess CVR in each individual.

The prelude to an acute event is the formation of atheromatous plaques in large and medium-sized arteries, which begins early in life and progresses silently over several years. The detection of subclinical atherosclerosis, which can be easily assessed using mostly non-invasive imaging tests, is one of the main strategies employed to individualise this risk. The presence of atheromatous plaques is associated with incident cardiovascular events in studies on large population cohorts without diabetes [6][7][8]. It allows us to identify young individuals at high CVR who may benefit from a long-term preventive strategy, knowing that they could benefit most from CVR control such as low-density lipoprotein cholesterol (LDLc) levels or blood pressure [9][10]. This is important because statins [11] and PCSK9 inhibitors [12][13] can delay the process of atherosclerosis, stabilise plaques already formed and reduce the likelihood of cardiovascular events. In this sense, the main clinical guidelines for cardiovascular prevention consider subclinical atherosclerosis detection as a risk-modifying factor, primarily in intermediate or borderline risk patients, both up- and down-regulating, with the consequent changes in treatment and follow-up that this entails [14][15]. In addition, the visualisation of atherosclerotic plaques by patients themselves is not only useful for the clinician but can also improve adherence to lifestyle measures and treatments with proven cardioprotective effects (e.g., lipid-lowering, antihypertensive and antiplatelet therapy) [16].

People with T1D have a four to eight times higher risk of CVD than the general population [17][18]. The physiopathology of T1D is characterised by the rapid and early autoimmune destruction of pancreatic beta cells, resulting in hyperglycaemia and the requirement for lifelong insulin replacement therapy. Hyperglycaemia is one of the most important CVR factors; however, even those with optimal glycaemic control (time-updated haemoglobin A1c (HbA1c) ≤ 6.9% or 51.9 mmol/mol) have a three-fold increased risk of CVD death compared with their counterparts without diabetes [19]. This fact suggests the existence of other factors involved in the pathogenesis of CVD in T1D such as exposure to hypoglycaemia, glycaemic variability, quantitative and qualitative abnormalities of lipoproteins, immune dysfunction, inflammation or cardiac autoimmunity, among others [20][21].

2. Physiopathology of Atherosclerosis in Diabetes

Atherosclerosis is a complex and not fully understood process. In brief, the evidence seems to state that it begins with the penetration and accumulation of apolipoprotein B-100-containing particles, mainly LDL particles, into the intimal layer of the arterial wall. In this new environment, they are oxidised and modified, leading to an inflammatory and immunogenic activation. Although the exact mechanisms are not fully understood, several processes, such as increased oxidative stress [22] and the degeneration of the endothelial glycocalyx [23], have been implicated. Subsequently, circulating T lymphocytes and monocytes enter the intimal layer through a dysfunctional endothelium. The latter mature into macrophages expressing scavenger receptors that recognise these modified lipoprotein particles and internalise them, notably increasing the cholesterol content of macrophages, turning them into foam cells. These foam cells release a plethora of proinflammatory cytokines that promote the process of atherosclerosis [24].

These leukocytes produce various mediators. The mediators cause smooth muscle cells to move from the media layer to the intima. There, the smooth muscle cells can grow and produce extracellular matrix molecules that increase the size of the plaque. From here, inflammation is perpetuated, and multiple processes occur that influence the progression of atherosclerosis. Finally, there are mainly two plaque complications: intraluminal growth with vascular stenosis and rupture or erosion with intravascular thrombus formation [25].

Various factors enhance and/or accelerate several of the above processes in people with diabetes. For example, hyperglycaemia leads to the glycation of various proteins, which undergo multiple reactions culminating in the formation of advanced glycation end products (AGEs). AGEs have been implicated in several steps in the development of atheromatous plaques, including accelerated monocyte migration, the glycation of lipoproteins facilitating the recognition by macrophages, an increased production of inflammatory cytokines and procoagulant effects, among others [26]. In addition, the increased productions of sorbitol and fructose (polyol pathway) also increase the production of AGEs. Further, AGEs are hardly degradable and may persist over time, which may explain why those who have had poor glycaemic control are at increased risk of vascular complications despite a better current control; this is known as the legacy effect [27][28].

Notwithstanding, through various mechanisms, mainly intracellular hyperglycaemia, there is an increase in oxidative stress with an increased production of reactive oxygen species, which react with various structures such as nucleic acids and proteins, increasing the expression of adhesion and inflammatory factors and affect genes involved in the pathogenesis of atherosclerosis [29][30]. There is an increased synthesis of pro-inflammatory cytokines in people with diabetes and several inflammatory markers have been associated with atherosclerosis in T1D [31][32][33]. In addition, elevated glucose levels and other processes increase the production of diacylglycerol, which, together with calcium, activates protein kinase C. Its activation has been implicated in several steps of atheroma plaque formation [26][30][34]. Furthermore, people with diabetes have qualitative and quantitative changes in the lipoprotein metabolism that have been implicated in the process of atherogenesis [35][36][37]. Most of the above processes are interrelated and promote each other. This perpetuates and accelerates the process of atherosclerosis.

Finally, people with diabetes not only have a greater atherosclerotic burden than the general population [38], but also have a greater inflammatory infiltrate, necrotic core and calcification that have been linked with increased plaque vulnerability [39]. Several of these changes are due to hyperglycaemia, but the high residual risk indicates that other agents are also involved. Even a recent Mendelian randomisation study suggests a possible causal role of T1D in peripheral and coronary atherosclerosis after adjusting for confounders (comorbidities, classic CVR factors, lipid and inflammatory variables), with a partial mediation of the effect through hypertension [40].

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