Acta Scientific NUTRITIONAL HEALTH (ISSN:2582-1423)

Volume 9 Issue 6 June 2025

Review Article

Type 2 Diabetes Mellitus and Cardiovascular Disease: Unraveling the Complex Interplay (Part II of II)

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Received: May 13, 2025

Published: May 26, 2025

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Abstract

In the setting of peripheral insulin resistance (IR) characteristic of diabetes, vascular dysfunction and atherosclerotic lesions result from the loss of insulin signaling in the endothelium [1]. Some authors have suggested that the implementation of pharmacological strategies that allow the control of endothelial changes can block vascular inflammation and oxidative stress (OS) and thus prevent metabolic disorders. This action may guarantee the physiological release of oxide nitric acid (NO) and capillary reorganization, as well as greater delivery and better tissue insulin sensitivity, improving the evolution of the disease and reducing the impact or appearance of complications, such as the cardiovascular [2-4]. This is so because the role of genetic alterations induced by factors of a highly varied nature, such as the NF-kB transcription factor in OS, vascular dysfunction, inflammation, and even reduced glucose uptake by some tissues, is shown to be determinants and, therefore, axial in deciding the type of intervention in type 2 diabetes mellitus (T2DM) [5,6].

Keywords: Diabetes Mellitus; Cardiovascular Disease; Unraveling; Interplay

Introduction

Part of these expectations seem to be answered in a large study in 2022 whose results advocate that diabetes continues to be an important cardiovascular risk factor rather than an equivalent to cardiovascular disease (CVD), suggesting a change in strategy towards another with a modern multifactorial approach to diabetes. According to this study, mortality directly related to CVD has changed favorably, although with limited data, perhaps in relation to better blood pressure controls or the routine use of protective factors such as statins [7].

In the previous delivery we analyzed the insulin resistance, dyslipidemia, hyperglycemia, oxidative stress and, inflammation. Now, endothelial dysfunction, an alteration that is central and permeates tangentially to cardiovascular and insulin functions, will be seen as the cause and consequence of intrinsic disorders of T2DM and CVD. Any effort addressed to stop, correct of prevent this disorder will grant multiple benefit to the patients. We will deal with this final topic along with a short revision of cardiovascular risk factor within the T2DM universe.

Endothelial dysfunction (ED)

The endothelium fulfills numerous functions in vascular regulation through multiple and complex actions that include endocrine functions, such as the release of surfactant substances, and that of maintaining blood fluidity, which it does thanks to sensors and local mediators that respond to a wide variety of stimuli. The endothelium itself limits the proliferation of smooth fibers and inflammation, largely thanks to nitric oxide (NO) whose stability is guaranteed by endothelin 1 (ET-1), angiotensin II (A-II), prostacillin and endothelium-derived hyperpolarizing factor (EDHF) [8]. These functions prevent extreme and sustained vasoconstric-

tion, hypercoagulability, oxidative stress (OS), and inflammation; all these recognized factors associated with the development and perpetuation of DMT2 and CVD (Figure 1).

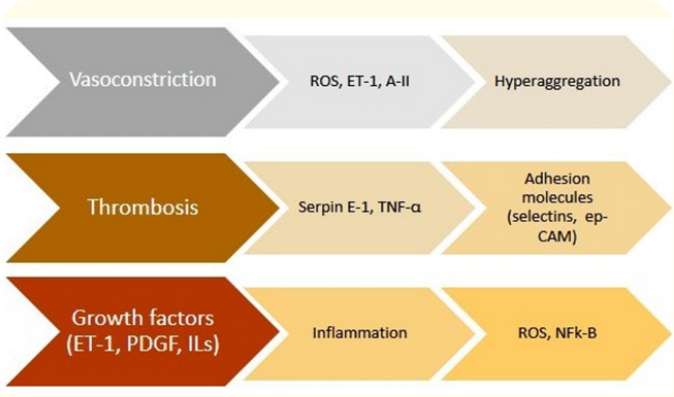

Figure 1: Summary of the effects of endothelial dysfunction and tissue response (ROS: Reactive Oxygen Species; ET-1: Endothelin 1; A-II: Angiotesin II; Serpin E-1: Endothelial Plasminogen Activator Inhibitor; TNF-α: Tumour Necrosis Factor Alpha; EP-CAM: Epithelial Cell Adhesion Molecule; PDGF: Platelet-Derived Growth Factor; Ils: Interleukines; NF-κB: Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cell)

The state of endothelial function is a good indicator of CVR or CVD in the face of multiple environmental aggressions and genetic factors that maintain a constant process of damage and repair. Through invasive and non-invasive methods, this can measure and estimate the degree of vascular injury and thus assess the patient's prognosis.

Indirect methods are easy and non-invasive and provide information on the vasodilator response, arterial response to stimuli that increase the release of NO, endothelial damage indices and inflammation, such as the determination of biomarkers (BIOM) and stimulation with vasodilators [9]. One of the BIOMs with the greatest predictive and safety capacity in the diagnosis of ED is the determination of endothelial progenitor cells (EPc).

Diabetes induces a decrease in the number of EPc, which contribute to endothelial replacement. This decrease impairs, at an early stage, the reendotheliziation process at sites of injury, being part of the ED installation and the development of cardiovascular complications. During the diabetic clinical course, ED takes place as hyperglycemia (HG), IR and dyslipidemia promote the EPc dysregulation [10]. On these grounds, diabetes clearly impairs all the processes involved in EPc mobilization, migration, homing and function, for which this BIOM deserves close attention, as it may be one important resource to estimate the degree of cardiovascular involvement in T2DM.

When EPc levels decrease, endothelium-derived microparticles (EMP) increase, especially in cases of DMT2 [11]. EMPs are small remnants of membranes detached from the surface of endothelial cells that circulate at physiological levels because of cell activation, endothelial damage, or apoptosis. Its elevation is a marker of endothelial hyperactivity, therefore, of significant damage in the development of CVD and/or T2DM. Other findings link to this BIOM to the potential role of EMP-associated miRNA signatures in body fluids or peripheral blood as biomarkers that predict metabolic diseases. Additionally, EMPs are significantly higher in arterial hypertension (AHT) with T2DM than in normotensive and non-DM controls [12]. They are also elevated in hypertriglyceridemia, acute coronary artery syndrome, and peripheral vascular diseases, which suggest the involvement of a common pathogenesis factor. The applicability of this BIOM is still a matter of much further studies, but some evidence of its possible use as an indicator of the therapy success reported. Nomura., *et al.* [13]. found that the level of plasma EMPs decreased significantly in T2DM patients with hyperlipidemia and high angiopoietin-2 after 6 months of eicosapentaenoic acid treatment, compared with the control group.

OS-specific markers have used successfully in the assessment of the development and onset of ED, such as the measurement of superoxide dismutase (SOD) activity, which is the major antioxidant system of the vascular wall. The clearance of ROS is largely dependent on this enzyme and it is clearly linked to the degree of endothelial compromise. A decrease in SOD activity contributes to reduced NO availability favoring ED, thereby, it is considered an indicative of potential or present CVD, since is a marker of cardiovascular changes in hypertensive and diabetic patients, as demonstrated by the changes in its serum levels that correlate with alterations in vascular structure and function [14]. Other BIOM include NO product, second messenger of NO production, and inflammation markers. Despite measurement of a BIOM does not reflect endo-

thelial function with total accuracy, its use as part of the diagnostic tools is advantageous for the assessment of endothelial function by physiological and pharmacological stimuli methods. The identification of one or more specific BIOMs in the future will undoubtedly enhance the predictive value of the BIOM for ED.

Direct evaluation by measuring the quality of the coronary response to intraluminal infusion of acetylcholine is an invasive method that, using quantitative angiography, measures vascular diameter with great precision.

However, being an invasive method that requires commodification has limitations for its much greater use.

From the pathophysiological point of view, when the endothelium loses or decreases its homeostatic capacities, ED occurs. In this state of abnormality, the endothelium allows leukocyte and platelet adhesion, favoring thrombosis and inflammation; in addition, an imbalance is established between the vasodilator substances derived from the endothelium, availability of ON and regulatory vasoconstriction, especially in the presence of IR [15]. The disorder in synthesis and/or degradation is, in part, the result of the local production of ROS by the different mechanisms described above, creating a fatal circadian rhythm that repeats continually until the metabolic disturbance or cardiovascular repercussion is controlled.

The excessive OS seen in T2DM oxidizes tetrahydrobiopterin (BH4), a nitric oxide synthetase (NOS) cofactor closely linked to the production and regulation of ON. The loss or oxidation of BH4 is associated with the uncoupling of NOS, resulting in the production of superoxide instead of NO, over and over again [16]. This vicious circle is perpetuated, oxidative species are formed and the consumption of NO is extended, which will consequently increase the OS. Additionally, the production of NO is reduced by high levels of symmetrical dimethyl-arginine (SDMA) in the pathological oxidative cycle, a BIOM that acts by inhibiting NO, since it competes with L-arginine required for the normal synthesis process [17]. Through PI3-kinase/Akt, insulin stimulates endothelial production of NO but, due to IR, the synthesis activities are impaired, which obviously promotes ED. This deterioration deepens or accelerates to the extent that the release of vasoconstrictor substances, such as ENT-1 and A-II, increases in the presence of compensatory hyperinsulinemia, which, in turn, conditions and promotes AHT [18].

ED follows an inexorable course if diabetes is not effectively controlled, since the dyslipidemia, OS and inflammation will exert their negative effects on endothelial homeostasis in a highly unfavorable environment of HG, AHT and IR. In any case, the OS and the activation of the various pathways of inflammation are the determinants of greater impact that lead to endothelial damage, since through them acts most of the triggers. These ultramicroscopic aspects are an additional therapeutic objective to interventions on healthy lifestyles and habits, since it implies a management from the very pathogenesis of ED.

The persistence and permanence of the determinants or triggers of ED, even in subclinical form, work together and with time and aging, both, in pathological conditions (T2DM, CVD) and by the natural process of life, ED will be the unfavorable result (Figure 2). The difference in the speed of installation will be established by the aggressiveness of the factors that drive it, which in turn, is related to the pathophysiological substrates.

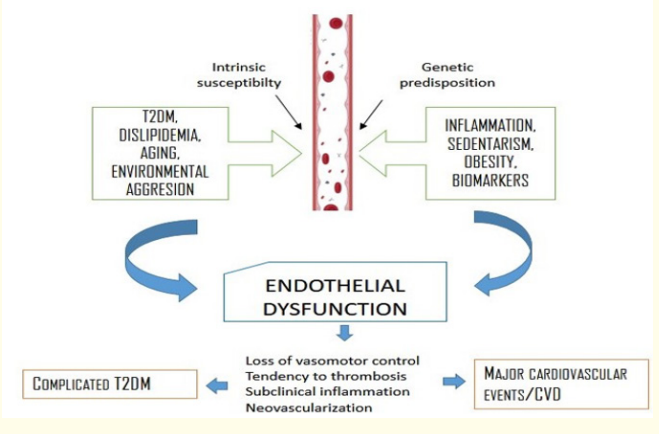

Figure 2: Factor Conditioning and triggering endothelial dysfunction in relation to age, environment or pathological situations.

In DMT2 patients, BIOM have been identified in peripheral and coronary blood that indirectly reflect endothelial damage, such as E-selectin, vascular cell adhesion molecule 1 (VCAM-1) and intracellular molecular adhesion molecule (ICAM), which are indicative of vascular inflammation [19]. Also indicative of ED are von Willeband factor elevation (vWF) and microalbuminuria, widely used as a predictor of vascular damage diffusion in diabetes. Dyslipoproteinemia, OS and inflammation synergize with AHT, obesity, IR, HG, and high levels of SDMA to determine the route to T2DM and/or CVD, although all these factors may act individually.

In summary, free fatty acids (FFA) and HG profoundly uphold metabolic deterioration, favoring the decoupling of oxidative phosphorylation in mitochondria, the decomposition of the regulatory system in the formation of ATP and the production of superoxide radicals and triggering of a linear OS, which is the last major substrate of the immediate events to the installation of the DE [19,20]. Therefore, T2DM increases all forms of CVR, affecting morbidity and mortality rates in this population group, in which ED plays the most determinant role as a common denominator of microvascular damage, thus being an independent predictor of CVR. Insulin is crucial in endothelial signaling in adipose tissue and skeletal muscle and disorders in its signaling pathways decrease ON synthesis and release, and GLT4 glucose transporter translocation is reduced in these tissues. In general, all the alterations described in T2DM that lead to metabolic and cardiovascular disarrangement work negatively on endothelial function due to their effect on the development of a persistent and systemic OS (Figure 3).

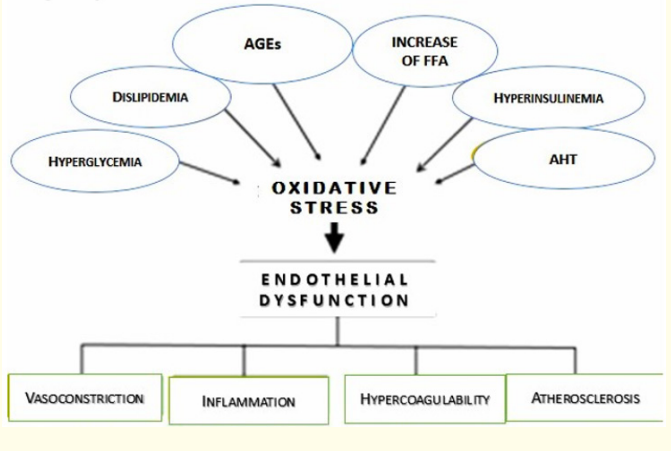

Figure 3: Pathogenesis of endothelial dysfunction in relation to oxidative stress of T2DM and its consequences (Source: Woodman., et al. [12]).

In the present, the comprehensive management of T2DM contemplates reversing the effects of ED and its triggering or conditioning factors, that is, to combat the physiological distortions that underlie in diabetic vasculopathy, such as dyslipidemia, OS, inflammation, visceral obesity, IR, HG and AHT, as a more holistic way of looking at the individual.

Risk factors and cardiovascular disease in T2DM.

T2DM accelerates atherosclerotic changes throughout the vascular bed and therefore increases the risk of developing a major cardiovascular event. CVD not only occurs more frequently in the diabetic population, but its presentation is much earlier, with a more rapid evolution and greater severity than in people without diabetes, as we have already pointed out. T2DM is also associated with an increased prevalence of other cardiovascular risk factors (CVRF), such as AHT, decreased high-density lipoprotein (HDL), obesity, hypertriglyceridemia, microalbuminuria (MA), inflammation, IR, HG; in addition, the increase of lipo-A, thrombogenic factors and low-density lipoprotein (LDL), all of which can upsurge up to eight times the relative risk of death in the presence of diabetes.

Based on the study by Haffner., *et al.* [22]., T2DM was considered equivalent to CVRF, especially due to its effect of increasing coronary deaths in the first cardiac event, and that even some patients with T2DM of short duration under 40 years of age still carry levels of CVD risk, although low [23]. However, most of the today guidelines do not consider T2DM as equivalent to coronary disease (CD) and in other cases stratification for patients with diabetes is recommended, when the ages range between 40 and 75 years, within 2 categories of risk, using a global system for evaluation [24]. For example, the American College of Cardiology (ACC) and American Heart Association (AHA) state that in patients 40 to 75 years of age with T2DM and LDL-C 70 mg/Dl, moderate-intensity statin therapy should be initiated without calculating the 10-year risk of atherosclerotic cardiovascular disease (ACVD). In higher-risk T2DM patients, such as those with multiple risk factors or those of 50 to 75 years of age, it is reasonable to use a high-intensity statin to reduce LDL-C by 50%. Below this limit, the protocol is moderately aggressive management and seeks to bring the LDL to values between 30 and 50% of the initial measurement. In patients under 40 and over 75 years, the benefit is unclear [23]. The intention to apply individualized treatments, once the risk has stratified, would reduce micro and macrovascular complications and offer better prognoses for people with T2DM.

With few variants since 2009, the American Diabetes Association (ADA) and a scientific statement of the ACC Foundation and the AHA supported a risk factor-based approach to deciding on the initiation of statin therapy, across three variables: age, previous cardiovascular events, and the presence or absence of ACVD. The ADA considers stratifying risks, LDL greater than 100 mg/dL, AHT, smoking, overweight/obesity and the family history of premature ACVD. All cases with ACVD events receive aggressive therapy, regardless of age [25].

Age and *sex* are non-modifiable factors, the former having the greatest impact. To consider a low risk condition in a diabetic (<10% in 10 years) based only on age, this must be ≤35 years for men and ≤45 years for women, without any other associated risk. Patients above these age limits are candidates for the greatest preventive efforts[22]. Despite the fact that men are more affected by myocardial infarction (MI), the relative risk of fatal CD associated with diabetes is 50% higher in women than in men [26]. T2DM in females poses greater diagnostic challenges since it tends to have a more silent evolution and traditional diagnostic tests are less sensitive and specific, therefore the prevalence of obstructive CD and atherosclerotic burden are higher. In recent years, a diagnostic method based on the implementation of an artificial intelligence interpretation of vectorcardiographic reading (CARDISIO®) has been used which seems to promise higher accuracy for the silent CD cases [27].

The *family history of CD* is a highly considered factor, since its presence in any first-line family member is a greater CVRF for diabetics than for non-diabetics [23]. *Smoking* constitutes a reversible CVRF, but it is one of those with the highest incidence in fatal outcomes due to CVD. Smoking induces oxidative processes, negatively affects platelet function, leads to fibrinolysis and inflammation, and impairs vasomotor function, effects that alone or together are potent atherogenics capable of doubling the 10-year risk of fatal events in smokers compared to non-smokers [28]. The relative risk of mortality from CVD and in diabetics exposed to cigarette smoke is reported to be between 1.36 and 1.83, above the non-smoker population [29]. The combination of diabetes and smoking constitutes the highest level of risk of developing CVD and death due to a major cardiovascular event or stroke (up to 50% more than in non-smoking diabetics) that, although it can reverse with the cessation of the habit, residual effects remain dependent on its duration [30]. *Obesity* very frequently coincides with T2DM in a one-to-one relationship. The risk of developing T2DM rises by 20% for every 1 kg/m^2 of body mass index (BMI) increase, but when the BMI is between 27.2 and 29.4 kg/m^2 reaches 100% [31]. A large part of this seems to be due to the close relationship between obesity and inflammation that we have described previously in the first part of this review.

AHT is a common finding in T2DM. Its prevalence can be of the order of 60%, with a close causal relationship with *diabetic nephropathy* (DN) [32]. DN, for its part, results from nephron involvement initiated by HG that culminates in final damage to the glomerular basement membrane, which translates into MA and chronic compensatory activation of the renin-angiotensin-aldosterone system that progresses to AHT and AHT itself enters into a vicious circle that deepens glomerular damage, aggravates ND, and can progress to nephrotic syndrome. When nephrotic syndrome develops, other unfavorable factors add, such as proteinuria, hypercoagulability, and hyperlipidemia, all of which contribute to diabetic CVD. Dyslipidemia was already discussed in the first part of this review. It aggregates as a CVRF and is determined by the loss or decrease of metabolic control of FFA, which, in the presence of IR, are dangerously increased, thus promoting the production of triglycerides (TG) that, in turn, stimulates the secretion of ApoB, LDL and VLDL. HG's glycosylating and oxidative effects diminish vascular adaptation and favor aggressive ACVD, where ROS are the primary determining factors [1]. Dyslipidemia, therefore, is a high-impact factor that largely explains the elevated prevalence of CVD in T2DM.

Left ventricular dysfunction (LVD) is an echocardiographic parameter indicative of incipient or present congestive heart failure (CHF). Its subclinical presence is frequent in T2DM and obesity would be a causal factor. Obesity, an in minor degree the overweight, leads LVD with preserved ejection fraction. However, despite the importance of myocardial energetics and steatosis in LVD, obesity appears not to be the primary cause of concentric hypertrophy, as reported [33]. Ofstad *et al* studied one hundred patients with T2DM

without clinical signs of CHF who compared with a non-diabetic obese group, identifying a subclinical impairment of diastolic function that is significantly more advanced in the diabetic cohort [34]. T2DM induces remodeling of the left ventricle (LV) independently of other risk factors and co-morbidities with increased LV mass and wall thickness [35], which are well-known contributors to the development of CHF, even more commonly found in patients with diabetes., maybe due to the HG that, in sequence, associates by itself with CHF [36]. The explanation for this may be partly due to a specific myocardial dysfunction called *diabetic cardiomyopathy* (DCM).

Adipose tissue and body organs interconnect and regulate through the action of a group of endocrine substances secreted by adipose tissue known as adipocytokines. DCM is potentiated by the high levels of these cytokines, particularly resistin and leptin, which usually accompany hypertrophic changes in cardiac fiber [37]. In obesity and T2DM, increases in leptin concentration and reductions level of adiponectins are described; the latter are important for the control of glucose absorption and lipid metabolism, since it reduces gluconeogenesis and favors glycolysis and oxidation of fatty acids in the liver. When obesity and T2DM coexist, this effect is much more significant [38]. The value of this finding lies in the fact that TG accumulation exacerbate in all tissues, including cardiac muscle, leading to myocardial steatosis and impaired cardiac calcium homeostasis, negatively affecting diastolic function, part of which would explain the high incidence of diastolic dysfunction in T2DM patients [39].

The structural and functional myocardial alterations of DCM does not relate to any other cardiac condition but aggravate or quickly progress when AHT and obesity are present. The subclinical diastolic dysfunction accounted in more than 50% in some cohort studies where higher prevalence appeared in the longer lasting diabetes [40]. It advances asymptomatically over several years and associates with increased mortality and risk of overt CHF [41]. Mitochondrial dysfunction and lipotoxicity work together in the OS environment as part of the T2DM pathophysiology. Concentric remodeling of LV is an additional result of these metabolic alterations, and all of them relate to higher levels of FFA within the IR of the myocardium and in the presence of ED.

Cardiovascular autonomic neuropathy (CAN) is a type of surreptitious-onset dysfunction commonly found in people with diabetes. It results from damage to the nerves that regulate cardiac and vasomotor activity that can cause coronary ischemia, arrhythmias, silent heart attacks, and sudden death. Its prevalence is reported with wide variations that can reach up to 75% in some studies, highlighting the poor glycemic control, the presence of peripheral neuropathy, nephropathy and retinopathy, the high levels of blood pressure, obesity, smoking and dyslipidemia as strong conditions for its appearance and severity [42]. The T2DM cases with the longest evolution show the highest prevalence, but those cases that have undergone early intervention or in which HG, AHT, dyslipidemia and MA control more effectively, show better protection from developing CAN [43]. Its cause seems to link to the same factors described up to here, and that lead to disruption of oxidative and inflammation control and of the endothelial homeostasis, thereby reducing neurovascular perfusion and causing cell dysfunction and abnormal apoptosis. Such disorders severely deteriorate the autonomic nervous system, with the already indicated repercussions on cardiovascular function, one of which is the loss of end-diastolic and systolic volumes preservation, a primary situation in the development of CHF and sudden cardiovascular death ocurrence [44].

The clinical manifestations of CAN usually go unnoticed or are mostly subclinical, and may include resting tachycardia, postural hypotension, exercise intolerance, QT elevation and frequent dynamic instability, all of them related to exaggerated or uncontrolled sympathetic activity. This disorder can further be part of the pathogenesis of CMD and works as a predictor of the severity of T2DM, as it can increase the five-year mortality rate from CVD when present [45]. Based on these findings, CAN is considered an independent risk marker for the presence of LVD in patients with diabetes and its timely and accurate management could be a factor for improving the final prognosis of these cases.

MI occurs much more frequently in the diabetic population than in the non-diabetic population, considerably increasing mortality rates in this group (most common cause of death), because ACVD is more extensive in T2DM and LV hypertrophy and LVD are highly prevalent. Due to the high prevalence of CD in these patients, their risk of a first MI is greater than 20% within 10 years of developing

the disease, double of that in compared populations without diabetes, while recurrence is above 40% [46]. In the first place, these statistics indicate the need for aggressive management aimed at reducing the risk of MI, focusing therapy primarily and not viewing the CD of T2DM as a comorbidity, but rather as a consequence of pathophysiological changes within the diabetic spectrum. As indicated in previous paragraphs, the immediate control of HG in the safest and most effective way will result in early benefits.

T2DM increases myocardial susceptibility to ischemia damage, which negatively changes the post-infarction prognosis. Some authors emphasize that the higher frequency of post-infarction deaths in diabetics relates to the larger size of infarctions seen in some reports of infarcted T2DM patients. Clinical experiences in infarcted subjects who underwent reperfusion showed infarctions up to 70% larger in diabetics than in non-diabetics [47], indications of a high myocardial susceptibility factor that may partly explain the poor prognosis of MI in diabetics in the short and long term. However, the high mortality due to MI in T2DM is independent of the clinical conditions known, including the extent of infarction. The permeability of coronary arteries after reperfusion is not a permanent or safe guarantee, since the overload and overdischarge of ROS at the time of reperfusion lead to irreversible loss of mitochondrial functions and cell necrosis, the same as isolated chronic HG. It may be that a kind of distortion in cell signaling is maintained failing to stop cell death and, on the contrary, sustaining a state of subliminal damage in the quality of myocardial repair response to ischemia.

The combination of dyslipidemia (TG and HDL), AHT, IR, HG and central obesity is known as *metabolic syndrome* (MS). It constitutes a risk in itself for CVD since it growths all-cause of mortality up to 1.75 times when it is present. Conversely, the risk of death from CVD in cases of MS can be up to 3.66 times higher than in the general population, depending on age and sex variables. In addition, MS is associated with an increased risk of CVD morbidity and hospitalization [50]. Regardless of the cause, the MS identifies individuals with a high risk of ACVD, whose magnitude varies according to the individual components of the syndrome present, in addition to the non-metabolic factors that the subject carries. In addition to having a predictive value for undiagnosed diabetes, MS represents a therapeutic target in comprehensive management strategies. With this approach, it is possible to reduce the risk of CD, stroke, T2DM or another event within the cardio-metabolic sphere, by adjusting lifestyle and applying therapeutic protocols for cholesterol and fats reduction and peripheral tolerance improvement to glucose, in addition to specific cardiovascular treatments.

Finally, a deteriorating *glomerular filtration rate* (GFR) and the appearance of MA are independent risk factors that indicate a high risk of CD development and its severity, evenly applicable for all-cause mortality and for CVD mortality in selective groups of diabetics [51]. Statins significantly decrease albuminuria and urinary albumin excretion rates, for which it appears as an opportunity to reduce cardiovascular morbidity and mortality related to impaired renal function. Although there are certain controversies about its diabetogenic risk related to high doses and its multiple drug interactions, especially those statins that interact with the cytochrome p450 group of enzymes, some beneficial actions are reported to reduce CVRF in T2DM patients, while in those with nephropathy the efficacy on renal function depends on time of evolution [52].

CVR calculation in T2DM

The use of risk calculators allows estimating the global CVR based on the specific weight of each factor that enters into the equation. Although there are many CVR calculation models and about 50 calculators are available for diabetes, Prediction systems that are specifically designed for variables that directly impact diabetes are recommended by the International Diabetes Federation (Table 1).

The engine for calculating CVR resulting from the United Kingdom Prospective Diabetes Study (UKPDS) is perhaps the most widely used. Its patient stratification to measure the risk of CD at 10 years made it a very reliable CVD predictor instrument in T2DM, despite the years, which adjust and update on several occasions to make it useful in special situations [53,54]. AHA/ACC developed an engine for the risk assessment of ACVD, the Atherosclerotic Cardiovascular Disease risk score (ASCVD), available for use electronically since 2013 and modified in 2018. This calculation system allows the estimation of the risk at 10 years and lifetime for ACVD, defined as coronary death or non-fatal MI or fatal and non-fatal stroke, based on the Pooled Cohort Equations and the work of Lloyd-Jones., *et al*. The information required to develop the algorithm with which to run the estimate using age, sex, race, total cholesterol, HDL, systolic blood pressure, use of antihypertensive

Age	> 60 yr
Microalbuminuria	>20 mcg/min or albumin/creatinine ratio >2.5 mg/mmol for men, and >3.5 mg/mmol for women*
Moderate chronic or severe nephropathy	Persistent proteinuria or GFR <45 mL/min/1.73 m^2
History of dyslipidemia	Previous diagnosis of familial hypercholesterolemia in the individual
Blood pressure levels	Systolic pressure ≥180 mmHg o diastolic pressure ≥110 mmHg
Cholesterol	>290 mg/dL
* Two measurements	

Table 1: Most relevant clinical findings suggesting high risk in patients with DMT2 [53].

medication, diabetes status, and smoking status. Despite the fact that the population studied to generate the database was quite heterogeneous and had age groups between 40 and 79 years, this engine, like others, can over or underestimate values due to ethnic, geographic or population characteristics [55].

The components of the UKPDS engine are age, duration of diabetes and HbA1c values, sex, systolic pressure, total cholesterol, HDL, smoking, race and presence or not of atrial fibrillation, with which risk estimation and 95% confidence interval are generated for T2DM individuals without known CVD, for fatal and non-fatal CD and for fatal and non-fatal stroke. The highest degree of sensitivity (89.8%), but with low specificity (30.3%), is obtained when the calculation is equal to or greater than 15%, with an overestimation range of 108.8% in men and 51.3% in women [55]. Its use is recommended in conjunction with the Framingham Score, since certain subgroups at high risk of cardiovascular events for their comorbidities may be underestimated if a single calculation model is used [54].

Conclusion

A global perspective, in which 578 million T2DM patients are expected by 2030 and with still very high risks of CVD, despite the decreasing trend of complications related to it, points to the need to implement energetic and early interventions that stop, reduce or prevent the development of ACVD. If risk factors such as obesity are not controlled, the global prevalence of T2DM is estimated to be 10.2% in 2045 [56]. T2DM patients have up to a 4 times higher rate of suffering from CVD compared to the non-diabetic population, which means that the risk in the diabetic population older than 30 years would potentially affect more than 300,000 people per year. The greater risk of MI and/or CD in T2DM with a worse evolution in the post-event produces mortality rates as high as 55%, against 30% of the non-diabetic population. The common factor between CVD and T2DM is the atherogenic tendency added to cardiovascular conditions such as AHT and LVD, and alterations related to IR and ED. The progress of complications in T2DM, such as nephropathy and CMD, can slow by timely and comprehensive therapeutic measures together with food hygiene and better lifestyle habits. The use of statins in conjunction with oral hypoglycemic agents strengthen these measures and can change the long-term prognosis of diabetics by establishing their preventive use once the risk has been identified and quantified**.** Combining them with innovative therapy is already necessary to relegate the progression of ED and the effect of IR.

Understanding the relationship of IR is essential to treat vascular complications related to diabetes. Sodium-glucose transport protein 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) agonists can promote brown fat from WAT and protect against ED. Although this mechanism still requires greater knowing, it is a promising opportunity to refocus current treatments. Present treatments are limited, as the best available therapy reduces CVR by as much as 30% and remains virtually ineffective in reducing the excess risk associated with diabetes. All pharmacological strategies rely on lifestyle modifications, prioritizing the management of IR and HG with the intention of controlling, reducing or containing dyslipidemia.

The increasingly rational comprehension of the role of OS and inflammation should stimulate more researchers in the hunt for biomarkers that are definitively useful for categorizing oxidative

risk and possible therapeutic interventions. An antioxidant is a substance or system that inhibits or reduces the oxidation of a substrate, which mostly derive from natural sources. For years, the possibility of applying exogenous antioxidants as adjuvants for numerous chronic conditions has raised, and T2DM is one of them and possibly the one that would benefit the most. More studies and more observation time in future works may provide standardized measurement methods for reliable screening of OS versus risk of disease or complications. Antioxidants can be one of those innovative resources to fight the inner and common pathophysiological changes of T2DM and CVD, aiming to offer a promising future for these patients. More enthusiasm needed from researchers and sponsors for this future be a reality.

Conflicts of Interest

The author declares no conflict of interest.

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