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Review Article

Type 1 Diabetes Mellitus and Premature Coronary Artery Disease

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ABSTRACT

Cardiovascular disease, which affects more than half of all diabetics, is the leading cause of morbidity and mortality in patients with type 1 and type 2 Diabetes Mellitus (DM). Around 55% of diabetes patients are thought to have it, in comparison to 2-4% of the general population. A significant risk factor for the development of Coronary Artery Disease (CAD) exists in people with Type 1 Diabetes Mellitus (T1DM). However, it is worth noting that the present Models of risk prediction for T1DM have a variety of flaws. CAD risk is expected to double or quadruple over the next two to four decades, and diabetes mellitus is the third most significant risk factor for the etiology of illness. As a result, diabetes increases the chance of developing Acute Coronary Syndromes (ACS), whose incidence surpasses 20% after seven years, compared to a rate of 3.5 percent in non-diabetics – a rate comparable to individuals who have already experienced an Acute Myocardial Infarction (AMI). Additionally, it is crucial to identify any well-defined specific risk factors for T1DM as well as any extra subclinical atherosclerosis that may influence these patients at an advanced stage of disease progression. T1DM patients have more severe lesions, a lower left ventricle (LV) ejection fraction, a higher risk of cardiac events, and a higher rate of silent ischemia when compared to non-diabetics. They continue to have impaired microcirculation and endothelial function, both of which contribute to tissue perfusion problems.

1. Introduction

Cardiovascular disorders are the major cause of morbidity and mortality in more than half patients with type 1 and type 2 diabetes mellitus. It is expected to affect approximately 55% of patients with diabetes, compared to only 2-4% of the general population.1When compared to the general population, the mortality rate for people with type 1 diabetes (T1DM) is nearly three times higher. In both men and women, premature atherosclerosis is the leading cause of excess mortality, with cardiovascular events happening more than a decade earlier. A recent meta-analysis determined that the standardized mortality ratio attributed to Cardiovascular Disease (CVD) is 11.[3] for women and 5.7 for men with type 1 diabetes. Notably, it appears as though the relative risk is unrelated to the duration of the disease. Even among young patients with T1DM, the annual incidence of CVD is approximately 1–2. Patients with T1DM had a tenfold increase in the risk of mortality from cardiovascular disease regardless of glycemic control, and an eightfold increased risk at various ages compared to the general population. The prevalence of cardiovascular disease (CVD) is determined by the length of diabetes, the level of glycemic control, and the age of patients in cohorts.[1]

Type 1 Diabetes Mellitus is a major risk factor for development of coronary artery diseases. The predictor model for the occurrence of coronary artery disease due to T1DM is currently still vulnerable to various limitations.[2]

Diabetes is the third most significant risk factor for the development of coronary artery disease and increases the risk by two to four times compared to patients without diabetes mellitus.[3] As a result, diabetes increases the risk of developing Acute Coronary Syndrome (ACS), the incidence of which reaches 20% after seven years, compared with 3.5 percent in individuals without diabetes at a rate comparable to that of people who have had an Acute Myocardial Infarction (AMI).[4]
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Even though study by the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) has found that prior intensive glycemic control reduces the risk of CVD, it is still important to identify any of the well-established specific risk factors for type 1 diabetes (T1DM) and additional subclinical atherosclerosis that may already be affecting these patients in the later stages of disease progression.[5,6]

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2. Definition and Pathophysiology

T1DM is a T-cell mediated autoimmune disease in which the destruction of pancreatic -cells causes insulin deficiency, resulting in hyperglycemia and a proclivity for ketoacidosis. Individuals who are at a higher risk of developing type 1 diabetes can be identified by genetic markers as well as the presence of specific autoantibodies. Islet-cell autoantibodies, as well as autoantibodies to insulin, glutamic acid decarboxylase (GAD), or tyrosine phosphates IA-2 and IA-2, and ZnT8, are antibody markers of -cell autoimmunity. The human leukocyte antigen (HLA) genes DQA and DQB are strongly linked to disease susceptibility. Environmental factors have also been proposed to play a role in the development of T1DM. Some of the most commonly cited environmental factors include a reduction in gut microbiota, obesity, early exposure to fruit or cow milk as a child, gluten, toxins, vitamin deficiency, and viruses.[7]

T1DM develops as a result of the immune system's activation against beta-cell antigens and the initiation of proinflammatory responses. Chronic immunological responses occur after antigen presenting cells (APCs) present beta-cell antigens to the immune system due to inefficient regulation of immunological reactions, which leads to beta-cell destruction. Beta-cell death caused by viruses or physiological mechanisms causes antigen release and the initiation of immune responses against other beta cells. Dendritic cells (DCs) typically take up these antigens and present them to T cells. Only autoreactive T cells that have escaped thymic negative selection can mount an auto-immune response. Autoreactive T cells stimulate autoreactive cytotoxic T and B cells after being activated by DCs. Finally, the collective cooperation of DCs, macrophages, T, B, and natural killer (NK) cells is required for the effector mechanism of beta-cell destruction.[7]

2. Risk Factors for Coronary Artery Disease due to Type 1 Diabetes Mellitus

It is generally well-established that diabetes mellitus raises cardiovascular risk. Numerous epidemiological studies have established that specific risk factors, such as systemic arterial hypertension, diabetes, dyslipidemia, smoking, sedentary behavior, central obesity, family history, and insufficient fruit and vegetable consumption, all contribute to cardiovascular disease, roughly 90% of coronary artery disease cases in the global population. Glycemic control's role as a risk factor for coronary artery disease is still debatable. Numerous clinical trials have been undertaken over the last few decades to determine the therapeutic efficacy of extreme hyperglycemia in type 1 diabetes in terms of reducing cardiovascular risk. Although the precise role of hyperglycemia in the pathogenesis of cardiovascular disease (CVD) is unknown, relevant studies such as the Diabetes Control and Complications Trial/The Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study have demonstrated the benefit of glycemic control through intensive insulin treatment in reducing macrovascular events. After 17 years of follow-up, it was discovered that rigorous diabetes care significantly decreased the incidence of CVD in 42% of patients and non-fatal myocardial infarction and cerebrovascular accidents in 57% of patients. This risk reduction is primarily due to the drop in glycohemoglobin levels linked with DCC.[8] Another study showed no statistically significant connection between fasting plasma glucose or glucose exposure time and coronary artery disease risk (CAD).[8]

Another study found that inadequate glycemic control is related with cardiac autoimmunity in patients with DMT1, as demonstrated by the presence of more than two cardiac autoantibody (Aab) types, which is corelated with an elevated risk of coronary artery calcification and cardiovascular disease events. Positivity for more than two autoantibodies also identified patients with DMT1 who had an elevated high-sensitivity C reactive protein, implying that cardiac autoimmunity is connected with an inflammatory state, however this mechanism was not observed in type 2 diabetes.[9] Glycemic variability may potentially contribute to the acceleration of coronary artery calcification and disease events in patients with type 1 diabetes.[9]

Another significant study, the European Diabetes Study (EURODIAB), verified albuminuria's predictive value in the pathogenesis of coronary artery disease (CAD) in individuals with type 1 diabetes. Additionally, we discovered a higher connection between macroangiopathy and metabolic syndrome markers than we did with hyperglycemia and macroangiopathy in this investigation. Additionally, gender-specific risk variables for SAP (Systolic Arterial Pressure), triglycerides (or HDL cholesterol), and waist-to-hip ratio were found to be linked with the development of CAD. The primary take-home lesson from our findings is that treating hyperglycemia completely and promptly results in cardiovascular benefits in patients with short-term diabetes and minimal cardiovascular risk.[10]

As has been noted for many years, nephropathy clearly appears as a significant predictor.[6] Nephropathy is a one of significant risk factor that has been recognized, associated, and established with an increased risk of death from any cause, primarily cardiovascular disease. Apart from indicating an increase in insulin resistance, which may be a factor in the development of coronary artery disease in T1DM, microalbuminuria is also a risk factor for developing early renal failure, as reported by the Steno Investigators.[11] Endothelial dysfunction, which typically precedes microalbuminuria, is most likely the cause of the prevalent renal and cardiovascular problems associated with T1DM.[5]

Cardiovascular Autonomic Neuropathy (CAN) is another condition frequently related to a higher risk of coronary artery disease. In patients with long-standing type 1 diabetes, the response of myocardial blood flow to sympathetic stimulation is decreased in parts of the heart with autonomic dis-innervation, implying a poor coronary-resistance vascular vasodilator response. On the other hand, autonomic nervous system abnormalities are significantly connected with renal illness, which may account for a substantial portion of the increased risk of death associated with autonomic neuropathy, as Ewing's landmark work originally discovered. Numerous causes may lead to early cardiac death in patients with coronary artery disease, including relationship with advanced subclinical coronary atherosclerosis, aberrant coronary vasomotor capacity, and changes in systolic and diastolic function. Another mechanism is life-threatening arrhythmias, which have a lower threshold when sympathetic tone is increased relative to baseline, as is frequently found in diabetic patients with sympathovagal imbalance.[12]

Cardiovascular Autonomic Neuropathy (CAN) has been linked to an increased risk of mortality in patients with myocardial infarction.[13] Dyspnea, tiredness, palpitations, hypotonia, nausea, and vomiting are all possible symptoms in patients with CAN who have had a myocardial infarction.[14] While CAN may be used to categorise coronary artery risk and screening for coronary artery disease may be useful in those with CAN, there is currently no consensus on this subject. The cost-effectiveness of the strategy has not been determined. Screening for CAN can be used to further stratify individuals' risks following myocardial infarction.[15]

Heart rate variability, a marker for autonomic dysfunction, was also associated with coronary artery calcification.[14] If autonomic dysfunction is involved in the pathogenesis of atherosclerosis, this has substantial implications for our understanding of coronary

atherosclerosis in diabetic patients. Autonomic dysfunction could likely have a direct effect on atherosclerosis. Sympathetic denervation may result in the dedifferentiation of vascular smooth muscle cells and a shift to a phenotype associated with the creation of extracellular matrix and migration to the intima, alterations seen in atherosclerosis.[16] A crucial question is whether preventing CAN also benefits patients with diabetes mellitus by lowering their risk of coronary heart disease.15 Early diagnosis of CAN at DCCT closeout is related with increasing incidence of later CVD events, although it is not a reliable predictor of CVD risk in comparison to HbA1c. Because HbA1c is a significant predictor of CAN in T1DM, diagnosing CAN over time identifies persons with T1DM at increased risk for serious CVD events.[17]

In DM, the tendency to unstable plaques is a result of the patients' aberrant metabolic circumstances, which result in endothelial, inflammatory, and smooth muscle cell differentiation.[18] Additionally, thrombosis is a significant risk factor as a result of functional alterations in platelets and the coagulation cascade.[19] Increased fibrinogen levels are related with the advancement of CAC in type 1 diabetes mellitus patients. In young people, increased fibrinogen levels have been linked with future atherosclerosis as measured by carotid thickness and CAC. Atherosclerotic plaques contain fibrinogen, fibrin, and LDL cholesterol, demonstrating the existence of a common mechanism for fibrinogen and lipoprotein entry into the vessel wall. The demonstration that fibrinogen disrupts and migrates endothelial cells, increases smooth muscle proliferation, and enhances the release of endothelial cell–derived growth factors supports the possibility that fibrinogen contributes to the genesis of atherosclerosis.[20]

Another factor that contributes to type 1 diabetes' increased risk of coronary artery disease is that existing risk factors' effects are altered. In type 1 diabetes, HDL cholesterol levels are typically 10 mg/dl higher, which is likely owing to a number of variables, including increased lipoprotein lipase activity and decreased hepatic lipase activity due to systemic insulin delivery, as well as altered HDL metabolism.[6]

The oxidative modification of LDL and the immunological response that results may be one of these critical components, as there has been a documented link between antibodies to oxidized LDL and incident CAD. Increased levels of oxidized LDL immune complexes were related with an increased risk of myocardial infarction and major cardiovascular events.[21] Another study found a positive correlation between the concentration of small, dense LDL particles and internal carotid IMT in men (evidence class III level A in the 2019 European Society of Cardiology (ESC) and European Association for the Study of Diabetes (EASD) in a subgroup of patients from DCCT/EDIC).[22] Another study found that patients in the upper quartile of AGE-LDL immune complex values had a three-and-a-half-fold increased risk of IMT progression compared with those in the lowest quartile. The association between oxidized LDL immune complexes and AGE-LDL immune complexes and IMT development was found to be independent of glycemic management, plasma lipids, and other conventional risk factors.[23]

Inflammation plays a crucial role in the development of atherosclerosis in DMT1. It may produce foam cell production and endothelium damage by stimulating macrophages and endothelial cells and disrupting nitric oxide's physiological activity, resulting in vascular cell cytotoxicity. Monocyte adhesion is also a vital stage in this process, and it's worth mentioning that E selectin has a significant, independent prognostic value for cardiovascular disease in type 1 diabetes. Another emerging biomarker of atherosclerosis is plasma levels of cell adhesion molecules such as soluble intercellular adhesion molecule-1 (sVCAM-1) are much higher in patients with type 1 diabetes.[24]

Tumor necrosis factor (TNF), interleukin (IL)-6, and interleukin (IL)-1 all act as regulators of adhesion molecules. These inflammatory markers have not been thoroughly investigated in order to determine their relationship to the development of coronary artery disease. However, after correcting for gender, age, HbA1C, systolic blood pressure, and diabetes mellitus duration, the EURODIAB study group demonstrated a significant difference between those with and without CAD (P 0.001) using a Z score based on combined IL-6, C-reactive protein, and TNF- levels. Furthermore, there was no cross-sectional correlation between level of homocysteine and CVD in EURODIAB, and tissue plasminogen activator inhibitor-1 or plasminogen activator inhibitor-1 failed to provide an independent predictor of CAD in the EDC study. However, in type 1 diabetes, a measure of T-cell activation by soluble IL-2 receptor expression, has been linked to the progression of CAC. Additionally, type 1 diabetes has been linked to increased of soluble CD40 ligand overexpression and CD40 ligand expression25 , which appears to be involved in the stimulation of endothelial cells and monocyte recruitment.[6]

Adiponectin has gained considerable attention due to its preference for accumulation in the subintimal region of the artery wall following injury to the vascular endothelium. It dose-dependently reduces TNF-induced cell adhesion and cellular adhesion molecule synthesis in human aortic endothelial cells and may act as an anti-inflammatory and antiatherogenic agent. Type 1 diabetes research is debatable and scarce, as despite high rates of atherosclerosis, type 1 diabetes has been associated with much greater adiponectin levels than normal glucose tolerance or type 2 diabetes mellitus. Given that insulin is involved in the regulation of adiponectin production, the very high systemic insulin levels associated with type 1 diabetes are thought to have a role. In the type 1 diabetes mellitus populations, increased macroalbuminuria rates could play a role, as elevated adiponectin levels have been associated with renal disease. Despite this, the EDC investigation discovered a substantial 63% reduction in CAD risk (per 1 SD; 6.3 ug/ml) increase in serum adiponectin levels among type 1 diabetic people after controlling for recognized risk factors such as urine albumin excretion. Additionally, Coronary Artery Calcification in Type 1 Diabetes (CACTI) study discovered that reduced plasma adiponectin levels were independently associated with an increased risk of developing CAC in T1DM.[6]

Numerous investigations have proven that type 1 diabetes mellitus has a familial effect on the risk of coronary artery disease. The receptor for advanced glycation end products situated on chromosome 6p21.[3] in the major histocompatibility complex class III area and is a crucial locus for type 1 diabetes pathogenesis. It plays a critical role in the development of vascular disease in chronic hyperglycemia. The AA promoter region genotype has been associated with lowering risk of cardiovascular disease in type 1 and type 2 diabetes, and the general population as compared to the TT-TA genotype. The relationship between this polymorphism and coronary artery disease is complicated and inconsistent. The ACE II genotype being associated with a considerably lower risk of MI in some studies. The situation is complicated further by the relationship of the D allele with nephropathy and the I allele with insulin resistance, the leading risk factor for coronary artery disease in T1DM. Leu7Pro, leucine to proline polymorphism, in the neuropeptide Y gene on chromosome 7p15.1 may contribute to type 1 diabetes patients' inherited propensity to coronary heart disease (CHD), possibly through impairing glucose control and lipid metabolism. However, another recent study in nondiabetics showed no evidence of a link to A1C. In a variety of populations, the 480C/T or 514C/T, depending on the transcription start localization identification, hepatic lipase promoter polymorphism, a functional variant affecting hepatic lipase activity, has been associated with an increased prevalence of CAC

in type 1 diabetes and premature CAD, as well as CAC. Intriguingly, those carrying the 480C mutation have a higher risk of coronary artery disease and lower HDL levels than those carrying the 480T variant. Recently, it was discovered that the LIPC 480C/T polymorphism is associated with insulin resistance. In type 1 diabetes patients, a common genetic variation in the hepatic lipase gene (LIPC480C>T) is associated with a more than twofold increase in subclinical coronary artery disease.[26]

ApoA-IV (Apolipoprotein A-IV) is a structural glycoprotein present in chylomicrons, VLDL, and HDL that participates in the process of reverse cholesterol transport from peripheral cells to the liver. Due to a frequent polymorphism of glutamine to histidine at position 360 near the carboxyl terminus, two isoforms of apoA-IV are formed: apoA-IV2 (360His) and apoA-IV1 (360Gln). The former was associated with a significantly elevated risk of subclinical coronary artery disease progression in type 1 diabetes mellitus patients (relative risk 3.3; p=0.003) and MI in type 2 diabetes mellitus patients, but not in control subjects without diabetes. The Von Willebrand factor Thr789Ala polymorphism has been associated with an increased incidence of coronary artery disease (CAD) in long-term type 1 diabetic patients (OR 4.2 for Ala/Ala homozygotes). A carrier of coagulation factor VIII, Von Willebrand factor, has been identified as a risk factor for MI in the general population.[12]

Haptoglobin (Hp) is a protein whose major role is to regulate the extracorpuscular hemoglobin's destiny and toxicity. The Hp protein is polymorphic, with two distinct allele classes denoted by the letters 1 and 2. After an 18-year follow-up, T1DM patients with haptoglobin genotype 2-2, which indicates decreased antioxidant capacity, had a greater prevalence of coronary artery disease (CAD) than those with genotype 1-1.27 Furthermore, a recent meta analysis discovered that the haptoglobin genotype 2-2 confers a twofold greater risk of cardiovascular events such as myocardial infarction and stroke when compared to genotypes 1-1 and 2-1. Another study discovered that HLA class II genes expressed on smooth muscle cells in atherosclerotic plaques and infiltrating inflammatory are associated with cardiovascular events and death in an independent manner.[5] HLA class II expression is increased or changed in a variety of autoimmune disorders, which may help explain why autoimmunity has a higher prevalence of cardiovascular disease. A increasing body of evidence suggests that various immune system components contribute to atherosclerosis; indeed, atherosclerosis has been hypothesized to be an inflammatory autoimmune disease. Autoantigens, particularly heat shock proteins (HSPs) and oxidized LDL, are frequently detected in patients with CVD (oxLDL). Internalized oxLDL is presented to CD4 T cells via HLA II molecules on infiltrating macrophages, which exacerbate the continuing inflammation in the arteries by secreting pro-inflammatory cytokines and chemokines.[28] On chromosome 6p21.3, the highly polymorphic HLA class II locus is the main genetic component related with type 1 diabetes. Particular HLA class II alleles increase vulnerability to type 1 diabetes, whereas others protect against its development. Similar features of the HLA have been observed in the general population in relation to the development of coronary artery disease. Thus, genetic variations affecting susceptibility to type 1 diabetes may also be connected with the cardiovascular problems reported in type 1 diabetes patients.[28]

Gender is another critical factor to consider. Although studies indicate that diabetes affects women more than men, the magnitude of these differences is still contested. Coronary artery disease was responsible for mortality in 8% and 11% of male and female, respectively, before the age of 40 in an English cohort of over 23,000 T1DM patients.[31] This and other studies show the influence of T1DM on mortality in younger age, particularly female patients. Women's coronary artery disease (CAD) detection is important because 40% of all CVD events in female patients result in death. Additionally, 67 percent of women who die of abrupt coronary artery disease have no prior symptoms. On the other hand, during coronary angiography, only 50% of individuals with suggestive angina symptoms had serious obstructive lesions. These studies highlight how difficult it can be to diagnose coronary artery disease (CAD) in females. Interestingly, risk factors such as obesity, smoking, and most crucially, diabetes mellitus have a considerably larger effect on women than on men. Additionally, prognosis of women post AMI is worse than men's, with a 38 percent death rate in the first year compared to 25% for men. These findings may be explained by the fact that women with T1DM had an increased prevalence and severity of coronary calcification. The gender variations in fat deposition and distribution of HDL and LDL cholesterol may help to explain why diabetes increases coronary calcification and the prevalence of coronary artery disease (CAD) in women more than men.[29]

3. Management of Type 1 Diabetes Mellitus

Diabetes care and management aims to help people with type 1 diabetes live long and healthy lives. The management strategies to achieve this goal broadly include: Effectively delivering exogenous insulin to maintain glucose levels as close to the individual's target range as is safely possible to prevent the development and progression of diabetes complications, Effectively managing cardiovascular risk factors, Providing approaches, treatments, and devices that reduce the psychosocial burden of living with type 1 diabetes and, as a result, diabetes-related distress, Management strategies should evolve in response to new therapies and technologies as they become available, taking into account the wishes and desires of the diabetic.[30]

In the future, therapies such as islet stem cell transplantation must be developed. Immunotherapy approaches are being studied for their potential use in Stage 1 (two islet autoantibodies but no dysglycemia) or Stage 2 (autoantibodies and dysglycemia) type 1 diabetes to prevent Stage 3 clinical type 1 diabetes, as well as to preserve beta cell function before and shortly after the onset of Stage 3 clinical type 1 diabetes. Many interventions have been tested in clinical trials, but the anti-CD3 monoclonal antibody teplizumab, low-dose anti-thymocyte globulin (ATG), and the anti-TNF drug golimumab have yielded the most promising results to date. These have been shown to preserve beta cell function in people with newly diagnosed type 1 diabetes, and teplizumab has also been shown to delay the clinical onset of type 1 diabetes. Several other trials are underway in the hopes of not only preserving but also improving beta cell function and interdicting the type 1 diabetes disease process sufficiently to prevent the disease from developing.[30]

4. Conclusion

Type 1 diabetes is well established to be associated with an increased risk of coronary artery disease (CAD), which develops at an early age. This higher risk is explained by a number of modifiable risk factors, including both general risk factors for coronary artery disease (blood pressure, cholesterol, and smoking) and particular risk factors. While the link between T1DM and cardiovascular disease is well established, the underlying mechanisms remain unknown, and the necessity for more aggressive therapy is frequently overlooked. Additionally, clinicians must recognize that men and women with T1DM are equally at risk of developing cardiovascular disease. While treatment with glucose-lowering medications, statins, blood pressure control, and lifestyle adjustments has improved results, people with T1DM continue to suffer a significantly elevated risk of cardiovascular events and death when compared to the general population.

As a result, this residual risk may be mitigated by improving the detection of 'at risk' persons and finding novel treatments.

5. Declarations

5.1. Ethics Approval and Consent to participate
Not applicable.

5.2. Consent for publication
Not applicable.

5.3. Availability of data and materials
Data used in our study were presented in the main text.

5.4. Competing interests
Not applicable.

5.5. Funding source
Not applicable.

5.6. Authors contributions
Idea/concept: DAI. Design: DAI. Control/supervision: CT, NK, SW, VYSP. Data collection/processing: DAI. Analysis/interpretation: CT, NK, SW, VYSP. Literature review: CT, NK, SW, VYSP. Writing the article: DAI. Critical review: CT, NK, SW, VYSP. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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