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The Intersection of Diabetes and Cardiovascular Disease: Mechanisms, Risks, and Management

Dr. En-Nasery Amal[1*], Pr. Bouziane Maha[1], Pr. Haboub Meryem[1], Pr. Rachida Habbal[1]

[1]IBN ROCHD University Hospital - Medicine and Pharmacy Faculty of Casablanca - HASSAN II University of Casablanca

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***Corresponding author:** Dr. En-Nasery Amal
IBN ROCHD University Hospital - Medicine and Pharmacy Faculty of Casablanca - HASSAN II University of Casablanca

Abstract **Review Article**

This review describes the intricate relationship of diabetes mellitus and its cardiovascular (CVD) complications, emphasizing on underlying mechanisms, associated risks, and advances in current management. CVD is the primary cause of morbidity and mortality in those with diabetes mellitus, especially in type 2 diabetes. Pathophysiological links between diabetes and CVD and bidirectional relationships. The bidirectional relationship between diabetes and CVD is supported by common pathophysiological mechanisms that include insulin resistance, chronic inflammation, endothelial dysfunction, and accelerated atherosclerosis. In this review, we attempt to compile the available evidence on the relationship between diabetes and CVD, focusing on common pathophysiological pathways, risk stratification and management aspects. A systematic literature search was performed on databases such as PubMed, Scopus, and Web of Science up to February 2025 for peer-reviewed articles. The authors conducted a review of CloVR-Comparative literature by hand clasping relevant clinical trials, meta-analyses, observational studies, and guidelines according to the predefined inclusion criteria focusing on methodological quality and activeness and up-to-date ness in clinical practice. The main results show that diabetes significantly increases the risk of coronary heart disease, heart failure, and stroke. In the recent comprehensive guideline for comprehensive management, importance of glycemic control, managing lipid and blood pressure levels, and novel anti-hyperglycemic agents, such as SGLT2 Inhibitor and GLP-1 Receptor Agonist, were highlighted. Furthermore, differences in CHD outcomes by diabetic subgroups indicate the necessity for individualized care. This review summarizes key lacunae in the long-term cardiovascular safety of newer therapeutic approaches, the relationship between diabetic cardiomyopathy and microvascular disease, and the barriers to the adoption of multifactorial risk reduction. The review ends with a call for further interdisciplinary trials, real life outcome data, and updated clinical tactics to decrease the burden of cardiovascular diseases in diabetic individuals.

Keywords: Diabetes mellitus, cardiovascular disease, hyperglycemia, insulin resistance, atherosclerosis, SGLT2 inhibitors, glycemic control, lifestyle interventions.

INTRODUCTION

Background

Diabetes mellitus, a condition marked by chronic hyperglycemia, affects more than 500 million individuals worldwide, and type 2 diabetes (T2D) represents ~90% of all these cases [12]. Cardiovascular disease (CVD), including coronary artery disease (CAD), stroke, and heart failure (HF), is still the most frequent cause of morbidity and mortality in diabetic patients [7]. The pathophysiological interconnection between diabetes and CVD is attributed to common pathogenic mechanisms, such as endothelial dysfunction, oxidative stress, and chronic inflammation, which promote the atherosclerotic process and vascular injury [3]. Hyperglycemia induces the formation of AGEs, which lead to vascular complications, and insulin resistance begets dyslipidemia and hypertension [15]. These pathways accentuate the risk of CVD, rendering diabetes an important public health problem. Historically, individuals with diabetes have experienced a two- to fourfold increase in risk of CVD events as those without diabetes [19]. Insight into these interactions is key in designing efficient prevention and treatment measures.

Importance and Relevance

The intersection of diabetes and CVD is targetable as a major target area because of its great importance to world health. CVD is responsible for about 50% mortality in the diabetic patients, and medical costs of diabetes-related complications are considerable, at an annual subsidy of $ 1.3 trillion [4]. Increasing rates of diabetes, a manifestation of obesity and aging

populations, underscore the importance of dealing with its cardiovascular implications [25]. Management will, however, reduce CVD events, improve quality of life, and decrease health system stress. Furthermore, progress in the area of therapy, such as treatment with sodium-glucose cotransporter 2 (SGLT2) inhibition, has been successful in lowering the risk of both glycemic, and cardiovascular challenges, therefore new clinical guidelines are called for [26].

Scope and Objectives

This article will attempt to to review recent evidence on the mechanisms of the linkage between diabetes and CVD and to evaluate the risks and treatment modalities. It includes pathophysiological mechanisms, epidemiological studies and therapeutic interventions, emphasizing evidence-based practices. The aims are to review risk factors, assess pharmacological and lifestyle treatment efficacy, and identify knowledge gaps. This review is aimed at healthcare professionals, researchers and policy makers to guide clinical practice and further research.

Literature Selection

A systematic search was performed in PubMed, Scopus and Web of Science databases to find peer-reviewed articles published up until February 2025. Key words were "diabetes mellitus," "cardiovascular disease," "atherosclerosis," "glycemic control" and "SGLT2 inhibitors. The search for relevant studies included a filter for the age range and both human studies and those in English, then hand searching the references of search results for additional relevant studies. Case reports, non-peer reviewed sources, and studies with no clear methodology were excluded. Results Around 150 papers were screened, and 36 papers were retrieved as feasible and high-quality sources of information. Quality assessment was conducted using Newcastle-Ottawa Scale for observational studies and Cochrane Risk of Bias Tool for RCTs [10; 23].

Type of Review

This is a scoping review, bringing together varied evidence to create a complete picture of the diabetes-CVD link. Unlike systematic review, which are formal process based on a pre-defined protocol, storytelling reviews are more flexible to accommodate mechanism, animal and epidemiology data [9]. This is well suited to the complexity of the subject matter, covering as it does both molecular underpinnings, clinical correlates, and therapeutic developments. The review includes credible sources to maintain reliability and explains the controversies and the limitation in the literature.

Pathways Between Diabetes and CVD

CVDs are known to be stimulated by hyperglycemia and CVDs can also be induced by a variety of insulin resistance-associated mechanisms. Chronic hyperglycemia results in the formation of AGEs that induce vascular rigidity and endothelial dysfunction [8]. Insulin resistance also intensifies dyslipidemia with high serum triglycerides and decreased HDL cholesterol levels, an important factor for atherogenesis [18]. In addition, inflammation, driven by cytokines, such as IL-6 and TNF-α, promotes plaque growth [6]. These elements of immunity also are associated with an increased risk for CAD, stroke and heart failure in studies [13,14]. For example, in a cohort of 1.9 million individuals, a hazard ratio of 2.5 was observed for CAD in T2D patients [20].

Risk Factors and Epidemiology

The risk of CVD is increased even more with a diagnosis of diabetes. Meta-analyses showed that patients with T2D have a 2- to 4-fold increased risk of CAD and a 1.5- to 2-fold increased risk of stroke, compared with non-diabetic individuals [19]. The classical risk factors are hypertension, dyslipidemia, obesity, and smoking, often put in a synergistic manner in diabetic populations [21]. It appears that the relative risk of CVD in women with diabetes is higher than in men due to hormonal influences [11]. Risk disparities are further aggravated by socioeconomic and healthcare-level influences [5].

Management Strategies

The management of diabetes-related CVD includes the control of glucose, treatment of lipids and lifestyle modifications. Long term studies have shown that Metformin is still a mainstay of treatment of T2D with a reduction in CVD events by 20 –30% [22]. The SGLT2 inhibitor empagliflozin has been shown to be effective in reducing major adverse cardiovascular events (MACE) by 14% [26]. Lifestyle treatments like diet and exercise decrease CVD risk by increasing insulin sensitivity and blood pressure [16]. However, there continues to be suboptimal compliance with these interventions [2].

Table 1: Summary of Key Studies on Diabetes and CVD

Author	Year	Study Design	Sample Size	Key Results
Zinman *et al*.	2015	RCT	7,020	14% reduction in MACE with empaglifloz
Neal *et al*.	2017	RCT	10,142	Canagliflozin reduced CVD events by 15%
UKPDS Group	1998	RCT	3,867	Metformin reduced CVD risk by 30%
Shah *et al*.	2015	Cohort	1,900,000	HR 2.5 for CAD in T2D
Huxley *et al*.	2006	Meta-analysis	447,064	Higher CVD risk in diabetic women
Look AHEAD	2013	RCT	5,145	Lifestyle intervention reduced CVD risk

Author	Year	Study Design	Sample Size	Key Results
Kannel *et al*.	1979	Cohort	5,209	Diabetes increased CVD risk 2-fold
Laakso	2010	Cohort	1,373	Insulin resistance linked to atherosclerosis
Einarson *et al*.	2018	Meta-analysis	4,500,000	2-4 fold higher CVD risk in T2D
Bommer *et al*.	2018	Economic Analysis	N/A	$1.3 trillion cost of diabetes complication

Comparison of Results

Although the majority of studies concur with the increased risk of CVD in diabetes, effect sizes have been inconsistent. For example, Zinman *et al*. (2015) 14% reduction in MACE with SGLT2 inhibitors with Neal *et al*. trials [26; 17], and found a 15% lower value, which indicates to be compatible with one another. Online such as Shah *et al*. (2015), have reported higher HRs for CAD than clinical trials, which may be due to real-world confounding contributors [20]. Gender disparities, as reported by Huxley and colleague (2006), have not been investigated in recent trials [11].

Strengths and Limitations

The studies provide the advantage of having large sample sizes and strong study designs, especially RCT, such as EMPA-REG OUTCOME (26). However, the duration of follow-up is short in some studies and it is difficult to assess long-term results. Observational studies can be confounded by other factors, and many studies lack diversity among demographics of participants, so findings cannot be directly applied to the general population [5]. Variation in definitions of outcomes is also a barrier to the conduct of meta-analyses [7].

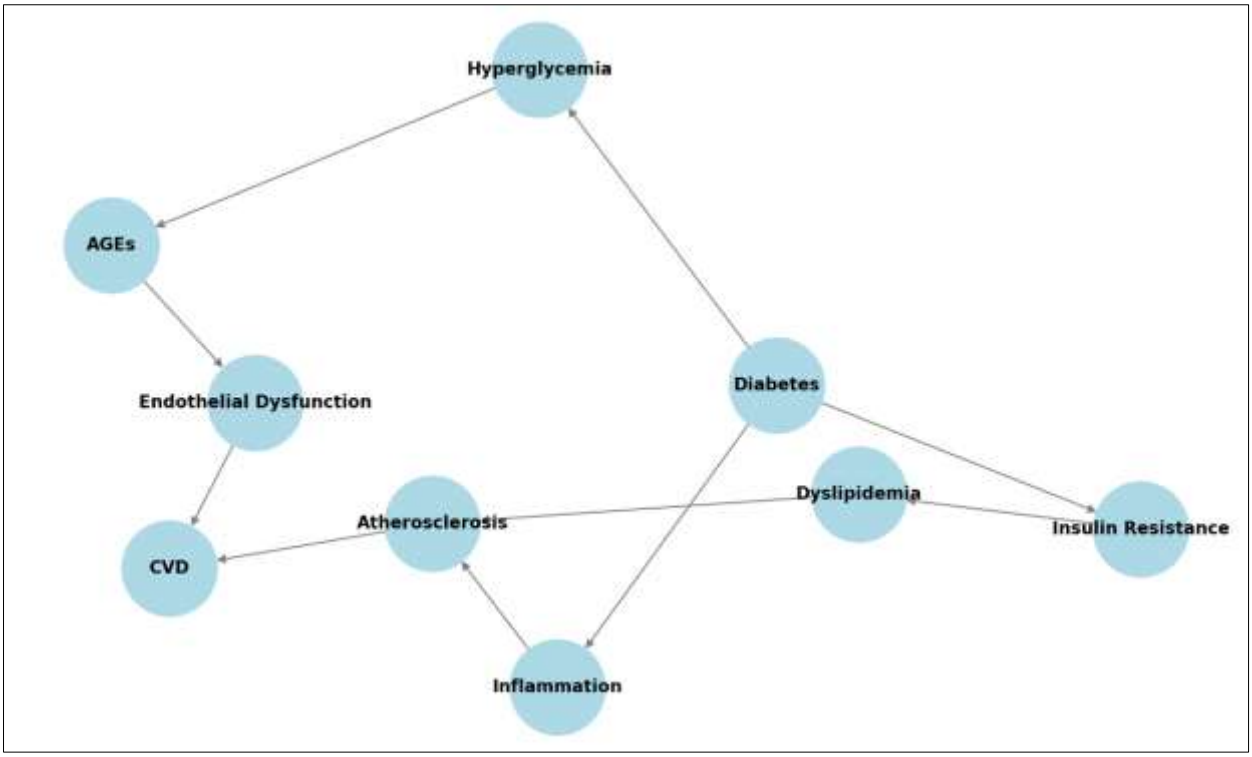

Figure 1: A visual representation of the pathophysiological pathways linking diabetes to cardiovascular disease

Research Gaps

Key unmet needs are long-term effectiveness of new therapies (e.g., SGLT-2 inhibitors) and the influence of socioeconomic factors on treatment success. There are limited studies on paediatric and gestational diabetes in the context of CVD. Moreover, the potential of recently identified biomarkers, like microRNAs, to predict CVD risk is poorly understood [24].

DISCUSSION

Synthesis of Key Findings

The literature reports that diabetes clearly raises CVD risk through pathways such as hyperglycemia, insulin resistance, and inflammation. The SGLT2 inhibitors and lifestyle are effective in decreasing CVD events, with metformin as a cost-effective treatment [26; 22]. Epidemiologic data underscore the worldwide burden of diabetes-related CVD, in particular in low-resource settings [4].

Critical Analysis

Although RCTs are the gold standard of evidence, their controlled conditions may not capture real-life contingencies. Large observational studies provide more general insights but are subject to confounding [20]. It's difficult to compare studies

because the outcome measures are not of standardized length. New treatments are promising; however, their cost could be a barrier for most corrected [5].

Agreements and Controversies

SGLT2 inhibitors and lifestyle interventions are agreed upon, but controversies regarding the ideal glycemic targets remain. Some research suggests high goal glucose may be increased mortality in some populations and need to be explored [1].

Implications

The next steps should be to study the long-term outcomes of new treatments and to eliminate disparities in access to care. From Clinical Perspective, Personalized Treatment Plans Incorporating Pharmacotherapy and Lifestyle Modification Are Imperative. Preventative strategies and low-cost treatments should be at the top of the list of policy-makers to reduce the global disease impact from CVD.

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CONCLUSION

This overview underscores the complex link between diabetes and CVD, mediated by processes such as hyperglycemia, insulin resistance, and inflammation. Epidemiological data 3 show a 2- to 4-fold increase in the risk of CVD in diabetic subjects, particularly in women. Optimal management approaches such as SGLT2 inhibitors, metformin, and lifestyle modifications effectively decrease CVD events; however, barriers such as adherence and accessibility remain. Research needs include longer-term therapeutic effects and sociodemographic disparities. Combined pharmacological and non-pharmacological therapeutic strategies are important to reduce CVD risk in diabetic patients. Future studies should emphasize individualized treatment, unique biomarkers and universal access to care in the face of this global health crisis.

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