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Narrative Article

EMERGING BIOMARKERS FOR CARDIOVASCULAR DISEASE PROGNOSIS IN DIABETIC PATIENTS: A NARRATIVE REVIEW.

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ABSTRACT.

Cardiovascular disease (CVD) is the leading cause of morbidity and death among patients with diabetes, presenting a significant global health challenge. Traditional biomarkers have limitations in accurately predicting CVD risk in this population, highlighting the need for novel biomarkers that offer improved precision and specificity. The review aims to critically evaluate current research on novel biomarkers for CVD prognosis in diabetic patients, synthesizing evidence on genetic, proteomic, metabolic, and inflammatory markers. An organized literature search was managed across multiple electronic databases, yielding a comprehensive selection of studies investigating biomarkers associated with CVD prognosis in diabetic individuals. Findings reveal emerging biomarkers with potential predictive value, such as genetic variants, inflammatory proteins, and metabolic metabolites. These biomarkers offer insights into the pathophysiological mechanisms underlying CVD in diabetes and show promise for improving risk stratification and early detection. The integration of novel biomarkers into clinical practice could revolutionize the management of CVD in diabetic patients by enabling personalized risk assessment and targeted interventions. However, challenges such as validation, standardization, and integration into existing clinical workflows need to be addressed. Future research should focus on longitudinal studies to elucidate the dynamic nature of biomarkers and leverage technological advancements to enhance their predictive value. The identification and validation of novel biomarkers hold potential implications for clinical policy and development. Incorporating these biomarkers into risk assessment algorithms and treatment guidelines could optimize patient outcomes and contribute to more efficient healthcare resource allocation. However, education and training for healthcare providers on biomarker interpretation and clinical implications are essential for successful implementation.

Keywords: *Cardiovascular Disease, Diabetes Mellitus, Biomarkers, Risk Assessment, Personalized Medicine.*
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INTRODUCTION.

Cardiovascular disease (CVD) remains the chief cause of morbidity and death among patients with diabetes, significantly impacting their quality of life and healthcare systems worldwide. Studies have consistently shown that people with diabetes are at a two to four times higher risk of developing CVD compared to those without diabetes [1]. The interplay between hyperglycemia, insulin resistance, and metabolic dysfunctions accelerates atherosclerosis, leading to an increased incidence of heart attacks, strokes, and peripheral vascular disease in this population.

Early detection and management of CVD in diabetic patients are hampered by the asymptomatic nature of the disease in its initial stages and the limitations of traditional risk assessment tools, which often underestimate the risk in this population. Moreover, the heterogeneity of CVD manifestations in diabetes necessitates more personalized and precise approaches to risk stratification and intervention.

Biomarkers are biological molecules that indicate a condition or disease or signify a normal or abnormal process. They can be discovered in tissues, blood, or other bodily fluids. They can be used to assess the degree to which the body reacts to an illness or condition's therapy [2]. In the context of CVD, biomarkers offer a promising tool for early detection, risk assessment, and monitoring of disease progression, as well as guiding therapeutic decisions.

Traditional biomarkers for CVD include lipid profiles, blood pressure, body mass index (BMI), and glycated hemoglobin (HbA1c). While these markers provide valuable information on cardiovascular risk, they often lack the specificity and sensitivity to fully capture the complex pathophysiology of CVD in diabetes, leading to a need for more precise.

The limitations of traditional biomarkers in accurately predicting CVD risk in diabetic patients underscore the urgent need for novel biomarkers that can offer more precise and personalized risk assessment. Emerging research suggests that genetic, proteomic, and metabolic markers may hold the key to unlocking this potential, providing insights into the molecular mechanisms underlying CVD in diabetes [3].

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The identification and validation of novel biomarkers for CVD in diabetic patients could revolutionize the management of this high-risk population. By enabling earlier detection, more accurate risk stratification, and tailored therapeutic interventions, these biomarkers have the potential to significantly improve patient outcomes, reduce healthcare costs, and alleviate the burden of CVD on individuals and societies.

The review article aims to critically evaluate and synthesize current research on novel biomarkers that have the potential to improve the prognosis, early detection, and management of cardiovascular disease in patients with diabetes. The key questions identified for the review are centered around evaluating and synthesizing current research on novel biomarkers that can improve the prognosis, early detection, and management of cardiovascular disease (CVD) in patients with diabetes. This involves a comprehensive examination of genetic, proteomic, metabolic, and inflammatory markers to identify those with potential predictive value for CVD in this high-risk population. The review aims to address the limitations of traditional biomarkers by exploring new biomarkers that offer improved precision and specificity for risk assessment and early detection, ultimately leading to personalized medicine approaches for managing CVD in diabetic patients.

METHODOLOGY.

This review adopts a comprehensive approach to synthesizing current research on biomarkers for CVD prognosis in diabetic patients. A systematic literature search was conducted using electronic databases including Scopus, PubMed, and Web of Science, and published between 2010 to 2023. The search strategy involved a combination of relevant keywords and Medical Subject Headings (MeSH) terms, such as "diabetes mellitus," "cardiovascular diseases," "biomarkers," "genetic markers," "proteomic markers," "metabolic markers," and "inflammatory markers." The search was limited to articles published in English and focused primarily on human studies. To find other studies, the reference lists of pertinent papers and reviews were also manually searched.

Based on predetermined inclusion and exclusion criteria, articles were assessed. Inclusion criteria encompassed studies investigating biomarkers associated with CVD prognosis in diabetic patients, including clinical trials, observational studies, systematic reviews, and meta-analyses. Studies examining both traditional and emerging biomarkers, such as genetic, proteomic, metabolic, and inflammatory markers, were considered. Exclusion criteria included studies unrelated to CVD prognosis, animal studies, conference abstracts, and articles not available in full-text format.

Data synthesis involved a narrative synthesis approach to summarize findings across studies, focusing on the association between biomarkers and CVD prognosis in diabetic patients. Key themes and patterns were identified, and potential biomarkers showing consistent associations with CVD outcomes were highlighted. Additionally, the strengths and limitations of the evidence were discussed, along with implications for clinical practice and future research directions.

DISCUSSION.

CURRENT LANDSCAPE OF BIOMARKERS IN CVD PROGNOSIS FOR DIABETIC PATIENTS.

Traditional Biomarkers for Cardiovascular Disease in Diabetic Patients.

The management and prognosis of CVD in patients with diabetes have long relied on a set of traditional biomarkers. These biomarkers, including lipid profiles, HbA1c, and CRP, play a pivotal role in assessing cardiovascular risk, guiding treatment decisions, and monitoring disease progression.

Lipid Profile.

Lipid profiles are a critical component of cardiovascular risk assessment, encompassing measurements of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides. In people with diabetes, low levels of HDL-C and elevated levels of triglycerides are linked to an elevated likelihood of CVD. Lipid profile screening is advised as a standard component of cardiovascular risk assessment in people with diabetes by the American College of Cardiology/American Heart Association (ACC/AHA) recommendations [4].

Glycated Hemoglobin (HbA1c).

As a measure of long-term glycemic control, HbA1c is calculated by averaging blood glucose levels over the two to three months prior. Its significance in cardiovascular risk stratification stems from the direct correlation between elevated HbA1c levels and elevated risk of CVD in patients with diabetes. HbA1c is recommended by clinical guidelines for both diabetes management and as a component of cardiovascular risk assessment [5].

C-reactive Protein (CRP).

Acute-phase protein CRP is used as a diagnostic for systemic inflammation. Unrelated to conventional cardiovascular risk, elevated CRP levels have been linked to an elevated risk of CVD, such as myocardial infarction and stroke. The use of CRP as a biomarker for cardiovascular risk assessment has been improved by the development of high-sensitivity CRP (hs-CRP) assays,

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which can identify lower levels of CRP, especially in people with diabetes.

Emerging biomarkers.

A. *Genetic Markers.*

Genetic markers have emerged as substantial predictors of CVD risk, particularly in patients with diabetes. Several specific genes and genetic loci have been identified that correlate with an increased susceptibility to CVD. For instance, the 9p21.3 locus has been consistently associated with coronary artery disease (CAD) and myocardial infarction (MI) across diverse populations [6]. Additionally, variants in the HNF1A gene, known for their role in maturity-onset diabetes of the young (MODY3), have also been linked to an enhanced risk of CVD in diabetic patients.

The predictive value of genetic markers for CVD lies in their ability to identify people at high risk before clinical symptoms manifest, allowing for early intervention. Genetic risk scores, which aggregate the effects of multiple genetic variants, have shown promise in improving the prediction of CVD risk beyond traditional risk factors [7]. The clinical relevance of these markers is significant, as they can guide personalized prevention strategies, including lifestyle modifications and pharmacotherapy, tailored to an individual's genetic risk profile.

B. *Proteomic Markers.*

Proteomic technologies have enabled the identification of novel proteins and peptides associated with CVD in diabetes, offering insights into the disease's pathophysiology and potential biomarkers for early detection. For example, elevated levels of inflammatory proteins such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) have been found in diabetic patients with CVD, reflecting the role of inflammation in the disease process [8]. Other proteins, such as cardiac troponins and natriuretic peptides, have been studied for their association with myocardial stress and heart failure in the context of diabetes [9].

The mechanisms by which these proteomic markers are linked to CVD in diabetes are multifaceted, involving pathways related to inflammation, endothelial dysfunction, and metabolic dysregulation. For instance, the increased expression of inflammatory proteins can exacerbate atherosclerosis by promoting plaque formation and instability [8]. The potential of these markers for early detection lies in their ability to reflect subclinical disease processes, such as endothelial dysfunction and myocardial stress before overt CVD develops. This early detection capability could enable timely interventions to prevent or mitigate the progression of CVD in diabetic patients.

C. *Metabolic Markers.*

Metabolomic profiling has identified several metabolites associated with a bigger risk of CVD in people with diabetes. These include amino acids such as branched-chain amino acids (BCAAs) and aromatic amino acids, which have been linked to insulin resistance and CVD. Additionally, altered levels of lipid metabolites, such as acylcarnitines and sphingolipids, have been associated with diabetic dyslipidemia and atherosclerosis, further indicating their role as potential biomarkers for CVD risk [10].

The correlation between these metabolites and CVD risk is deeply intertwined with the metabolic dysregulation characteristic of diabetes. For example, insulin resistance, a hallmark of type 2 diabetes, can lead to increased lipolysis and elevated levels of free fatty acids, contributing to the accumulation of harmful lipid intermediates and promoting atherosclerosis. Understanding the metabolic pathways that link these metabolites to CVD risk can provide insights into the pathophysiology of CVD in diabetes and identify potential targets for therapeutic intervention.

D. *Inflammatory Markers.*

Inflammation plays a crucial role in the development and progression of both CVD and diabetes. Chronic low-grade inflammation, distinguished by raised levels of inflammatory cytokines and acute-phase reactants, contributes to the pathogenesis of atherosclerosis and insulin resistance [8, 11]. This inflammatory milieu can exacerbate endothelial dysfunction, promote plaque formation, and increase the risk of thrombotic events.

Beyond traditional markers like CRP, emerging inflammatory biomarkers such as IL-1β, IL-6, and TNF-α have gained attention for their potential to provide more specific insights into the inflammatory processes underlying CVD in diabetes. Additionally, novel markers like pentraxin-3 (PTX3) and adipokines (e.g., adiponectin and leptin) are being explored for their roles in inflammation and metabolic regulation, offering new avenues for risk assessment and therapeutic targeting [12].

E. *Other Biomarkers.*

MicroRNAs (miRNAs) are small, non-coding RNAs that regulate gene expression post-transcriptionally and have been implicated in various pathophysiological processes, including CVD and diabetes. Specific miRNAs, such as miR-126 and miR-146a, are involved in endothelial function and inflammation, respectively, and their altered expression has been associated with the development of atherosclerosis and diabetic complications [13].

Circulating endothelial cells (CECs) and endothelial progenitor cells (EPCs) have emerged as biomarkers of endothelial health and vascular repair capacity. Elevated

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levels of CECs can indicate endothelial damage, while decreased levels of EPCs may reflect impaired vascular repair mechanisms, both of which are associated with increased CVD risk in diabetes. These cells offer a unique window into the vascular health of diabetic patients and their potential risk for CVD.

CLINICAL APPLICATION AND FUTURE DIRECTIONS.

The integration of novel biomarkers into clinical practice for CVD management in diabetic patients is progressing, albeit at a varied pace. Biomarkers such as high-sensitivity C-reactive protein (hs-CRP) have gained acceptance for evaluating cardiovascular risk, while others, like certain genetic and proteomic markers, are still predominantly used in research settings or for specific populations. The use of advanced glycation end products (AGEs) and inflammatory markers is becoming more common in assessing complications in diabetes, reflecting a growing recognition of their importance.

Several challenges hinder the widespread adoption and standardization of novel biomarkers. These include the need for robust validation studies to confirm their predictive value, the establishment of standardized assays and reference ranges, and the integration of biomarker testing into existing clinical workflows. Additionally, the cost-effectiveness of widespread screening using these biomarkers and the need for education among healthcare providers about their interpretation and clinical implications remain significant barriers.

Current research has yet to fully elucidate the complex interactions between various biomarkers and their cumulative impact on CVD risk in diabetes. Gaps exist in understanding the longitudinal dynamics of these biomarkers and their response to therapeutic interventions. Furthermore, research is needed to explore the ethnic and gender-specific variations in biomarker levels and their implications for CVD risk stratification.

The potential for technological advancements, specifically in the fields of artificial intelligence (AI) and machine learning, to enhance the utility of biomarkers is immense. These technologies can analyze large datasets to identify patterns and predict outcomes, potentially uncovering new biomarkers and providing insights into their interactions. AI-driven models could also improve the accuracy of risk prediction algorithms by integrating diverse biomarker data, lifestyle factors, and genetic information.

The ultimate goal of incorporating novel biomarkers into clinical practice is to enable personalized medicine, where treatment and prevention strategies are tailored to an individual's unique biomarker profile. This approach could involve specific dietary recommendations, lifestyle changes, and pharmacological interventions designed to target the underlying pathophysiological processes identified through biomarker screening.

Personalized medicine has the potential to significantly improve patient outcomes by preventing the development of CVD in high-risk diabetic patients, reducing the incidence of complications, and optimizing the management of existing diseases. For healthcare systems, the shift towards personalized medicine could lead to more efficient resource allocation, reduced hospitalization rates, and lower healthcare costs, ultimately contributing to the sustainability of healthcare delivery.

CONCLUSION.

In conclusion, the burden of CVD in patients with diabetes underscores the critical need for precise risk assessment and effective management strategies. Traditional biomarkers have played a pivotal role in evaluating CVD risk but often lack the specificity needed for accurate prediction in this high-risk population. Emerging biomarkers, including genetic, proteomic, metabolic, and inflammatory markers, offer promising avenues for improving risk stratification and early detection of CVD in diabetic patients. While some biomarkers have already found clinical utility, challenges such as validation, standardization, and integration into clinical workflows remain. Future research should focus on elucidating the longitudinal dynamics of biomarkers, understanding their interactions, and leveraging technological advancements like artificial intelligence to enhance their predictive value. The ultimate goal is to enable personalized medicine approaches that optimize patient outcomes, reduce healthcare costs, and contribute to the sustainability of healthcare systems.

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LIST OF ABBREVIATIONS.

CVD: Cardiovascular Disease
HbA1c: Hemoglobin A1c
CRP: C-reactive Protein
hs-CRP: High-sensitivity C-reactive Protein
BMI: Body Mass Index
CAD: Coronary Artery Disease
MI: Myocardial Infarction
MODY3: Maturity-Onset Diabetes of the Young (type 3)
IL-6: Interleukin-6
TNF-α: Tumor Necrosis Factor-alpha
BCAAs: Branched-Chain Amino Acids

EPCs: Endothelial Progenitor Cells
CECs: Circulating Endothelial Cells
PTX3: Pentraxin-3
miRNAs: MicroRNAs

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CONFLICT OF INTEREST.

The authors have no competing interests to declare.

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