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Novel Biomarkers in Early Prediction of Diabetic Nephropathy: A Systematic Review

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Abstract

Diabetes mellitus (DM) is a metabolic illness that is highly prevalent and intricate. Because of the high incidence of diabetic complications and disease mortality, the condition is one of the biggest medical and social issues in the world. Due to its rising prevalence, diabetes mellitus (DM), which raises blood glucose levels, is one of the world's health challenges and is anticipated to impact 495 million people. Diabetic kidney disease, or DKD, is a widespread ailment all over the world. It is the main cause of end-stage kidney disease (ESKD) and one of the most common consequences of diabetes mellitus (DM). Three essential elements play a role in its pathogenesis: the inflammatory, metabolic, and hemodynamic axis. Clinically, DKD is characterized by persistent albuminuria and a gradual reduction in glomerular filtration rate (GFR). These changes, however, are not unique to DKD, emphasizing the necessity to find new biomarkers originating from the disease's pathophysiology to support diagnosis, monitoring, treatment response, and prognosis. Cystatin C, also known as CysC, is a member of the cysteine protein inhibitor family and is a low-molecular-weight protein with 122 amino acids. The CST3 housekeeping gene, which is found on chromosome 20 (20pl1. 2, encodes it. Protein turnover, pro-protein processing, bone remodeling, antigen presentation, and apoptosis are among the physiological processes in which cysteine cathepsins are involved.

Keywords: Diabetic Nephropathy; Biomarkers; Serum Cystatin C; Neutrophil Gelatinase-Associated Lipocalin; Plasma Kidney Injury Molecule

1. Introduction

Diabetes mellitus (DM) is a metabolic illness that is highly prevalent and intricate. Because of the high incidence of diabetic complications and disease mortality, the condition is one of the biggest medical and social issues in the world [1]. Due to its rising prevalence, diabetes mellitus (DM), which raises blood glucose levels, is one of the world's health challenges and is anticipated to impact 495 million people [2]. Diabetic kidney disease, or DKD, is a widespread ailment all over the world. It is the main cause of end-stage kidney disease (ESKD) and one of the most common consequences of diabetes mellitus (DM). Three essential elements play a role in its pathogenesis: the inflammatory, metabolic, and hemodynamic axis [3]. Clinically, DKD is characterized by persistent albuminuria and a gradual reduction in glomerular filtration rate (GFR). These changes, however, are not unique to DKD, emphasizing the necessity to find new biomarkers originating from the disease's pathophysiology to support diagnosis, monitoring, treatment response, and prognosis [4]. Early identification of inflammatory biomarkers is crucial to minimizing complications associated with diabetes mellitus since the condition is an inflammatory one that affects more areas of the body than just the classic hemodynamic and metabolic axis. The advancement of DKD towards its terminal stages, which necessitate renal replacement therapy and result in mortality, can be postponed with early detection and the optimization of currently available therapeutic alternatives. Thus, the purpose of this review is to examine the disease's molecular components

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as well as the clinical applicability and function of novel biomarkers in DKD treatment [5]. Elevated blood vessel glucose levels are critical to the development of diabetic neuropathic pain because hyperglycemia produces too many reactive oxygen species (ROS), it causes metabolic dysfunctions in the mitochondria and the glucose metabolic pathway [6]. Through glycation, high glucose concentrations cause covalent adducts to form with plasma proteins. Advanced glycation end products (AGEs) are one of these events and a significant risk factor for complications from diabetes. After prolonged exposure to hyperglycemia, podocytes—a crucial part of the glomerular filtration barrier—can develop abnormalities. One of the early glomerular morphologic alterations is the loss of podocytes, which is crucial to the development of diabetic nephropathy (DN). Clinically speaking, diabetic people with DN exhibit proteinuria and reduced kidney function [7]. Pathologically, DN patients typically have glomerular sclerosis, interstitial fibrosis, extracellular matrix protein deposition, thickening of the basement membrane, and kidney hypertrophy. Even while blood pressure and glucose management can help manage DN patients, many of them eventually develop renal failure. Therefore, it will be crucial to comprehend the pathophysiology of DN and create new biomarkers to diagnose DN early [8,9]. Biological substances known as biomarkers are employed to identify the conditions of healthy or sick cells, tissues, or people. From a clinical standpoint, biomarkers significantly influence the treatment of patients with or without obvious disease, as well as those who are suspected of having a disease. Nowadays, biomarkers—such as genes, proteins, metabolites, glycans, and other molecules—are employed at the molecular level and are useful for prognosis, illness diagnosis, and the creation of numerous therapeutic interventions [10,11].

2. The Perspectives and Epidemiology of Diabetic Kidney Disease

As one of the most prevalent chronic, non-communicable diseases, diabetes mellitus (DM) has become one of the fastest-growing worldwide health catastrophes in recent decades. Recent statistics from the International Diabetes Federation (IDF) shows that 537 million adults in the world between the ages of 20 and 79 have diabetes in 2021, accounting for 10.5% of the total population. By 2030, this figure is anticipated to increase to 643 million [12]. However the time between the development of DM and its diagnosis is frequently 4–7 years, and additional time elapses before any clinical harm manifests. Thus, there is a lot of interest in the development of earlier diagnostic techniques. About 30–40% of patients with type 1 or type 2 diabetes mellitus (DM) also have diabetic kidney disease (DKD) [13]. The inflammatory, metabolic, and hemodynamic axes are the three main axes involved in the etiology and development of diabetic kidney disease (DKD). Of these, the data supporting the inflammatory axis as a potential therapeutic target is growing [1]. Since diabetes mellitus is an inflammatory condition that affects more than only the usual hemodynamic and metabolic axes [3], identifying inflammatory biomarkers early on is crucial to minimizing the disease's associated consequences. The advancement of DKD towards its terminal stages, which necessitate renal replacement therapy and result in mortality, can be postponed with early detection and the Optimization of currently available therapeutics alternatives [4]. Thus, the purpose of this review is to examine the disease's molecular components as well as the clinical applicability and function of novel biomarkers in DKD treatment.

3. Challenges with Traditional Biomarkers

Serum creatinine levels are used to determine the estimated glomerular filtration rate (eGFR), and the diagnosis of DKD depends on the presence of albuminuria. Significant glomerular damage and a drop in renal function lead to a decline in eGFR. Albuminuria is often the most reliable marker for prognosis prediction and treatment success among those used to measure DKD. Albumin excretion in the urine (UAE) is measured to determine the degree of albuminuria and is used for risk grading [5]. The degree of structural damage and renal function are clearly correlated, especially at modest levels of eGFR decline during DKD [9]. However, when albuminuria is modest or eGFR decline is minor in the early stages of the disease, this connection is less evident. This suggests how important is to find novel biomarkers for early prediction of DKD.

4. Novel Biomarkers for Diabetic Nephropathy

Without a doubt, risk management to enhance prognosis and decelerate the advancement of kidney disease linked to diabetes mellitus depends on early diagnosis. However, as previously mentioned, there are significant limits to conventional diagnostic testing that frequently lead to a delayed diagnosis [14]. As a result, the ongoing quest for novel biomarkers in serum and urine based on metabolomics and proteomics has become more important in recent years. This is because our knowledge of the pathophysiology and mechanisms behind the development of DKD has improved [15]. Many biomarkers have been proposed as a result of progress in understanding the molecular mechanisms behind both acute and chronic kidney injury. These could be important in the assessment of individuals with diabetic kidney disease (DKD), even though they have primarily been found in cases of acute kidney injury (AKI). These biomarkers can potentially improve the accuracy of evaluating the onset and course of DKD, an area where traditional biomarkers,

including serum creatinine, which is used to assess GFR and albuminuria, have limits. The data supporting the utility of novel biomarkers that possess strong diagnostic and discriminative power, good sensitivity and specificity, and the ability to detect minute changes in renal structure and function is still inconsistent and contentious [16,17]. Furthermore, it is significant to remember that the AKI consensus states that biomarkers are not a substitute for appropriate clinical examination and conventional testing. Instead, they function as supplemental exams that enable the early detection and personalisation of groups that can profit from interventions for the treatment and prevention of cardiovascular risk. We go over the biomarkers that have been suggested for various DKD conditions in the sections that follow [17].

4.1. Conventional Markers

As mentioned, albuminuria and the eGFR, calculated using creatinine, are two common diagnostic procedures for DKD [18]. Nonetheless, a number of clinical variables are predictive of both the advancement of DKD and the drop in glomerular filtration rate [19]. Age, the length of diabetes, glycosylated hemoglobin (HbA1c) levels, systolic blood pressure (SBP), albuminuria, prior eGFR, and the existence of other microvascular problems such as diabetic retinopathy are among these factors. Robust predictive equations to forecast the onset of DKD are not yet available, despite the existence of these factors. This underscores the need for enhanced risk management beyond the understanding gained from epidemiologically based studies on the risk of eGFR decline linked to these factors [20, 21]. Additionally, various diagnostic tests are required to determine the presence of DKD due to the limitations in the use of creatinine and albuminuria as well as the occurrence of the normoalbuminuric phenotype of DKD.

4.1.1. Serum Cystatin C (CysC)

Cystatin C, also known as CysC, is a member of the cysteine protein inhibitor family and is a low-molecular-weight protein with 122 amino acids. The CST3 housekeeping gene, which is found on chromosome 20 (20pl1. 21), encodes it [22]. Protein turnover, pro-protein processing, bone remodeling, antigen presentation, and apoptosis are among the physiological processes in which cysteine cathepsins are involved [23]. The most prevalent and effective endogenous inhibitor of these enzymes' activity within and outside of cells, CysC is involved in a variety of pathological processes, including inflammation and cardiovascular disease [24]. Every nucleated cell in the organism produces and releases CysC into the plasma at the same rate. Its tiny size and positive charge allow it to be freely filtered at the glomerular level, where it is fully reabsorbed and destroyed by the renal tubules without being secreted [25, 26]. Serum CysC may therefore serve as a biomarker for the early detection of AKI and may indicate early alterations in enal function and decline in eGFR. Its estimated sensitivity and specificity are 71% and 53%, respectively, in situations like the first six hours of the postoperative phase following a cardiovascular procedure. When compared to other biomarkers, such as creatinine changes, CysC allows for an earlier diagnosis of AKI; nonetheless, its utility is restricted [27, 28].

4.1.2. Neutrophil Gelatinase-Associated Lipocalin (NGAL)

NGAL, a 25 kDa lipocalin protein, is also referred to as neutrophil gelatinase-associated lipocalin. In response to nephron injury, it is specifically released into the blood and urine by both injured epithelial cells of the nephron and neutrophils [29]. Through the glomerular filtrate, NGAL is separated from plasma and subsequently reabsorbed by endocytosis through

The proximal tubules megalin system. Serum and urine damage indicators were tested in 94 diabetic patients and 45 non-diabetic control subjects in a cross-sectional study. The results showed that NGAL levels were 1.5 times greater in the diabetic patients than in the healthy participants. Additionally, regardless of eGFR, this investigation discovered that markers of tubular and glomerular damage were linked to the prevalence of albuminuria, indicating that both glomerular and tubulointerstitial damage may cause albuminuria [30]. Additionally, NGAL has been suggested as a possible biomarker for recognizing and detecting DKD in its early stages. Diabetes patients may experience tubular injury prior to glomerular disease, and NGAL may be a helpful diagnostic for the early identification of diabetic nephropathy (DN). Changes in early stages of nephropathy can be identified by NGAL before proteinuria. Both serum and urine measures of NGAL were used in a study of 144 individuals with type 2 diabetes mellitus, and both were able to predict the onset of albuminuria, enabling the early diagnosis of DN. Furthermore, Carvalho et al. discovered that patients with type 2 diabetes mellitus who had normal or slightly elevated albuminuria had higher levels of uKIM-1 and urine NGAL, indicating that tubular and glomerular damage might be happening even in the early stages of DKD [31].

4.1.3. Plasma Kidney Injury Molecule – 1 (KIM – 1)

Patients with tubular injury tend to have higher serum levels of injury molecule 1 (KIM-1), a type I transmembrane glycoprotein expressed in the apical membrane of the proximal renal tubular cells [32]. Baseline blood KIM-1 levels, after correcting for baseline urinary albumin-to-creatinine ratio levels, eGFR, and Hb1Ac, were a substantial predictor

of eGFR loss and ESKD during the 5 to 15 years of follow-up in a cohort analysis of individuals with type 1 diabetes mellitus and proteinuria [33]. Furthermore, independent of other factors like systolic blood pressure (BP), HbA1c, AER, eGFR, and TNFR1, plasma KIM-1 levels predicted an early reduction in eGFR and the progression of kidney disease in a cohort study that included 462 patients, of whom 259 had normoalbuminuria and 203 had microalbuminuria [34]. However, the available findings are poor and needs more study to establish its correlation between urinary KIM-1 and DKD [32].

4.1.4. Additional DKD Diagnostic Biomarkers

Numerous biomarkers, linked to inflammatory processes and fibrosis, may be useful in the context of diabetic kidney disease (DKD). These include pigment epithelium-derived factor (PEDF) and fibroblast growth factors 21 and 23 (FGF21, FGF23). Furthermore, a decrease in the eGFR may be correlated with markers of endothelial dysfunction, such as the mid-regional fragment of pro-adrenomedullin (MR-proADM), and markers of cardiac damage, such as N-terminal pro-B-type natriuretic peptide (NT-proBNP). Copeptin, a biomarker produced from arginine vasopressin, is an independent marker of eGFR decline and even the progression to end-stage renal disease (ESRD) and has been linked to the advancement of DKD. Although there is a growing list of biomarkers that may be useful in DKD, there hasn't been any clinical confirmation of these indicators [35].

4.2. Biomarkers for Therapeutics Outcome

It is critical to look for biomarkers that can assess a person's risk prediction and anticipate how they will react to suggested treatments while treating and managing patients with DKD. Nevertheless, several studies that assess and forecast the course of the disease fail to identify patients who are more susceptible to unfavourable side effects or secondary events from the therapeutic intervention under study, or to offer information about how participants responded to the medications under evaluation. Furthermore, the clinical response of individual individuals to medications or treatment procedures can vary widely. As a result, when prescribing a medication, knowing biomarkers of treatment response can save time and money [36]. Commonly employed indicators of clinical response in many research are the decreases in blood pressure, albuminuria, hyperglycemia, or cholesterol levels. These indicators might not be enough on their own, therefore, to identify persons that could benefit from drug usage prior to beginning or who are more likely to have negative effects. In research designs assessing the true impact of new medications, like SGLT2 inhibitors, or earlier interventions, like aldosterone receptor antagonists, surrogates of therapeutic response have demonstrated limitations. Angiotensin-converting enzyme II polymorphisms have been shown to predict populations with varying degrees of pharmacological response [37]. Therefore, a clinical issue is to define improved indications of therapy response. Potential therapeutic targets and prognostic markers have been found through the investigation of pathophysiological mechanisms during DKD, particularly inflammation, which presents chances to expand therapy options for these patients [3]. The innate immune response's activation of neutrophil processes, which results in DNA decondensation and histone citrullination by PAD-4, a histone deaminase, is of special interest. As a result, neutrophil proteases such myeloperoxidase (MPO) and neutrophil elastase (NE) are secreted together with DNA, histones, and other components. It has been suggested that NETs are mechanisms that, independent of an infection response, promote the development of DKD and cardiovascular illnesses through inflammation. According to recent studies, blocking NETs may be a novel target for treatment as well as a biomarker for DKD prognosis and follow-up [38].

A continuous process is required for the identification and investigation of biomarkers for prognostic purpose, with metabolomic and proteome analysis being used to pinpoint clinically significant molecules.

4.3. Prognostic and Monitoring Biomarkers

Let's start by talking about tubular injury biomarkers, which include L-FABP, NGAL, α-1-microglobulin, NAG, cystatin C, and KIM-1 [4]. One of the most researched markers is KIM-1; studies have included a prospective cohort study (n = 1156) using banked baseline plasma samples from participants in randomised controlled trials of early (ACCORD) and advanced (VA NEPHRON-D) DKD, as well as a nested case–control study (n = 190 cases of incident DKD and 190 matched controls) [59]. According to the findings of these investigations, KIM-1 is a reliable indicator of glomerular filtration rate reduction in both early and severe DKD [39]. Furthermore, elevated plasma levels of KIM-1, TNFR-1, TNFR-2, MCP-1, suPAR, and YKL-40 were linked to an increased risk of DKD development in the Chronic Renal Insufficiency Cohort (CRIC) Study, which included 894 patients; TNFR-1 is covered in more detail in a later section [40]. To find compounds of clinical significance, more study on therapeutic response biomarkers—such as proteome and metabolomic responses—is still required. Finding biomarkers for tubular damage, oxidative stress, inflammation, and fibrosis holds the potential for identifying DKD high-risk populations and creating successful intervention and prevention plans. Nevertheless, more research is required to determine the clinical use of these indicators and to track the effectiveness of novel compounds created to treat diabetes mellitus.

5. Application Barriers of Novel Biomarkers

The development of medicine has led us to this stage, where molecules that can aid in subpopulation classification and therapeutic intervention optimization are being sought after in order to develop personalized intervention strategies. However, a lot of the information now available regarding biomarkers for DKD is based on research conducted on animals, cells, and in vitro, and the findings of large population studies remain debatable [35].

The cost-effectiveness of employing these biomarkers is an additional important consideration that is outside the purview of this study. The restricted global availability of these markers hinders their extensive application. Furthermore, it is critical to take into account the possible variability arising from diagnostic test studies and the execution of each test, since these factors may change how the results are interpreted [41].

Finding appropriate biomarkers for diagnosis, treatment response, follow-up, and prognosis becomes more difficult as a result of new research showing that diabetes mellitus (DM) can impair biomarkers' ability to predict the onset of kidney disease [42]. However, a number of obstacles, including the cost, lack of approval from national and international regulatory organisations, inconsistency in testing methodologies and findings, and the availability of test platforms, limit the adoption of these biomarkers [43].

6. Conclusion

New DKD therapy possibilities have emerged recently, and efforts are being made to find possible therapeutic targets for prognosis, follow-up, and prevention. But further research is required to prove these biomarkers' usefulness, thus their application in clinical practice is still in its early stages. However, the creation of new compounds and therapeutic approaches is encouraging, and it is anticipated that in the future, medical professionals will have greater access to a greater variety of efficient and customised interventions for DKD patients.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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