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Review Article

Early Laboratory biomarkers for the Quick Detection of Diabetic kidney Disease.

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Abstract

The significance of early identification of Diabetic Kidney Disease (DKD), a significant complication leading to End-Stage Kidney Disease (ESKD), is highlighted by the increasing frequency of diabetes worldwide. Using search phrases such as "diabetic kidney disease," "early biomarkers," and "laboratory markers," this study synthesizes material from PubMed, Medline, and Google Scholar to examine early laboratory biomarkers for quick Diabetic Kidney Disease (DKD) identification. The ability to detect early DKD is limited by the use of conventional markers such as albuminuria and Estimated Glomerular Filtration Rate (eGFR). Reflecting the underlying inflammatory processes, inflammatory biomarkers such as Monocyte Chemoattractant Protein-1 (MCP-1) and Tumor Necrotic Factor-Alpha (TNF-α) have emerged as possible early indications of DKD development and progression. Furthermore, tubular damage-related indicators including Kidney Injury Molecule-1 (KIM-1) and Vitamin D-Binding Protein (VDBP) have the potential to identify early renal impairment. Beta-2 Microglobulin (B2M) and urine type IV collagen are examples of glomerular damage indicators that are linked to structural abnormalities in DKD, which may help with early identification. Pentosidine and the oxidized DNA nucleoside 8-oxodG are two examples of oxidative stress indicators that show promise in predicting macrovascular and microvascular problems in DKD. These biomarkers provide light on the etiology and course of DKD, giving medical professionals useful instruments for prompt intervention and treatment.

Introduction

Globally, the incidence of diabetes is still rising quickly, and by 2045, it is predicted to affect about 700 million people [1]. One of the main causes of End-Stage Kidney Disease (ESKD) and Chronic Kidney Disease (CKD) worldwide is diabetes [2]. Up to 40% of diabetics have Diabetic Kidney Disease (DKD), which is linked to a considerable risk of morbidity and death, especially from ESKD and Cardiovascular Disease (CVD) [3] Two well-established indicators of kidney function are albuminuria and Estimated Glomerular Filtration Rate (eGFR) [4] However, a rising body of research has cast doubt on their validity as DKD indicators, raising concerns about their usefulness in recent years [5]. Now that it is well known that DKD may develop into ESKD without first causing an increase in albuminuria, albuminuria is a less accurate indicator of the disease's development. Furthermore, a poor predictor of early kidney function decrease in Type-1 Diabetes (T1D), microalbuminuria is prone to swings between normoalbuminuria and microalbuminuria, which is considered an early sign of DKD [6] Conversely, measured GFR (mGFR) is not well reflected by eGFR, particularly when mGFR is more than 60 ml/min/1.73 m2, which may result in a mistaken categorization of kidney function. A possible function for cystatin C, either alone or in conjunction with creatinine, has been suggested by some research, casting doubt on the efficacy of using blood creatinine as a surrogate measure for eGFR [7]. The search for the identification

of DKD biomarkers has received a lot of interest lately. It has been observed that a number of biomarkers are associated with eGFR and albuminuria, or that they perform better in terms of prediction or diagnosis than eGFR and albuminuria. These have mostly been identified as biomarkers connected to the kidney damage and inflammatory pathways of DKD [12]. Research on biomarkers has entailed assessing one or more panels of potential indicators. Recent breakthroughs in the fields of proteomics, metabolomics, and genomes have changed the landscape of biomarker identification and shown promise for DKD [8]. These innovative methods make it possible to examine a significant quantity of data on the disease's molecular cause, which makes them useful instruments for comprehending complex biological systems. One such instance is the urine CKD273 proteomic classifier panel, which consists of 273 peptides and has shown a great deal of promise in the prediction of renal outcomes in diabetes [9].

Methodology

Using resources including PubMed, Medline, and Google Scholar, a thorough literature search was carried out to investigate early laboratory biomarkers for the quick diagnosis of Diabetic Kidney Disease (DKD). Throughout the search, terms including "diabetic kidney disease," "early biomarkers," "laboratory markers," "diabetes mellitus," and "kidney function tests" were used. The inclusion criteria were peer-reviewed publications, review papers, and clinical research studies that focused on laboratory biomarkers for the early identification of DKD. Research examining the effectiveness, benefits, and results of several laboratory markers in the early identification of DKD were taken into consideration for the review.

Inflammatory biomarkers in DKD

It is acknowledged that inflammation plays a significant role in the development of DKD [10] Pro-inflammatory cytokines, chemokines, adhesion molecules, different growth and nuclear factors, and other molecules are involved in the inflammatory response. These molecules together provide the molecular signature of inflammation. Several biomarkers have been studied, including Vascular Cell Adhesion Molecule-1 (VCAM-1), adhesion molecules, C-Reactive Protein (CRP), monocyte chemoattractant protein-1 (MCP-1), interleukins-1,6,8,17,18,19, and many others. Inflammatory cytokines also include Tumor Necrosis Factor Receptors (TNFRs). This is an appealing route to search for new biomarkers since the large number of biomarkers not only shows the existence of the inflammatory processes involved in DKD, but also their complexity [11]. One important cytokine implicated in the etiology of Diabetic Kidney Disease (DKD) is tumor necrotic factor-alpha (TNF-α). It contributes to apoptosis, inflammation, and changes in intraglomerular blood flow since it is expressed in glomerular and tubular cells. According to a meta-analysis conducted by Qiao et al., T1DM patients exhibit considerably higher levels of TNF-α in comparison to healthy controls [12]. Additionally, it has been shown by Navarro JF et al. that serum TNF-α is raised in patients with advanced renal impairment and is correlated with the excretion of urine proteins, indicating a significant role for this cytokine in the beginning of proteinuria in these individuals [13].

Moreover, TNF-α has been connected to diabetes patients' microvascular and macrovascular problems, such as diabetic [14]. As a result, TNF-α levels in the blood and urine might be useful biomarkers to determine the extent of microalbuminuria and renal impairment in diabetics. DKD development is significantly influenced by tumor necrotic factor-alpha receptors, such as TNF-α receptor 1 and TNF-α receptor 2. These receptors contribute to renal failure and the ultimate development of End-Stage Renal Disease (ESRD) via being implicated in inflammatory pathways and apoptosis [15]. Research has shown that there are robust associations between microalbuminuria and serum TNF-α receptors in individuals with type 1 and type 2 diabetes, suggesting that these receptors may serve as prognostic indicators for the advancement of the illness (Purohit et al. 2018) [16,17]. Furthermore, TNF-α receptors have been linked to diabetic retinopathy, highlighting their significance in microvascular problems related to diabetes. The pro-inflammatory cytokine Monocyte Chemoattractant Protein-1 (MCP-1) is also connected to the etiology of diabetic kidney disease. MCP-1, which is produced by renal epithelial cells and mononuclear leukocytes, is involved in tubular atrophy, glomerular damage, and renal inflammation [18]. Patients with diabetes have been shown to have elevated urine MCP-1 levels, especially in those who have microalbuminuria and increasing renal deterioration [19]. MCP-1 could be a useful marker for anticipating diabetes microvascular problems and early renal failure. Hyperglycemia induces Connective Tissue Growth Factor (CTGF), which is linked to renal fibrosis and the formation of extracellular matrix in Diabetic Kidney Disease (DKD). Patients with diabetes have been shown to have elevated urine CTGF levels, especially if they are at a higher risk of developing end-stage renal disease and have progressive renal dysfunction [20]. In addition to being a predictor of diabetic retinopathy, CTGF may function as an independent predictor of ESRD and mortality in DKD. One important immunoregulatory cytokine linked to mesangial proliferation in DKD is interleukin-6 (IL-6). Even before albuminuria develops, studies on diabetic patients have shown increased blood IL-6 levels, which have been linked to macrovascular problems and the advancement of the illness [21,22]. Elevated IL-6 levels may act as indicators for the beginning of microalbuminuria, early progressive renal deterioration, and the prediction of macrovascular problems in diabetes. In two studies including patients with Type-2 Diabetes (T2D), substantially greater levels of ICAM-1 were found in macroalbuminuria and microalbuminuria compared to normoalbuminuria and controls, $p = 0.00140$ [23,24]. In contrast, no significant difference in ICAM-1 was identified in T1D participants with microalbuminuria and normoalbuminuria, $p > 0.0542$. Additionally, a research with

1950 T2D participants reported no correlation of ICAM-1 with both eGFR, p = 0.506 and albuminuria, p = 0.06143 [25] Aside from ICAM-1 and CRP, the other often reported inflammatory biomarkers include MCP-1, IL-6 and TNFRs .

Unlike with ICAM-1 and CRP, consistent correlation was established for these biomarkers with altered kidney function in diabetes. For instance, a Japanese research revealed substantial correlation of both TNFR1 (OR 2.32; p < 0.001) and TNFR2 (OR 2.40; p < 0.001) with eGFR <60 ml/min/1.73 m2 [26] Other inflammatory biomarkers studied, namely the adhesion molecules VCAM-1 and Activated Leucocyte Cell Adhesion Molecule (ALCAM), Cluster Of Differentiation 36 (CD36) which is expressed by various cells including monocytes and Platelets, Pentraxin 3 (PTX-3) an acute phase inflammatory protein, and the cytokines IL-1, 8, 9, 17, 18 and 19, have also exhibited significant association with DKD [27,25].With respect to ESKD, a notable publication by Niewczas et al. identified 17 kidney risk inflammatory signature (KRIS) proteins of which five, namely TNFR-1, TNFRSF-27, IL-17F, TNFSF-15 and chemokine ligand 15 (CCL15) were found to predict progression to ESKD over 10 years, with a combined hazard ratio (HR) > 1.20, p < 0.1 [28]. Of the five markers, TNFR-1 displayed the best predictive potential for ESKD boosting the C-statistic from 0.81 to 0.84 which was verified in three different cohorts encompassing both T1D and T2D participants. The C-statistic or Area Under The Receiver Operating Characteristic (AUROC) is a number ranging from 0.5 to 1 where any value near to 1 signifies that a biomarker or prediction model is successful at identifying persons at high risk of developing the endpoint or outcome of interest [29].

Biomarkers related to tubular damage

The plasma protein known as Vitamin D-Binding Protein (VDBP) is involved in a number of physiological processes in the body, such as the immune system, inflammation, and the transportation of vitamin D3 metabolites through the bloodstream. It also binds and absorbs actin. Increased excretion of VDBP in urine was linked to tubular dysfunction, according to Tian et al. [30]. Consequently, it is believed that individuals with diabetic renal disease may similarly have an increase in VDBP excretion. According to their research, as compared to the healthy control group, type-2 DM patients with varying degrees of albumin secretion had a considerably higher quantity of VDBP in their urine. These outcomes matched those of earlier research. In addition to increased urine, the microalbuminuria group also had substantially higher VDBP concentrations. VDBP in serum and urine demonstrates a correlation with the UACRProximal tubular epithelial cells express KIM-1, a transmembrane protein with an immunoglobulin-like domain and a mucin domain. It may be used as a marker to assess renal tubular damage in individuals with diabetic kidney disease [31]. According to Gohda et al, KIM-1 serum concentration was significantly higher than KIM-1 urine concentration in individuals with renal insufficiency and was associated with a superior eGFR value [32]. Moreover, there is a correlation between the length of time a person has had diabetes and the level of KIM-1 in their blood; people with diabetes for less than five years had higher levels of this marker. According to the findings, KIM-1 may be used as a biomarker in the early stages of diabetic kidney disease. The potential of Neutrophil Gelatinase-Associated Lipocalin (NGAL) as a biomarker for diabetic kidney disease is covered in three publications in this review. Research has been done on its potential as a biomarker for diabetic kidney disease by Kaul et al. and Li et al. [33,34]. Both studies' findings showed that as diabetic kidney disease worsened, the amount of NGAL in urine rose. The results of correlation analysis indicate a relationship between NGAL and eGFR and albuminuria. Furthermore, individuals with diabetic kidney disease also showed higher levels of NGAL in their serum and plasma. Cellular toxicity in diabetics may result from megalin's endocytosis of Advanced Glycation End Products (AGEs) in proximal tubular epithelial cells. Megalin's tubular biomarker studies revealed a correlation between the severity of diabetic kidney disease and elevated megalin concentrations in urine [35].

Biomarkers related to glomerular damage

In diabetic kidney disease, beta-2 microglobulin (B2M) has shown a potential capacity to identify glomerular injury. Patients with diabetes who had normal renal function (eGFR of 90 mL/min/1.73 m2) had higher B2M [36]. The incidence of glomerular structural abnormalities, particularly in mesangial cell failure, was linked to Glypican-5 and Smad1. According to an in vivo investigation, mice with diabetes were shown to have considerably higher levels of GPC5, particularly in the kidney podocytes and mesangial cells. GCP5 concentrations were significantly higher in diabetic patients than with the healthy control group. Following a 52-week observation period, GCP5 was shown to have a robust connection with reduced eGFR values (r = −0.786) and albumin secretion (r = 0.346) in individuals with diabetic renal disease. As a result, GCP5 may be used as a biomarker for kidney damage caused by diabetes [31]. However, further research is required to determine the mechanism behind GCP5's correlation with other clinical indicators. Urinary type IV collagen was statistically linked with both the tubulointerstitial damage score and the mesangial expansion score, indicating that the pathogenic processes of diabetic kidney disease are represented in the rise of this protein. As the illness advanced, Tomino et al. found in an Asian multicenter research that urine Type IV collagen gradually increased from normo-micro-macroalbuminuric phases [37]. With overt proteinuria excluded, Ijima et al. examined the urine type IV collagen in the normo-microalbuminuric group.

Microalbuminuria occurred in the normoalbuminuric group with a greater amount of urinary type IV collagen excretion after a year of follow-up. The results of the aforementioned research point to the significance of type IV collagen as a biomarker for microalbuminuria onset diagnosis.Furthermore, Morita et

al. contend that type IV collagen was independently linked to microalbuminuria in the T1DM group [38]. Araki S et al., however, found no evidence of a substantial alteration in type IV collagen with the advancement of DKD in a follow-up research including patients with type 2 diabetes [39]. But type IV collagen serum levels were shown to be greater in diabetic retinopathy, suggesting a role for type IV collagen in the prognosis of microvascular problems [40]. Urinary type 1V collagen is a predictor of early start and disease progression in individuals with type 1 and type 2 diabetes, according to the research stated above. Its increased content in the serum signals the beginning of diabetic nephropathy. Due to their ability to keep klotho in a balanced state throughout the body, the kidneys are crucial to this process. The soluble Klotho (sKlotho) concentration was observed to drop in the early stages of the illness but to continue to decline as the disease advanced in a cross-sectional examination of individuals with chronic renal failure [41] Patients with low sKlotho concentrations decreased their eGFR values from baseline more quickly than patients with greater concentrations, according to a research done on patients with diabetic kidney disease [42]. On the other hand, Bob et al. investigation produced inconsistent findings. In individuals with eGFR values <60 mL/min/1.73 m2, sKlotho shown an increase in concentration [43].

Since commercially available kits lack uniformity, it is assumed that the variances in the study's findings are the consequence of technical differences in the biomarker measurement process. Furthermore, it's important to keep in mind that when a condition worsens, the concentration of biomarkers does not necessarily drop. Consequently, further research is required to ascertain if Klotho can forecast the long-term course of diabetic kidney disease [41]. Changes in the concentration of biomarkers in urine, serum, and plasma suggest that these indicators are involved in several disease pathogenesis processes, including inflammatory events and structural changes in the tubules and glomerulus. Furthermore, the individual biomarkers included in this study are linked to either lower eGFR levels or albumin excretion in the urine. When discovered in its soluble form in plasma, fibrillar protein fibrnectin, which is present on cell surfaces, is linked to constriction of the glomerular extracellular matrix. Research has shown that in diabetes individuals, it is upregulated in the glomerulus's capillaries and mesangium [41]. From normoalbuminuric to microalbuminuric individuals, plasma fibronectin levels have been shown to gradually rise, with a notable increase linked to overt proteinuria. Urinary Fibronectin (U-FN) has been shown to have predictive value for both renal and vascular issues. It has been associated with micro- and macrovascular sequelae, including retinopathy, neuropathy, and cardiovascular events in diabetic patients [44]. A component of mesangium and glomerular basement membranes, laminin has been linked to the growth of the mesangial matrix in Diabetic Kidney Disease (DKD) [45]. Research has shown that people with normoalbuminuria had greater levels of laminin, indicating that laminin may be a useful diagnostic for predicting albuminuria [46]. Diabetic retinopathy has been linked to elevated serum laminin levels, suggesting a role for laminin in microvascular problems [47]. According to these results, serum laminin may be used as a marker to detect the beginning and development of diabetic microangiopathy and DKD. Cystatin C, often known as CysC, is a low-molecular-weight protein that has gained attention as a possible substitute indication for Glomerular Filtration Rate (GFR) estimation [48]. Research has shown the diagnostic value of serum CysC in individuals with normoalbuminuria, indicating its ability to predict renal impairment prior to the manifestation of symptoms [30]. In patients with type 1 and type 2 diabetes mellitus (DM) and chronic kidney disease (CKD), serum CysC has also been shown to be a predictor of the development of end-stage renal disease (ESRD) [49]. Furthermore, in patients with type 2 diabetes, serum CysC has been linked to retinopathy and cardiovascular risk, indicating that it may serve as a predictor of both microvascular and macrovascular consequences of the disease [50]. The glomerular basement membrane's (GBM) negative charge and perm selectivity are largely attributed to GAGs, which include heparan sulfate [51]. These functional groups are lost as a consequence of endothelial dysfunction in DKD, which causes hyperfiltration and albuminuria [51]. Research has shown that diabetic patients with microalbuminuria and macroalbuminuria excrete more GAGs—especially heparan sulfate—in their urine than those with normoalbuminuria, which may indicate that GAGs are predictive of microalbuminuria [52]. Additionally, there is evidence linking the examination of urine GAG to diabetic retinopathy, suggesting that this marker may have predictive value for microvascular problems associated with diabetes [53].

Biomarker of oxidative stress

Studies using mechanistic and epidemiological evidence indicate that oxidative stress is a major mediator of problems and progression. As a result, markers associated with ROS generation offer a great deal of promise for DKD stage stratification. Oxidized DNA nucleoside 8-oxodG is created in live cells as a result of oxidative stress. Urinary 8-oxodG has been linked to an increased risk of diabetes, atherosclerosis, and cancer, according to a number of studies [54]. In a research including T2DM patients with diabetic nephropathy, Xu et al. discovered that individuals with microalbuminuria had greater urine 8-oxodG levels [55]. Patients with greater urine 8-oxodG levels had significantly faster development of diabetic kidney disease, according to clinical trial with a 5-year follow-up [56]. It has been shown that urinary 8-oxodG has a pathogenic role in the development of diabetic retinopathy in patients with both T1DM and T2DM [57]. According to Etiane et al., 8-oxodG has an AUC of 0.836, making it a diagnostic tool for assessing microvascular problems in diabetes patients [58]. Moreover, this marker has been linked to macrovascular problems in type 2 diabetes. According to the aforementioned research, urine 8-oxodG excretion may be a reliable indicator of the onset

of microvascular and macrovascular problems associated with diabetes as well as the course of the illness.

The covalent interaction of amino groups with the glucose moiety results in the formation of pentosidine, an advanced glycoxidation product [59]. Serum pentosidine levels were shown to be more pronounced in advanced stages of nephropathy and microalbuminuria by Miura et al. (Miura et al. 2003) [60]. Patients with microalbuminuria and an early reduction in GFR had greater excretion in their urine, according to Bruce A. et al. [61]. It has been shown that diabetic individuals with elevated pentosidine levels are independent predictors of cardiovascular disease, all-cause mortality, and diabetic retinopathy 62]. According to these data, measuring the amount of pentosidine in serum and urine may serve as a foundation for identifying individuals who are susceptible to an early drop in GFR and may also prove to be a useful biomarker for the micro- and macrovascular problems associated with diabetes.Numerous clinical research has focused on uric acid's role in the prognosis of DKD since it is created by purine metabolism and has been shown to have an independent role in predicting the course of the disease. Early hyperuricemia is a significant predictor of DKD development, according to research by Bartakova et al. [63]. According to an analysis by Zoppini et al., hyperuricemia, which is thought to be an independent risk factor in the progression of the disease and a strong predictor of GFR decline, was associated with a significantly higher cumulative incidence of CKD with GFR decline among T2DM; additionally, T1DM with higher serum uric acid levels developed persistent macroalbuminuria [64]. Based on this data, individuals with type 1 and type 2 diabetes may be able to use serum uric acid as an independent predictor of the development of macroalbuminuria in the future.

Conclusion

The study concludes by highlighting the significance of early test indicators in the prompt identification of Diabetic Kidney Disease (DKD). By investigating indicators for inflammation, tubular damage, glomerular damage, and oxidative stress, this work offers potential paths for improving DKD diagnosis and treatment. By providing prospective targets for early intervention techniques and significant insights into the etiology of diabetic kidney disease, these biomarkers have the potential to improve patient outcomes in the long run.

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