Fetuin-A as a Biomarker for Diabetic Nephropathy: Insights and Clinical Implications

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Abstract

Diabetic nephropathy (DN) remains one of the leading causes of end-stage renal disease globally, representing a major microvascular complication of diabetes mellitus. Early detection and intervention are critical for slowing disease progression and reducing morbidity and mortality. In recent years, the hepatokine glycoprotein Fetuin-A has emerged as a potential biomarker for DN, providing insights into its pathophysiological role in kidney damage among diabetic patients. Fetuin-A, primarily produced in the liver, plays a dual role in metabolic regulation and inflammation, both of which are central mechanisms in the development of DN. Elevated serum Fetuin-A levels have been associated with insulin resistance, chronic inflammation, and vascular calcification, all of which contribute to the progression of diabetic kidney disease. Recent studies have demonstrated a significant correlation between increased Fetuin-A levels and renal function, albuminuria, and declining glomerular injury in patients with type 2 diabetes mellitus (T2DM). Additionally, Fetuin-A interacts with key signaling pathways, including the insulin signaling cascade and inflammatory cytokines, which are implicated in the pathogenesis of DN. Its ability to modulate mineral metabolism and prevent ectopic calcification in the kidneys further highlights its complex role in renal health and disease. Despite promising findings, the exact mechanistic pathways linking Fetuin-A to DN remain incompletely understood. Some studies have reported conflicting results, suggesting the possibility of context-dependent effects of Fetuin-A depending on the stage of diabetes and nephropathy. This underscores the need for further longitudinal studies and larger patient cohorts to validate Fetuin-A as a reliable biomarker for DN diagnosis, disease monitoring, and therapeutic targeting. Clinically, the measurement of serum Fetuin-A levels could provide an additional tool for risk stratification and early intervention in diabetic patients predisposed to

nephropathy. Furthermore, targeting Fetuin-A-related pathways may open novel therapeutic avenues to mitigate renal injury in diabetic individuals.
This review aims to summarize the current evidence regarding the association between Fetuin-A and diabetic nephropathy, elucidate its biological roles in disease progression, and explore its potential utility as a biomarker and therapeutic target. Future research directions and clinical implications are also discussed to provide a comprehensive understanding of Fetuin-A's role in diabetic kidney disease.

Keywords: Fetuin-A, diabetic nephropathy

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Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and impaired insulin secretion, leading to hyperglycemia [1]. The global prevalence of T2DM has been steadily increasing over the past few decades, largely driven by rising obesity rates, sedentary lifestyles, and aging populations [2]. According to the International Diabetes Federation (IDF), approximately 537 million adults were living with diabetes in 2021, with T2DM accounting for over 90% of these cases [3]. The disease imposes significant economic and healthcare burdens, particularly in low- and middle-income countries where healthcare systems are often ill-equipped to manage chronic diseases effectively [4].

The incidence of T2DM varies significantly across regions and populations, with higher rates observed in urban areas compared to rural ones [5]. Genetic predisposition, ethnicity, and environmental factors all play pivotal roles in determining susceptibility to T2DM [6]. Studies have shown that individuals of South Asian, Middle Eastern, and African descent are at higher risk compared to Caucasians [7]. Additionally, lifestyle factors such as poor dietary habits, physical inactivity, and excessive alcohol consumption contribute significantly to the rising incidence of T2DM [8]. Public health interventions targeting modifiable risk factors are essential for reducing the burden of this disease [9].

Diagnosing T2DM is primarily based on plasma glucose criteria or glycated hemoglobin (HbA1c) levels [10]. The American Diabetes Association (ADA) recommends diagnosing diabetes if fasting plasma glucose (FPG) is ≥126 mg/dL, 2-hour plasma glucose is ≥200 mg/dL during an oral glucose tolerance test (OGTT), or HbA1c is ≥6.5% [11]. Symptoms of hyperglycemia, such as polyuria, polydipsia, and unexplained weight loss, combined with a random plasma glucose level of ≥200 mg/dL, also confirm the diagnosis [12]. HbA1c is particularly useful as it provides an average measure of blood glucose control over the past two to three months [13].

Screening for T2DM is recommended for individuals with risk factors such as obesity, family history of diabetes, hypertension, dyslipidemia, and a history of gestational diabetes [14]. Early diagnosis is crucial, as many individuals with T2DM remain asymptomatic for years, leading to delayed treatment

initiation and an increased risk of complications [15]. Routine screening programs, especially in high-risk populations, can facilitate early intervention and prevent long-term complications [16].

Obesity remains the most significant modifiable risk factor for T2DM, with excess adipose tissue contributing to insulin resistance and chronic low-grade inflammation [17]. Visceral fat, in particular, is strongly associated with impaired glucose metabolism [18]. Weight reduction through lifestyle interventions, including a balanced diet and regular physical activity, has been shown to significantly reduce the risk of developing T2DM [19]. Pharmacological treatments, such as metformin, may also be considered in high-risk individuals [20].

The pathophysiology of T2DM involves complex interactions between genetic and environmental factors, leading to insulin resistance in peripheral tissues and beta-cell dysfunction in the pancreas [21]. Chronic hyperglycemia and lipotoxicity exacerbate beta-cell failure over time, contributing to disease progression [22]. Pro-inflammatory cytokines and oxidative stress play significant roles in this process, highlighting the importance of anti-inflammatory therapies in managing T2DM [23].

In recent years, continuous glucose monitoring (CGM) and advanced diagnostic tools have improved our ability to detect and manage T2DM more effectively [24]. CGM provides real-time glucose readings, enabling better glycemic control and reducing the risk of hypoglycemia [25]. Point-of-care testing for HbA1c has also become widely available, offering a convenient and reliable diagnostic tool in both clinical and community settings [26].

The economic burden of T2DM is substantial, with costs associated with medical care, medications, and diabetes-related complications [27]. Indirect costs, including loss of productivity and premature mortality, further contribute to the societal impact of the disease [28]. Effective prevention and early intervention strategies are critical to reducing healthcare expenditures and improving patient outcomes [29].

T2DM is associated with numerous complications, including cardiovascular disease, neuropathy, retinopathy, and nephropathy [30]. Early diagnosis and optimal glycemic control are essential for preventing or delaying these complications [31]. Regular monitoring of blood glucose, blood pressure, and lipid profiles is crucial for managing the disease effectively [32].

The role of primary care physicians in managing T2DM cannot be overstated. Early diagnosis, patient education, and consistent follow-up care are critical components of effective diabetes management [33]. Multidisciplinary care teams, including dietitians, diabetes educators, and endocrinologists, play a significant role in improving outcomes [34].

Technological advancements, including digital health platforms and telemedicine, have improved access to diabetes care, particularly in remote and underserved areas [35]. Smartphone applications for self-monitoring of blood glucose, medication reminders, and lifestyle tracking have empowered patients to take an active role in managing their condition [36].

Preventive measures, including community-based education programs and health promotion campaigns, are essential for reducing the incidence of T2DM [37]. Awareness about the importance of regular physical activity, healthy eating, and routine health check-ups can significantly impact diabetes prevention efforts [38].

In conclusion, T2DM remains a significant global health challenge with rising incidence rates driven by lifestyle and environmental factors. Early diagnosis and effective management are crucial for preventing complications and reducing healthcare costs. Continued research, innovative technologies, and public health interventions are essential for addressing the growing burden of T2DM worldwide [39].

Diabetic nephropathy (DN) is one of the most significant microvascular complications of diabetes mellitus, contributing substantially to end-stage renal disease (ESRD) worldwide. Its prevalence has been steadily increasing, in parallel with the global diabetes epidemic. Studies indicate that approximately 30-40% of diabetic patients will develop nephropathy during their lifetime, with type 2 diabetes mellitus (T2DM) being the primary contributor to the rising incidence [40]. The condition progresses through well-documented stages, from microalbuminuria to macroalbuminuria and eventually ESRD. Early intervention and routine monitoring are essential for delaying progression and improving patient outcomes, but these measures remain suboptimal in many clinical settings [41].

The pathophysiology of diabetic nephropathy involves a complex interplay of metabolic and hemodynamic factors, leading to structural and functional kidney damage. Hyperglycemia-induced activation of the polyol pathway, formation of advanced glycation end-products (AGEs), and activation of protein kinase C (PKC) play pivotal roles in kidney damage [42]. Additionally, intraglomerular hypertension and podocyte injury further exacerbate glomerular sclerosis and fibrosis. These mechanisms underscore the need for robust biomarkers that can accurately detect and predict disease progression in its early stages [43].

Traditional diagnostic markers for diabetic nephropathy include urinary albumin excretion (UAE), estimated glomerular filtration rate (eGFR), and serum creatinine levels. Microalbuminuria remains the gold standard for early detection, despite its limitations in sensitivity and specificity [44]. Some patients with advanced diabetic kidney disease (DKD) may not exhibit albuminuria, a condition referred to as non-albuminuric DKD, which complicates diagnostic accuracy. Serum creatinine and eGFR are also limited by their dependence on muscle mass and other non-renal factors, highlighting the urgent need for better diagnostic tools [45].

Recent research has focused on identifying novel biomarkers that can improve the early diagnosis and risk stratification of diabetic nephropathy. Biomarkers such as kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and cystatin C have shown promise in identifying kidney damage before significant changes in albuminuria occur [46]. Additionally, urinary exosomal microRNAs and inflammatory cytokines, including transforming growth factor-beta (TGF-β), have emerged as potential candidates for early detection. However, these biomarkers are yet to be fully validated for routine clinical use [47].

Despite these advancements, significant gaps remain in the diagnostic approach to diabetic nephropathy. One major challenge is the lack of universally accepted cut-off values and standardized assays for novel biomarkers. Moreover, the cost and accessibility of advanced diagnostic tools pose barriers to widespread implementation, particularly in resource-limited settings [48]. Another critical limitation is the inability of current biomarkers to differentiate between diabetic nephropathy and

other forms of chronic kidney disease (CKD), which often share similar clinical and biochemical features [49].

Genetic and epigenetic factors are also gaining attention as potential contributors to diabetic nephropathy susceptibility and progression. Genome-wide association studies (GWAS) have identified several genetic loci associated with increased risk of DN, including variants in the ELMO1 and SLC12A3 genes [50]. Epigenetic modifications, such as DNA methylation and histone acetylation, are also implicated in DN pathogenesis. These findings open new avenues for personalized medicine, where genetic and epigenetic profiles could guide early interventions [51].

Current guidelines emphasize the importance of routine screening for albuminuria and eGFR in diabetic patients. However, there is a clear need to incorporate novel biomarkers into existing diagnostic algorithms to improve sensitivity and specificity. Point-of-care testing for these biomarkers could further streamline early diagnosis and monitoring. Integration of artificial intelligence (AI) and machine learning models is also being explored to predict DN risk based on large datasets, potentially revolutionizing the diagnostic landscape [52,53].

Therapeutic strategies for diabetic nephropathy primarily focus on glycemic and blood pressure control, along with the use of renin-angiotensin-aldosterone system (RAAS) inhibitors. Despite these interventions, a significant proportion of patients progress to ESRD, underscoring the limitations of current treatments. Sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RAs) have shown promising renal protective effects beyond glycemic control, offering hope for improved outcomes [54,56].

The heterogeneity of diabetic nephropathy poses a challenge in both diagnosis and treatment. Personalized medicine approaches, incorporating genetic, epigenetic, and biomarker data, are likely to play a pivotal role in addressing these challenges. Collaborative efforts between researchers, clinicians, and policymakers are essential to overcome current barriers and ensure equitable access to advanced diagnostic and therapeutic tools [57,58], diabetic nephropathy remains a major global health concern, with rising incidence and substantial diagnostic challenges. While significant progress has been made in identifying novel biomarkers and therapeutic strategies, further research is needed to bridge existing gaps. Integrating advanced diagnostics, precision medicine, and innovative therapeutic approaches will be crucial in improving outcomes for patients with diabetic nephropathy [59].

Despite extensive research highlighting the role of Fetuin-A in inflammation, insulin resistance, endothelial dysfunction, and vascular calcification in diabetic nephropathy (DN), significant gaps remain in understanding the context-specific dual role of this glycoprotein. Fetuin-A exhibits paradoxical functions, acting as both an anti-calcification agent and a pro-inflammatory molecule. However, the molecular mechanisms governing these opposing actions are poorly understood. There is a critical need to determine the specific pathological conditions, such as different stages of DN or varying degrees of hyperglycemia, under which Fetuin-A exerts protective versus deleterious effects. A clearer understanding of these mechanistic pathways would provide valuable insights into targeted therapeutic interventions.

Genetic and epigenetic factors influencing Fetuin-A expression and function represent another underexplored area. Current studies rarely consider how genetic polymorphisms or post-translational modifications might alter the biological activity of Fetuin-A in DN. Investigating these genetic and epigenetic influences could shed light on individual variations in DN susceptibility and progression, potentially paving the way for personalized medicine approaches in diabetes care.

Furthermore, the interaction between Fetuin-A and other known biomarkers of DN, such as kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and adipokines like adiponectin, remains inadequately studied. While Fetuin-A has been individually linked to various inflammatory and metabolic pathways, its role within a broader biomarker network has not been fully elucidated. A multi-biomarker approach incorporating Fetuin-A may significantly enhance diagnostic accuracy and risk stratification in DN patients.

Therapeutic modulation of Fetuin-A is another promising yet under-researched avenue. While preliminary studies have suggested that lifestyle changes and pharmacological interventions, such as SGLT2 inhibitors and GLP-1 receptor agonists, can indirectly influence Fetuin-A levels, there is little evidence on whether direct modulation of Fetuin-A could improve renal outcomes. Rigorous clinical trials are required to explore the therapeutic potential of targeting Fetuin-A pathways for better DN management.

The role of Fetuin-A in pediatric diabetic nephropathy also remains largely unexplored. Early alterations in Fetuin-A levels have been observed in children with diabetes, but age-specific reference ranges and longitudinal studies are lacking. Research focusing on pediatric populations could uncover unique insights into the early stages of DN and provide opportunities for early intervention.

Finally, most existing studies on Fetuin-A and DN are cross-sectional in nature, which limits their ability to establish causal relationships. Longitudinal studies are essential to determine whether elevated Fetuin-A levels precede DN progression or simply reflect ongoing renal damage. Prospective cohort studies are needed to validate Fetuin-A as a reliable predictive biomarker for disease progression and therapeutic response.

Addressing these research gaps will not only enhance our understanding of the multifaceted role of Fetuin-A in DN but also improve its clinical utility as both a diagnostic and prognostic biomarker. Additionally, these insights could open new therapeutic avenues, ultimately contributing to better disease management and improved outcomes for diabetic patients

Fetuin-A, a glycoprotein primarily synthesized in the liver, has emerged as a potential biomarker for diabetic nephropathy (DN), a common complication of diabetes mellitus. Its role in inflammation, insulin resistance, and vascular calcification links it to the pathophysiology of DN. Elevated levels of Fetuin-A have been observed in patients with type 2 diabetes, and its association with renal dysfunction suggests its potential as an early diagnostic marker for DN. This glycoprotein participates in multiple metabolic and inflammatory pathways, making it a significant molecule for understanding disease progression and prognosis [60].

The pathogenesis of diabetic nephropathy involves a complex interplay of hyperglycemia, oxidative stress, and inflammation. Fetuin-A, known to inhibit insulin receptor tyrosine kinase activity,

contributes to insulin resistance, which is a major driver of diabetic complications. Studies have demonstrated that elevated serum Fetuin-A levels correlate with reduced kidney function and increased urinary albumin excretion, suggesting its direct involvement in renal damage [61]. Additionally, Fetuin-A modulates the release of pro-inflammatory cytokines, amplifying the inflammatory response in DN [62].

Inflammation plays a critical role in the onset and progression of diabetic nephropathy. Fetuin-A is a recognized inhibitor of ectopic calcification, but paradoxically, it also stimulates inflammatory pathways via Toll-like receptor 4 (TLR4). This dual role raises questions about the exact mechanisms through which Fetuin-A contributes to DN. Clinical studies have shown that increased Fetuin-A levels are associated with higher levels of C-reactive protein (CRP), further establishing its inflammatory role in DN progression [63].

Beyond its role in inflammation and insulin resistance, Fetuin-A is also implicated in endothelial dysfunction, another hallmark of DN. Elevated Fetuin-A levels impair nitric oxide bioavailability, contributing to vascular dysfunction. This impairment can exacerbate kidney damage by reducing renal blood flow and increasing glomerular pressure. Studies suggest that therapies targeting endothelial function may need to consider the modulatory effects of Fetuin-A on vascular health [64].

Emerging evidence indicates that Fetuin-A levels may serve as a predictive biomarker for the severity of DN. Longitudinal studies have demonstrated a positive correlation between serum Fetuin-A levels and progression from microalbuminuria to overt proteinuria. This relationship highlights the potential utility of Fetuin-A measurements in predicting renal outcomes and tailoring early interventions in diabetic patients [65].

Fetuin-A also interacts with adipokines and other metabolic regulators, adding another layer of complexity to its role in DN. It has been shown to inhibit adiponectin, an anti-inflammatory adipokine with renoprotective effects. Lower adiponectin levels, combined with elevated Fetuin-A, create an imbalance in pro- and anti-inflammatory signals, accelerating renal damage in diabetic patients [66].

The clinical implications of Fetuin-A as a biomarker extend beyond diagnostic utility. Therapeutic strategies aimed at modulating Fetuin-A levels could offer novel approaches for DN management. Preliminary studies suggest that lifestyle interventions, including weight loss and improved glycemic control, may reduce serum Fetuin-A levels, potentially mitigating renal damage [67].

Additionally, pharmacological interventions targeting inflammatory and metabolic pathways associated with Fetuin-A are being explored. Agents such as SGLT2 inhibitors and GLP-1 receptor agonists, known for their renal protective effects, may exert their benefits partially through modulation of Fetuin-A levels. Further studies are needed to clarify these mechanisms and optimize therapeutic strategies [68].

Recent meta-analyses have reinforced the association between Fetuin-A and diabetic nephropathy. Data from diverse populations indicate that higher Fetuin-A levels are consistently associated with poorer renal outcomes. However, variability in study designs, patient demographics, and analytical

methods warrants standardization before Fetuin-A can be universally adopted as a clinical biomarker [69].

Fetuin-A's dual role as both a protective and deleterious factor in DN underscores the need for a nuanced understanding of its biology. While it prevents vascular calcification, its pro-inflammatory and insulin-resistance-promoting properties complicate its therapeutic targeting. Researchers are increasingly focused on identifying specific conditions under which Fetuin-A's protective effects can be maximized while minimizing its harmful consequences [70].

Technological advances in proteomics and metabolomics have enabled more precise measurements of Fetuin-A levels in serum and urine. These tools have facilitated the identification of Fetuin-A isoforms and post-translational modifications, which may have distinct biological activities and clinical implications in DN. Such insights are expected to refine the utility of Fetuin-A as a biomarker [71].

In pediatric populations with diabetes, early alterations in Fetuin-A levels have been reported, suggesting its potential as an early biomarker for DN in younger age groups. This observation highlights the need for age-specific reference ranges and longitudinal studies to confirm its predictive value in pediatric diabetes [72].

Fetuin-A's association with cardiovascular complications in DN patients further enhances its relevance as a biomarker. Cardiovascular disease remains a leading cause of mortality in DN, and elevated Fetuin-A levels are linked to increased arterial stiffness and vascular calcification. Integrating Fetuin-A measurements into cardiovascular risk assessment models may improve patient outcomes [73].

Despite the promising evidence, limitations exist in the current understanding of Fetuin-A in DN. Most studies are cross-sectional, limiting the ability to establish causality. Moreover, the influence of genetic polymorphisms on Fetuin-A expression and function remains poorly understood. Addressing these knowledge gaps is essential for advancing its clinical application [74].

Fetuin-A also shows potential as a therapeutic target. Animal models have demonstrated that genetic or pharmacological modulation of Fetuin-A expression can reduce renal inflammation and fibrosis. Translating these findings into clinical practice, however, requires rigorous human trials [75].

Furthermore, the interplay between Fetuin-A and other biomarkers of DN, such as kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL), needs to be elucidated. A multi-biomarker approach may enhance diagnostic accuracy and prognostic precision [76, 77].

In conclusion, Fetuin-A represents a promising biomarker for diabetic nephropathy, with significant potential in diagnosis, prognosis, and therapeutic monitoring. Its multifaceted role in inflammation, insulin resistance, and endothelial dysfunction positions it as a key player in DN pathophysiology. However, further research is necessary to standardize measurement techniques, clarify mechanisms, and validate clinical applications

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