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PROTEOMIC ANALYSIS OF URINARY PROTEIN MARKERS FOR PREDICTING DIABETIC KIDNEY DISEASE

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Abstract
Diabetic kidney disease (DKD) is a common microvascular complication, affecting 20–40% of individuals diagnosed with type 2 diabetes, leading to high morbidity and mortality rates. DKD is diagnosed based on persistent proteinuria, an albumin-to-creatinine ratio exceeding 30 mg/g creatinine, decreased estimated glomerular filtration rate (eGFR), and progressive decline in renal function. Identifying biomarkers of renal functional damage that can predict kidney disease at early stages and monitor disease progression remains a pressing issue.

Keywords: Serum zinc-alpha-2-glycoprotein (ZAG), diabetic nephropathy (DN), albumin, urinary ZAG, mg/g creatinine, eGFR.

Introduction

The pathogenesis of diabetic kidney disease involves three main components: hemodynamic, metabolic, and inflammatory axes [1,5]. Clinically, DKD is characterized by persistent albuminuria accompanied by progressive reduction in glomerular filtration rate (GFR). An early-stage diagnostic marker for detecting DN is critical, as timely intervention can slow renal function loss and reduce adverse outcomes. DN is diagnosed based on persistent proteinuria, albumin-to-creatinine ratio above 30 mg/g, decreased eGFR, and progressive renal function deterioration. The appearance of small amounts of albumin in the urine, termed

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microalbuminuria, has been accepted as the earliest marker of DN development. Since DN is a leading cause of end-stage renal disease, identifying reliable biomarkers that can guide diagnosis and treatment is of paramount importance. However, it has been reported that a significant portion of renal dysfunction occurs even before microalbuminuria appears [10,12]. Albuminuria is associated with several confounding factors, such as physical exercise, urinary tract infections, acute illnesses, and heart failure. Furthermore, albuminuria has been observed in non-diabetic individuals, indicating that it is not entirely specific for predicting diabetic kidney disease [7].

Thus, there is an urgent need to develop novel non-invasive biomarkers that can assess the risk of future DN or detect the disease at its earliest stages. Given these limitations, additional urinary biomarkers are needed for optimal clinical management of diabetes, which can predict DN at a very early stage, even before microalbuminuria occurs [1,3,4]. Interestingly, in chronic cases of diabetic nephropathy, kidney function correlates better with the degree of tubulointerstitial damage than with glomerular lesions, suggesting that researchers should focus on tubular biomarkers to identify patients with diabetic nephropathy.

There is growing interest in identifying alternative biomarkers that could provide more powerful and rapid means for detecting the progression of diabetic nephropathy. In this context, various researchers have proposed biomarkers reflecting tubular injury.

Zinc-alpha-2-glycoprotein (ZAG) is a 41–43 kDa glycoprotein belonging to the family of major histocompatibility complex-related proteins. ZAG is present in various epithelia and is secreted into multiple bodily fluids. It is known that ZAG stimulates lipolysis by activating adenylate cyclase via a guanosine triphosphate-dependent process through binding to β3-adrenergic receptors.

Proteomic analyses indicate that urinary ZAG levels are elevated specifically in patients with diabetes and may serve as a biomarker for precise and specific clinical assessment of diabetic nephropathy [2,8,9,10]. Immunohistochemical studies have shown that ZAG is primarily expressed in the renal tubules of humans [13,14].

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Currently, it is hypothesized that urinary ZAG concentration may be associated with early stages of diabetic nephropathy progression, before microalbuminuria becomes evident. This can be detected in type 2 diabetes patients prior to significant albuminuria. Interest in using biomarkers for early DN detection arises from the observation that type 2 diabetes patients may already experience renal impairment at diagnosis due to a prediabetic phase. Although microalbuminuria is considered the earliest clinical marker of DN, 29.1–61.6% of individuals with type 2 diabetes may have renal impairment before microalbuminuria appears. Therefore, it is essential to implement diverse strategies for early DN detection in type 2 diabetes patients to slow disease progression and improve outcomes. Elevated urinary biomarkers may be detected in type 2 diabetes patients before significant albuminuria and can serve as early indicators of renal damage in diabetic nephropathy, playing an important role in effective management and treatment approaches. This is also due to the weak correlation between albuminuria and eGFR, as urinary albumin lacks both sensitivity and specificity for detecting early stages of DN.

In the present study, as shown in Table 1, urinary ZAG concentration was significantly elevated in DN patients compared to healthy controls. These new findings suggest that increased urinary ZAG may reflect renal injury earlier than microalbuminuria in patients with diabetic nephropathy and may serve as a potential novel biomarker for this diabetes complication.

Study Objective

To evaluate the diagnostic value of urinary proteomic markers in the early detection of diabetic nephropathy and to assess the significance of these biomarkers in predicting the disease.

Materials and Methods

The study involved 58 patients with type 2 diabetes attending the nephrology department of TMA. Eighteen healthy control subjects, with a mean age of 51.6 ± 8.6 years, also participated. The study was conducted in a multidisciplinary TMA clinic in collaboration with endocrinologists, urologists, and nephrologists.

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Immunoenzymatic, clinical, and biochemical analyses were performed using automated analyzers from Mindray and diagnostic kits from Human BioChemMac, alongside highly sensitive mass spectrometry methods.

As evident from the results (Table 1), urinary ZAG content in examined patients significantly increased to 53.64 ± 5.57 mg/L. In the control group, the mean value was 28.17 ± 2.18 mg/L, approximately twice the baseline level.

Table 1 Urinary Proteomic Marker Levels in Patients with Diabetic Nephropathy, M±m

Parameter	**Healthy Subjects (n=18)**	**Patients with DN (n=58)**
Blood urea nitrogen, mmol/L	5,48 ± 0,45	7,31 ± 0,64
Creatinine, µmol/L	70,13 ± 6,54	86,54 ± 7,47
Body mass index, kg/m²	24,86 ± 2,63	27,83 ± 2.47
C-reactive protein, mg/L	1,18 ± 0,17	2,14 ± 0,19
eGFR, mL/min/1.73 m²	108,24 ± 9,67	104,63± 9,58
Serum zinc-alpha-2-glycoprotein (ZAG), mg/L	22,13 ± 2,46	34,67 ± 2,98*
Urinary ZAG, mg/g creatinine	28.17 ± 2.18	53,64 ± 5,57 *

*Note: * – statistically significant difference, $p < 0.05$ compared with healthy subjects.

Changes in urinary ZAG concentrations observed in the present study may indicate tubular damage that occurs at the early stages of diabetic nephropathy, preceding the processes that lead to microalbuminuria. Consequently, this protein could potentially serve as a biomarker for specific and precise clinical assessment of diabetic nephropathy.

In the next stage of the study, DN patients were stratified into three groups: those with normal albuminuria (urinary albumin-to-creatinine ratio < 30 mg/g, n = 18),

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those with microalbuminuria (30 mg/g < urinary albumin-to-creatinine ratio < 300 mg/g, n = 16), and those with macroalbuminuria (urinary albumin-to-creatinine ratio ≥ 300 mg/g, n = 14).

In our study, urinary ZAG levels were significantly elevated in DN patients compared to the control subjects. Notably, urinary ZAG concentration increased earlier than albuminuria, as evidenced by elevated urinary ZAG in patients with normal albuminuria who still had higher eGFR levels.

These findings suggest that elevated urinary ZAG may reflect renal damage earlier than microalbuminuria in patients with diabetic nephropathy, highlighting its potential as a novel biomarker for assessing this diabetic complication. There were no significant differences in mean urinary ZAG concentration between patients with normal albuminuria and healthy control subjects. However, mean urinary ZAG levels in patients with microalbuminuria (67.48 ± 5.87 mg/g) and macroalbuminuria (81.24 ± 7.98 mg/g) were approximately two to three times higher than those in healthy controls ($P < 0.01$).

Table 2 Urinary Zinc-Alpha-2-Glycoprotein (ZAG) Concentration in DN Patients Relative to Urinary Albumin Levels

Parameter	**Healthy Subjects (n=20)**	**Normoalbuminuria (urinary albumin-to-creatinine ratio < 30 mg/g, n=18)**	**Microalbuminuria (30 mg/g < urinary albumin-to-creatinine ratio < 300 mg/g, n=16)**	**Macroalbuminuria (urinary albumin-to-creatinine ratio ≥ 300 mg/g, n=14)**
Urinary ZAG, mg/g	28,17±2,18	36,23 + 2,56	67,48 ± 5,87*	81,24 ± 7,98*

*Note: * – statistically significant difference, $p < 0.05$ compared with healthy subjects.

Consequently, proteomic studies have suggested that the elevation of urinary ZAG may be associated with the pathogenesis of non-albuminuric diabetic nephropathy, as ZAG is primarily expressed in proximal convoluted and straight tubules.

The changes in urinary ZAG concentrations observed in our study may reflect damage not only to the glomeruli but also to the renal tubules, occurring at the

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early stages of diabetic nephropathy, preceding those processes that lead to microalbuminuria.

Our proteomic analysis data provide the opportunity to identify potential urinary biomarkers for diabetic nephropathy, representing a significant step forward in advancing precise diagnostics and disease characterization. Alternative biomarkers, distinct from urinary albumin and creatinine, can help detect early-stage DN, including protein-based biomarkers present in urine.

Numerous biomarkers identified to date have demonstrated strong diagnostic potential, including urine-based proteomic biomarkers, which have shown excellent promise. Increasingly, clinical laboratories now have access to diagnostic methods capable of independently and accurately predicting microalbuminuria associated with DN.

These proteomic biomarker analyses are often simpler and less invasive than standard diagnostic procedures, potentially reducing the need for kidney biopsy as a primary diagnostic tool for DN. These strategies also provide a theoretical foundation for more reliable treatment approaches and for preventing disease progression.

However, despite such promise, proteomic biomarker panels are not yet routinely implemented in most clinical chemistry laboratories. Further studies focusing on these proteomic biomarkers will guide early and non-invasive diagnosis of DN, allow more reliable patient monitoring, and support improved patient outcomes at multiple levels.

We anticipate that continued research into the role of targeted proteomics in diabetic kidney disease will lead to new breakthroughs in the field, with undeniable clinical value.

Conclusion

This study, involving several dozen patients, highlights the potential of individual biomarker panels in the clinical diagnosis of diabetic nephropathy. The human urinary peptidome database presented here represents an important step toward establishing proteomics as a diagnostic tool in clinical practice.

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It is important to note that proteomic biomarkers are often simpler and less invasive than standard diagnostic methods, potentially reducing the need for kidney biopsy as a primary diagnostic tool for DN. Moreover, they enable more reliable patient monitoring and support improved treatment outcomes at multiple levels.

Conclusions: Identification of these biomarkers will allow for earlier detection of renal functional impairments and help define patient groups that particularly require effective therapeutic interventions.

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