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Biomarkers of diabetic nephropathy detection, today and future

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Introduction

Diabetic nephropathy (DN) is the common cause of mortality due to end stage of kidney failure. According to the International Diabetes Federation's Diabetes Atlas Report in 2015, more than 415 million people suffer from diabetes (1).

Up to 40% of the patients with type I and type II DM present diabetic kidney disease (2). Today early diagnosis of diabetic kidney disease is one of the most important aim of investigators. Biomarkers have a notable importance for the prediction, diagnosis and the therapeutic success of various diseases such as diabetic kidney disease (3). The best source of renal biomarkers are urine and serum, but urine is an ideal source of biomarkers, chiefly for renal diseases and urinary tract.

The most important urinary biomarkers for early diagnosis and progression of diabetic kidney disease that introduced by scientists are illustrated in Table 1.

At present, diagnosis of diabetic kidney disease in clinical settings relies upon the assessment of kidney function, usually by calculating estimated glomerular filtration rate (GFR), and the assessment of renal injury, usually by assessment of urinary albumin-to-creatinine ratio (14).

While albuminuria today remains the gold standard for diagnosing and categorizing diabetic kidney disease, however, it has many limitations. Urinary albumin excretion may also increase for reasons other than diabetic kidney disease such as physical activity, diet pattern, infection, fever, congestive heart failure, marked hyperglycemia, menstruation, and marked hypertension. Serum creatinine levels are also affected by the muscle mass and diet pattern especially meat intake, and therefore may interfere with the GFR calculation (14). Additionally, most recent studies fail to show that changes in microalbuminuria predict nephropathy progression, and there is a contentious, ongoing debate about the predictive value of microalbuminuria, and the relative importance of using microalbuminuria as a renal endpoint in clinical trials. This debate concentrates on three concerns, including (1) a large number of patients with microalbuminuria revert to normal albumin excretion, (2) only a small percentage of patients with microalbuminuria progress to proteinuria, and (3) progressive renal functional decline is already present in one-third of patients that progress into microalbuminuria (4).

Implication for health policy/practice/research/ medical education

According to the limitation of biomarkers in early detection of diabetic kidney disease, it should be remembered that no gold standard biomarker and technique in early detection and diagnosis of diabetic kidney disease was existed. Hence, large longitudinal cohort studies are still required to validate the abilities of the aforementioned novel early diagnosis and prediction techniques.

Keywords: Biomarkers, Diabetic nephropathy, End-stage of renal disease, Diabetic kidney disease

However, unfortunately in diabetic kidney disease, kidney tubular damage develops over years before clinical and laboratory abnormalities like albuminuria, hypertension, or diminishing glomerular filtration rate appear (15), and waiting for clinical or laboratory manifestation of kidney disease before beginning treatment may hinder the attempts that prevent progression to end-stage kidney failure (16). Thus, tubular biomarkers seem to play an important role in the early diagnosis of diabetic kidney disease. In type 2 DM urinary NAG excretion increases proportionally to the duration of diabetes. It occurs much earlier than albuminuria. NAG can be considered as an early tubular biomarker (17). Urinary NAG is the most sensitive biomarker for detecting early damage in diabetic patients (18).

Although numerous investigators mentioned different types of biomarkers in diabetic kidney disease prediction, however all biomarkers have some limitations (14) in early detection of diabetic kidney disease and there are no enough clinical trials studies for validity of these biomarkers.

Conclusion

According to the limitation of biomarkers in early detection of diabetic kidney disease, it should be remembered that, no gold standard biomarker and technique in early detection and diagnosis of diabetic kidney disease was

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Table 1. Urinary biomarkers in diabetic nephropathy

Urinary biomarkers of DN	Example
Markers of glomerular injury	Adiponectin, ceruloplasmin, laminin, transferrin, immunoglobulin G, glycosaminoglycans, lipocalin-type prostaglandin D synthase (L-PGDS), fibronectin, vascular endothelial growth factor/VEGF (4), type IV urinary collagen (5), podocyte number, podocyte-specific proteins (nephrin, synaptopodin) (6).
Markers of tubular injury	Neutrophil gelatinase-associated lipocalin (NGAL)(7), N-acetyl-β-D glucosaminidase (NAG), kidney injury molecule-1 (KIM-1), α1- and β2-microglobulin, liver-type fatty acid binding protein (L-FABP), retinal binding protein 4 (RBP4), angiotensinogen, cystatin C (4).
Biomarkers of kidney fibrosis and inflammation	Collagen type IV, transforming growth factor-β, proinflammatory molecules, chemokines such as monocyte chemoattractant protein-1 (MCP-1), and cytokines such as tumor necrosis factor-α (TNF- α), tumor necrosis factor receptor-1 (TNFR1), interleukin-6 (IL-6), interleukin-18 (IL-18), IL8, IP10, G-CSF, EOTAXIN, RANTES, urinary orosomucoid and BMP7 (3), TGF-β1-to-BMP-7 ratio (8).
Biomarkers of oxidative stress	8-hydroxy- 20-deoxyguanosine (8-OHdG), 8(F2a)-isoprostane, 4-hydroxy-2-nonenal, 3-nitrotyrosine peptides as well as AGEs including carboxymethyl lysine and pentosidine, heart fatty acid binding protein (H-FABP), uUrinary advanced glycation products (UAGE) (3,9).
Proteomics	Urinary (IL-6, IL-8, MCP-1, interferon gamma-inducible protein (IP-10), macrophage inflammatory protein-1δ, inositol pentakisphosphate 2 kinase (IPP2K), zona occludens 3 (ZO-3), cadherin-like protein FAT tumor suppressor 2, three peptides that were decreased, including α-1(IV) and α-1(V) collagen and tenascin-X (10,11). Specific collagen fragments, β2-microglobulin, ubiquitin, proinflammatory cytokines, RBP4, transthyretin, apolipoprotein A1, apolipoprotein C1, cystatin C (12).
Micro RNA	miR-15b, miR-34a and miR-636 (13).

existed. Hence, large longitudinal cohort studies are still required to validate the abilities of the aforementioned novel early diagnosis and prediction techniques.

By reviewing of mechanisms involved in diabetic kidney disease pathogenesis (19), biomarkers and the fact that tubular injury in diabetic kidney disease take place years before changes of laboratories urinary and serum tests, theoretically may be said that sum of three biomarkers; urinary NAG (tubular biomarker), urinary AGEs (pentosidine) and microalbuminuria with together are the best reliable biomarkers for early detection, diagnosis and treatment of diabetic kidney disease. This theory will be studied in future as clinical trial research for validating of these biomarkers in DN early detection.

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Authors' contribution

MT was the single author of the manuscript.

Conflicts of interest

The author declared no competing interests.

Ethical considerations

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