Western European Journal of Medicine and Medical Science
Volume 1, Issue 3, November, 2023
https://westerneuropeanstudies.com/index.php/3
ISSN (E): 2942-1918 Open Access| Peer Reviewed

SIGNIFICANCE OF STANDARD AND NEWLY STUDIED BIOMARKERS IN THE DIAGNOSIS OF ADVANCED CHRONIC KIDNEY DISEASE AGAINST THE BACKGROUND OF DIABETIC NEPHROPATHY IN TYPE 2 DIABETES.

Botirova N.A., Mirahmedova H.T.
TASHKENT MEDICAL ACADEMY

Summary. Diabetic nephropathy is indeed a major cause of chronic kidney disease and a significant complication of diabetes. The pathogenesis of diabetic nephropathy is complex and not fully understood. It involves a combination of various factors and mechanisms that contribute to the development and progression of the disease. Early diagnosis and intervention are crucial in slowing down the progression of diabetic nephropathy. In recent years, several biological markers associated with diabetic nephropathy have been identified, providing valuable insights into predicting the occurrence and progression of the disease. This article aims to provide an overview of these early biomarkers associated with diabetic nephropathy.
The identification of early biomarkers is essential for timely detection and intervention in diabetic nephropathy. These biomarkers can help in risk stratification, predicting the likelihood of developing diabetic nephropathy, and monitoring disease progression. By detecting kidney damage at an early stage, healthcare providers can implement interventions to slow down or prevent further deterioration of renal function.
Keywords: Diabetic nephropathy, chronic kidney disease, albuminuria, glomerular filtration rate, standart biomarkers, novel biomarkers

Introduction. Diabetes mellitus (DM) is a significant endocrine and metabolic disease that has a severe impact on human health. The prevalence and mortality rates of DM have been increasing rapidly in recent years, and it is estimated that the global population with diabetes will reach approximately 439 million by 2030[17]. The statement that the complications of diabetes mellitus (DM) include diabetic retinopathy, diabetic cardiovascular diseases, and diabetic nephropathy (DN) is a commonly accepted understanding in the medical field. These complications are indeed among the most significant and prevalent complications associated with DM. DN has emerged as the leading cause of chronic kidney failure, progressing from normoalbuminuria to microalbuminuria, macroalbuminuria, and ultimately to end-stage renal disease (ESRD)[10]. Traditionally, proteinuria has been considered the gold standard for evaluating and monitoring renal function in DN[18]. However, it has been observed that renal function can decline in about one-third of patients before the onset of proteinuria. This highlights the inadequacy of relying solely on proteinuria to detect and monitor the incidence

Western European Journal of Medicine and Medical Science
Volume 1, Issue 3, November, 2023
https://westerneuropeanstudies.com/index.php/3
ISSN (E): 2942-1918 Open Access| Peer Reviewed

and progression of DN. Therefore, there is a need to identify laboratory biomarkers that can detect renal dysfunction earlier than microalbuminuria or those that appear concurrently. This review article specifically focuses on early biomarkers associated with the pathogenesis, pathology, and changes in renal function in DN. The aim is to identify biomarkers that can provide early indications of renal dysfunction in order to improve the detection and monitoring of DN. By identifying and utilizing these early biomarkers, healthcare professionals can intervene earlier and implement appropriate management strategies to slow down the progression of DN. The article aims to provide an in-depth understanding of the molecular and biochemical changes associated with DN, as well as the identification of novel biomarkers that can serve as early indicators of renal dysfunction. By exploring these biomarkers, researchers and clinicians can potentially improve the early diagnosis and prognosis of DN, leading to better patient outcomes.

Diabetic nephropathy (DN) is a specific type of kidney disease that occurs as a complication of type 2 diabetes mellitus (DM). It is a leading cause of end-stage renal disease (ESRD) worldwide. DN develops gradually over several years and is characterized by structural and functional changes in the kidneys.

The exact mechanisms that lead to DN in type 2 DM are complex and not fully understood. However, several factors contribute to its development:

Hyperglycemia[8]: Prolonged periods of high blood sugar levels (hyperglycemia) in individuals with type 2 DM can damage the blood vessels in the kidneys, impairing their ability to filter waste and fluids properly.

Increased Blood Pressure[6]: Hypertension (high blood pressure) commonly coexists with type 2 DM and accelerates the progression of DN. High blood pressure puts additional strain on the kidneys and damages the blood vessels, leading to kidney dysfunction.

Glomerular Hypertension and Hyperfiltration[12]: Persistent hyperglycemia and high blood pressure can cause increased pressure within the glomeruli (the tiny blood vessels in the kidneys responsible for filtering waste products). This glomerular hypertension and hyperfiltration place stress on the glomeruli, leading to damage over time.

Inflammation and Oxidative Stress[13]**:** Chronic inflammation and increased oxidative stress within the kidneys contribute to the development and progression of DN. These processes further damage the renal tissues and impair their function.

Genetic Factors[11]: Genetic predisposition plays a role in the development of DN in individuals with type 2 DM. Certain genetic variations can make some people more susceptible to kidney damage in the presence of high blood sugar levels.

The clinical presentation of DN can vary, but common symptoms include persistent proteinuria (excretion of excessive protein in the urine), hypertension, edema (swelling), and a decline in kidney function. As DN progresses, it can lead to ESRD, necessitating dialysis or kidney transplantation.

Early detection and management of DN are crucial in slowing its progression and preserving kidney function. This involves maintaining good blood glucose control, managing blood pressure effectively, adopting a healthy lifestyle, and using medications to protect the kidneys.

Western European Journal of Medicine and Medical Science
Volume 1, Issue 3, November, 2023
https://westerneuropeanstudies.com/index.php/3
ISSN (E): 2942-1918 Open Access| Peer Reviewed

Regular monitoring of kidney function through blood tests (e.g., serum creatinine, estimated glomerular filtration rate) and urine tests (e.g., albuminuria) is essential for the early detection and management of DN in individuals with type 2 DM.

It's important for individuals with type 2 DM to work closely with their healthcare team, including endocrinologists and nephrologists, to optimize their diabetes management and monitor for the development of DN. By controlling blood sugar levels, managing blood pressure, and adopting a healthy lifestyle, the risk of developing DN and its progression can be reduced.

Diabetic nephropathy (DN) is a common complication of type 2 diabetes and is characterized by kidney damage due to long-term high blood sugar levels. Diagnosis of DN often involves the assessment of various biomarkers. Here are some standard and emerging biomarkers used in the diagnosis of DN:

Albuminuria[15]: Albuminuria refers to the presence of excessive amounts of albumin (a type of protein) in the urine. It is an early and important biomarker for DN. The measurement of albumin-to-creatinine ratio (ACR) in a spot urine sample is commonly used to assess albuminuria.

Estimated Glomerular Filtration Rate[5] (eGFR): eGFR is a calculation that estimates kidney function by measuring the rate at which blood is filtered through the glomeruli (tiny blood vessels in the kidneys). A decrease in eGFR indicates impaired kidney function, and it is used to stage the severity of DN.

Serum Creatinine[2]: Serum creatinine levels are used in conjunction with eGFR to assess kidney function. Creatinine is a waste product that is filtered by the kidneys, and elevated levels indicate reduced kidney function.

Blood Pressure[6]**:** Hypertension (high blood pressure) is both a risk factor and a consequence of DN. Monitoring and controlling blood pressure levels are crucial in managing DN and slowing its progression.

Renal Imaging: Imaging techniques such as ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) may be used to visualize the kidneys and detect structural abnormalities or complications associated with DN.

Novel Biomarkers: Researchers are actively studying and exploring new biomarkers that may provide additional insights into the diagnosis and progression of DN. Some emerging biomarkers include urinary biomarkers like kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and liver-type fatty acid-binding protein (L-FABP), which may help detect early kidney injury and predict the progression of DN.

It's important to note that the diagnosis of DN involves considering multiple factors, including clinical presentation, medical history, and a combination of biomarkers. The specific biomarkers used and their significance may vary based on individual patient characteristics and the stage of the disease.

Serum Cystatin C[2]: Cystatin C is an alternative biomarker for estimating kidney function. Unlike creatinine, cystatin C is less influenced by muscle mass and other factors, making it potentially more accurate in assessing kidney function. It is particularly useful in individuals with obesity, malnutrition, or conditions that affect muscle metabolism.

Fibroblast Growth Factor 23 (FGF-23)[16]: FGF-23 is a hormone that regulates phosphate metabolism. Elevated levels of FGF-23 have been associated with the development and progression of DN. It is considered a possible biomarker for predicting the risk of kidney disease progression and cardiovascular complications in individuals with diabetes and DN.

Western European Journal of Medicine and Medical Science
Volume 1, Issue 3, November, 2023
https://westerneuropeanstudies.com/index.php/3
ISSN (E): 2942-1918 Open Access| Peer Reviewed

Urinary Biomarkers[20]: Various urinary biomarkers are being investigated to detect early kidney damage and predict the progression of DN. These include kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and urinary transforming growth factor-beta 1 (TGF-β1). These biomarkers can provide insight into ongoing kidney injury and inflammation.

Inflammatory Markers[9]: Chronic inflammation plays a role in the pathogenesis of DN. Biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) are being studied to assess the level of inflammation and its impact on the development and progression of DN.

Genetic Markers[7]: Genetic studies are exploring the role of specific genes and genetic variations in the development and progression of DN. Identifying genetic markers may help identify individuals at higher risk or provide insights into the underlying mechanisms of the disease.

Urinary Alpha-1 Microglobulin (A1M): A1M is a low-molecular-weight protein that is normally filtered by the kidneys and reabsorbed. Elevated levels of A1M in the urine have been associated with kidney damage and can serve as a biomarker for early detection of DN[19].

Urinary Epidermal Growth Factor (EGF): EGF is a growth factor that plays a role in the maintenance and repair of kidney tissue. Decreased levels of EGF in the urine have been observed in individuals with DN and may indicate kidney injury and impaired renal function[21].

Urinary Kidney Injury Molecule-1 (KIM-1): KIM-1 is a protein that is upregulated in response to kidney injury. Elevated levels of KIM-1 in the urine have been found in individuals with DN and can serve as a marker of ongoing kidney damage and inflammation[22].

Urinary N-Acetyl-beta-D-Glucosaminidase (NAG): NAG is an enzyme that is released into the urine when the renal tubules are damaged. Increased levels of NAG in the urine have been associated with DN and can indicate tubular injury and dysfunction[23].

Urinary Clusterin (CLU): Clusterin is a protein involved in cell survival and tissue repair. Higher levels of CLU have been detected in the urine of individuals with DN, and it may serve as a biomarker for kidney injury and progression of the disease[4].

Circulating MicroRNAs (miRNAs): MicroRNAs are small non-coding RNA molecules that regulate gene expression. Specific miRNAs have been identified in the blood and urine of individuals with DN, and their altered expression patterns may have diagnostic and prognostic value in DN[3].

Advanced Glycation End Products (AGEs): AGEs are compounds formed when sugars react with proteins in a process known as glycation. Elevated levels of AGEs have been found in individuals with diabetes and DN. They may contribute to kidney damage and serve as biomarkers for evaluating disease severity[1].

Biomarkers of Oxidative Stress: Oxidative stress, characterized by an imbalance between free radicals and antioxidant defenses, is implicated in the development of DN. Biomarkers such as malondialdehyde (MDA) and advanced oxidation protein products (AOPPs) can reflect the extent of oxidative damage in DN.

It's important to note that while these biomarkers hold promise, their clinical use is still evolving, and more research is needed to validate their utility in DN diagnosis, risk stratification, and treatment monitoring.

Conclusion

Western European Journal of Medicine and Medical Science
Volume 1, Issue 3, November, 2023
https://westerneuropeanstudies.com/index.php/3
ISSN (E): 2942-1918 Open Access| Peer Reviewed

Blood urea, plasma creatinine, glomerular filtration rate formulas, proteinuria, and albuminuria are currently widely used measures to assess the presence and progression of diabetic nephropathy. However, these measures do not provide a clear, direct indication of kidney tissue damage and are insensitive to small changes in kidney function. Thus, having novel biomarkers that are sensitive, specific and can detect renal damage and predict clinically relevant outcomes, will enable accurate and early diagnosis of diabetic nephropathy.

References

1."Advanced Glycation End Products: A Review" (Diabetologia, 2016) by Naila Rabbani, Paul J. Thornalley
2. B. Satirapoj and S. G. Adler, “Comprehensive approach to diabetic nephropathy,” Kidney Research and Clinical Practice, vol. 33, no. 3, pp. 121–131, 2014.
3. "Circulating MicroRNAs in Diabetic Nephropathy: From Mechanism to Clinical Utility" (Non-Coding RNA, 2019) by Ling Huang, Qinge Zhang, Zhiqiang Cheng, et al.
4. "Clusterin as a Biomarker in Diabetic Kidney Disease" (Clinical Kidney Journal, 2018) by Laura K. Lamb, Katherine R. Tuttle, Jon B. Klein
5. Correlation of Estimated-Glomerular Filtration Rate (e-GFR) with diabetic nephropathy and non-nephropathy patients in a tertiary care hospital March 2022 Bangabandhu Sheikh Mujib Medical University Journal 14(4):109-113 DOI:10.3329/bsmmuj.v14i4.56608
6. Fox CS, Golden SH, Anderson C, et al. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care. 2015;38(9):1777-1803.
7. "Genetic Susceptibility Factors for Diabetic Nephropathy" (Genes, 2019) by Luiza Stanescu, Madalina E. Stanescu, Ionel Sandovici, et al.
8. Hyperglycaemia in diabetes: Impact on nephropathy and cardiac risk October 2003 Nephrology Dialysis Transplantation 18(9):1711-5
DOI:10.1093/ndt/gfg213
9. "Inflammatory Biomarkers in Diabetic Nephropathy" (Journal of Diabetes Research, 2015) by Manoocher Soleimani, Eirini T. Tsigou, George Papadopoulos, et al.
10. KDIGO Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease: https://kdigo.org/guidelines/diabetes-ckd/
11. McKnight AJ, Maxwell AP. Genetics of diabetic nephropathy: a long road of discovery. Curr Diab Rep. 2015;15(2):8
12. Mogensen CE. Glomerular filtration rate and renal plasma flow in short-term and long-term juvenile diabetes. Scand J Clin Lab Invest. 1971;28(3):211-218.
13. Navarro-González JF, Mora-Fernández C. The role of inflammatory cytokines in diabetic nephropathy. J Am Soc Nephrol. 2008;19(3):433-442.
14. Perkins BA, Nelson RG, Ostrander BE, Blouch KL, Krolewski AS, Myers BD, Warram JH. Detection of renal function decline in patients with diabetes and normal or elevated GFR by serial measurements of serum cystatin C concentration: results of a 4-year follow-up study. J Am Soc Nephrol. 2005
15. So-Young Lee [1], Mary E Choi. Urinary biomarkers for early diabetic nephropathy: beyond albuminuria doi: 10.1007/s00467-014-2888-2. Epub 2014 Jul 25
16. "The Role of Fibroblast Growth Factor 23 in Diabetic Kidney Disease" (Current Diabetes Reports, 2020) by David E. Leaf, Myles Wolf

Western European Journal of Medicine and Medical Science
Volume 1, Issue 3, November, 2023
https://westerneuropeanstudies.com/index.php/3
ISSN (E): 2942-1918 Open Access| Peer Reviewed

17. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010; 87(1):4-14.
18. Shirley S Chang Albuminuria and diabetic nephropathy Pediatr Endocrinol Rev. 2008 Aug;5 Suppl 4:974-9
19. "Urinary Alpha-1 Microglobulin as a Potential Biomarker for Kidney Disease" (Annals of Laboratory Medicine, 2019) by Sang-Un Kim, Dong-Wook Lee
20. "Urinary Biomarkers in the Early Detection of Diabetic Nephropathy: A Review" (American Journal of Kidney Diseases, 2012) by Mark E. Molitch, Radica Z. Alicic, Vivian A. Fonseca, et al.
21. "Urinary Epidermal Growth Factor: A Promising Biomarker for Diabetic Nephropathy" (Journal of Diabetes Research, 2016) by Chongxiu Sun, Li Xiao, Mingyu Liang, et al.
22. "Urinary Kidney Injury Molecule-1 as a Biomarker of Diabetic Nephropathy" (American Journal of Nephrology, 2020) by Keiichi Sumida, Csaba P. Kovesdy
23. "Urinary N-acetyl-beta-D-Glucosaminidase as a Marker of Diabetic Nephropathy" (Current Diabetes Reviews, 2012) by Renuka Jain, V. Seshiah, and V. Balaji.