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Advancement in Biomarkers for Diabetic Nephropathy: Pathophysiology Mechanism and Early Diagnostic Tools

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Abstract: Diabetic nephropathy is a significant challenge of affecting blood glucose regulation which may result in chronic renal impairment and ultimately lead to ESRD. It arises due to the persistent hyperglycemia & involves complex mechanism such as mechanical, hemodynamic changes. It includes risk factor such as modifiable which includes hyperglycemia, hypertension, obesity, smoking and non-modifiable include genetic, age, sex etc. Diabetic nephropathy progress through stages, from early enlargement of the glomerular basement membrane to advanced glomerular damage and reduced GFR. The diabetic nephropathy is classified with GFR and urine albumin level, stages range from normal to the last stage of kidney dysfunction dependent on dialysis therapy or transplant. Biomarkers in diabetic nephropathy reflect different type of kidney damage such as glomerular (urinary transferrin, type IV urinary collagen), oxidative (pentosidine, heart fatty acid binding protein), tubular (Neutrophil gelatinase-associated lipocalin, kidney injury molecule 1, cystatin-c), inflammation (Tumor Necrosis Factor alpha, urinary, orosomucoid) biomarker serve as a important component in the early identification, diagnosis, monitoring & assessment of treatment effectiveness in diabetic nephropathy. Traditionally, microalbuminuria has served as the early biomarker for the diabetic nephropathy. Recent advances highlight several promising urinary and serum biomarkers, including zinc-alpha-2 glycoprotein, NGAL, KIM-1. These biomarkers have proven effective in identifying the conditions in its initial phase, before the occurrence of microalbuminuria. Emerging biomarker approaches involving microRNAs, long noncoding RNAs, and urinary exosomes provide additional insight into pathogenies and early diagnosis. The development of biomarkers could improve early detection, therapeutic intervention, and reduce the burden of complicated diabetic nephropathy.

Keywords: Diabetic Nephropathy, Diabetes Mellitus, Biomarkers, Chronic Kidney Disease, End-Stage Renal Disease, Diabetic Kidney Disease, Advanced Glycation End Products.

INTRODUCTION

Diabetic nephropathy (DN) is the prevalent challenge associated to cardiovascular disorders and is a lead to cause of cardiovascular mortality. The people with diabetes mellitus, it severely affects renal function. Renal replacement treatment is necessary for many individuals with long term kidney disorder diagnosed with ESRD [1]. Researcher indicates that individual with type 1 diabetes advance to the final phase of the kidney failure earlier than individual diagnosed with type 2 diabetes, while diabetic nephropathy (DN) occurs among individuals with medical record of diabetes & kidney failure over several years [2]. Among the most prevalent ongoing effects of persistent hyperglycemia is diabetic nephropathy [3]. Accordingly, a number of pathophysiologic variables, including hemodynamic factors, metabolic factors, growth factors/cytokines, transcription factors and cell signaling, autophagic activity, inflammation and oxidative stress are responsible for the advancement of the kidney disease in diabetes [4,5]. Among these, oxidative stress is acknowledged as an essential element in the progression

of the diabetic nephropathy along with its persistence despite adequate glycemic control. This may be because of accumulating reactive molecules that are difficult to eliminate [5,6]. Oxidative stress commonly results from increased activity of the polyol pathway, autoxidative glycosylation, and the production of advanced glycation end-products (AGEs) linked to chronic diabetes [6]. Consequently, it has been hypothesized that by scavenging free radicals, antioxidant supplements may provide some protection against this problem. Many naturally occurring phenolic compounds and plant secondary metabolites with antioxidant properties have been identified in recent decades [7].

Diabetic nephropathy is described as elevated urinary albumin excretion (UAE) without the presence of another kidney disease. The first medical sign of renal disorder is microalbuminuria, also known as incipient nephropathy, defined as abnormally low amount of albumin in urine (>30 mg/day or 20 µg/min, or a urinary albumin/creatinine ratio [ACR] >3.0 mg/mmol). Advancement to macroalbuminuria or severe kidney disease, takes place when UAE exceeds 300 mg/day or 200 µg/min (urinary ACR >30 mg/mmol) & is linked to gradual reduction in GFR alongside the emergence of hypertension. Severe diabetic nephropathy affects 15–40% of individual identified with type 1 diabetes with the highest prevalence occurring 15–20 years after diagnosis. [8]

For DN, risk factor was categorized as either modifiable or non-modifiable. Modifiable factors consist of dyslipidemia, glycemic control and hypertension. Furthermore, smoking was shown to be another modifiable risk factor by Scott and Bornhorst ethnicity, age, pregnancy period, genetic factor and gender are non-modifiable. The disease was more susceptible to developing in patients with a family record of kidney disease related to diabetes.

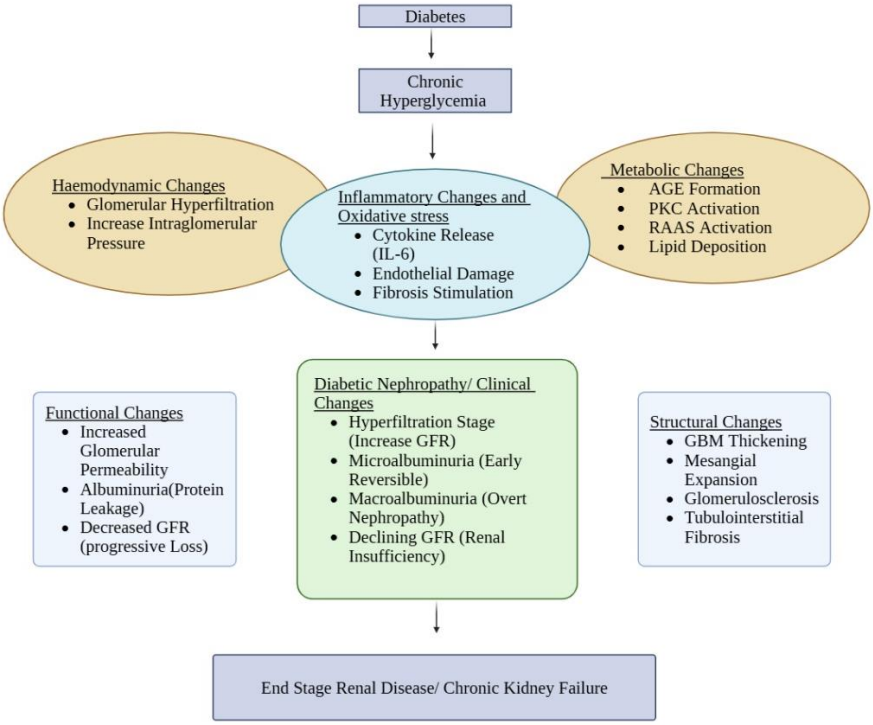

Figure No.1: *Pathophysiology of Diabetic Nephropathy*

The first sign of DN refers to the thickening of glomerular basement membrane. GFR stays normal during this phase, which can continue up to five years and there is usually no albuminuria or hypertension. About two years after GBM thickening and mesangial proliferation began the second stage is marked by mild to severe mesangial expansion. GFR is still normal at this point and no other notable clinical signs are present. The tertiary stage is characterized by glomerular damage & increase microalbuminuria levels, varying from 30 to 300 mg/day. This stage called nodular sclerosis which usually appears 5–10 years after GBM thickening starts and can happen to diabetic people with or without hypertension. Prominent vascular and tubulointerstitial lesions are indicative of the fourth stage, advanced diabetic glomerulosclerosis. A GFR below 15 mL/min/1.73 m^2 indicates total renal failure which is the last stage of DN [9].

Pathophysiology of Diabetic Nephropathy

Hemodynamic & metabolic mechanisms can lead to diabetic nephropathy. Through processes like cellular hypertrophy increased permeability of endothelial cells and increased synthesis of matrix protein hyperglycemia aids in its growth. Furthermore, hyperglycemia raises the synthesis of prostaglandins that dilate blood vessels which raises intraglomerular

pressure and renal perfusion and finally results in hyperfiltration.

The kidney's aldose reductase enzyme transforms extra glucose into sorbitol. Afferent arteriolar vasodilation elevated renal circulation and elevated glomerular capillary pressure are the results of a decrease in intracellular myoinositol caused by elevated intracellular sorbitol levels. Additionally, hyperglycemia promotes the growth of diabetic nephropathy by raising the activity of protein kinase C in smooth muscle cell of blood vessels and endothelial cells. Diabetic nephropathy becomes more severe by hypertension because it results in glomerular hypertension. Elevated arterial pressure is directly linked to a rapid reduction in glomerular filtration rate. Hemodynamic variables that impact the activity of glomerular, mesangial and epithelial cells cause increased formation of mesangial matrix and thickening of the basement membrane. Elevated glomerular permeability, proteinuria, glomerulosclerosis & extracellular matrix buildup are all consequences of elevated systemic arterial pressure. It is also believed that there is a hereditary component to the advancement of diabetic nephropathy. Decreased serum ACE levels may be the consequence of polymorphisms in the gene controlling the generation of the angiotensin-converting enzyme (ACE), according to one theory. ACE inhibition becomes less efficient as a result, and angiotensin II activity rises.

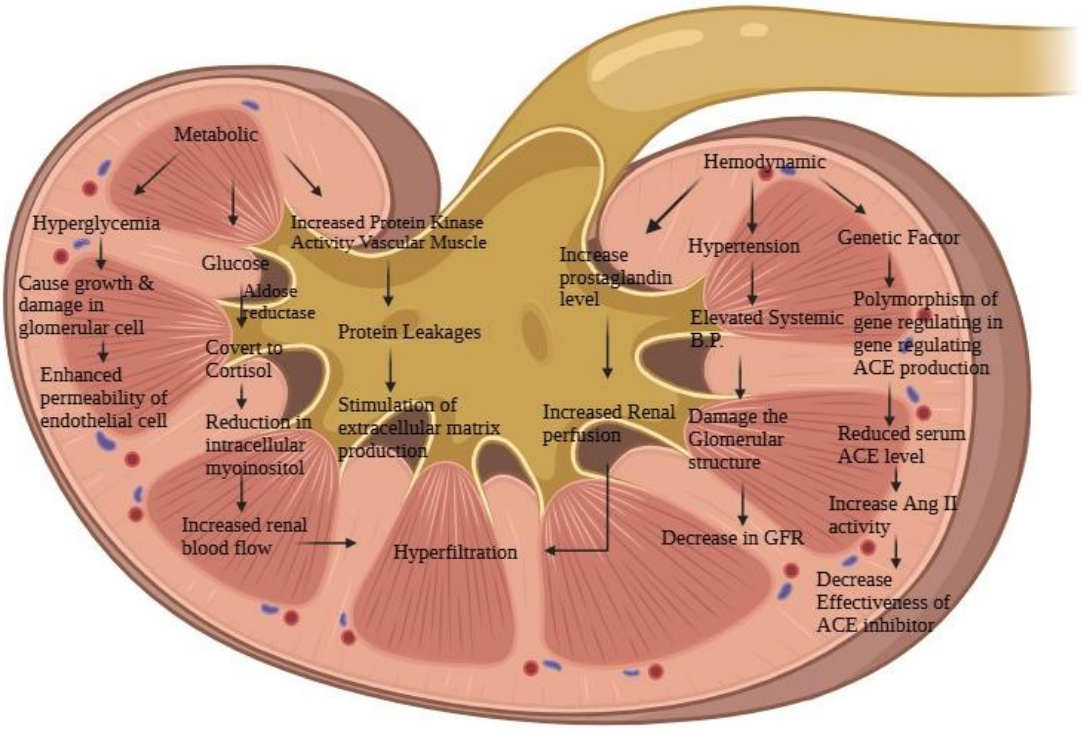

Figure No.2: *Mechanism of Diabetic Nephropathy*

Elevated cholesterol and cigarette smoking are factors linked to diabetic nephropathy. People with nephropathy usually see their condition worsen more quickly than people who don't smoke. Additionally, lipid abnormalities including raised levels of lipoprotein, total cholesterol, elevated LDL cholesterol and diminished HDL cholesterol, are commonly observed in diabetic individuals with microalbuminuria. It has been established that both LDL and total cholesterol are separate contributing factor to onset of renal disease [10].

Microalbuminuria, or the existence of albumin traces found in the urine is the initial therapeutic feature of DN. The initial stage of diabetic renal disorder in type 1 diabetes is identified as persistent albuminuria between 30 and 299 mg/day, which also predicts the establishment of kidney impairment associated with type 2 diabetes. A urinary albumin elimination rate ≥300 mg/day is indicative of overt or clinical nephropathy, which affects approximately 80% of patients diagnosed with type 1 diabetes who experience persistent microalbuminuria. After developing severe nephropathy, more than half of people having type 1 diabetes progress ESRD within a decade, and over 75% do so within 20 years. In contrast, because many people diagnosed with type 2 diabetes have encountered the disease for years without being identified, a higher percentage of individuals with the disease are diagnosed with microalbuminuria or overt nephropathy shortly after being diagnosed with their diabetes detection. 20-40% of individual having type 2 diabetes who have microalbuminuria will establish kidney disease. But only 20% of people with overt nephropathy will eventually evolve to ESRD [11].

Classification of Biomarkers of Diabetic Nephropathy

Diabetic Nephropathy is also referred as Chronic renal failure, it is a serious and fatal side effect of both T1D & T2D. The

presence of albuminuria has historically served as the basis for its therapy, early sign of microvascular problems, microalbuminuria (MA) indicates a higher chance of developing advanced comorbidities. However, MA is not always a good indicator of DKD, especially when it comes to younger individuals or DKD that is not albuminuric. Therefore, in order to identify kidney disease and injury before MA emerges, glomerular and other indicators of renal impairment are being used. Along with urinary albumin (UAE), the development of new biological markers may aid in the early stages of DKD, providing chances for therapeutic or preventive measures that may slow or stop the development of irreversible long-term health problems and lower CKD-related death rate and illness rate [12,13]. Approximately 40% of people diagnosed with diabetes have CKD which is the primary reason of CKD globally. Even though the majority of the outcome of diabetic renal impairment is ESRD, the most patients pass away from infections and heart related conditions prior to the requirement of kidney transplant treatment. Glomerular hyperfiltration is the initial stage of diabetic kidney disease, which progresses naturally to increasing albuminuria, decreasing glomerular rate and finally end stage renal disease. These abnormalities are triggered by the metabolic changes linked to diabetes [14].

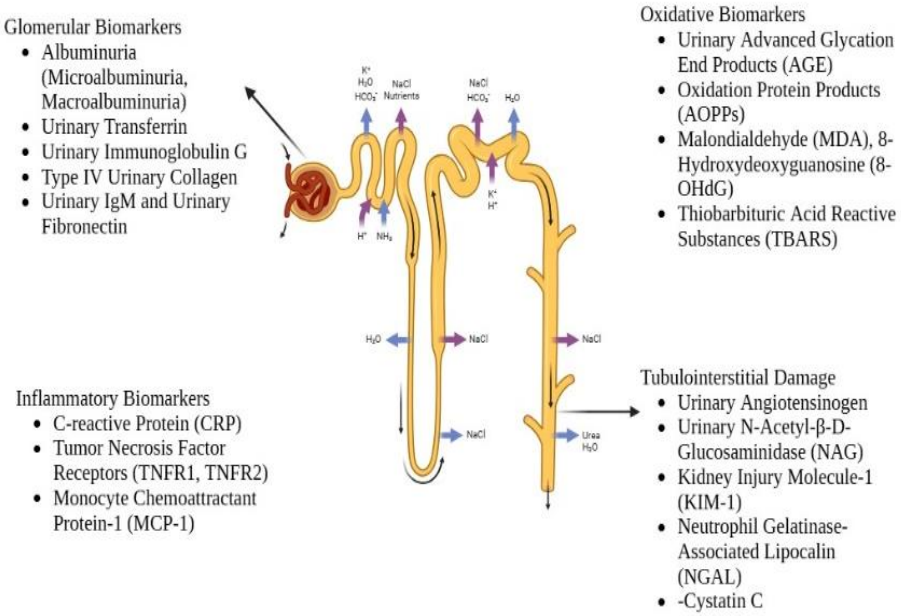

Figure No. 3: *Classification of Biomarkers*

Glomerular Injury

The most well-known biomarker for diabetic nephropathy (DN) is microalbuminuria, which is essential for early identification. In diabetes mellitus (DM), microalbuminuria is a sign of extensive endothelial dysfunction, which connects kidney involvement to problems with the heart and brain. As filtered albumin is reabsorbed in the renal tubules, over time, it has been shown that microalbuminuria is indicative of both tubular and glomerular deterioration. Furthermore, new biomarkers for tubular damage in diabetes mellitus have been investigated across type 1 & type 2 diabetes, these tubular markers have been found early in renal failure, even before microalbuminuria appears.

Currently many biomarkers are involved in early DN diagnosis, which capture the progression from normoalbuminuria to microalbuminuria and beyond renal impairment throughout microalbuminuria and macroalbuminuria. These new biomarkers are widely recognized, they are typically evaluated alongside albuminuria levels, particularly microalbuminuria. Biomarkers of inflammatory and oxidative processes associated with diabetes mellitus & diabetic nephropathy are under investigation.

Our focus is restricted in the beginning of phase of DN, despite the large body of research on biomarkers showing renal failure across different phases of DM progression. Urinary biomarkers in early DN must be updated in order to demonstrate their value in early diagnosis, which has important therapeutic and preventative ramifications. Because they are simple to collect, allow for population-wide screening, and can identify tubular damage which happens early in the progression of diabetes mellitus, urinary biomarkers are very useful. Proteomics also presents encouraging developments for assessment.

There are several sources of the biomarkers used to assess renal involvement in diabetes mellitus (DM). Some of the biomarkers that are important to the nephron include the following:

(i) markers at the level of epithelial cells (podocytes), such nephrin and podocalyxin;
(ii) markers linked to GBM, such as collagen and laminin;
(iii) endothelial markers, like vascular endothelial growth factor (VEGF);

(iv) tubular cell-level markers, like kidney injury molecule-1 (KIM-1), N-acetyl-β-D-glucosaminidase (NAG), and neutrophil gelatinase-associated lipocalin (NGAL) [15,16].

Certain biomarkers like angiotensinogen can be generated by both tubular cells and podocytes indicating a mixed origin [17]. Certain biomarkers like transferrin, ceruloplasmin immunoglobulins G & M, are found in the bloodstream. Due to glomerular injury increases permeability to plasma proteins, these proteins end up in the urine. Numerous categories have been put out to handle the variety of urine biomarkers associated with diabetic mellitus (DM). Matheson groups these biomarkers according to their origin as well as the pathological conditions that impact the nephron like inflammation, oxidative stress and kidney damage:

(i) Kidney dysfunction biomarkers
(ii) Inflammatory biomarkers including cytokines & chemokines
(iii) Oxidative stress biomarkers [18].

Microalbuminuria (Moderately increased Albuminuria) in Type 1 Diabetes Mellitus-
Type 1 DM typically appears 5–10 years earlier to the progression of microalbuminuria. Patient with microalbuminuria and type 1 diabetes, kidney biopsies frequently show normal histological results in only a few patients, diabetic nephropathy lesions have been found [19,20].

McKenna and Thompson suggested that, microalbuminuria is a predictor of when ESRD will emerge. Microalbuminuria can either stay constant, advance to albuminuria or relapse to normoalbuminuria [21,22]. Contributing factor usually exert a major influence on the advancement of microalbuminuria to macroalbuminuria, which is frequently linked to arterial hypertension and decreased GFR. A greater probability of developing heart-related conditions and ESRD are associated with persistent microalbuminuria. It's crucial to remember that, although microalbuminuria usually causes a fall in GFR there are instances where this decline happens even when normoalbuminuria is present [23,24].

Microalbuminuria (Moderately Increased Albuminuria) in Type 2 Diabetes Mellitus-
Microalbuminuria is frequently identified in population-based screening programs and is a significant indication for type 2 DM. As per the review by Newman, that included 28 studies with 10,294 participants, 26% of people with a ten-year illness duration had microalbuminuria. Microalbuminuria is more common in Asian and Hispanic people who have type 2 diabetes mellitus (43%) than in White people (33%) according to a study that included 24,000 participants [25]. Microalbuminuria can proceed to macroalbuminuria, return to normal levels, or stay in a stable state. After a follow up of 6-year, Araki found that microalbuminuria regressed in 51% of cases & proceeded to substantially elevated albuminuria in 28% of cases in research with 216 patients [26]. Compared to patients with normoalbuminuria, those with microalbuminuria are more likely to develop significantly elevated albuminuria. Furthermore, people with significantly elevated albuminuria experience a greater drop in GFR than people with microalbuminuria. The onset of microalbuminuria is significantly influenced by the administration of ACE inhibitors and ARBs to manage arterial pressure, along with efficient glycemic control. Interestingly, microalbuminuria is acknowledged as a glomerular function indicator [27,28].

5.1. Glomerular Biomarkers

5.1.1. Urinary Transferrin- Transferrin, which has a molecular weight of 76.5kDa, is capable to easily move across the glomerulus due to its small molecular size & ionic charge. In advance of the development of microalbuminuria elevated amount of urine transferrin, urinary ceruloplasmin, and immunoglobulin G have been found in normoalbuminuric individual having type 2 DM. This indicates its potential at an early stage of diagnostic for DN. Urinary transferrin levels rise even more in patients with microalbuminuria. Enhanced level of these substances is identified in patients with type 2 diabetes who also experience vascular issues such heart disease and eye disease. Interestingly, microalbuminuria is more common in patients with initially elevated urine transferrin excretion than in those with normal levels [29,30].

5.1.2. Urinary Immunoglobulin G- The negatively charged plasma protein has limited ability to transverse the glomerular barrier with a molecular weight of 150kDa [31]. Urinary IgG may be eliminated earlier than the development of microalbuminuria, accompanied by elevated levels of urine transferrin, ceruloplasmin, and orosomucoid. Thus, elevated excretion of IgG in the urine might be an indicator of microalbuminuria in patients with DM [32].

5.1.3. Urinary Ceruloplasmin- Ceruloplasmin is a protein found in serum that transports Cu that has difficulty filtering through the glomerulus due to its greater negative charge [33]. Ceruloplasmin has been detected in certain patient having type 2 diabetes who have normoalbuminuria, it may be used to identify kidney damage early on, even before albuminuria appears. Like urine transferrin and immunoglobulin G, it could be a sign of diabetic nephropathy prognosis in people diagnosed with type 2 diabetes. Yamazaki determined that that as albuminuria worsens, both the urine rate of excretion and the elimination of ceruloplasmin rise. Indeed, increased levels of urine transferrin, immunoglobulin G, and ceruloplasmin may be linked with type 2 diabetes [34,35].

5.1.4. Type IV Urinary Collagen- Type IV Urinary Collagen is an important part of mesangial matrix & GBM [36]. Damage happens at the mesangial and glomerular capillary levels in diabetic nephropathy (DN). Urine excretion of type IV collagen is expected to be sign of kidney damage associated with DN. It has already been found that individuals having type 1 diabetes who are normoalbuminuric have higher urine level of type IV collagen which indicated that this protein could be serving as a marker to identify diabetic nephropathy in its early stage. Patients with type 1 diabetes also showed elevated secretion of type IV collagen & laminin according to other studies [37]. There have also been reports of normoalbuminuric people with poor glucose tolerance excreting more type IV collagen in their urine. Patients diagnosed with type 2 diabetes may have structural alterations in their kidneys that are reflected in urinary type IV collagen. Urinary type IV collagen levels in these patients have been found to be linked with the severity of histological lesions. Urine containing type IV collagen is identified as a specific indicator for diabetic nephropathy in its early stages. It could assist distinguish DN from glomerulonephritis where its levels are usually lower and help detect DN in type 2 diabetes patients [38].

5.1.5. Urinary Laminin- Basement membranes normally contain the 900 kDa glycoprotein known as laminin. It is believed that urine laminin is produced by the kidneys and that serum laminin can't pass through the typical glomerulus. Immunohistochemistry has demonstrated that laminin is found in the thicker capillary basement membranes and mesangial expansion that are characteristic of diabetic nephropathy. As expected, the excretion of type IV collagen is the primary component of GBM, coincides with the excretion of laminin. Since laminin is also found in the basement membrane of the tubules, a correlation among urinary laminin excretion and tubular injury markers (such as NAG, alpha 1 microglobulin, beta 2 microglobulin & kappa light chains) should be expected. Before microalbuminuria appears, diabetic patients excrete more urinary laminin than healthy controls. Particularly in persons over 60, urinary laminin excretion rises with aging. It has a strong correlation with arterial pressure, glycemic management, and the length of diabetes. Type 2 diabetic patients having a sign of nephropathy exhibited a significantly elevated laminin or albumin ratio than the patient with non-diabetic nephropathy, although urinary laminin secretion is elevated in non-diabetic chronic nephropathy compared to control. This suggests that urinary laminin excretion might aid distinguish between diabetic & non-diabetic nephropathy [39].

5.1.6 Urinary Glycosaminoglycans- Glycosaminoglycans is a significant constituent of GBM and extracellular matrix. Even people with normal albuminuria, diabetes mellitus causes alterations in these components that result in increased excretion of glycosaminoglycans. The tubular foundation membrane contains them as well. Additional tubular markers like Tamm-Horsfall protein shows distal tubular dsyfunction in diabetes patients, are connected to urinary glycosaminoglycans [40].

5.1.7. Lipocalin-Type Prostaglandin-D Synthase- This biomarker indicates the glomerular capillary walls higher permeability and is linked to damage to those walls. It is less important as an early sign of diabetic nephropathy, even though it is regarded as a marker for renal abnormalities [41].

5.1.8. Urinary IgM and Urinary Fibronectin- These biomarkers have been investigating only, with insufficient evidence to establish their utility as early indicators of diabetic nephropathy (DN). Patients with DM only exhibit a considerable increase in urinary fibronectin excretion when microalbuminuria is present. One indicator of compromised renal function is IgM. Urinary glomerular biomarkers have been found in certain patients with normoalbuminuria, despite the fact that they are not yet often employed in clinical practice. This implies that the most sensitive glomerular biomarker might not be albuminuria. However, high-caliber research is required to confirm their clinical usefulness [42,43].

Tubular Biomarkers

The main characteristic of diabetic nephropathy is the presence of developed glomerular lesions, the previously mentioned biomarkers can be found during the initial phase of diabetic nephropathy. The important characteristic of DN is the presence of developed glomerular lesions. In the preliminary phase of diabetic nephropathy progression, the biomarkers mentioned previously can be identified. In DN, tubular injury frequently coexists with tubulointerstitial damage and Tubular dysfunction can occur early, according to tubular biomarkers, even before glomerular damage in certain cases. Compared to microalbuminuria, the gold standard biomarker for DN, these biomarkers have demonstrated higher sensitivity. Notably, microalbuminuria is now understood to be a sign of tubular dysfunction besides serving as a glomerular biomarker [44].

6.1. Neutrophil Gelatinase-Associated Lipocalin (NGAL)- A glycoprotein called NGAL is found in renal tubule cells and guards against kidney injury [45]. Urinary NGAL is a biomarker used to evaluate tubular damage in diabetes mellitus. Elevated levels are detected in the initial stage of the disease and even in people with normoalbuminuria [46]. Elevated urine NGAL levels can occur earlier than the beginning of microalbuminuria in individuals diagnosed with type 1 DM. Urinary NGAL levels in patients having type 2 diabetes are increased in those with normoalbuminuria, and they rise gradually in those with microalbuminuria and macroalbuminuria. Likewise, kidney injury molecule-1 levels increase concurrently, indicating both early and increasingly severe renal damage [47]. According to Fu et al., study revealed that individuals having hyperfiltration in type 2 DM have increased urine level NGAL & urine KIM-1 than people with normal

glomerular filtration rates (GFR). Urinary NGAL may help to assess the progression of type 2 diabetes in patients and emphasizes the early development of tubular impairment in prediabetic patients [48].

6.2. Urinary Alpha-1-Microglobulins- It is a small molecular size (27 kDa) serum protein, urinary alpha-1-microglobulin readily penetrates the glomerular capillary wall. After reaching at the proximal tubule, it is usually digested and reabsorbed. But this reabsorption is inhibited by tubular dysfunction, which raises urine excretion [49]. Hong et al. examined 590 patients with type 2 DM with a cross-sectional design discovered 33.6% of those with normoalbuminuria had higher urine alpha-1-microglobulin levels. This implies that alpha-1-microglobulin is a more sensitive and early urine biomarker because tubular damage may happen before the development of microalbuminuria. It is essential to remember that some people with albuminuria may not have alpha-1-microglobulin [50]. Urine albumin and other urine biomarkers are frequently evaluated in conjunction with alpha-1-microglobulin. Urinary alpha-1-microglobulin, beta-2 microglobulin & the albumin/creatinine ratio did not correlate with plasma asymmetric dimethylarginine, indicating that tubular and endothelial dysfunction may be dissociated. In the initial phase of diabetes mellitus, alpha-1-microglobulin also play an important role in prediction of DN. It is also a reasonably priced biomarker for DN early detection [51,52].

6.3. Urinary Kidney Injury Molecule-1 (KIM-1)-
The transmembrane glycoprotein KIM-1 is present in the cells of proximal tubules. When this area gets damaged, it gets eliminated in the urine. A highly sensitive biomarker that has proven useful in identifying acute kidney damage is KIM-1 [53]. According to Petrica study, patients with normoalbuminuric type 2 DM possesses greater urine KIM-1 level, which suggests proximal tubule impairment early in the illness. Furthermore, compared with individual experiencing normoalbuminuria, those with microalbuminuria had greater urine KIM-1 levels [54]. According to de Carvalho study, patient with type 2 DM who had normoalbuminuria had higher KIM-1 levels, which gradually increased in people experiencing microalbuminuria and macroalbuminuria. Similar forms of growth were observed in NGAL levels evaluated in conjunction with KIM-1. Additionally, type 2 DM patients experiencing hyperfiltration exhibit high KIM -1 excretion than those with normal GFR, and NGAL showed a comparable pattern. KIM-1 and NGAL are two biomarkers that could point to a detrimental impact of hyperfiltration on the proximal tubule [55]. However, in patients with type 1 DM, Nielsen failed to find a urine KIM-1 value that might forecast the development of glomerular function (GFR). Their results also show that KIM-1 has little predictive value for an individual affected by type 2 diabetes [56].

6.4. Urinary N-Acetyl-β-D glucosaminidase (NAG)- The lysosomes of proximal tubular cells contain the enzyme NAG [57]. For tubular damage, NAG is a sensitive biomarker because it is secreted into the urine in a larger amount when these cells are injured or malfunctioning. In Patient with type 1 DM, this rise in NAG levels may happen before the onset of microalbuminuria [58]. Only normoalbuminuric patients nor the control group showed elevated urine NAG activity & serum Cystatin C (Cys C) levels. Additionally, patient with microalbuminuria exhibited elevated levels of urine ALP and LDH activity [59]. Urinary NAG has not been found to have substantial clinical relevance as a preliminary biomarker for diabetic nephropathy (DN) by other researchers, including Ambade et al. Excretion of urinary NAG rises proportionately in addition with hoe long a person had type 2 diabetes & happens significantly sooner than albuminuria. Consequently, NAG may be regarded as an early indicator of tube injury [60]. According to Assal study he determined that the most effective biomarker for identifying damage early in urinary NAG in diabetes patients [61].

6.5. Urinary Angiotensinogen- The pathophysiology of diabetic nephropathy (DN) involves the RAAS. The kidneys contain the RAAS components, which combine to form a local RAAS. One potential biomarker for RAAS activation in diabetic mellitus (DM) is urinary angiotensinogen [62]. Elevated urine angiotensinogen levels in type 1 DM may be a prognostic diagnostic in patients with normotension since they occur before the progression of microalbuminuria. Urinary angiotensinogen levels are greater in patients with normoalbuminuric type 2 diabetes than controls and they gradually rise in patients with microalbuminuria, particularly those with macroalbuminuria. Therefore, one early indicator of DN is urine angiotensinogen. Furthermore, there is a correlation between urine angiotensinogen levels & alpha-1-microglobulin in patient with type 2 diabetes [63,64]. The progression of DN may be impacted by RAAS activation, the use of ACE inhibitors is encouraged. These results emphasize the need for further research to validate urinary angiotensinogen as a biomarker. Additionally, elevated urinary angiotensinogen may be a risk element for renal and heart related problems, and it may be a valuable indicator for assessing the renal impact of alogliptin that are protective among individuals with type 2 DM [65,66].

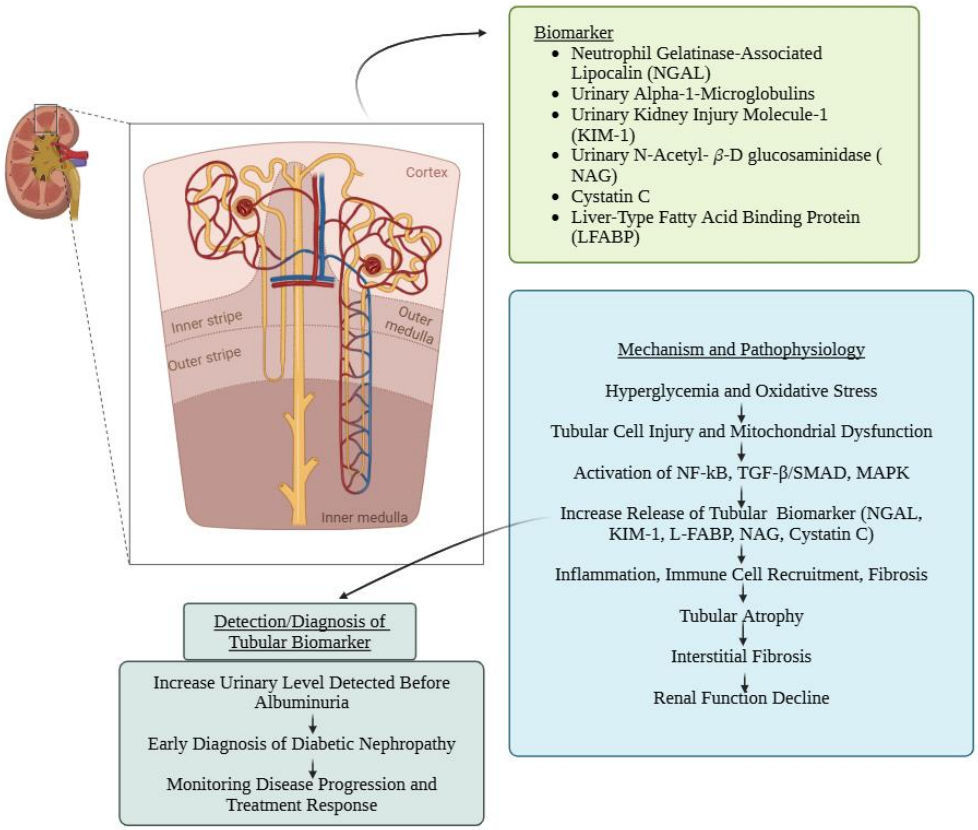

Figure No.4: *This Figure shows the types of Tubular Biomarkers, Mechanism or Pathophysiology of Tubular Biomarker and Diagnosis of Tubular Biomarker.*

6.6. Cystatin C- Cystatin C is a protein with a small molecular size that functions as a cysteine protease. It is synthesized by nucleated cells throughout the human body. Patients with type 2 diabetes who have normoalbuminuria, especially those with GFR of <60 mL/min/1.73 m², may rely on elevated urine cystatin C levels as a separate measure of kidney dsyfunction. In patient having type 2 DM, urine cystatin C and serum are effective indicators for evaluating early nephropathy [67]. Cystatin C is reabsorbed in the tubules after being filtered at the glomerular level. It is frequently employed to evaluate renal functions. The effective utilization of cystatin C to measure GFR is considered to be independent of body mass and is frequently seen to be on level with or even more accurate than techniques based on serum creatinine [68]. Serum cystatin C is regarded as a specific biomarker that can identify even slight glomerular damage. However, urinary cystatin C rises at an early stage in both diabetes and pre-diabetic nephropathy and indicates tubular injury [69,70]. Urine cystatin C levels are greater in microalbuminuric patients than in non-microalbuminuric patients. The evolution of diabetic nephropathy (DN) can be predicted by urinary cystatin C [71].

6.7. Liver-Type Fatty Acid Binding Protein (LFABP)- The cytoplasm of human proximal tubular cells contains the low-molecular-weight protein known as urinary L-FABP. A crucial biomarker for diagnosis of diabetic nephropathy is urine L-FABP, which is also raised in patient with type 2 DM who have normoalbuminuria. In reality, Japan's Ministry of Health and Welfare has formally acknowledged urine L-FABP as a tubular biomarker [72]. The liver produces L-FABP. Patients with type 1 DM who have normoalbuminuria has been found to show elevated urine L-FABP levels, which are predictive of the development from normoalbuminuria to microalbuminuria and from microalbuminuria to macroalbuminuria [73]. Recent research has shown that measuring plasma and particularly urine L-FABP may act as a valuable biomarker for early recognition of acute kidney damage (AKI), which can be brought on by a number of things, including heart surgery, cardiopulmonary bypass surgery or critically unwell people [74].

It has been hypothesized that the kidney's endogenous antioxidant L-FABP can inhibit tubulointerstitial damage. In the context of CKD, its excretion in the urine is also elevated. It has been demonstrated that urine L-FABP (uL-FABP) release is linked to both structural and functional tubular damage by immunohistochemically staining renal biopsy tissues. This has been verified in several disease processes such as minimal change nephrotic syndrome, lupus nephritis & diabetic kidney disease, where there is substantial proteinuria that results in tubular destruction and CKD. Proximal tubules are under tremendous amounts of stress due to the which eliminated the amount of filtered protein crossing the glomerular barrier which speeds up L-FABP excretion into urine from the tubular compartment. Therefore, the severity of

tubulointerstitial damage is largely reflected in the level of L-FABP. Additionally, a strong correlation exists between uL-FABP and chronic kidney disease progression. Consequently, uL-FABP is likely to be a helpful indicator of tubulo-interstitial injury. under proximal tubules under different proteinuric conditions to many free fatty acids attached to albumin could potentially cause oxidative stress, which would further aggravate the injury. By the way, human proximal tubules express L-FABP which is involved in intracellular FFA metabolism and may have antioxidant impact on the development of tubular-interstitial damage. Therefore uL-FABP is present only in the kidney tubules it may be a helpful biomarker of tubular damage. However, glomerular compartment injury must be excluded out. In recent year, the therapeutic use of uL-FABP as a predictive marker in diabetic nephropathy has also been analyzed. In those with small amount of albumin excretion, UL-FABP levels were high, correctly reflecting the extent of DN in patient with type 2 DM. Furthermore, increased UL-FABP excretion was considered to be a key contributor to the development of DN. The excretion of uL-FABP is unaffected by serum L-FABP levels, indicating that the tubular cells are the primary source of the L-FABP detected in urine. With declining renal function, uLFABP excretion rises independently of urine protein/albumin excretion. However, even in the absence of kidney dysfunction, patients with diabetes or hypertension had higher levels of uL-FABP. Moreover, when proteinuria was taken into account, DN uL-FABP did not independently correlate with a deterioration in renal functioning. Thus, further investigation is required to determine whether uL-FABP is a valid clinical biomarker for tracking the development of DN [75].

6.8. Nephrinuria- A transmembrane protein called nephrin play important role in the formation of the slit diaphragm [76]. Diabetic nephropathy (DN) is classified as a podocytopathy because podocyte dysfunction occurs in diabetes mellitus (DM). Nephrinuria is the result of damage to the slit diaphragm. Some patient with diabetes mellitus (DM) may experience nephrinuria before the development of microalbuminuria. Additionally, it has been observed in some patients diagnosed with type 2 diabetes have normoalbuminuria [77,78]. Nephrinuria is a sign of early glomerular injury and is linked to podocyte destruction. Patient with diabetic nephropathy (DN) may experience nephrinuria prior to the onset of microalbuminuria due to abnormalities in nephrin regulation within podocytes [79].

Inflammatory Biomarkers

Diabetes mellitus (DM) is associated with persistent inflammation that impacts the whole body including the kidneys. These processes involve inflammatory factor like cytokines & chemokines, some of which can act as indicators of inflammation.

7.1. Tumor Necrosis Factor Alpha (TNF Alpha)- Patient diagnosed with type DM who have microalbuminuria and macroalbuminuria had greater urinary TNF alpha levels than those who have normoalbuminuria. Furthermore, there is a correlation between urine TNF alpha and urinary NAG, a tubular injury marker [78]. Cherney conducted a thorough investigation in which they looked at 42 urine cytokines and chemokines in patients with normoalbuminuric type 1 diabetes. He discovered that the patients with a normal albumin-creatinine ratio did not have changed urine levels of RANTES, IL6, IL8, or platelet derived growth factor. Nonetheless, microalbuminuria was correlated with increase excretion of these indicators in the urine. According to Cherney et al., these indicators may be useful in determining a patient's risk of developing diabetic nephropathy (DN) if they have type 1 diabetes. Additionally, they discovered that higher secretion of inflammatory cytokines & chemokines is linked to renal hyperfiltration among patient with type 1 diabetes [81,82]. As per Tashiro the patients with type 2 Diabetes, MCP-1 levels rise in the final phase of the disease but IL8 levels are higher in the early stages of DN [83]. Research findings shows that the type 2 DM the patients with microalbuminuria and normicroalbuminuria, IL8, IP10, MCP-1, G-CSF, EOTAXIN & RANTES levels were elevated in patients with microalbuminuria compared to those with normicroalbuminuria or the control group. Diagnosing and treating diabetic nephropathy (DN) early may benefit from measuring these indicators [84]. Additionally, Ibrahim and Rached discovered that patients with microalbuminuria had greater urine MCP-1 levels than either normoalbuminuric or healthy controls [85].

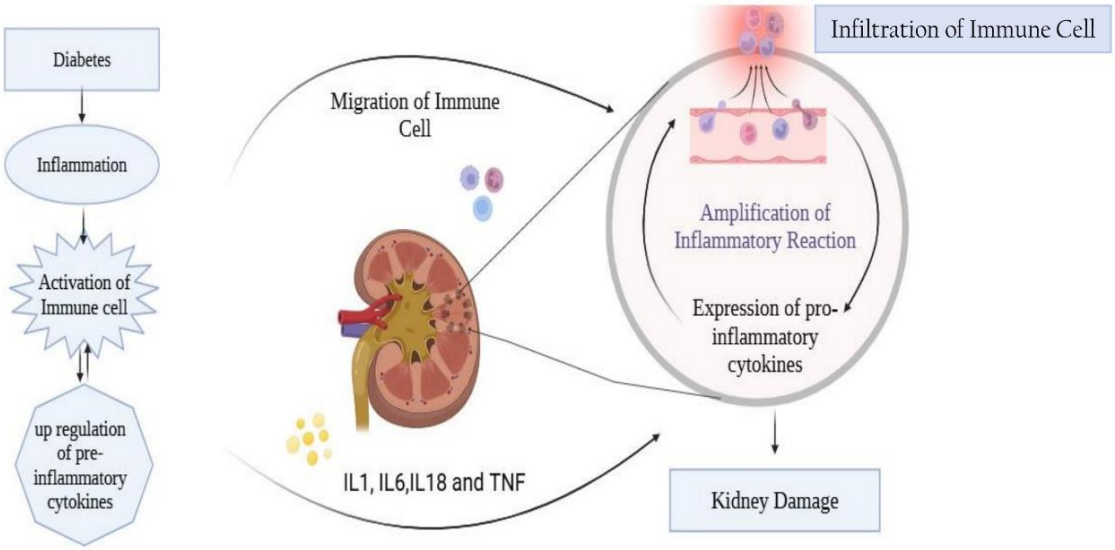

Figure No.5: *Pathophysiology of Inflammatory Biomarker*

Urinary Orosomucoid- A glycoprotein called orosomucoid plays a role in inflammatory mechanism. Urinary Orosomucoid levels are greater in patients with type 1 diabetes who have normoalbuminuria than in controls. In individuals with microalbuminuria and macroalbuminuria these levels rise much more [86]. Orosomucoid excretion is increased among patients diagnosed with type 2 diabetes accompanied by immunoglobulin G, ceruloplasmin, and transferrin excretion. Orosomucoid may be a preliminary sign of renal damage and is a crucial and distinct element for diabetic microvascular problems, according to El-Beblawy Furthermore, cardiovascular death rate in patient with type 2 diabetes is predicted by the rate at which orosomucoid is eliminated in the urine. In the beginning or first stage of diabetic nephropathy, urinary inflammatory indicators are useful for evaluating inflammatory processes [87,88].

Oxidative Stress Biomarkers-

Oxidative stress includes lipid peroxidation and substantial changes to proteins and DNA that contribute to cellular malfunction. Under diabetes circumstances, it is closely associated with increased reactive species (ROS) generation in several tissues. One of the main effects of oxidative stress in diabetes represent the excessive production of superoxide in endothelial cells. This increased generation of superoxide triggers a several pathways that results in the development of adverse effect including the polyol pathway enhanced production of AGEs, enhanced expression of AGE receptor and its ligands, activation of protein kinase C isoforms increased function of hexosamine pathway & DNA damage including oxidized bases, DNA strand breaks and DNA-protein crosslink formation [89,90]. Additionally, it has been found that hyperglycemia reduces the body's natural antioxidant defenses and causes the synthesis of free radicals, both of them have an impact on endothelial dysfunction [91].

8.1. 8-hydroxy-2′-deoxyguanosine (8-OHdG)- Oxidative stress significantly affects DNA in addition to damaging cellular proteins leading to various modifications of its bases [92]. Both mitochondrial and nuclear DNA from blood cells and tissues are commonly impacted by oxidative degradation. Guanine is the most susceptible to oxidation among all the purine and pyrimidine bases. 8-hydroxy-2′-deoxyguanosine (8-OHdG) is created when hydroxyl group binds to the guanine molecule's eighth position during oxidation. This oxidatively altered product is a common indicator of DNA damage brought on by free radicals. 8-OHdG is released in the urine after being easily filtered by the glomerulus membranes, which makes it a helpful biomarker of systemic oxidative DNA [93,94]. Additionally, it is proposed that 8-OHdG is a trustworthy biomarker for assessing DNA damage caused by oxidation in diabetes in vivo. Compared to healthy controls, patients diagnosed with type 2 diabetes have noticeably increased urine excretion levels. Furthermore, a favorable correlation exists among urine 8-OHdG levels and HbA1c levels [95,96]. Elevated 8-OHdG levels and increased oxidative stress were linked to both immediate and extended term glycemic variations. One useful biomarker for both microvascular & macrovascular problems in type 2 diabetes is urinary 8-OHdG. Its efficacy in comparison to urine albumin for the initial identification and prognosis of diseases like diabetic nephropathy and cardiovascular disease has not yet been evaluated [97].

8.2. Pentosidine - The glycation of protein amino groups without the use of enzymes in conjunction with oxidation processes results in advanced glycation end products, or AGEs. The two major molecular components of AGEs are pentosidine and N-carboxymethyl-lysine. Although AGE development is a natural aspect of aging, chronic diseases like

diabetes mellitus, Alzheimer's disease, atherosclerosis & kidney failure greatly increase its production and accumulation. The usefulness of AGEs especially pentosidine is reliable indicators of oxidative stress in diabetes is supported by research. Furthermore, research has demonstrated the use of pentosidine as a marker for diabetes issues. Calabrese for example, determined that type 2 patients with diabetic nephropathy had noticeably higher urine and plasma pentosidine levels than controls. Similarly, Piarulli discovered that microalbuminuria patients diagnosed with type 2 diabetes exhibit significant elevated serum pentosidine levels than those without, indicating that pentosidine levels are influenced by renal function and glycemic management. Pentosidine's function as a diagnostic indicator for microvascular problems in type 2 diabetes was further highlighted by Kerkeni et al. The buildup of particular AGE subclasses, like N-carboxymethyl-lysine & pentosidine, within mesangial expansions and nodular lesions in DN is one mechanism causing oxidative stress in diabetes. Although pentosidine has promise as a DN marker, more investigation is necessary to confirm its clinical usefulness [98].

8.3. Heart Fatty Acid Binding Protein (H-FABP)- H-FABP, serve as a marker of distal tubular damage. Nauta evaluated the connection between albuminuria and GFR and indicators of glomerular damage (IgG), proximal tubular injury (urinary KIM-1, NAG, NGAL & cystatin C) and distal tubular damage (urinary H-FABP) in a study that looked at individual with type 1 and 2 DM. the researcher revealed that urine cystatin C levels was noticeably low in normoalbuminuric patients, urinary NAG, NGAL & H-FABP exhibited higher level in these patients as compared to the controls [99].

8.4. Urinary Advanced Glycation End Product (AGE)- Tubular dysfunction is caused by AGEs, which are harmful to the tubules. and are eliminated in the urine. Elevated urine alpha-1-microglobulin & KIM-1 levels were observed in type 2 diabetes mellitus individuals with normoalbuminuria due to tubular dysfunction that occurred before microalbuminuria developed. These indicators were correlated with higher urine AGE levels at the same time. One of AGEs' components, pentosidine acts as a biomarker for the development and buildup of AGEs [100,101].

8.5. Podocytes- Diabetes mellitus and diabetic nephropathy are classified as podocytopathies because they cause podocyte destruction. The quantity of podocytes in the urine or certain urine biomarkers like nephrin & podocalyxin can be used to assess podocyte damage. According to a study conducted on DM patients, there was little variation in the quantity of urine podocytes between normoalbuminuric people and controls urine podocyte counts were higher and correlated with urine osteopontin and IgM levels in patients with microalbuminuria and nephrotic syndrome. It was discovered that DM patients with microalbuminuria exhibited higher urinary level of podocalyxin, which is produced from the apical surface of podocytes in vesicular form, than those with normoalbuminuria [102]. More over half of the normoalbuminuric participants in another study on DM patients had higher urine podocalyxin levels. Those with macroalbuminuria and microalbuminuria had much greater amounts. Additionally, there was a link between the levels of beta-2 microglobulin and urine NAG and urine podocalyxin [103]. According to Hara Urinary podocalyxin may be useful for preliminary indicator for identifying early podocyte damage in DM individuals whereas Zheng explored the urinary microRNA profile of podocyte related molecules, including synaptopodin, podocalyxin, CD2-AP, α-actin4 & podocin, to find potential biomarkers in individuals with normoalbuminuria, microalbuminuria & macroalbuminuria [104].

8.6. Vascular Endothelial Growth Factor (VEGF)- One podocyte biomarker VEGF, a proangiogenic substance that is mostly generated by podocytes in the nephron. Urinary alpha-1-microglobulin is a sign of proximal tubular injury, has been shown to be related with urinary VEGF levels among patients with type 2 diabetes. According to Kim research, patients with normoalbuminuric type 2 diabetes had greater levels of VEGF excretion than controls, with microalbuminuria and macroalbuminuria patients having increasingly higher amount [105].

8.7. Fetuin A - Fetuin A is a glycosylated glycoprotein that has been demonstrated to increase insulin resistance and prevent ectopic calcium deposition. In people with diabetes mellitus, it also stops atherosclerotic plaques from calcification which is a crucial component for the advancement of diabetic nephropathy is elevated urine excretion of fetuin A [106,107].

9. Emerging biomarkers:

9.1. MicroRNA - For diabetic nephropathy (DN), microRNAs (miRNAs) are showing promise as diagnostic biomarkers. By adhering themselves to the 3′ untranslated regions (3′ UTR) of target mRNAs and resulting in destruction or translation restriction these tiny noncoding endogenous RNAs (20–30 nucleotides) control gene expression [108,109]. Apoptosis, DNA repair, oxidative stress response, cancer & cellular development are all impacted by miRNAs, which are essential for the post-transcriptional control of gene expression. Recent research has shown that miRNAs target genes involved in oxidative stress, fibrosis & inflammation across in vivo & in vitro model of DN. Patients with diabetes have been show to possess altered amounts of certain miRNAs in their urine or serum. According to these animal research, Pezzolesi and associates discovered that early-stage type 1 diabetics, who are more prone to develop ESRD quickly, have abnormal plasma levels of a number of TGF-β-regulated miRNAs [110,111]. Studies involving diabetic nephropathy (DN) mice models have observed that miRNAs play a crucial role in the advancement of diabetic nephropathy by acting downstream of the TGF-β/Smad signaling cascade. In particular, TGF-β1 signaling enhances the expression of miR-192, miR-200b/c, miR-216a & miR-217 in mesangial cells and glomeruli in mice with type 1 and type 2 diabetes induced by STZ [112].

Remarkably, further research has discovered that miR-192 increases the production of other miRNAs as well as extracellular matrix and fibrotic effector genes such Col1a2 & Col4a1. The TGF-β signaling pathway & related fibrotic response are further strengthened by this miRNA expression amplification [113]. High amounts of miRNAs, including let-7b-5p, miR21-5p, miR-29a-3p & let-7c-5p were found to be in blood flow. According to these findings, circulating miRNA levels could potentially forecast when diabetic nephropathy (DN) may proceed to ESRD [114].

9.2. Long noncoding RNA - Noncoding transcripts that do not encode proteins and range in length from 200 nucleotides to 100 kbp are referred to as long noncoding RNA (lncRNA). In studies of diabetic nephropathy models, it has been discovered that the expression of miRNAs is connected with the expression of lncRNAs. It has been demonstrated that PVT1 in particular increases the buildup of extracellular matrix (ECM) by modifying TGF-β signaling in mesangial cells [115]. Numerous investigations have indicated that the pathophysiology of diabetic nephropathy (DN) may involve plasmacytoma variant translocation 1 (PVT1) lncRNA. PVT1 has been recognized as a possible gene associated with type 2 diabetes related ESR [116]. The expression of five miRNAs (miR-1204, miR-1205, miR-1206, miR-1207 & miR-1208) rises in interaction with human mesangial cell to high blood sugar & PVT1 is found in a region connected to ESRD. As a result of their great stability in biofluids and ease of detection, long noncoding RNAs (lncRNAs) hold promise as both possible therapeutic targets and prognostic biomarkers for diabetic nephropathy (DN) [117,118].

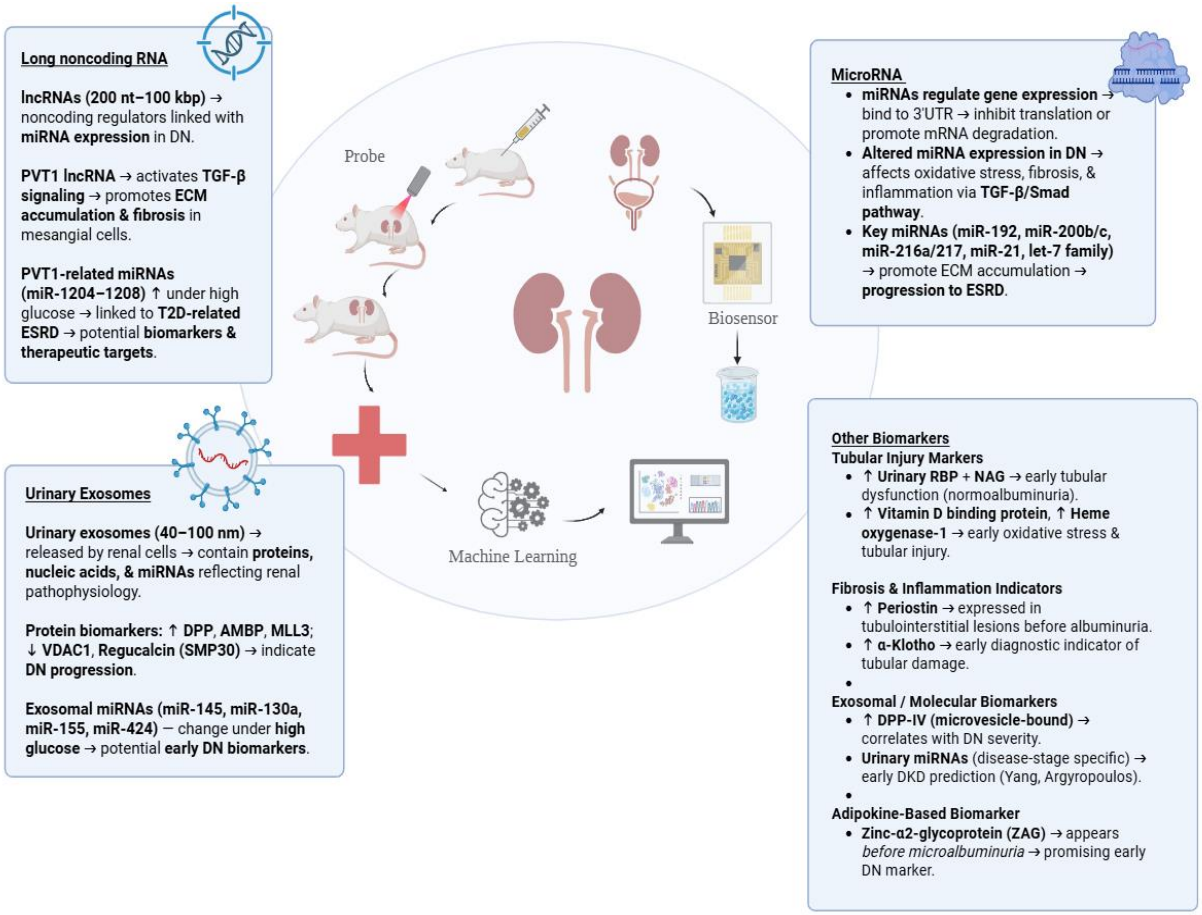

Figure No.6: *This Figure shows the types of Emerging or Early Evaluating Biomarker for Diabetic Nephropathy.*

9.3. Urinary Exosomes- Urinary exosomes are the microscopic vesicles (40–100 nm) secreted by a variety of renal cells. Along with nucleic acids, they also contain a variety of cytosolic, membrane & transport proteins [119]. Exosomes show promise as a non-invasive source of diabetic nephropathy biomarker and a marker of disease stage and advancement because they represent the pathophysiological condition of their originating cells. Therefore, Pisitkun was the first who identified them in urine samples of healthy person interest in studying urinary exosomes has risen substantially in tandem with developments methods for isolating, purifying and examining their molecular makeup [120,121]. One possible prospective biomarker for DN is dipeptidyl peptidase, an enzyme essential for T-cell activation. Both plasma and urine exosome samples from diabetes individuals had higher quantities of it [122].

A study by Raimondo analyzed the protein profiles from isolated urinary exosomes of ZDF rats. A type 2 diabetes model,

using liquid chromatography or mass spectrometry. The study revealed different expression of several proteins' protein like major urinary protein 1 & Xaa-Pro dipeptidase. Recent proteomic techniques have extended the variety of new proteins linked to urinary exosomes [123]. In a related investigation, Zubiri and associates detected 352 various proteins in human's urine exosomes using the LC-MS/MS approach proceeded by validation by selective monitoring of reaction. Among these, it was discovered that the patients with DN had different levels of histone lysine N-methyltransferase (MLL3), VDAC1, and α-microglobulin/bikunin precursor (AMBP) than control participants. VDAC1 levels decreased while those of AMBP and MLL3 increased [124]. The same research team recently published a study on a protein called regucalcin, which is also referred to as senescence marker protein-30 (SMP30). Zubiri and colleagues discovered that the kidneys of people with diabetic nephropathy (DN) have downregulated regucalcin expression through the use of animal models and a human pilot investigation. Human urine exosomes also showed these alterations [125]. Additionally, urinary exosomes are sources and carriers of miRNAs. 22 exosomes of miRNAs, comprising miR-145, miR-130a, miR-155, and miR-424, was found to express differently among type 2 diabetic patient in comparison to control groups in a study by Barutta & colleagues that looked at miRNA expression of urinary exosomes in diabetic patients with diabetic nephropathy. MiR-145 levels in mesangial-derived exosomes elevated under high glucose circumstances, according to mechanistic investigations conducted in the STZ induced diabetic nephropathy rat model and cultured mesangial cells. This suggests that screening urinary exosomes use as an early diagnostic method to identify the progression of diabetic nephropathy [126].

9.4. Microparticles- Extracellular vesicles known as microparticles (MPs) are discharged from cell surfaces in reaction to injury or stress. They are between 0.1 to 1 µm in size, larger than exosomes, and have a unique molecular makeup that includes phosphatidylserine exposed on their surface [127]. Before the onset of DN, microparticles (MPs), which are secreted by renal cell under diabetic circumstances, found in urine and plasma. MPs have drawn interest as possible biomarkers for DN progression prediction because of their capacity to be extracted from fluids using noninvasive techniques. The potential of urinary podocyte derived MPs as early sign of glomerular injury in diabetic nephropathy was highlighted in recent investigation by Burger and colleagues. They demonstrated that elevated glucose and mechanical stretch caused the release of podocyte MPs into the urine throughout the early phase of diabetic renal injury even before alteration in albuminuria were noticed. They did this using a variety of mouse models of type 1 diabetes, type 2 diabetes & diabetes-induced stress conditions [128].

Early Evaluating Biomarker of Diabetic Nephropathy-

A diverse range of urine indicators have been recommended for evaluating early-stage diabetic nephropathy, and some of these have only recently been put into use.

- In patients with normoalbuminuria, higher amounts of the small molecular size protein urinary retinol-binding protein have been identified in the urine coupled with NAG, suggesting tubular dysfunction in the initial phase of DN [129].
- It is essential to highlight the importance of serum retinol- binding protein 4 as an indicator for evaluating the extent of coronary artery disease [130].
- Potential biomarker for type 2 diabetes is urinary vitamin D binding protein which may help detect diabetic nephropathy early [131].
- Urinary heme oxygenase-1 could be an early indicator for diabetic nephropathy because it has been observed in type 2 diabetic individuals before they exhibit substantial albuminuria. This result is consistent with the expected impact of oxidative stress activation to the progression of DN [132].
- Periostin, a cell adhesion molecule typically absent in healthy kidneys, becomes expressed in renal system during tubulointerstitial lesions and is subsequently excreted in the urine. This makes urinary periostin a potential indicator of injury at this site. Elevated concentration of periostin have been detected in diabetes patients before the development of substantial albuminuria, suggesting its role as a biomarker for renal impairment [133].
- Urinary alpha- klotho concentration is raised in normoalbuminuric type 2 diabetes mellitus patients compared to control, indicating its capability as a diagnostic indicator for diabetic kidney damage [134].
- According to Sun he observed that urinary levels of micro vesicle bound dipeptidyl peptidase-IV correlate with the extent of DN in a study involving normoalbuminuric, microalbuminuric & macroalbuminuric type 2 diabetes mellitus patients [135]. Recent research highlights the potential use of urine specific microRNAs as markers for the early identification of diabetic kidney disease. According to the reviews of existing studies, Yang proposed the theory that urine specific microRNAs might be serve as indicators for the initial phase of the disease [136].
- The predictive usefulness of urine microRNAs in detecting the start of microalbuminuria in individuals with type 1 diabetes was recently highlighted by Argyropoulos [137].
- Zinc-alpha-2 glycoprotein, an adipokine, is linked to the major histocompatibility complex class I protein [138]. It is a urinary adipokine, emerges prior to microalbuminuria in diabetic nephropathy, highlighting its potential for early detection biomarker for diabetic renal disease

[139]. Lim also recognize zinc-alpha-2 glycoprotein as a promising new urinary biomarker for normoalbuminuric DN [140].

CONCLUSION

Diabetic nephropathy continues to be one of the most severe side effects of diabetes, contributing significantly to chronic kidney disease (CKD) and end-stage renal disease (ESRD). While traditional markers like microalbuminuria have been helpful in detecting kidney damage early, they still have limitations that highlight the urgent need for more sensitive and precise biomarkers. New approaches using urinary and blood biomarkers, such as NGAL, KIM-1, and microRNAs, are showing promise in identifying kidney damage at even earlier stages often before clinical symptoms appear.

In addition, recent breakthroughs in understanding the underlying causes of diabetic nephropathy like oxidative stress, inflammation, and glomerular dysfunction have established the foundation for the development of innovative diagnostic tools. Technologies such as urinary exosomes and long non-coding RNAs are opening up exciting possibilities for personalized medicine and tailored treatment.

The potential integration of these advanced biomarkers into routine clinical practice could transform how we detect, assess risk, and manage diabetic nephropathy. This would not only improve patient outcomes by slowing disease progression and reducing complications but also help lessen the financial and social burden of diabetes-related kidney disease.

FUTURE ASPECTS

The future of diagnosing and managing diabetic nephropathy is centered on exciting innovations, like advanced biomarkers, precision medicine and cutting-edge technologies. Emerging biomarkers, urinary exosomes, micro RNAs & non-coding RNAs, shows great promise in detecting kidney damage on early on before symptoms like microalbuminuria even show up. These tools, paired with molecular profiling, will allow doctors to assess risk more personally and tailor treatments to each patient.

The role of AI and machine learning in this transformation can't be overstated. By analyzing vast amount of data these technologies will help to identify individuals at risk, improve diagnostic accuracy and create more effective predictive models. Non-invasive tools such as advanced urine and blood tests and wearable device, could make monitoring kidney health simpler more accessible and less intrusive for patients.

Moreover, combining biomarkers research with telemedicine and digital health platforms has the potential to expand care, especially in areas where healthcare resources are limited. New treatments guided by biomarkers, targeting process like oxidative stress, inflammation & fibrosis could stop or even reverse the damage from diabetic nephropathy. Global collaboration and data sharing will speed up research while ensuring privacy pushing us closure to breakthrough. By focusing on detecting the disease early and embracing these innovations the future of diabetic nephropathy care will be more focused on prevention and personalized treatments and better outcomes for patients worldwide.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The author declares no conflict of interest

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ABBREVIATION

- ESRD-End-Stage Renal Disease
- GFR-Glomerular Filtration Rate
- DN-Diabetic Nephropathy
- AGE-Advanced Glycation End-Products
- UAE-Urinary Albumin Excretion
- ACE-Angiotensin-Converting Enzyme
- MA- Microalbuminuria
- DKD- Diabetic Kidney Disease
- CKD-Chronic Kidney Disease
- DM-Diabetes Mellitus
- VEGF-Vascular Endothelial Growth Factor
- GBM-Glomerular Basement Membrane
- KIM-1-Kidney Injury Molecule-1
- NGAL-Neutrophil Gelatinase-Associated Lipocalin
- NAG-N-acetyl-β-D-glucosaminidase
- Cys C- Cystatin C
- RAAS-Renin-Angiotensin-Aldosterone System
- LFABP-Liver-Type Fatty Acid Binding Protein
- AKI-Acute Kidney Damage
- TNF Alpha-Tumor Necrosis Factor Alpha
- DNA-Deoxyribonucleic acid
- 8-OHdG-8-hydroxy-2′-deoxyguanosine
- H-FABP-Heart Fatty Acid Binding Protein
- RNA-Ribonucleic acid
- lncRNA-long Noncoding RNA
- ECM- Extracellular Matrix
- PVT1-plasmacytoma variant translocation 1
- STZ-Streptozotocin
- AMBP-α-microglobulin/bikunin precursor
- MPs-Microparticles

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