ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at: www.ijmacr.com

Volume – 4, Issue – 3, May – June - 2021, Page No. : 119 – 132

Diagnostic Biomarkers of Nephropathy in Diabetes Mellitus: A Review

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How to citation this article: Dr Yadav KS, Dr Khot VV, Dr Toshniwal PA, Dr Kamble P S,"Diagnostic Biomarkers of Nephropathy in Diabetes Mellitus: A Review", IJMACR- May – June - 2021, Vol – 4, Issue -3, P. No. 119 – 132.

Type of Publication: Review Article

Conflicts of Interest: Nil

Abstract

Diabetes is a fast-growing metabolic disease across the globe. In 2000, 31.7 million people with diabetes mellitus and 62 million in 2007 topped the world. Diabetic kidney disease is dreadful condition and develops complications in 20% to 40% of all diabetics causing end stage renal diseases. The prevalence of diabetes around the world affects more than 8% of the global population. It was predicted that over 550 million people by the year 2035 and more than 40% of people will develop chronic kidney disease. Early-onset diabetic cases are responsible for the development of various post-diabetes complications, commonly called diabetes nephropathy. Currently blood urea and serum creatinine has low predictive value and it is difficult to reach the conclusive diagnosis of kidney diseases based on them. The evolution of novel biomarkers addresses to such paucity, viz., Calprotectin, Cystatin-C, Interleukin-18, Kidney injury molecule-1, Liver-type fatty acid-binding protein, Neutrophil gelatinase-associated lipocalin, Urinary angiotensinogen, Urinary micro-RNA, Asymmetric dimethylarginine, micro-RNA, Uromodulin, β-trace protein and many more. These novel biomarkers are categorized in tubular injury and tubular reabsorption biomarkers. Therefore, diagnosis and prognosis are the utmost priority of the medical profession to minimize renal morbidity. Data presented in this article is taken through online search from PubMed, Scopus, Medline, Google Scholar, Research gate, Google search and many more publication sites. The purpose of publishing this review is to facilitate existing research work to help clinicians for diagnosis and use of novel biomarkers on diseased for better health delivery.

Keywords: Diabetes mellitus, diabetes nephropathy, conventional-novel biomarkers

Introduction

According to the WHO Guidelines 2014, diabetes mellitus (DM) is a group of metabolic disorders characterized by a high blood sugar level. In 2014, 9% of adults aged 18 years and above had diabetes (WHO Reports, 2000-2002, 2012, and 2014). Diabetes is a fast-gaining epidemic in India, 62 million individuals were diagnosed as diabetes in 2007[1]. As per the Wild et al. (2004), the prevalence of diabetes in India has been predicted to double globally from 171 million in 2000 to 366 million in 2030 (fig 1).

Diabetic Nephropathy

The complication arising from diabetes called as diabetic nephropathy (DN) and is considered the prominent cause of death among end-stage renal disease (ESRD)[2]. Diabetic kidney disease (DKD) is a dreadful disease and develops complications in 20% to 40% of all diabetics. Literature survey on DN concluded that poor glycaemic control was one of the important risk factors for the development of DN[3].

Pathophysiology of diabetes nephropathy [4]

The key pathophysiological event in DN is basement membrane damage (fig.2). In renal damage there is the progressive thickening of the basement membrane damage, pathological change in mesangial-vascular cells, formation of advanced glycation end products (AGEs), accumulation of polyols via the aldolase reductase pathway and activation of protein kinase C. Passage of macromolecules through the basement membrane activate inflammatory pathways that contribute to the kidney damage.

Symptoms of kidney disease include poor appetite, upset stomach, sleep disturbances, weakness, and difficulty concentrating. Puffiness of the face and periorbital edema appears at a later stage. US Renal Data System (USRDS) 2012 and Annual Data Report Standards of medical care in diabetes, 2013 constituted almost 45% of the incident in the United States. Currently; this disease is not recognized at an early stage because of inadequate diagnostic tools. Therefore, it is an acute need of highly sensitive biomarkers for the detection of DN.

Use of Biomarkers in diagnosis

National Institutes of Health Biomarkers Definitions Working Group in 1998 defined biomarker as an indicator of normal biological, pathogenic processes, or pharmacologic responses to therapeutic intervention. There are two major types of biomarkers: biomarkers of exposure and biomarkers of disease. Biomarkers of exposure are used in risk prediction, and biomarkers of disease are used in screening, diagnosis and monitoring of disease progression.

Table 1: Diabetes nephropathy is divided into four hierarchical glomerular lesions [5]

Class	Description and criteria
I	Mild or nonspecific changes on light microscopy and conformed glomerular basement membrane (GBM) thickening proven by electron microscopy: GBM > 395 nm (female), GBM > 430 nm (male).
IIa	Mild mesangial expansion in >25% of the observed mesangium; area of mesangial proliferation < area of capillary cavity.
IIb	Severe mesangial expansion in >25% of the observed mesangium; area of mesangial proliferation < area of capillary cavity.
III	At least one convincing nodular sclerosis (Kimmelstiel-Wilson lesion).
IV	Advanced diabetes glomerulosclerosis in >50% of glomeruli.

Table 2: Conventional markers of kidney diseases and their predictive role.

	Description and Use	Limitations
GFR	GFR measures the rate at which the glomeruli filter the plasma and remove waste products from it. The normal value for GFR is up to 120 mL/min.GFR is the best marker for the detection of kidney disease, understanding its severity, making decisions about diagnosis, prognosis, and treatment. If the kidney is injured, the GFR gradually declines the glomerular function used for measuring the GFR.	A measure of GFR by using exogenous substances has limitations. Estimation of GFR (eGFR) is based on serum creatinine and is further limited to variation in creatinine production. Therefore eGFR does not reflect the early stage of renal disease because routine clinical tests do not measure the degree of GFR.
Albuminuria	Albumin, a small molecule produced in the liver and the circulating life span is of 12 to 20 days. The turnover rate is around 15 g/d. A significant amount was filtered in the glomeruli, but most of it is reabsorbed by the proximal tubular cells. Normal urine contains 20 mg albumin/L and the normal range of MAU is 30 to 300 mg in a 24-hour urine collection. An increase in albuminuria should not only be considered as a risk factor for DN but also as evidence of early organ damage. MAU has been recognized as a predictor of progression to ESRD in T1DM and T2DM.	Recent studies have raised growing concerns about the value of MAU as a predictable marker of progression to ESRD. MAU may represent an initial reversible phase of kidney damage rather than the inevitability of progression to ESRD. Thus, while MAU may be an indicator of renal injury, considerable doubt has emerged that it is a predictor of ESRD in patients with diabetes.
Creatinine	Creatinine is a breakdown product of the phosphocreatine in muscle. Approximately 2% of the body's creatine transformed into creatinine. Serum creatinine normal range is 0.8 to 1.4 mg/dL in adult males and 0.6 to 1.2 mg/dL in adult females. Creatinine is a fairly reliable indicator of kidney function because a high creatinine level in the blood is associated with poor clearance of creatinine by the kidneys.	The use of serum creatinine as an indirect marker is limited because several factors influence serum creatinine levels to include age, race, gender, pregnancy, muscle mass, drug metabolism, protein intake, medications (corticosteroids), drugs. Its sensitivity is poor at the early stages of the disease. GFR may deteriorate by more than 50% before a significant rise in serum creatinine.

Blood Urea Nitrogen (BUN)	Urea is a waste product of protein metabolism. Urea is filtered through kidneys and excreted in the urine. The normal level of BUN is 7-20 mg/dL. Elevated BUN levels could be an indicator of kidney damage and dysfunction. The BUN-creatinine ratio is an accurate measurement of kidney function.	Several factors that influence blood volume and renal blood flow may impact on BUN levels: febrile illness, high protein diet, alimentary tube feeding, alcoholic addict, gastrointestinal bleeding, dehydrated patients, and drugs. Because the synthesis of urea depends on the liver, severe liver disease can cause a decreased BUN.
Cystatin C	CysC is a low-molecular-weight (13 kDa) protease inhibitor produced by all nucleated cells. Kidney glomerulus filters CysC that is metabolized by proximal renal tubular cells. Normal range of serum CysC is 0.6-1.0 mg/L. It is useful to detect early and mild even before the development of MAU. Its levels are correlated with GFR and are unaffected by muscle mass. It is a sensitive marker of early DN when eGFR remains > 60 mL/min.	The measurement of CysC level is currently not routinely used due to the higher cost of the immunoassay. Both these factors limit its use in clinical practice at present. Some factors can also influence CysC levels, such as alterations in thyroid function. Consequently, CysC should not be considered for the evaluation of GFR without assessing thyroid function tests. They are also liable to change in patients with CKD receiving glucocorticoids.

Classification of novel biomarkers of diabetes nephropathy

Biomarkers have been classified based on the various stages of exposure to disease. They are also useful in the investigation of the natural history and prognosis of a disease. Apart from the etiology of the disease, biomarkers have the potential to identify disease at the earliest stage, reducing pathogenesis and helps in risk prediction. Biomarkers can also provide insight into disease progression, prognosis, and response to therapy.

Characteristics of the novel biomarkers

- Availability of source material, blood, urine, etc.
- Biologically reliable and accurate judgment on the underlying disease mechanism.
- Diagnostic and prognostic utility.
- High sensitivity and specificity.
- Non-invasive, easily measured, inexpensive, and produce rapid results.

Novel Biomarkers for diagnosis of Diabetes nephropathy

Commonly biomarkers for diagnosis and monitoring targeted drug therapy in DN are categorized as given below;

A. Novel Biomarkers of AKD

B. Novel Biomarkers of CKD

C. Biomarkers of Glomerular Diseases

D. Biomarkers of Nephrotoxicity

The combination of different types of technologies provides more effective methods to identify and validate new disease biomarkers in blood or any other body fluids.

A. Novel Biomarkers of Acute Kidney Disease

AKD is an abrupt or rapid decline in renal filtration function associated with a significant increase in morbidity, mortality, and cost of care.

Calprotectin	Calprotectin is a pleiotropic molecule in acute and chronic inflammation. Its levels are seen to rise within 2 hrs and reach a peak in 48 h in surgery for kidney tumors. Elevated levels of calprotectin sustain in post-operative period for 5 days. Due to calprotectin role in AKD is yet to be incompletely defined, its interpretation need extra caution in DN as it is increased in rheumatoid arthritis, inflammatory bowel disease, prostate cancer, etc.[6]
CysC	Cystatin C (CysC) is filtered freely by the glomerulus, completely reabsorbed and metabolized in the proximal tubule. The level of CysC is independent of muscle mass over other kidney markers, which becomes important in patients with prolonged hospitalizations[7].
TIMP-2 x IGFBP7	Urinary Tissue Inhibitor of Metalloproteinases–2(TIMP-2) x Insulin like Growth Factor–Binding Protein 7 (IGFBP7) has been recently discovered and validated as sensitive biomarkers to predict stage 2 or 3 AKD in high-risk patients [8]. In the long-term follow-up of the SAPPHIRE validation study, the authors showed that TIMP-2 x IGFBP-7 levels in ICU admission were predictive of a composite of death or receipt of renal replacement therapy during the next 9 months in patients who developed AKD [9]. The clinical utilization of urinary TIMP-2 × IGFBP-7 was demonstrated in the PrevAKD trial in Kidney Disease Improving Global Outcomes (KDIGO) guidelines in patients undergoing cardiac surgery with high risk for AKD [10].
IL-18	Interleukin-18 **(**IL-18) is a key mediator of innate and acquired immunity and candidate urine biomarker for renal parenchymal injury formed in the proximal tubules [11]. Recent reports addressing the role of IL-18 in kidney diseases indicate the involvement of this cytokine in acute tubular necrosis and renal vasculitis[12].
KIM-1	Kidney Injury Molecule 1(KIM-1) has low basal expression in the normal kidney but is up-regulated in post ischemic injury in the proximal tubule. The extracellular domain of KIM-1 appears in the urine shortly after ischemic injury and can be readily detected by a KIM-1 urinary dipstick [13]. In a study conducted by Ichimura et al it was established that KIM-1 was recognized as apoptotic cell surface-specific epitopes expressed by apoptotic tubular epithelial cells and subsequently phagocytosed apoptotic bodies and necrotic debris[14].
L-FABP	Liver-type Fatty Acid–Binding Protein (L-FABP) level is seen increased in urine in patients who sustained AKD following cardiac surgery. The L-FABP gene is altogether expressed in renal cortex and is induced by hypoxia. In renal transplant recipients, urinary L-FABP strongly correlates with ischemic time, hence the proposed potential marker of renal hypoxia[15] . A study conducted in critically ill patients with early AKD found that L-FABP improved the prediction model for AKD progression, dialysis, and death within 7 days[16].
NGAL	Neutrophil Gelatinase-associated Lipocalin (NGAL) raised has been documented in thick ascending limb of the loop of Henle and the intercalated cells of the collecting duct are the primary sites of NGAL production in the kidney [17]. In human studies, the expression of the NGAL mRNA and protein has been shown to be significantly increased in the kidney tubules in the Ischemic, septic, or post-transplantation AKD, 2-6 hours after cardiopulmonary bypass surgery[18].

AGT	Urine Angiotensinogen (AGT) is a promising biomarker for AKD progression in acute decompensated heart failure [19]. Yang et al investigated that AGT along with other biomarkers like NGAL, KIM-1, and IL-18 and AGT outperformed with an AUC 0.78 for AKD progression and 0.85 for progression with death [20].
miR	MicroRNA (miR), microRNA 21 (miR-21) in urine and serum is a biomarker of AKD progression; urine miR-21 was a better outcome predictor than plasma miR-21. Various other forms of microRNA have been evaluated and their values were found to be altered several days before abnormal serum creatinine. Several micro RNA have been demonstrated to be independent predictors of mortality in AKD patients requiring renal replacement therapy [21].

B. Novel Biomarkers of Chronic Kidney Disease (CKD)

In CKD, progressive interstitial kidney inflammation with fibrosis develops renal failure with anemia, proteinuria, hyperphosphatemia, hypertension, cardiac hypertrophy, and ultimate death. ESRD is the renal pathologic process independent of the underlying cause of the disease.

ADMA	Increase level of Asymmetric Dimethylarginine (ADMA) results in decline in nitric oxide production, which in turn is associated with endothelial dysfunction and kidney damage[22]. A study on patients CKD and diabetes mellitus showed that reduction of proteinuria is accompanied by a lower ADMA level in serum, suggesting that increased cell death may contribute to ADMA formation and endothelial dysfunction in diabetes CKD[23].
Cystatin C (CysC)	CysC is a protease inhibitor used in the measurement of renal function and determination of the eGFR. At present serum creatinine and GFR are the two parameters being used to diagnose, evaluate prognosis, and monitor the response to treatment has certain limitations[24] . Equations combining CysC and serum creatinine perform better than either measurement alone in the diagnosis of CKD. Combining serum creatinine, CysC, and urine albumin-to-creatinine ratio also improves risk stratification and assessment of CKD progression and mortality[25].
KIM-1	KIM-1 expressions promote kidney fibrosis and establish a link between acute and recurrent injury with progressive CKD. In a study of DN, serum KIM-1 level predicts the risk of ESRD during 5-15 years of follow-up, identifying KIM-1 as a marker for CKD [26]. After the proximal tubule injury, tubular cell polarity is lost and KIM-1 may be released directly into the interstitium. Further, increased transepithelial permeability leads to the leak of tubular contents into the circulation[27].
L-FABP	L-FABP is predominantly expressed in human renal proximal tubules and can be detected in the urine only when the kidney is damaged[28]. Kamijo and colleagues reported that urinary L-FABP levels in CKD patients were correlated in proteinuria and the progression of CKD measured by serum creatinine[29]. A study done by Tamami Tanaka et al[15] stated that urinary L-FABP showed correlations with BUN and pathological changes, whereas other conventional urinary markers failed to detect the interstitial damages.
miRNA	Recent literature showed more than two thousands of miRNAs has been identified in humans[30] . Khurana et al observed in this research several other noncoding RNA classes, like transfer RNAs (tRNAs), tRNA fragments (tRFs), mitochondrial tRNAs, or long intergenic noncoding RNAs (lincRNAs), and identified nearly 30 differentially expressed noncoding RNAs in CKD patients as suitable biomarkers for early diagnosis. Of these, miRNA-181a appeared to be the most robust biomarker for CKD[31].
NGAL	Davide Bolignano et al[32] indicated that NGAL represents a novel risk marker of CKD progression. A study done by S, Zang X, et al[33] suggested that NGAL, cystatin C, β2-MG, α1-MG showed good correlation with eGFR. Median concentrations of the 4 markers progressively increased across various stages of CKD. Zang and colleagues reported that NGAL inhibits elevation of serum creatinine and blood urea nitrogen and reduces renal tubular epithelial cells apoptosis.

Uromodulin	Uromodulin (Tamm–Horsfall protein) a glycoprotein produced in the tubular cells of the distal tubule and released into the tubular lumen. CKD is characterized by interstitial fibrosis and tubular atrophy suggesting lower levels of uromodulin. Thus, uromodulin may represent intact renal mass rather than renal function. Steubl et al showed that plasma concentration of uromodulin was a marker for intact renal mass and used for identification of early stages of CKD[34].
β-PT	β-Trace Protein (β-TP) is a protein isolated from the cerebrospinal fluid, as well as in low concentrations in serum and urine. A study done by Dajak M and colleagues stated that β-TP may be a useful and reliable urinary marker of tubular damage[35] [35]. Studies in CKD patients demonstrated that serum β-TP is an adequate marker of GFR impairment with a diagnostic accuracy similar to those of serum creatinine, CysC, and β2-microglobulin (β2M)[36].

C. Biomarkers of Glomerular Diseases

Glomerular diseases fall into two major categories; Glomerulonephritis describes the inflammation of the membrane tissue, and Glomerulosclerosis describes the hardening of the blood vessels within the kidney. DN is the leading cause of glomerular disease and total kidney failure.

FSGS	Focal segmental glomerulosclerosis (FSGS) is the leading cause of ESRD in the United States. The diagnosis and evaluation of FSGS rely on the correlation of the clinical history, laboratory measurements of serum albumin, urine protein, viral markers, and renal histopathology. Proteinuria may be in the nephrotic or subnephrotic range [37].
(IgAN)	IgA Nephropathy (IgAN) is considered as a common form of primary glomerulonephritis. IgA and is a predictable marker from minor urinary abnormalities to ESRD. IgA nephropathy develops when IgA protein accumulates in kidneys causing inflammation. The inflammation leads to excretion of blood and protein into kidneys dysfunctions. Approximately 20-40% of patients with IgAN may develop ESRD within 20 years [38].
LN	Lupus Nephritis (LN) is a major risk factor for morbidity and mortality in SLE and 10% of patients with LN will develop ESRD[39]. Avihingsanon and colleagues reported that measurement of urinary messenger RNA (mRNA), levels of chemokine and growth factor genes could identify active class IV LN more accurately and could be used to follow response to therapy[40].
MN	Membranous nephropathy (MN) is a common cause of idiopathic nephrotic syndrome in adults. The formation of sub epithelial immune deposits and complement activation causes alterations of the basement membrane structure and damage to the filtration barrier, causing proteinuria [41]. A study conducted by Weisong Qin et al [42] concluded that anti-PLA2R is a specific marker of idiopathic MN in Chinese patients. In 2009, Beck and colleagues identified the M-type PLA2R, a transmembrane receptor that is highly expressed in glomerular podocytes, as a target podocyte antigen that triggers an antibody response in membranous nephropathy [43].

D. Biomarkers of Nephrotoxicity

Nephrotoxicity occurs when specific detoxification and excretion do not work properly due to the damage or destruction of kidney function by exogenous or endogenous toxicants. It includes molds and fungi, cancer therapeutics such as cisplatin, antibiotics such as aminoglycosides, metals such as mercury, arsenic, and lead, and drugs of abuse such as cocaine. It is a purely biological process induced by external factors or agents rather than metabolic alterations. Therefore, diabetes and any metabolic manifestations have no close role in dysfunctions of the kidney. Novel biomarkers of nephrotoxicity include the following:

- Alanine aminopeptidase (AAP)
- Gamma-glutamyl transpeptidase (GGT)
- Glutathione-s-transferase (GST)
- Kidney injury molecule 1 (KIM-1)
- Lactate dehydrogenase (LDH)
- N-acetyl-glucosaminidase (NAG)

Summary

Biomarker assays can be evaluated for analytical performance and clinical performance. Additionally, a biomarker assay is said to have clinical utility if it ultimately improves patient outcomes when used as intended. Innovation in nephrology is progressively being rejuvenated, as advances in the fields of proteomics, genomics, and metabolomics improve the ability of researchers to study various proteins, and these techniques become widely available, the results from biomarker discovery studies are much anticipated. Above mentioned potential novel biomarkers shall be used for routine diagnosis of DN in future. Though there is a limitation in terms of technical expertise and cost, the above biomarkers will prove their merits in diagnosis of DN.

Acknowledgement

This review was a manuscript after thoughts of utility of contents for well-being of patients by our own colleagues. So first of all, we are thankful to all sufferers who gave us an opportunity. Secondly, we are grateful to all scientists and researchers who have given their contribution for inventions and discoveries of new biomarkers of diabetes nephropathy. Last but not least, we would like to acknowledge: WHO, ADA, IDF, Medscape, Medline, Research Gate, Google Scholar and many more who have contributed for completion of this work.

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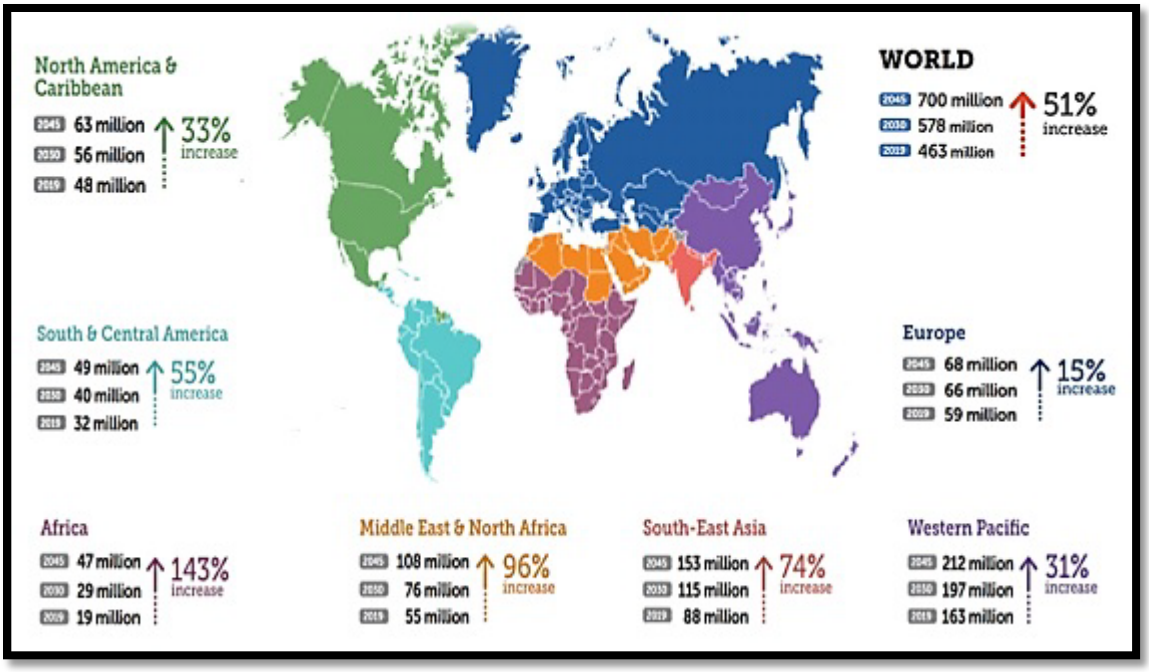
Legend Tables

Fig 1: Global burden of diabetes mellitus, 2010-2045.



(Source: International Diabetes Federation Diabetes atlas 9th edition, 2019)

Fig 2. Pathophysiology of diabetes nephropathy [4].

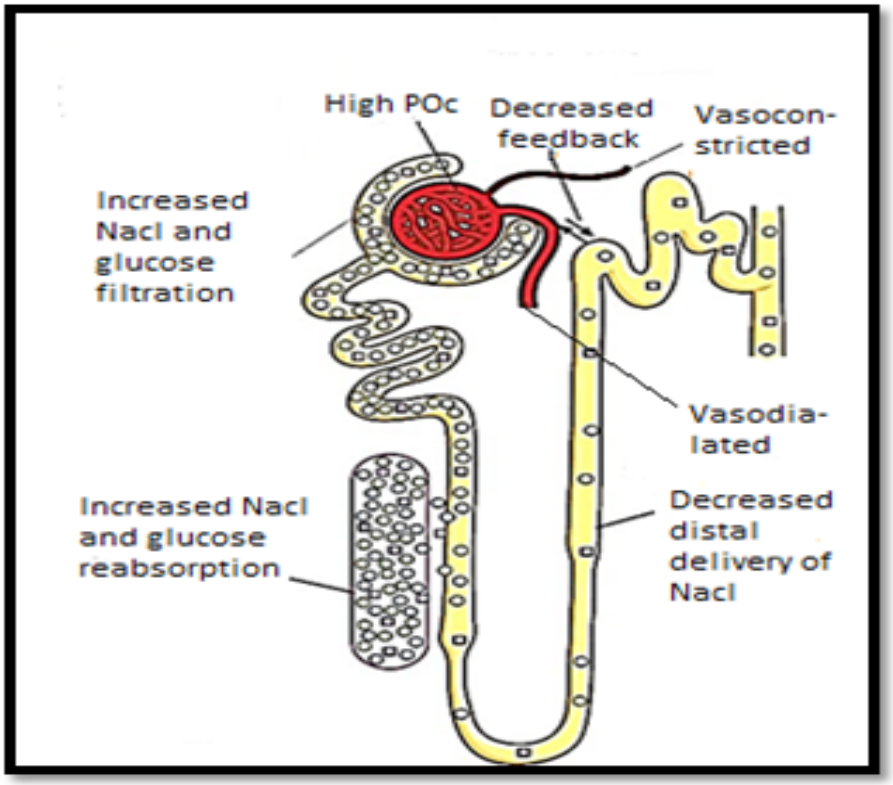
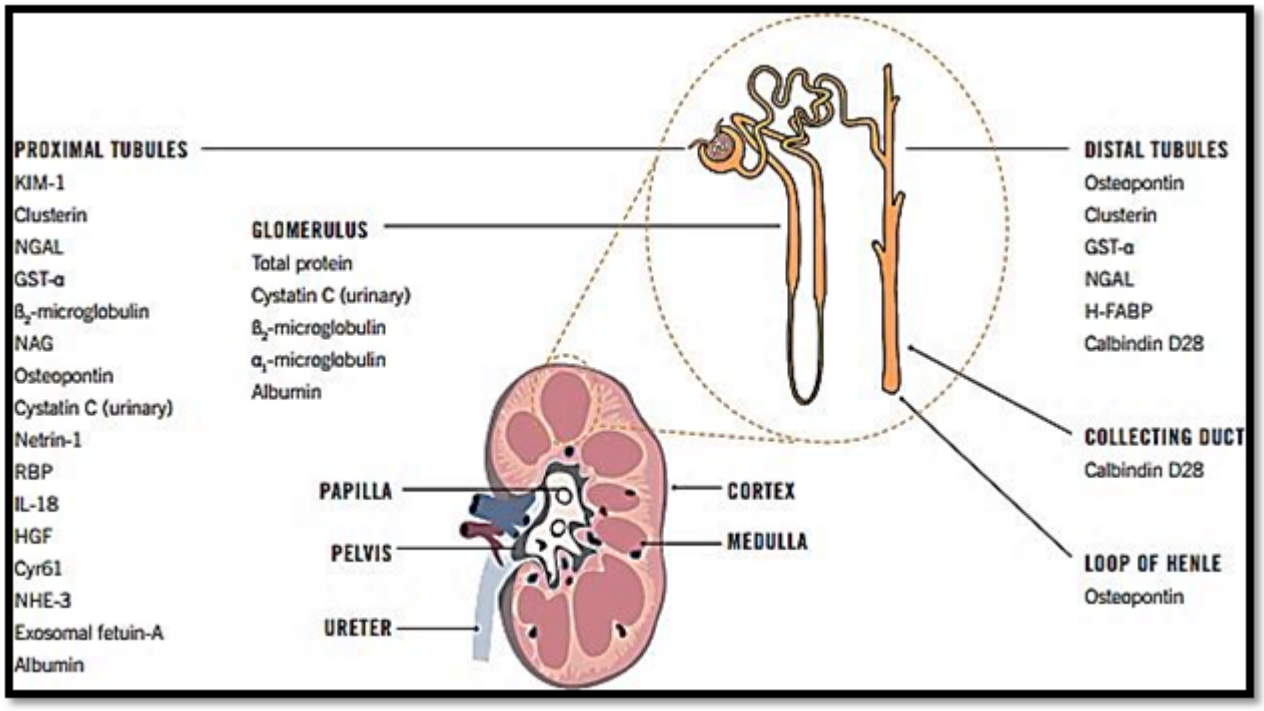


Fig 3: Diagram showing renal biomarkers reported in literature survey.



(Source: Novel biomarkers of DN pacific biomarkers, 2013)