REVIEW ARTICLE

Chinese Journal of Medical Research
Chinese J Med Res 2022; 5(1): 8-12

ISSN(e): 2618-091X
ISSN(p): 2663-8053

Diagnostic Utility of Urinary Kidney Injury Molecule 1 (KIM-1) as an early Predictive Biomarker for Acute Kidney Injury (AKI) in Diabetes Mellitus induced Nephropathy

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Received: January 22, 2022; Accepted: March 13, 2022

Abstract

Diabetic nephropathy (DN), also known as diabetic kidney disease (DKD), a major consequence of type 1 and 2 diabetes mellitus getting down to chronic kidney disease (CKD), In many settings acute kidney injury singly could be a health risk pre disposal factor for (CKD), Accumulated evidence implicates proximal tubules involvement in the pathogenesis of diabetes mellitus with persistent hyperglycemia as an indicator for possible renal tubule injury Moreover Kidney injury molecule (-1), is a protein mainly expressed at the proximal tubule cells at low levels in normal kidneys but it is significantly up regulated following kidney injury. The current review article mainly discusses the development process of diabetes mellitus caused nephropathy as well as the utility of urinary kidney injury molecule - 1 (uKIM-1), as a diagnostic biomarker for the timely detection of acute kidney injury before the development of overt renal dysfunction. Urinary (KIM-1), maybe capable of identifying renal dysfunction caused by diabetic nephropathy its utility is supported by many studies. However, it should be coupled with intricate clinical judgment in order to achieve the best outcome of the specific patient management.

Keywords: Diabetic nephropathy, Diabetes Mellitus, Chronic kidney disease, Acute kidney injury, Urinary KIM-1.

INTRODUCTION

Chronic kidney disease (CKD), is increasingly recognized as a big challenge to the global health care systems presenting with a high economic input but low output high risk factor for morbidity and mortality [1]. Recent figures estimated that globally (697.5), million people suffer from chronic kidney disease (CKD) [2]. In many settings (CKD), is considered as a downstream condition as an example acute kidney injury (AKI), singly could be a health risk pre disposal factor for (CKD), according to reports in several (CKD), studies [3]. Furthermore, diabetes mellitus may significantly affect kidneys consequently diabetic nephropathy is the most frequently-encountered entity among end stage renal diseases cases.

In this setting Diabetic nephropathy (DN), also known as diabetic kidney disease (DKD), a major consequence of type (1 and 2 diabetes), mellitus [4]. Incidence rates for (DN), is on the raise a big percentage of the majority patients necessitating a regular dialysis mode of treatment, diabetes mellitus (DM), is implicated as the main cause [5]. The structural and metabolic alterations of the nephron like thickening of glomerular basement membrane and loss of endothelial fenestrations are amongst the multiple kidney compartments lost integrity due to diabetes. In addition, mesangial matrix expansion, and loss of podocytes with effacement of foot processes are also highly regarded as outcomes of diabetes [6–8]. In turn these structural defects result into glomerular hypertrophy glomerulosclerosis, tubulointerstitial inflammation and fibrosis which finally contribute to acute kidney injury (AKI).

Acute kidney injury (AKI), on the other hand, is an abrupt clinical emergency which may range from a minor loss of kidney function to a complete kidney failure and happens within a few hours to days Clinically it is characterized by oliguria and in the course of an increase in serum creatinine (sCr), within 48 h of either (0.3mg/dL), or (50%), in relation to initial values within the first 7 days after exposure to potential nephrotoxic [9]. Taking into consideration that (AKI), is a reversible condition upon early detection urges for integrating reliable and efficient screening methods for accurate timely diagnosis and appropriate management moreover in individuals at high risk [10].

The current routine detection procedures blood urea nitrogen (BUN), serum creatinine (sCr), and creatinine clearance are limited as diagnostic assay for within the early stages of (AKI),

due to the late involvement of the specific metabolites in the course of the disease development [11]. Hence biomarkers warranting early detection and monitoring of acute kidney injury in diabetes is requirement an example of a biomarker that have proven because of its sensitivity and specific for timely involvement of proximal tubular cell injury in both humans and animal studies is the urinary concentration of Kidney Injury (Molecule-1), (KIM-1) [12–14].

Aim

This narrative review discusses the development course of diabetes mellitus caused nephropathy as well as the utility of urinary kidney injury (molecule-1), (uKIM-1), as a diagnostic biomarker for the timely detection of acute kidney injury before the development of overt renal dysfunction.

What is KIM-1

Kidney injury (molecule-1), a proximal tubule apical type 1 transmembrane glycoprotein basically primarily expressed on the surface of (T), cells possessing two extracellular domains, O-glycosylated mucin and (6-cysteine), domains [15, 16]. (KIM-1), protein is encoded for by the human KIM-1 gene located on chromosome (5p33.3), Furthermore it contains signal peptide prior to the N-terminal domain this in turn, is directly behind (KIM-1),'s location on the cell surface [17,18]. (KIM-1), protein is expressed at low levels in physiologically normal functioning kidneys but is highly upregulated in proximal tubule cells post injury to the kidney. After renal injury, there will be pathologically induced separation of the extracellular domains of (KIM-1), from the cell surface gaining access to urine through a metalloproteinase mediated-process [16]. The concentration of urinary (KIM-1), is reported to be markedly increased within few hours after renal injury [19]. The protein upregulation is mainly observed in the proximal tubule cells during acute tubular injury [13-20]. Therefore, identifying mechanisms of specifically detecting and quantifying the level of urinary (KIM-1), in diabetic patients may potentially be an effective method for the early diagnosis of (AKI), in patients of diabetic nephropathy.

Diabetic Nephropathy Progression to Acute Kidney Injury

Diabetic nephropathy (DN), has a significant contribution to the burden of (CKD), a number of studies have implicated (DN), progression to (AKI), especially in patients with persistent hyperglycemia [21, 22]. Sustained hyperglycemia is believed to be highly associated with advanced glycation end products (AGEs), oxidative injury hypoxia metabolic and energetic disturbances over activation of theremin-Angiotensin-Aldosterone System (RAAS). and the secretion of significant inflammatory and fibrotic factors like (TGF-β), which in turn drives the initiation and development of renal injury leading to fibrosis [8-23].

During the onset of (DN), associated with hyper glucose reabsorption hypertrophy of the proximal tubular cells combined with high levels reactive oxygen species (ROS), secretion oxidative injury and (TGF-β), production leads to (AKI) [24–26]. In addition diabetic environment in the nephron incites untimely proliferation of tubular cell, further introduction of more complex reactions of (TGF-β), and cyclin-dependent kinase inhibitors results in the arrest of (G1), phase of the cell cycle then switch to tubular hypertrophy and a senescence-like phenotype development as demonstrated in (figure 1), The typical phenotypic growth triggers rare feedbacks like the salt paradox a characteristic of diabetic kidney disease This molecular pathway activation likely initiate tubulointerstitial injury and diabetic nephropathy [25]. Moreover, it was hypothesized that diabetic tubular expansion in relation to molecular changes initiates diabetic nephropathy progressing to advanced (CKD), likely increasing the susceptibility to (AKI) [25-27].

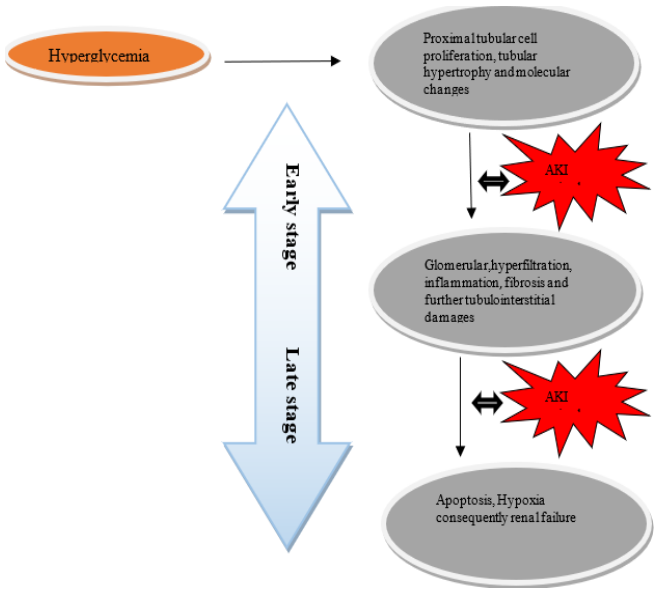

Figure 1: Schematic presentation of the pathological cellular and molecular alterations of the kidney tissues in response to hyperglycemia and the subsequent development of (DKD), progressing to Kidney failure. The process is potentially involved with episodes of acute kidney injury

Recently it was reported that (31.1%), of (292), diabetic kidney disease patients developed (AKI), at a certain stage of the disease [22]. In addition, higher incidences of (AKI), was reported among diabetic patients undergoing different forms of surgery [28,29]. on different forms of therapeutic prescriptions [30]. diabetic patients experiencing sepsis/septic shock [31]. and those without associated events [32]. Moreover (AKI), has also been reported to be independently associated with diabetes which make the need for its early detection a paramount [33,34].

The early-stage involvement of proximal tubule in (DKD), pathogenesis makes (KIM-1), a potential predictive (DKD), induced (AKI), biomarker Renal insults like diabetic nephropathy resulting in tissue injury may affect the kidney function upregulation of (KIM-1), protein and its substantial secretion in urine [35]. All studies reported a strong association between urinary (KIM–1), or plasma (KIM–1), with progressive decline in renal function in diabetic patients [36–40]. However, there were several variations in this relationship mainly attributed to severity of diabetes and the proportionality of renal impairment Moreover studies have reported an association between urinary (KIM–1), with urinary albumin although its concentration markedly increases in both albumin uric and non-albumin uric patients making it an independent biomarker in addition to decrease in estimated glomerular filtration rate [36-39].

Urinary KIM-1 as a Biomarker in AKI

A biomarker is a parameter of protein origin for detecting structural, biochemical, physiologic or genetic changes in the body It undergoes changes including up or down regulation which in turn is objectively measured and evaluated as an indicator for a particular pathological or physiological process disease or pharmacologic responses to a therapeutic intervention [41]. Currently blood urea nitrogen (BUN), serum creatinine estimated glomerular filtration rate (eGFR),

proteinuria and albuminuria measures are being used to assess for the presence and progression of kidney pathology However studies have evidently reported suboptimal outcomes with these biomarkers in terms of specificity and sensitivity at timely detection of kidney diseases [42,43]. Additionally, the imprecision lack of renal tissue injury specificity and lack of sensitivity to small changes in renal function lowers the utility potential of these measures.

Several characteristics of (KIM-1), qualify it as an absolute biomarker of acute kidney injury especially in persistently hyperglycemic patients Firstly lack of (KIM-1), expression in a normal functioning kidney Second it is highly upregulated following renal tubulointerstitial injury specifically in the apical membrane of the proximal tubule and lastly the capacity to remain highly concentrated in affected epithelial cells until completely recovered [12-44]. Evidence suggests (KIM-1), is highly sensitive biomarker responding to proximal tubular damages of different insults in a study evaluating kidney biopsy specimen of 6 patients with acute tubular injury (uKIM-1), levels was increased within 12 hours after renal dysfunction [45]. Comparably biopsies reported from various renal insults (102 cases), against seven (7), controls (uKIM-1), was significantly increased in all diseases versus control except in minimal changes and was confirmed to be associated with tubulointerstitial inflammation [46]. In patients with type (1 DM), with or without albuminuria elevated (KIM-1), was strongly associated with early progressive renal decline [40]. Similar findings were replicated in another cross-sectional study in which urine (KIM-1), proved to be more sensitive as compared to albuminuria measurements [36]. Furthermore, a comprehensive meta-analysis summarizing at least 11 studies and (2979 cases), authors reported a (uKIM-1), specificity and sensitivity for the diagnosis of (AKI), at (86.0%), and (74.0%), respectively [47].

In another study involving (4739), participants reported that during a mean follow-up period of above 16 years high (KIM-1), levels was associated with low (eGFR), Further proving the utility potentials of the biomarker at predicting renal function deteriorations moreover in middle-aged patients [48]. Moreover detecting (AKI), development in special patients' population, (uKIM-1), together with other biomarkers (N-acetyl-β-D-glycosaminidase), (NAG), and neutrophil gelatinase-associated lipocalin (NGAL), showed diagnostic value in predicting renal injury post-cardiac surgery [49,50]. Several studies also confirmed baseline urinary (KIM-1), concentrations to be significantly increased with detectable urine protein and correlated with its severity indicating possible hypersecretion in renal tubular damage [37-51]. Furthermore urinary (KIM–1), was found to be a good (AKI), predictor in adult patients with sensitivity and specificity of (74%), and (84%), respectively Moreover (uKIM–1), was reported to have a diagnostic performance of (85%), as a biomarker for early diabetic nephropathy in (765 T2DM), patients with normoalbuminuric [52,53].

Taking into consideration its specificity and sensitivity in early diagnosis and or prediction of renal injury urinary (KIM-1), maybe capable of identifying renal dysfunction caused by diabetic nephropathy and may even hold a predictive role in acute kidney injury.

Table 1: Acute kidney injury induced Diabetic Nephropathy incidences and respective findings in diabetic patients.

Condition, year, (reference)	Study type	Sample type, size (N)	Findings
Diabetic kidney disease (DKD), 2021.[22]	Retrospective – open cohort study	Humans (292)	31.1% of the patients followed up developed AKI and majority there was related sepsis, moreover AKI was associated to declining eGFR.
Type 2 diabetes mellitus, 2020.[36]	Cross-Sectional	Humans (602)	Urinary and serum KIM-1 were associated with increase in Albumin to creatinine ratio, however only serum KIM-1 was associated with lower eGFR.
DN with T2DM, 2020.[37]	Cross - section	Humans (90)	Urine KIM -1 and NGAL are independent markers for early diagnosis of DN
T2DM,2016.[38]	Case -control	Humans (48)	uKIM – 1 was suggested as a potential early biomarker for DN
Diabetic Nephropathy, 2019.[39]	Case - control	Humans (60)	KIM – 1 was observed to increase with progress in kidney damage with or without kidney function derangement.
T1DM, 2016.[40]	Cross - section	Humans (462)	Increase in plasma KIM – 1 level is strongly associated with risk of progressive renal decline in T1DM.
T1DM & T2DM after Coronary artery bypass grafting (CABG), 2015.[29]	Case - control	Humans (5581)	There was increased risk of AKI in T1DM compared to T2DM patients post CABG.

DKD = Diabetic kidney disease, AKI = Acute kidney injury, eGFR = estimated glomerular filtration rate, KIM – 1 = Kidney injury molecule 1, DN = Diabetic nephropathy, T2DM = Type 2 diabetes mellitus, T1DM = Type 1 diabetes mellitus, uKIM – 1 = Urinary kidney injury molecule 1, NGAL = Nitrophil gelatinase – associated lipocalin, CABG = Coronary artery bypass grafting.

The Origin and Detection Methods of Urinary KIM-1

KIM-1, possesses a single transmembrane domain in its structure and in a setting of ischemic or injury it undergoes metalloproteinase membrane-proximal cleavage leading to release of soluble KIM-1, ectodomain into the urine [54]. The secretion combined with high intrarenal synthesis of KIM-1, mRNA, and protein definitely hyper KIM-1, in the urine during and after AKI, episodes [19-55].

The presence of KIM-1, in urine as a soluble protein is detected using microbe-based assays Recent studies reported that KIM-1, protein can quantitatively be determined by enzyme linked immunosorbent assay ELISA, and immunoblotting [56,57]. Both methods require urine supernatant [38]. Quantifying of uKIM-1, can proceed either with freshly collected or preserved urine samples kept for up to a period of 6 months at -80℃ independent of the addition of protease inhibitors [58]. Importantly a prospective study discovered urinary KIM-1, concentration interference in association with the pre-freezing and thawing time Moreover repeated freeze–thaw cycles adversely affect KIM-1, measurement [59]. Therefore, authors recommend

determination of specific time urine samples should be stored at room temperature, frozen, and defrosted prior to measurement of the analyte [42-40].

CONCLUSION

The diagnostic potential of urinary KIM-1 in early identification and monitoring of DN associated AKI is of great importance. Given the acute nature and severity of the condition, there is a need for a more rapid method of its detection of which there is a possibility of developing a lateral flow immunochromatographic assay for KIM -1 as compared to the currently available assessment tools for AKI. This biomarker seems to be more sensitive and specific; its levels closely mirror the amount of renal tissue damage.

KIM 1 is expressed in urine in form of soluble protein; the quantification of the protein is more reliable due to availability of necessary requirements for the procedure. The utility of KIM 1 protein is more evident and supported by many studies. Therefore, application of uKIM-1 individually or alongside ordinary assays such as sCr, eGFR in clinical diagnosis will likely yield better risk detection and overall management.

In this review we hypothesize that kidney injury molecule 1 (KIM – 1) is secreted and can be excreted in urine shortly after renal tubule injury in diabetic patients proceeding diabetic nephropathy. Future studies are needed to test the hypothesis. Moreover, simplified and available techniques for detecting and quantifying urinary KIM – 1 are also needed. Additionally, well controlled studies with a larger sample size are warranted to validate its potential value across a broader scope of clinical settings.

Authors' contributions

Rogious Mbasani and Nelson Musilanga; Conceived the objective of the paper, reviewed literature and contributed in the write up of the paper. Both authors proof read and equally contributed to the final manuscript.

Conflict of Interest

All authors declare no conflict of interest.

Funding

No funding was received.

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