

Kidney manifestations of diabetes mellitus - A ReviewSwaminathan S.¹, Rajeswari S.² and Wasim Mohideen³¹Director of Laboratory Services & Consultant Biochemist, Techmed Health Centre & Diagnostic Pvt Ltd, No: 01, Siva Building, Krishna Street, off North Usman Road, T. Nagar, Chennai 600 017, India²Assistant Manager QA & QC, Triviron Health Care Pvt Ltd, A2 & A3 SIPCOT, Irrungattukottai, Sriperumbudur, Chennai, India³Director of Preventive & Wellness Medicine, Techmed Health Centre & Diagnostic Pvt. Ltd, No: 01, Siva Building, Krishna Street, off North Usman Road, T. Nagar, Chennai 600 017, India

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T. Nagar, Chennai 600 017, India***Article History:****Received:** 19/02/2018**Revised:** 02/04/2018**Accepted:** 04/04/2018**DOI:** <https://doi.org/10.7439/ijbr.v9i4.4657>**Abstract**

The prevalence of diabetes mellitus, especially T2DM is on the increase worldwide and in a developing country like India, as of date approximately 30 – 40% are identified to have DM. Sedentary life style, obesity, increased BMI, insulin resistance, hyperlipidemia, delayed diagnosis, metabolic syndrome are some of the factors that lead to the development of DM. Extensive research have been conducted in this field and still more studies are being undertaken. The first organ affected in all uncontrolled DM patients is the kidney, followed by liver and cardiac. Kidney disease predominantly account for increased mortality among T2DM and is the main cause of CKD as well as DN. Treatment of CKD due to uncontrolled T2DM is still controversial because of the scarcity of evidence available. MA plays a significant role in screening pre and established DM. Increased levels of urate are identified as one of the metabolic disturbances in T2DM. This review article highlights the research findings during the last two decades on the manifestations of kidney disease in T2DM.

Keywords: DM, T2DM, ESRD, CKD, GFR, HbA1C, MA.**1. Introduction**

Diabetes mellitus (DM) is a growing epidemic in a developing country like India. According to World Health Organization (WHO) statistics the numbers of people living with DM are increasing at the rate of 8% per year in India. The above figures have been arrived at from many epidemiological studies. Type 2 Diabetes Mellitus (T2DM) is prevalent compared to T1DM. The factors that influence the development of T2DM are obesity, secondary life style, hypertension and metabolic syndrome (MetS). The Progressive decline in uncontrolled T2DM starts with kidney, cardiac, liver and latter many organs. T2DM is now prevalent in developing countries compared to developed countries. Many risk factors will start if there is delayed diagnosis and treatment leading to many micro and macro vascular complications. It is therefore important to develop

efficient therapeutic treatment before organs like kidney, cardiac and liver start malfunctioning [1].

No correlation has been established to link MetS to renal function. Decreased Glomerular Filtration Rate (GFR) is the common finding in T2DM and there was no difference between patients with and without MetS. Waist Circumference (WC) will be useful indicator to assess its association to microalbuminuria (MA). MetS shows association to WC, but not to decreased GFR in a group of Japanese T2DM patients.[2]

Developing of Diabetic Nephropathy (DN) will progress to End Stage Renal Disease (ESRD) and such observation is prevalent worldwide. Non-Diabetic Renal Disease (NDRD) is a common finding in all DM patients. No uniform association exists between DN to renal and retinal relationship in T2DM.

While there is higher incidence of NDRD in T2DM patients, DN is less frequent and is a poor predictor of the type of DN under these conditions, renal biopsy is the method of choice for a precise diagnosis of DN in T2DM patients. [3]

In the recent past urinary stone disease have shown an increase solely due to dietary modifications. Based on life style and an increased prevalence have been observed in patients with DM. The mean Body Mass Index (BMI) is a useful marker and its level is higher in DM patients compared to BMI of non-DM. Uric acid (UA) calculi formation in DM was found to be significantly higher compared to non-diabetic. A strong association exists between UA stone formation and T2DM. Further correlations have been found between DM, BMI and urinary pH [4]. The common causes of ESRD are DM and hypertension. As long as Fasting Plasma Glucose (FPG) is < 140 mg/dL, glycemic control will be good. When PPPG is between 140-200 mg/dL, glycosylated hemoglobin (HbA1c) will be 6-7% in T1DM and 7-8% in T2 DM patients. Use of metformin for T2 DM is not recommended for patients with chronic renal failure as lactic acidosis will be induced by metformin. The alternate drugs of choice are glipizide and repaglinide [5].

Studies in the recent past have revealed that DN in T2DM patients is increasing worldwide. The largest number of patients requiring dialysis and renal transplantation in developed countries are from T2DM accounting to 50% of ESRD patients. Chronic Kidney Disease (CKD) in DM is considered as heterogeneous. A large number of patients suffer from proteinuric DN and a reduced GFR in the absence of proteinuria have been observed in an increasing number of T2DM patients. The survival of T2DM patients with DN depends upon cardiovascular comorbidity. It has been observed recently that both minor renal hemodynamic and morphological changes are seen even in prediabetes whose conditions do not fall in line with the definition of TDM [6]. Global scenario predicts that the cause for both CKD and ESRD is DN and many researchers have been conducted linking both basic and clinical therapeutics. [7] DM significantly increases the overall morbidity and mortality by elevating the CVD risk. The first organ affected in T2DM patients are the kidneys due to Intera renal - athero and arteriosclerosis together with non-inflammatory glomerular damage. In recent years, Acute Kidney Injury (AKI) has been identified as the clinical and prognostic problem even when mortality did not improve substantially. Of late, there are lacunae involving studies linking AKI to DM and T2DM. [8]

DN is characterized by microalbumin (MA) \geq 300 mg/dL with reduced GFR during pre-diabetes stage after the kidney has been exposed to chronic hyperglycemia. It is a common microvascular complication in all T2DM

patients and is the major cause of kidney failure. GFR < 60mL/min is considered as an independent risk factor for CVD and death. It is important to detect DN during its initial onset which helps early therapeutic interventions to prevent further complications. Further physicians should consider demographic factors, degree of kidney impairment, adverse drug effects, tolerability and interactions with other drugs or risk factors and comorbidities before prescribing drugs for T2DM patients. Regular follow up should be undertaken by adjusting the therapeutic regimen to control risk factors and patients should be taken care of by referral specialists. [9]

2. DN and Non-Protein Nitrogenous Substances (NPN)

Serum Creatinine (Cr) and Blood urea Nitrogen (BUN) are the two principal markers that are measured to diagnose GFR. These two levels usually increase in serum during advances stages of kidney dysfunctions and increase in the levels of beta 2 microglobulin (β 2M), BUN, Cr and glucose with a decrease in insulin were observed, while β 2M increase just one day after injection of streptozotoin injection BUN and Cr were found to be elevated at day two. These observations confirm that β 2M is a better diagnostic marker compared to the other two (BUN & Cr). [10] DM has a profound effect on renal impairment changes in older people. Routine blood markers of DM together with GFR and MA will help to identify renal impairment during different stages of DM populations and such markers should be used to identify DN especially in older population. Both the American Diabetes Association (ADA) and the National Institute of Health (NIH) recommend once a year to check eGFR using Cr value to detect the degree of kidney impairment. If conventional risk factors like age, sex duration of DM, smoking, obesity, Blood Pressure (BP), glycemic control and DN are adjusted, eGFR remains an independent and significant predictor of renal impairment. As the accuracy of Cr value is affected by methodological differences, cystatin C (CysC) is emerging as a future marker for DN. However, reference intervals for different age groups, especially for genetic population should be established before CysC is being put to use to diagnose DN. Many studies have stressed the importance of measuring MA, eGFR, Cr as well as Hemoglobin to confirm the diagnosis of ESRD. [11]

Abnormal urinary Albumin Excretion (UAE) is found in about 25% of T2DM patients and some were found to have azotemia. Albuminuria was found to be associated with long term duration of DM, poor glycemic controls as shown by increase in HbA1c level and elevated BUN. All these will lead to the progression of DN [12] A positive correlation exists between Cr and age in all DM patients and female patients show correlation between FPG and metabolic end products, BMI as well as to uric

acid(UA).[13] In renal disease, as well as in hypertensive nephropathic cases, salivary BUN and Cr could be used to screen such cases.[14] Insulin insensitivity in terms of phosphate transport has been observed in DM patients with renal insufficiency and it is related to GFR. Insulin insensitivity in such patients could be assessed by measuring the Factorial Excretion of Phosphate (Fe-P) and it probably occur in renal tubules. [15]

Insulin Resistance (IR) is the key pharmacological defect which leads to the development of T2DM. Significant association exists between serums Magnesium (Se-Mg) in diabetic patients compared to controls. Further, statistically significant association was found for Homeostatic Model of Assessment (HOMA) among the diabetic groups. An inverse significant association was also found between Se-Mg and fasting insulin level as well as a highly significant inverse correlation between HOMA and insulin level.

A positive correlation between Se-Mg and Quantitative Insulin Sensitivity Check Index (QUICKI) shows that Se-Mg level decreases with increase in IR. Further, a strong association was found between fasting insulin and insulin sensitivity indices due to a lower Se-Mg level in controls compared to diabetic patients. All these observations strongly recommend that T2DM patients need treatment to correct hypomagnesemia. [16]

Data from UKPDS indicates that Metformin treatment is the drug of choice to treat T2DM as it has low risk for hypomagnesaemia, highly effective, tolerability, low cost and effective in controlling cardiovascular mortality. Metformin is recommended for T2DM if the eGFR is >30 mL/min/m². However for patients with eGFR $> 30-60$ mL/min/m², frequent monitoring of renal function to be undertaken. Other drugs must be used carefully in T2DM patients with renal dysfunction. Sulphonyl ureas with active hepatic metabolites should be avoided since they are renally excreted and the drug of choice for such patients is Dipeptidyl Peptidase inhibitors. Such drugs do not cause hypoglycemia and they require dose reductions at various stages of renal diseases. [17]

In T2DM patients Cys C is significantly increased, High Density Lipoprotein Cholesterol (HDL-c) decrease while other lipid profile parameters were increased compared to controls. CysC is a useful marker for the evaluation of renal involvement in DM patients and shows significant lipoprotein abnormalities when compared to controls.[18] CKD is a common finding among T2DM patients as it is associated with age, male gender, BP and drugs such as statin use. More prospective observational studies are required to clarify the nature of the above associations. [19]

It has been pointed out that some relationship exists between vitamin D (Vit-D), insulin secretion, IR and β -cell function in T2DM patients; however, evidence

linking Vit-D and T2DM are contradictory and standardized well controlled studies are required. As Vit-D influences the rennin-angiotensin system, inflammation and Mineral Bone Density (MBD), it may be associated with the cause and progression of CKD. Available evidence shows that Vit-D deficiency may be a risk factor for DM and CKD. Supplementation with Vit-D has not shown any improvement in glycemic control or prevent incident DM. More clinical trials with large sample size, extended study period with optimal dose of Vit-D supplementation are needed. [20]

The predominant clinical feature of both early and late stages of DN is progressive renal decline and not albuminuria. Progressive renal decline is a unidirectional process that develops while patients have normal renal function. Decline in renal function progress at a steady state leading to ESRD, but at different rate among individuals leading to proteinuria. As animal model do not mimic progressive renal decline, studies must be conducted in human with Diabetes. Such studies may yield positive findings that will help to develop accurate methods for early diagnosis to select appropriate therapy. [21]

T2DM patients with kidney disease account for the increased mortality. Increased urine albumin excretion and impaired GFR are common among T2DM patients and such patients are prone to increased risk for CVD and mortality. Two recent studies have shown the critical effect of kidney disease on mortality of T1DM and excess mortality was confined only to the group with kidney disease. The degree to which kidney disease captures risk of adverse health problems has not been determined. Such findings in T1DM patients may not extrapolate to T2DM because the later is frequently associated with other comorbidities that affect mortality. [22]

Serum CXCL16 was found to be negatively correlated with eGFR, Creatinine clearance rate and albumin, but positively correlated with 24 hour urine proteins, BUN, Cr and UA after adjusting for age, gender and BMI in subjects with DN. [23]

It is important to control early multifactorial interventions such strict BP control, use of Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin two receptor blockers (A2RBs) and good metabolic control to attenuate CVD risk which will slow that rate of progression to renal disease.

However uncertainties prevail in the use of combined ACE and A2RBs as uncertainty still prevails in such treatment. Multidisciplinary management is required in treating T2DM management with CKD as such conditions are prevalent among chronic diseases which represents a significant public health problems. T2DM is the main cause of CKD and is also a comorbidity of DN. Due to scarcity of evidence available treatment of T2DM patients in controversial. [24]

3. Uric Acid

Association exists between UA calculi with prediabetes, diabetes and obesity. Further, it is also associated with urolithiasis patients undergoing surgical management. [25] Low urine pH, elevated BMI and increased acid intake are the contributing factors for urolithiasis observed in T2DM patients. However, low urine pH is not entirely the contributing factor. [26]

Based on the strong association between T2DM and UA stone formation, UA nephrolithiasis may be used as one of the conditions that may be associated with IR. Based on these observations it is important to screen patients with UA stones, especially if obese for the presence of T2DM or components of the MetS. [27] MetS defines a cluster of metabolic disturbances that increases the risk for T2DM and CVD. UA urolithiasis is highly prevalent among stone forming patients with features of MetS such as obesity and T2DM. Very low urine pH is found to be the first observation in the development of idiopathic UA stones. Low urine pHs in such patients is due to increased net acid excretion due to impaired buffering caused by defective ammonia excretion resulting in abnormally acidic urine. [28]

Urine analysis is especially with quantitative urine pH has emerged as a usual marker to evaluate UA urolithiasis. Fasting urine pH correlated inversely both with BMI and Low Density Lipoprotein Cholesterol [LDL-c]. Also total urine volume showed inverse correlation to age and disease duration and positively with BMI. Hence urine pH was found to be the main risk factors in urolithiasis in T2DM patients. Increased BMI further substantiate this observation. Data from more number of patients are required to confirm these findings. [29]

4. Microalbuminuria

Urinary Kidney Injury Molecule (KIM-1) play a significant role to differentiate T2DM patients and controls and it is highly significant based on the differences between normoalbumin uric, microalbumin uric and albumin uric. A positive correlation exists between KIM-1 and MA as well as microalbumin/Creatinine ratio. [30] MA patients have significantly higher BP and duration of diabetes compared to normoalbumin uric subjects. HDL-c was significantly lower in MA subjects while FPG, TGs, TC and VLDL-C were found to be marginally higher in microalbuminuric than normoalbumin uric. Every diabetic patient should be screened for MA as high prevalence exists and shows positive association with BP and altered lipid profile. Screening for MA will enable to take intervention and prevent further complications like ESRD and CVD.[31] Collaboration with primary health care centres are important as the prevalence of T2DM was found to be high along with CKD and albuminuria.

Hence screening of all prediabetic patients at health centres will enable common primary care to prevent complications related to kidney related diseases. [32]

Trace elements also play a part in T2DM and some chronic complications may be associated with alterations in the levels of element like copper in plasma, tissues and urine. DM along with MA may cause an increase in the urinary excretion of copper, which if not controlled may lead to DN.[33] A higher level of both serum Total Sialic Acid (TSA) and high sensitive C-reactive Protein (hs-CRP) was observed in DN nephropathic patients compared to controls. Both TSA and hs-CRP shows significant correlation to FPG, PPPG, HbA1c and MA in both DM and DN groups compared to normal controls. Logistic regression analysis showed that both TSA and hs-CRP were independently associated with DN and higher levels of these may increase the microangiopathic DN complications in T2DM. [34]

Diabetic kidney disease (DKD) is found to be more frequent among African-Americans, Asian-American as well as in native Americans. Progressive kidney disease is more frequent with T1DM than T2DM. Hyperglycemia is a well known risk factor along with sex, obesity, hypertension, chronic inflammation, IR, hypovitaminosis D, dyslipidemia and polymorphism in some genes. Even slight increase in BP is associated with MA signaling future CVD. MA together with IR may lead to MetS and MA is generally the first clinical sign of renal dysfunction in DM. Both renal dysfunction and CVD risk factors will be elevated even in the high normal range of MA. [35]

The earliest possible ESRD or CVD may develop based on the levels of some traditional markers such as BP, HbA1c, TC, hs-CRP and Pro-Brain Naturetic Peptide. All the above markers have been successfully applied in clinical practice with some usefulness. The principal renal biomarkers albuminuria and GFR are also found to be associated with renal and CVD in DM patients and could be easily used to identify those at risk of long term complications. Pharmacological interventions may control these biomarkers to reduce renal dysfunction and CVD. [36]

UAE as well as urinary albumin to Creatinine ratio measurements along with eGFR have clinical utility as biomarkers and they will serve as all-cause mortality to assess CVD, progressive CKD and ESRD in both diabetes and non diabetes. However, controversy still exists whether isolated MA in the absence of reduction in eGFR, urine sediments and structural renal disease could be regarded as kidney diseases. [37]

Presence of MA is the single most important marker for the development of macrovascular disease and progressive renal impairment.

Along with this Reactive Oxygen Species (ROS), inflammatory cytokines and growth factors also key players in this condition. Along with the presence of glomerular endothelial dysfunction, these markers will lead to the initiation of MA in diabetes.[38] A complex relationship exist between MetS and CKD and both should be viewed as a common progressive illness. IR, OS, increased proinflammatory cytokines, connective tissue growth, profibrotic factor, microvasuclar injury and renal ischemia are the factors that lead to the development of renal injury. Such factor also portends a higher CVD risk at all stages of CKD, renal insufficiency to ESRD. In the presence of CKD, the clinical interventions for MetS are weight reduction, dietary modification, increased physical activity, controlling CVD risk factors such as hypertension, dysglycemia and dyslipidemia. The relation between MetS and CKD still remains controversial and no solid association has been established now. More studies are needed to establish prophylactic and therapeutic interventions in this field. [39,40]

Males with higher UA shows risk for MA with decrease eGFR in older age, increased systolic BP, and low HDL-c are prone to get CKD and hence it is important to established clinical manifestations for CKD in diabetes.[41] Some potential factors contributing to rapid decline in renal function include ethnic/genetic, demographic, smoking, increased HbA1c, obesity, MA, anemia, low Se-Mg, increased phosphate, hypovitamin D, increased BP retionapthy and cardia autoimmune nephropathy.[42]

5. Conclusion

DM is a chronic disease caused by many factors and T2DM is a self induced disease by an individual due to non – control of several factors associated with it. DM is now emerging as the number one disease worldwide and uncontrolled DM will have severe manifestations on the functional level of kidney, liver and cardiac. Although extensive research is still being carried out in this field, mechanism underlying its effects on the alterations of kidney function is still not well standardized. Those with kidney disease predominantly account for increased mortality is T2DM and is the main cause of CKD as well as DN. Some association exists between UA calculi and DM status. The prevalence of T2DM in healthcare centers is higher with the presence of CKD and albuminuria. Both TSA and hs – CRP are associated with DN leading to complications in T2DM. MA is the first clinical sign of renal dysfunction in DM and it is clinically used as the future indicator for renal dysfunction. The independent risk identified for renal impairment in DM are sex, age, WC, BMI, insulin insensitivity, urine PH and dyslipidemia. More research is needed in this area to further explore standard treatment for CKD induced by T2DM.

Conflict of interest: None

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