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The Place and Use of Urinary Albumin-Creatinine Ratio (UACR) as a Diagnostic and Prognostic Marker for Diabetic Micro and Macro-Vascular Complications

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Abstract

UACR has been recommended by different guidelines as an important parameter for regular and routine clinical checkup for Diabetes Mellitus (DM) patients and kidney disease patients and also to assess the morbidity and mortality of patients of cardio-renal-metabolic diseases of different types. More and more studies are being published across the globe establishing the association of other DM complications with UACR and there are also different studies in non-diabetic patients. Moreover, different researchers have also come up with data showing association of adverse outcomes with much lower value of UACR which is considered normal today. The purpose of this review article with 36 published articles, is to highlight the importance of measuring UACR across the continuum of all types of diabetic complications and to stimulate more research in this direction and also towards the issue of lower values of UACR are also related to adverse outcomes even in non-diabetic patients.

Keywords: UACR: Urinary Albumin-to-Creatinine Ratio; DM: Diabetes Mellitus; CKD: Chronic Kidney Disease; ED: Erectile Dysfunction; CVD: Cardiovascular Disease; DR; DPN: Diabetic Peripheral Neuropathy

Abbreviations: DM: Diabetes Mellitus; RRT: Renal Replacement Therapy; CVD: Cardiovascular Disease; PAD: Peripheral Arterial Diseases; CKD: Chronic Kidney Disease; UACR: Urinary Albumin-to-Creatinine Ratio; KDQOI: Kidney Disease Quality Outcome Initiative; GFR: Glomerular Filtration Rate; DKD: Diabetic Kidney Disease; DPN: Diabetic Peripheral Neuropathy; ED: Erectile Dysfunction; ARB: Angiotensin Receptor Blocker.

Introduction

95% of the world's Diabetes Mellitus (DM) patients are Type 2 and the rest are Type 1 and others. The most important issue about the disease is that it reduces life span and increases early age morbidity due to devastating complications caused by organ damage. So, the management of DM includes glycemic control as well as screening for complications for their earliest possible detection, prevention and treatment. So, the importance of an investigation tool, which is valid across all types of complications for screening, monitoring and prognosticating, cannot be over emphasized.

Global Incidence and prevalence of Diabetes Mellitus (DM)

Followings are the data published by IDF 2021 atlas fact sheets: [1]

- 537 million adults (20-79 years) are living with diabetes worldwide-1 in 10.
- The total number of people with diabetes is predicted to rise to 643 million (1 in 9 adults) by 2030 and 784 million (1 in 8 adults) 2045.
- 4 in 5 people with diabetes (81%) live in low-income and middle-income countries.
- 68% of adults with diabetes live in the 10 countries with the highest number of people with diabetes.
- The countries with the largest number of adults with diabetes aged 20-79 years in 2021 are China, India and Pakistan. They are anticipated to remain so in 2045.
- Diabetes caused 6.7 million deaths in 2021-1 every 5 seconds.

A Brief Overview of Complications of Diabetes

Acute complications of diabetes are mainly related to the glycemic status of the patient, either hypoglycemia or hyperglycemia and they are metabolic in nature. Infections are also sometimes acute complications of the disease. Chronic complications on the other hand is due to vasculopathy, namely microvascular and macrovascular complications. Prevention and management of complications of diabetes is one of the facets of the management.

Microvascular Complications:

Retinopathy: It may range from impaired visual acuity to complete blindness. It may also include increased incidence of glaucoma and cataract.

Neuropathy: Can clinically present in many forms: right from involvement of cranial nerves to involvement of autonomic nervous system causing gastroparesis or orthostatic hypotension or even sudden cardiac death.

Nephropathy: It can manifest as increased level of proteinuria to different level of impairment of glomerular filtration, and ultimately end stage kidney disease requiring renal replacement therapy (RRT).

Macrovascular Complications:

- Cardiovascular Disease (CVD) in its all forms.
- Cardiomyopathies
- Heart Failure
- Cerebrovascular Diseases
- Peripheral Arterial Diseases (PAD)

Now the questions are:

- Can these complications be predicted and detected early?
- Can they be prevented?
- Is there any common marker to predict or detect them and follow their progress over time?

The pathologic hallmark of DM involves the vasculature leading to both microvascular and macrovascular complications [2]. Chronicity of hyperglycaemia is associated with long-term damage and failure of various organ systems mainly affecting the eyes, nerves, kidneys, and the heart [3]. Controlling the glycaemic status over a prolonged period of time is the cornerstone of the treatment. Different trials have already proved that. Although the UKPDS conclusively showed the benefit of improved glycaemic control in reducing the risk of microvascular disease, risk reductions for myocardial infarction and death from any cause were observed only with extended post-trial follow-up [1]. Similarly, in the ADVANCE trial [4], in which 11,140 patients with type 2 diabetes were randomly assigned to receive either intensive glucose control or standard glucose control, patients in the intensive-control group had a mean glycated haemoglobin level that was 0.8% lower than that in the standard-control group. However, at the same time, they had a reduction in major microvascular events of 14% but a non-significant reduction in major macrovascular events of only 6% after a median of 5 years of follow-up. In the randomized ACCORD trial [5], there was a nonsignificant reduction of 10% in the composite primary outcome of nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular causes among 10,251 patients with type 2 diabetes who were assigned either to a group with a target glycated haemoglobin level of less than 6.0% or to a group with a target level of 7.0 to 7.9% at the time the trial was stopped, after 3.5 years, because of an unexplained excess rate of death from any cause (22%, P=0.04). Both the ADVANCE and ACCORD trials involved high-risk patients who were 8 and 12 years older, respectively, than the patients in the UKPDS. In addition, in the ADVANCE and ACCORD trials, patients had been treated for diabetes for 8 and 10 years before randomization, respectively, whereas patients in the UKPDS had newly diagnosed disease. About a third of the patients in the ADVANCE and ACCORD trials had a history of macrovascular disease, as compared with 7.5% in the UKPDS [3]. Both the ADVANCE and ACCORD trials suggested that near-normal glycemia did not reduce cardiovascular events in the short term.

Also, over the last few years the introduction of GLP-1RA and SGLT-2 inhibitors have opened another frontier in treating diabetic patients regarding anti-atherosclerotic effect, prevention and treatment of heart disease and prevention of progression and treatment of chronic kidney disease (CKD).In fact, it has been a revolution for treatment of cardio-renal complications in patients with DM. The lack of one predictive parameter, which can predict organ damage for all the microvascular and macrovascular complications and prognosticate about premature death, is lacking any of the international guidelines. The most important debate or question remains whether both micro- and macrovascular complications are a continuum or they are different entities happening in diabetic patients independently. As discussed in an article by Chawla A, et al. [6] in The Indian Journal of Endocrinology and Metabolism [2], much attention has been

focused on the management of macrovascular complications such as stroke and acute coronary syndromes. It is well-recognized that vascular complications in a given tissue are often accompanied by evidence of pathology in other vascular territories. A linear relationship between microvascular complications and duration of disease was established by the authors where they documented the presence of micro-vasculopathy across different age groups in their study in 25-40% of diabetic patients aged >25 years with more than 5 years duration of diabetes [6]. Researchers such as Krentz AJ, et al. [7] and Al-Wakeel, et al. [8] have observed that both microvascular and macrovascular complications develop simultaneously in diabetes [7,8]. We will try to investigate the evidence in favour of any such parameter, like albuminuria.

Urinary Albumin-to-Creatinine Ratio (UACR)

A routine dipstick is not sensitive enough to detect small amounts of urine protein. Therefore, it is recommended that screening in adults with CKD or at risk for CKD be done by testing for albuminuria. Urinary Albumin-to-creatinine ratio (UACR) is the first method of preference to detect elevated protein. The recommended method to evaluate albuminuria is to measure urinary ACR in a spot urine sample. UACR is calculated by dividing albumin concentration in milligrams by creatinine concentration in grams. Although the 24-hour collection has been the "gold standard," alternative methods for detecting protein excretion such as urinary albumin-to-creatinine ratio (UACR) correct for variations in urinary concentration due to hydration as well as provide more convenience than timed urine collections. The spot specimen correlates well with 24-hour collections in adults [9].

Definitions of Abnormalities of Albumin Excretion

In spot urine samples, the normal level of UACR is below 30 mg/g. The normal UACR is less than or equal to 17 mg/g in men, but in women the normal value is slightly higher and is around 25 mg/g. This paragraph is to impress upon the readers about the fact that any rise in UACR value can indicate higher cardio-metabolic-renal risk. Nobody should get confused about the present definition of CKD as proposed by KDIGO (mentioned) in the next paragraph. So the definitions of Microalbuminuria and Macroalbuminuria across the globe are as per KDIGO guidelines, detailed below.

Moderately increased albuminuria, historically known as Microalbuminuria, (UACR 30-300 mg/g) refers to albumin excretion above the normal range, but below the level of detection by the tests for total protein. Severely increased albuminuria, historically known as Macroalbuminura, (UACR>300 mg/g) refers to higher elevation of albumin associated with progressive decline in glomerular filtration rate. The following chart lists the albuminuria categories in CKD.

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min/1.73 m²) Description and range			Persistent albuminuria categories Description and range		
			A1	A2	A3
			Normal to mildly increased	Moderately increased	Severely increased
			< 30 mg/g < 3 mg/mmol	30–300 mg/g 3–30 mg/mmol	> 300 mg/g > 30 mg/mmol
G1	Normal or high	≥ 90			
G2	Mildly decreased	60–89			
G3a	Mildly to moderately decreased	45–59			
G3b	Moderately to severely decreased	30–44			
G4	Severely decreased	15–29			
G5	Kidney failure	< 15			

Figure 1: Green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk. GFR, glomerular filtration rate. www.kidney-international.org CKD nomenclature Kidney International.

What we know about this parameter's importance in clinical practice and how it could help the clinician in the early diagnosis and prognostication about different complications of DM.

Kidney Disease

We already know that raised UACR is a marker of diabetes related Chronic Kidney Disease (CKD). Estimation of UACR and serial measurement is already recommended by different

guidelines to detect, assess and follow up CKD patients. The definition of CKD also involves UACR [9,10]. Kidney Disease Quality Outcome Initiative (K/DOQI), developed global consensus for the adoption of a simple definition and classification system. CKD is defined as kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for 3 months or more, irrespective of cause. Kidney damage in many kidney diseases can be ascertained by the presence of albuminuria, defined as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens. So, now it is a well-established fact across the globe and all the guidelines have advocated its use as a tool for screening, diagnosing, prognosticating and follow ups for Diabetic Kidney Disease (DKD) [11].

Cardiovascular Disease (CVD)

In the year 2000, when the HOPE (The Heart Outcomes Prevention Evaluation Study) study was published, people became gradually convinced about the relationship of UACR with cardiovascular events and mortality [12]. Albuminuria as a predictor of cardiovascular and renal outcomes in people with known atherosclerotic cardiovascular disease [13]. The study concluded, albuminuria is a continuous risk factor for CV events even below the level of microalbuminuria. Microalbuminuria predicts clinical proteinuria in nondiabetics. Authors of another landmark study concluded that, in a community-based sample of middle-aged non-hypertensive, nondiabetic individuals, low levels of urinary albumin excretion well below the current microalbuminuria threshold predicted the development of CVD. These observations strengthen the growing body of evidence that challenges the notion that UACR <30 μg/mg indicates "normal" albumin excretion. Microalbuminuria, defined as an urine albumin to urine creatinine ratio (UACR) of 30 to <300 μg/mg, is an established risk factor for cardiovascular morbidity and mortality and for end-stage renal disease in individuals with an adverse cardiovascular risk profile such as those with hypertension or diabetes mellitus. Accordingly, national and international guidelines recommend screening for microalbuminuria in patients with diabetes or hypertension" [14].

Retinopathy

A number of studies have found a significant association of Diabetic retinopathy (DR) with UACR. A Korean study found that UACR level was independently associated with DR and its severity in patients with type 2 diabetes. UACR levels differed according to the stage of DR, and tended to increase with severity of DR. Moreover, the study showed that normal-to-mildly increased albuminuria was a predictor of the risk for DR [15]. In several studies, the prevalence of DR in normal albuminuria has been reported to be 10-20% [16,17]. Another study reported that normal-to-mildly increased albuminuria is associated with future development of DR, indicating that the risk for DR gradually increases with UACR levels below the microalbuminuria threshold [18].

Peripheral Neuropathy

Diabetic peripheral neuropathy (DPN) can lead to neuropathic pain, which worsens the quality of life [19]. Many studies confirmed that the level of UACR, which represents one of the risk factors of early DPN [20], was higher in patients with neuropathy as compared those without this condition [21]. One of the group of researchers found that even in the normal range, UACR and the risk of DPN showed a positive correlation [22]. This group has another publication, where they concluded that the change in UACR and NCV was not related in patients without DPN and with DPN. However, change in UACR ≥30% suggested a risk for new-onset DPN [23]. So, both for micro- and macrovascular complications, UACR remains the only common association for screening, prognosticating and follow up tools, especially in diabetic patients.

Erectile Dysfunction

Another event in the life of longstanding, especially poorly-controlled DM is Erectile Dysfunction (ED) in male patients. This is a short of organ dysfunction due to DM and a very close association has been found with this disorder with UACR. Albuminuria is an important independent risk factor of ED in men with diabetes after adjustment of age and diabetes mellitus duration. Identification and control of albuminuria and other associated risk factors might play a role in the prevention or reversal of ED [24]. Not only in DM patients, it has also been found in non-diabetic patients, especially in patients of essential hypertension [25]. Another study has concluded the same findings related to ED, diabetic males with severe ED have a significantly higher age and poorer glycaemic control. Age at which DM was first diagnosed and duration of untreated DM was significantly more in ED cases, due to their general tendency to ignore their symptoms and delay treatment seeking, and is a possible explanation of poorer glycaemic control in ED cases [26]. Another study has concluded its relationship with ischemic heart disease, in type 2 diabetic men without clinically overt cardiovascular disease, the presence of ED predicts a new onset of CHD events. Symptoms of ED should be independently sought to identify high-risk subjects for comprehensive cardiovascular assessments [27]. So, age of the patient, duration of DM, level of glycemic control and presence of albuminuria are some of the factors associated with development of ED.

Mortality

A group of researchers found statistically significant positive associations between baseline UACR and death from all-cause mortality, endocrine nutritional and metabolic diseases,

and diseases of the circulatory system and possibly mental and behavioural disorders, and diseases of the respiratory and digestive system [28] Not only does DM increases CVD related mortality, it also increases all-cause mortality and it correlates with increased UACR values [29,30]. There were similar findings also in the HOPE and micro-HOPE studies, mentioned earlier in this article.

Now, it is well established fact that both microalbuminuria and macroalbuminuria are associated with adverse renal and cardiovascular outcomes [12] and ACE-inhibitors can favourably change such outcomes. The most recommendations from KIDGO and ADA also have placed SGLT-II inhibitors with evidence, like, Empagliflozin, Canagilozin, Dapagliflozin as agents to be used in both diabetic and non-diabetic kidney disease patient with albuminuria for slowing the progression of the kidney disease [31]. So, treating patients of albuminuria with agents irrespective of glycemic status to reduce albuminuria like ACE-inhibitors or ARB (Angiotensin Receptor Blocker), SGLT-II inhibitors, Finerenone can improve both cardiovascular and renal end points as have shown by multiple landmark trias,like Hope and Micro-HOPE [12,32-35]. The purpose of this review article is to explore whether UACR can be used to detect, prognosticate other microvascular complications of diabetes. Moreover, whether it can be used as a favourable outcome surrogate as have been seen in different kidney-specific trials.

The fallacy and the Controversy

Albuminuria and Urinary Tract Infection (UTI)

We researched the literature to answer the series of questions detailed in the following text:

- Whether asymptomatic UTI (Urinary tract Infection) is associated with albuminuria?
- Whether symptomatic UTI is associated with albuminuria?
- What is the nature of proteinuria in patients with UTI?

With the huge increase in incidence and awareness of renal disease, accurate screening for proteinuria in high-risk groups is now considered a valuable diagnostic and prognostic tool [36,37]. Although UTI is often associated with proteinuria, the relationship between proteinuria and UTI is not clearly defined. Despite the practice of excluding UTI in patients found to have proteinuria being universally recommended in management guidelines, we have found no evidence of an association between asymptomatic UTI and proteinuria. Further, among patients with diabetes there is evidence, based on sensitive and specific immunoassay technology, that asymptomatic bacteriuria does not cause albuminuria. Too much emphasis on the importance of exclusion of UTI may reduce the reliability of establishing the diagnosis of proteinuria by introducing several additional steps in the diagnostic pathway, like appropriate timing of the spot sample, extra laboratory tests, even for asymptomatic patients. Thus, delays and extra cost in such investigations may have a negative effect on the early detection of proteinuria in non-diabetic patients as well as in the higher-risk group of diabetic patients with possible deleterious consequences [38]. Moreover, it may also demotivate the health care provider against the important test of UACR.

Discussion

As DM burden is increasing globally, the health care system across the globe is being challenged by ever increasing complications and their ramifications. One of the core management principles of treating and managing a DM patient has been complications related to target organ damage, both micro- and macro-vascular. In this regard, there is an urgent need for global recommendation from all the related societies and guidelines for a uniform assessment tool. Till date, UACR has been mainly used for detecting and treating DKD patients. The researchers across the globe have presented multiple evidences in favour of the parameter of UACR and its association with multiple DM complications related to organ damage. Moreover, some have suggested its association is linear and progressive and there should be more investigations to reduce the cut-off value of 30 mg/gm, apart from the researchers of Hope and Micro-Hope trials [39,40].

Conclusion

The use of the parameter UACR should be reviewed in the light of new data and publications. It has definite potential to become a marker of different complications of diabetes and also a surrogate marker for treatment effects. Apart from the studies related to the cardio-renal complications, very good quality studies are lacking for other complications like, neuropathy, retinopathy or erectile dysfunction. So good quality studies are needed for role of UACR in relation to other complications of diabetes, like Distal peripheral Neuropathy, Retinopathy and erectile dysfunctions.

Limitations

This article is a review of 37 important and relevant publications. The authors of the article are of the opinion that more and larger Cohort-based studies are required to establish the role of UACR, both in diabetic and non-diabetic patients, for screening, monitoring, prognosticating different vascular complications and related organ damage and ultimately mortality.

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