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Diagnostic & Clinical Utilities of Serum βeta$_2$ Microglobulin and Urinary Albumin Creatinine Ratio for Identification of Pre-Chronic Kidney Disease

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ABSTRACT

Chronic Kidney Disease (CKD) burden is increasing rapidly worldwide. CKD develops over many years, with a long latent period when it is clinically silent. Routine investigations of renal function are unable to truly detect kidney dysfunction in early stages of CKD as pre-CKD. Thus, detection of pre-CKD still remains a challenge to clinicians. Hence a hospital based, cross sectional, observational study was planned to assess diagnostic and clinical utility of serum βeta$_2$Microglobulin (β_2M) and Urinary Albumin Creatinine Ratio (UACR) in 100 high risk CKD subjects who suffered either with hypertension, Diabetes mellitus or both for more than 5 years. β_2M and UACR were estimated and correlated with eGFR in study subjects. On basis of UACR and eGFR study participants were divided in 3 groups as Group I, Group II and Group III. Group I subject showed all normal values of serum creatinine 0.73 mg%, mean serum β_2M 1.87 µg/ml ± 0.62 and UACR as 25.9 ± 3.42 indicating no CKD. Group II subjects clinically asymptomatic having normal serum creatinine 1.48 mg%, but significantly ($p<0.001$) raised β_2Microglobulin (3.92 µg/ml ± 0.61) and UACR (47.4 ± 2.88) indicated as pre-CKD. All parameters were significantly raised in group III subjects when compared with group I and group II revealed advanced CKD. Serum β_2M with UACR possessed clinical diagnostic utility in patients with clinical hypertension, Diabetes mellitus or both to assess glomerular function and diagnose as pre-CKD in clinically asymptomatic stage and thus help in further preventing these subjects to progress to critical advanced stages of chronic kidney disease. Study concludes that an estimation of serum β_2M and UACR may be considered as a better predictor and diagnostic markers to assess glomerular function in adults for pre-CKD.

Keywords: Chronic kidney disease (CKD), Pre-chronic kidney disease, βeta2 Microglobulin, Urinary albumin creatinine ratio (UACR)

INTRODUCTION

Chronic Kidney Disease (CKD) is a global health issue which possess great threat to the health system. The definition of CKD was introduced by the National Kidney Foundation (NFK) in 2002 and later adopted by the International Group, Kidney Disease Improving Global Outcomes (KDIGO) in 2004 [1]. Prevalence of CKD is approximately 800 per million population (pmp) and incidence of End Stage Renal Disease (ESRD) is 150-200 pmp [2]. The definition of CKD requires a decrease in kidney function with a glomerular filtration rate (GFR) of less than 60 ml/min per 1.73 m^2 and/or kidney damage for 3 months or more. Eighty percent of chronic disease deaths worldwide occur in low and middle-income countries. In India, the projected number of deaths due to chronic kidney disease was around 5.21 million in 2008 and is expected to rise to 7.63 million in 2020. CKD is associated with age related renal function decline accelerated in patients with hypertension, diabetes, obesity and primary renal disorders [3]. The anti-aging gene Sirtuin (SIRT1) is a nicotinamide adenine dinucleotide-dependent deacetylase. It is repressed in the global chronic disease epidemic with relevance to kidney disease, non-alcoholic fatty liver disease (NAFLD), obesity, Diabetes and neurodegenerative diseases. SIRT1 is now closely connected to kidney disease [4,5]. Kidney damage refers to pathologic abnormalities documented by biopsy or imaging, alterations in urinary sediment or

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proteinuria (albuminuria/creatinuria>30mg/g) [6]. The criteria of pre-CKD are normal or high level of glomerular filtration rate greater than 90 ml/min when there are no symptoms to indicate kidney damage, which is well known as early stage of CKD. Pre CKD is reversible, and its progression can be delayed [7]. The staging criteria for CKD are primarily focused on the prognostic value of measured GFR (mGFR) or estimated GFR (eGFR) for predicting CKD progression, cardiovascular disease and other clinical outcomes [8]. Since quantification of GFR is a time-consuming job, and may not always be possible, two important markers, Serumβeta$_2$ Microglobulin (β_2M) and Urinary Albumin Creatinine Ratio (UACR) have been used for evaluating the progression of CKD.

β_2M is a non-glycosylated protein and possesses a negative charge. It is a component of MHC class 1 molecule which are present on almost all cells except in red blood cells. It is characterized to get freely filtered in the glomeruli and get reabsorbed and metabolized in the proximal tubules [9]. Levels of β_2M are elevated in kidney disease, in addition to other conditions such as malignancies, autoimmune diseases, infections and aging. Decrease in renal function results in a proportional rise in serum β_2M levels. It correlates more closely to GFR in all different levels of renal functions. It is therefore a highly suitable marker of renal dysfunction [10].
Microalbuminuria is defined as a urinary albumin excretion of 30-300 mg/day, measured in a 24 h urine collection. It is also defined as values between 20-200 mg/L or 30-300 mg/g (albuminuria/creatinuria) [11]. Measurement of it is of great benefit in individuals who are at risk for progressing symptoms of CKD. It may possibly help to get CKD diagnosed in an early phase, because it is widely known that CKD typically becomes symptomatic only in stage 4 and 5, with this context, it is noteworthy that most patients with CKD are not aware of having diseased kidneys. Staging of CKD by 2012 KDIGO guidelines is based on the linear association of albuminuria with progression of CKD, ESRD and all causes of mortality independent of eGFR, and albuminuria [12].

Assessment of Kidney function was commonly made by estimation of concentration of conventional markers like serum Creatinine (SCr), blood urea nitrogen (BUN) and serum cystatin C. However, there are evidence which demonstrate that these biomarkers are not optimal to detect pre-CKD a kidney disease in early stages [13]. Most of the commonly used parameters of renal function are able to detect kidney disease when GFR has already fallen substantially and so early detection of patients of CKD is still a challenge. Hence, the present study was planned to assess the diagnostic utility of serum βeta$_2$ Microglobulin (β_2M) and Urinary Albumin Creatinine Ratio (UACR) for early detection of pre-CKD patients.

MATERIALS & METHODS

The present study was a cross-sectional observational study carried out in Biochemistry Department, Medical College and Sir Sayajirao General (S.S.G.) Hospital, Baroda, Vadodara, in collaboration with the Medicine Department of S.S.G Hospital. Approval of Institute's Scientific Review Committee and Institutional Ethics Committee for Human, Research was obtained, and Ethical Clearance was taken for conducting the research.

Total 100 subjects were included in the study. Informed consent of subjects was obtained for participation in the study and for blood collection. Demographic data, detailed medical and clinical history of all the study subjects were observed during the study. Patients with Diabetes Mellitus or Hypertension or both for more than 5 years coming for routine follow up in medicine department were included as study subjects. Patients with ESRD, haemodialysis, renal transplant, pregnant females and individuals with any systemic diseases like malignancy were excluded from the study. Based on eGFR and UACR, study subjects were grouped, and sub grouped according to KIDGO classification as given in **Table 1**.

Table 1. Grouping of study subjects according to KIDGO classification.

Group I: No CKD	Group II: Early CKD	Group III: Advanced CKD
eGFR≥90 ml/min/1.73 m^2 **UACR<30mg/g**	**II (a)**: eGFR> 90 ml/min/1.73 m^2 UACR 30-300 mg/g (Stage I CKD)	**III (a)**: eGFR 30 - 44 ml/min/1.73 m^2 UACR 30-300mg/g (Stage IIIb CKD)
	II(b): eGFR 60-89 ml/min/1.73 m^2 UACR 30-300mg/g (Stage II CKD)	**III (b):** eGFR 15-29 ml/min/1.73 m^2 UACR > 300mg/g (Stage IV CKD)
	II(c): eGFR 45-59 ml/min/1.73 m^2 UACR 30-300mg/g (Stage IIIa CKD)	**III (c)**: eGFR 10-14 ml/min/1.73 m^2 UACR > 300mg/g (Stage V CKD)

5 mL of blood sample was collected in plain vacutainer from all the study subjects. After the clot formation serum was separated and assayed for serum urea, creatinine, albumin using clinical biochemistry diagnostic instruments. Serum β_2M was assayed by Sandwich ELISA on Micro lab Elisa Reader. 24 h urine samples were collected in 5 litres of plastic container added with thymol crystals as a preservative from all study subjects simultaneously on same day. Urinary micro albumin was measured using Immuno turbidimetric method, urinary creatinine was measured using Modified Jaffe's Kinetic method and serum urea was measured by enzymatic method. UACR was calculated using standard formula. Using modification of diet in renal disease (MDRD) study equatione-GFR was calculated. MDRD- GFR (ml/min/1.73m^2) was calculated from equation: 186 x Scr$^{-1.154}$ x age $^{-0.203}$ x 0.742 if female. From total 100 study subjects, 10 patients were excluded, as they were end stage renal disease (as on investigation eGFR< 10 ml/min/1.73 m^2) [12].

Statistical Analysis

Data was analysed using MedCalc statistical software. Continuous variables were calculated by description statistics and reported as mean ± standard deviation (SD). Urea and creatinine were not normally distributed hence median and interquartile range were calculated. Variables were compared across three groups by one- way analysis of variance (ANOVA). A p value of less than or equal to 0.05 was considered statistically significant. Pearson's correlation analysis was used to study correlation of serum β_2M and UACR with GFR.

RESULTS

The observations made with respect to various aspects of the study are given in **Table 2**.

Table 2 depicted that maximum number of cases were of group II and there was statistically significant difference in mean age of three groups ($p<0.05$). It showed the total no of males in the study group were 64 and females were 26. Most frequent risk factors observed in our study was hypertension (37%) followed by hypertension with Diabetes Mellitus (32%) and Diabetes Mellitus (31%).

Test of Significance - ANNOVA

Table 3 showed that there was statistically significant difference seen in urea, albumin, UACR and β_2M when compared with three subject groups ($p<0.05$). On basis of UACR and eGFR study participants were divided in 3 groups as Group I, Group II and Group III. Group I subject showed all normal values of serum creatinine 0.73 mg%, mean serum β_2M 1.87 µg/ml ± 0.62 and UACR as 25.9 ± 3.42 indicated no CKD. Group II subjects clinically asymptomatic reported normal serum creatinine 1.48 mg%, but raised β_2Microglobulin 3.92 µg/ml ± 0.61and UACR 47.4 ± 2.88 showing statistical significance ($p < 0.001$) indicated as pre-CKD. All parameters were significantly raised in group III subjects when compared with group I and group II revealed advanced CKD. There was no statistically significant difference in creatinine in group I and II study subjects and showed mean serum creatinine within the normal reference range.

Table 2. Demo graphic details of the subjects.

Variables	Group I (n=10) Mean ± SD	Group II (n=48) Mean ± SD	Group III (n=32) Mean ± SD
Age (years)	32.2±10.8	41.2±12.2	49.3±13.4
Sex (M/F)	8/2	35/13	21/11
History of hypertension	5	20	8
History of diabetes	3	16	9
History of both Diabetes and Hypertension	2	12	15

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Table 3. Biochemical parameters of all study groups.

Variables	Group I (n=10) Mean ±SD	Group II (n=48) Mean ±SD	Group III (n=32) Mean ±SD	p value
Urea (mg/dL)	28(28-38)	56(50-64)	96(89-146)	0.002
Creatinine (mg/dL)	0.73 (0.43-0.88)	1.48 (1.12-1.78)	4.27 (2.3-8.1)	0.07
Albumin (mg/dL)	3.3± 0.53	3.62 ± 0.70	3.92 ± 0.81	0.04
UACR	25.9 ± 3.42	47.4 ± 2.88	71.9 ± 3.66	<0.001
β_2Microglobulin (µg/ml)	1.87 ± 0.62	3.92 ± 0.61	7.49 ± 1.2	<0.001

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Table 4 revealed that in the present study there was a negative correlation between GFR, serum βeta$_2$Microglobulinand urinary ACR, which indicates that urinary ACR and serum β_2Microglobulin increased with decrease in eGFR. This negative correlation was moderate at low levels of urinary ACR and high with increased urinary ACR. The study also showed that this negative correlation was moderate at low levels of serum β_2M and very strong as the levels of serum β_2M increased.

Table 4. Correlation of serum βeta$_2$ Microglobulin & UACR with eGFR in all study subjects.

With eGFR	Serum β_2M	UACR
Correlation r- value	Group I -0.513 Group II -0.762 Group III -0.793 Group I, II& III -0.827	Group I -0.578 Group II -0.447 Group III -0.679 Group I, II& III -0.765

Figure 1 and **Figure 2** depicted that in the present study serum β_2M showed a strong negative correlation with eGFR as compared to moderate correlation with UACR in pre-CKD patients (Group II).

Table 5 showed that serum β_2M had a higher sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and likelihood ratio as compared to urinary ACR.

DISCUSSION

Chronic kidney disease (CKD) is recognized to have changed from a subspecialty issue to a global health concern. CKD is a type of kidney disease in which there is gradual loss of kidney function over a period of months or years. Early detection of CKD by screening for kidney disease in high risk patients, early referral to nephrologist, appropriate treatment of hypertension, DM and other risk factors, lifestyle modifications with specific emphasis on physical exercise and abstinence from smoking will retard progression of kidney disease to an advanced stage [14]. In search of an ideal marker for identification in early stages of CKD, which may overcome the limitations of the conventional markers like creatinine, the present study on serum β_2M and Urinary Albumin Creatinine Ratio (UACR) for early detection in pre-CKD patients was planned and conducted. Serum β_2M is recognised as an important

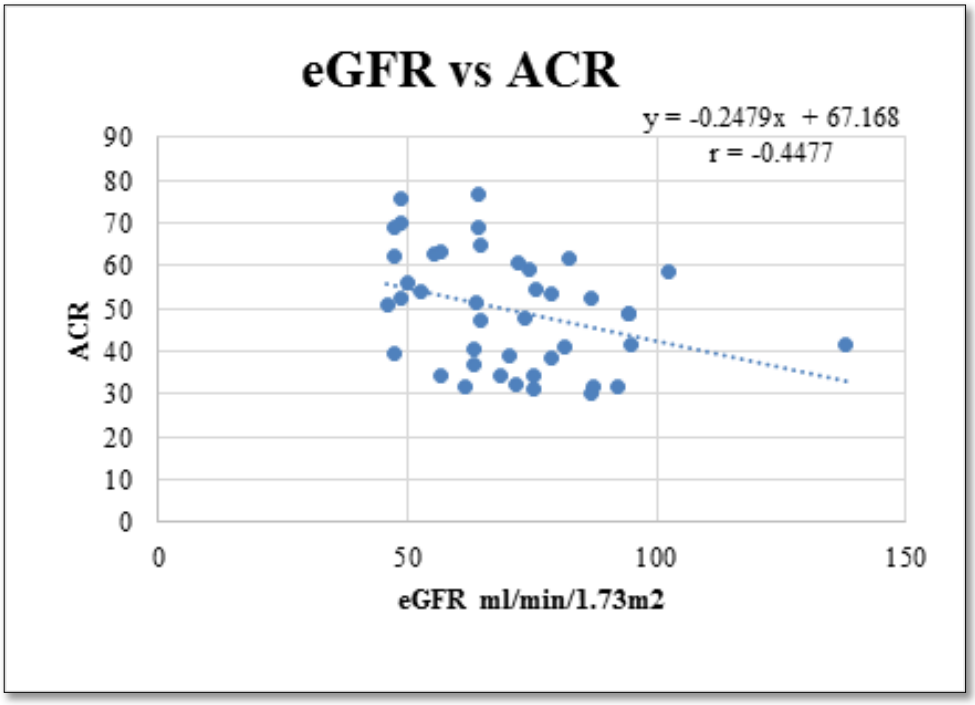

Figure 1. Correlation of UACR with eGFR in Pre CKD (Group II).

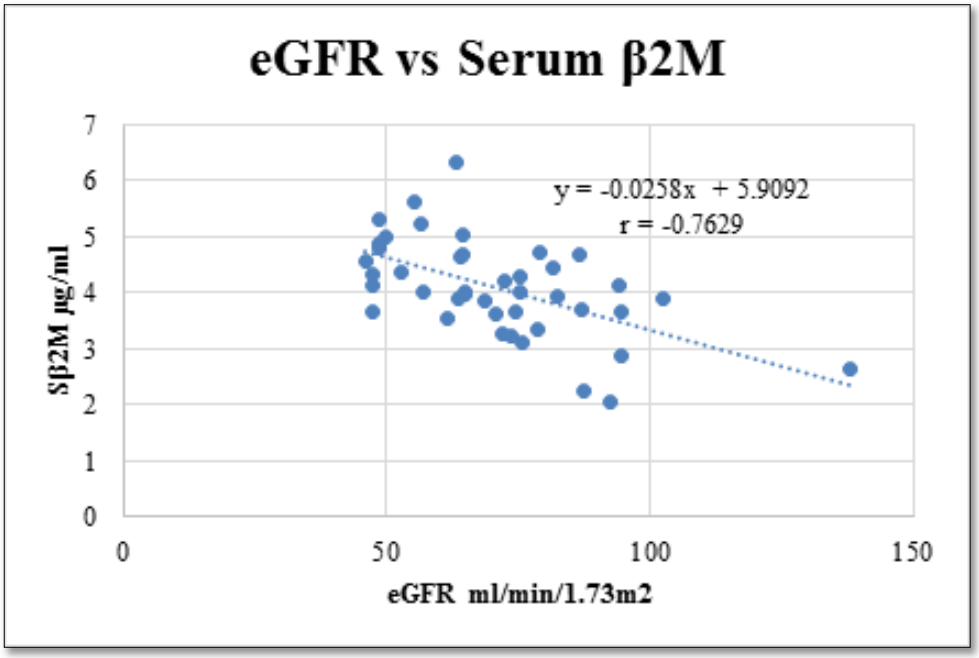

Figure 2. Correlation of serum β_2M increased with eGFR in Pre CKD (Group II).

emerging biomarker in numerous renal as well as non-renal diseases.

In this study, maximum numbers of cases were of pre-CKD (group II). The study subjects ranged in age group of 40-59 years of all three groups. The mean +SD of age of group I was 32.2 +10.8, group II was 41.2 + 12.2 and group III was 49.3 + 13.4 years. There was statistically significant difference in mean age of the three groups ($p<0.05$). Present study also confirmed that an association of past history and family history with hypertension was most common risk factor for pre-CKD.

Shahjahan et al. [15], in their study reported that the correlation of serum creatinine varied from (r=0.209) to (r=0.688), which remarked as a weak to moderate correlation in group II (creatinine clearance 69.90±3.56) and group III (creatinine clearance 44.80±1.65). Tazeen et al. also reported similar results [16]. According to present study serum creatinine was not of much utility in pre-CKD (group II) subjects, as there was a weak correlation between eGFR and serum creatinine. This study also depicted moderate correlation with subjects with advanced stages of CKD.

Table 5. Sensitivity, Specificity, PPV, NPV and LR ofurinary ACR and serum β_2Microglobulin.

	UACR	SB_2M	Combined
Sensitivity	93.75%	97.50%	98.75%
Specificity	60.0%	80%	70%
PPV	94.93%	97.50%	96.40%
NPV	54.54%	80%	87.5%
LR-	0.1	0.03	0.018

In this study, median for serum β_2M for subjects of Group I with no CKD was 1.77 µg/ml, for pre-CKD group II subjects (stage 1, 2 and 3a) was 3.98 µg/ml and subjects with advanced CKD, group III (stage 3 b, 4 and 5) was 7.49 µg/ml. There was statistically significant difference in serum β_2M levels between the three study groups ($p<0.001$). In present study serum β_2M of group I with No CKD was within reference value with slightly on the upper limit of reference range 0-2 µg/ml, signifying that the patient was at high risk of developing chronic kidney disease in very near future and preventive measures should be taken to halt this progression of CKD. Pre CKD, group II study subjects

showed raised serum β_2M, an approximately double the normal range signifying that although the conventional markers like serum creatinine in these patients was not raised, even then the patient was in an early stage of CKD. Group III subjects with an advanced CKD showed declined eGFR, increased serum creatinine, β_2M levels with high values than group I and II study subjects. These results clearly indicated more the damage to nephrons clinically more is biochemical elevations of related excretory parameters. In patients with no CKD (group I) there was a moderate correlation between eGFR and serum β_2M (r=0.5130), which justified that the utility of this biomarker was not only in early stages but also in patients who are at risk of developing CKD. In this study serum β2M was evidenced as a better and more précised biomarker for staging among patients of CKD.

Study subjects of group II with serum β_2M showed a strong negative correlation, whereas UACR showed a moderate negative correlation with eGFR whereas in advanced stage of CKD (group III) when there was an appreciable decreased eGFR, UACR also served as a good biomarker. The results also showed that serum creatinine is imprecise and not sensitive enough to detect early change of renal function, when active management is important. It may also be interpreted from these results that it is often not elevated until the injury to nephrons of kidneys is well established. Creatinine values may alter as its generation may not be simply a product of muscle mass but influenced by muscle function, muscle composition, activity, diet and health status. An increased tubular secretion of creatinine in some patients with kidney dysfunction could give false negative values [17].

According to a study by Zeng et al. [18], the sensitivity, specificity, NPV, PPV of serum β2M was 86.6%, 64.7%, 81.3% and 73.7% respectively. When compared to this study the statistical values of sensitivity, specificity, NPV and PPV of serum β2M were high in present study. Lee et al. [19], in his study documented 85.1% sensitivity of serum β2M which were much lower as compared to the 97.50% calculated in this study.

Global chronic disease like diabetes, chronic kidney disease, cardiovascular diseases have raised a global concern. Sirtuin 1 (SIRT1), a nicotinamide adenine dinucleotide (NAD+) dependent class III his tone deacetylase (HDAC)has a critical involvement in insulin resistance by targeting transcription factors such as p53 [20]. SIRT1, as an intracellular energy sensor, detects the concentration of intracellular NAD (+) and uses this information to regulate cellular energy. It has been reported that SIRT1 has enormous beneficial effects in regulating many biological processes involved in chronic kidney disease. These include cellular immunity to oxidative stress, reduction of fibrosis, suppression of inflammation, inhibition of apoptosis, regulation of metabolism and regulation of blood pressure [21]. SIRT1 has been found to be an essential factor in regulating metabolic homeostasis. In metabolic disorders like Diabetes Mellitus, kidneys are very likely to get affected. Diabetes is associated with reduced SIRT1 expression in the kidney, it is likely that the kidney may benefit from SIRT1 activation. It was demonstrated in a mouse model of diabetic nephropathy, that SIRT1 expression decreases in proximal tubules before albuminuria. These findings also suggested that decreased SIRT1 expression in proximal tubular cells causes abnormal nicotine metabolism and reduces the supply of nicotinamide mononucleotide from renal tubules to glomeruli. This further decrease expression of SIRT1 in glomerular podocytes and increases expression of a tight junction protein, claudin-1, which results in albuminuria [22-24].

The limitations of the present study were small sample size and lack of follow up. To reach a validated definite conclusion, patients of group I need to be followed up and the preventive measures should be taken with those who have raised serum β_2M. In future studies with a greater number of cases along with serial testing of serum β_2M and UACR as well as expression of SIRT 1 gene in order to follow up cases are required for more validated results of serum β_2M to implement as routine test for early diagnosis of CKD [25].

CONCLUSION

This study was carried out to assess role of serum β_2M and UACR for early detection of patients of CKD and its utility as predictive biomarker for pre-CKD. This study concluded that serum β_2M and UACR were raised maximum in group III cases of an advanced CKD, which clearly indicated that as eGFR decreased, kidney function was declined and these markers raised in proportion. Serum β_2M and UACR were raised in group II cases without symptoms of CKD, which indicated that the patients of group II are at a high risk of developing CKD. Individually serum β_2M turned out to be a better biomarker than UACR for early detection of CKD patients because of its high sensitivity, specificity and strong correlation with eGFR. On combining both these markers, there was a high sensitivity which indicated its diagnostic importance and utility in detection of early cases of CKD and its treatment. The study suggests that serum β_2M and UACR have very important role in detection of pre-CKD, where serum creatinine levels remain normal. Plasma and urinary β_2M levels can be reliably and cost effectively measured, which makes it as an ideal screening tool. From this study it could be concluded that an estimation of serum β_2M and UACR may be considered as a better predictor and diagnostic markers to assess glomerular function in adults with pre-CKD. However, along with serum β_2M and UACR, SIRT1 gene expression study may further facilitate the early detection of kidney disease and glomerular function.

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