

## Original Research Article

# Study of renal functions in metabolic syndrome and its correlation with various parameters

Anand N., Vidya T. A.\*

Department of Medicine, SRM Medical College Hospital and Research Centre, SRM IST, Kattankulathur, Kanchipuram, Tamil Nadu, India

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**\*Correspondence:**

Dr. Vidya T. A.,

E-mail: [tavidya@gmail.com](mailto:tavidya@gmail.com)

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### ABSTRACT

**Background:** Metabolic syndrome includes a constellation of various metabolic abnormalities that have been associated with cardiovascular disease, stroke and all-cause mortality in the general population. It has now been established that it is also associated with renal dysfunction. This study was done to assess renal function in metabolic syndrome in Indian population as well as its correlation with different parameters of the metabolic syndrome.

**Methods:** A cross-sectional study was conducted in a university hospital from 2014 - 2015. Renal functions were studied in 100 obese individuals, 50 with and 50 without metabolic syndrome after informed consent and the results were analysed.

**Results:** 100 obese individuals, 50 with and 50 without metabolic syndrome were compared. All underwent a physical examination and relevant investigations. All parameters of renal function showed significant derangement in cases as compared to controls. 38 patients (76%) among the cases (n=50) of metabolic syndrome had altered renal functions versus 9 patients (18%) among controls (n=50). Individually, there was a significant correlation of altered renal function (reduced estimated glomerular filtration rate (eGFR) and presence of microalbuminuria) with fasting blood glucose and systolic blood pressure (p=0.001), diastolic pressure (p=0.003) and triglyceride levels (p=0.036). High density lipoprotein-cholesterol levels did not show a significant correlation.

**Conclusions:** Obese individuals with metabolic syndrome have significant derangement of renal functions as compared to those without metabolic syndrome. Most parameters of the syndrome are also independently associated with alteration of renal functions.

**Keywords:** Chronic kidney disease, eGFR, Microalbuminuria, Metabolic syndrome

### INTRODUCTION

Metabolic syndrome also called syndrome X or insulin resistance syndrome is a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose deposition and function. International Diabetic Federation (IDF) criteria for metabolic syndrome are:<sup>1</sup>

- Central obesity-waist circumference > 90 cm for men and > 80 cm for women
- Plus any 2 of the following factors

- Raised Triglyceride level >150 mg/dl
- Reduced HDL cholesterol <40mg/dl in males and < 50 mg/dl in females
- Raised blood pressure: systolic BP >130 or diastolic BP >85 mmHg.
- Raised plasma fasting glucose >100 mg/dl or previously diagnosed type 2 diabetes

Metabolic syndrome is a risk factor for coronary heart disease, as well as for diabetes, fatty liver, and several cancers.<sup>2</sup> Apart from this, there also exist a relationship

between renal dysfunction and metabolic syndrome. Obesity and insulin resistance which are prominent features of the metabolic syndrome have been associated with secretion of inflammatory mediators and activation of inflammation-associated signalling pathways. Wisse implicated specific mediators in the pathogenesis of the metabolic syndrome, including leptin, IL-6, TNF- $\alpha$ , adiponectin and acylation-stimulating protein.<sup>3,4</sup>

Since many of the above mentioned cytokines have also been postulated to modulate renal pathophysiology, it is tempting to reason that progressive kidney disease could result from their presence in the context of the metabolic syndrome. Other mechanisms which adversely impact renal function in metabolic syndrome include physical compression of kidney parenchyma by adipose tissue, reduced birth weight and nephron number, enhanced glucocorticoid activity, or altered uric acid metabolism.<sup>5-7</sup> Most of the above-mentioned data have been compiled by Jeffrey R. Schelling and John R. Sedor in their study.<sup>8</sup> They come to a final conclusion that metabolic syndrome is a risk factor for chronic kidney disease not just indirectly through diabetes and hypertension but also directly.

This study was therefore undertaken to assess the renal status in metabolic syndrome and also the correlation of different parameters of metabolic syndrome with microalbuminuria and GFR.

## METHODS

A total of 100 individuals were included in this study. Study was conducted in a tertiary care university hospital from 2014 to 2015. Ethical clearance was obtained from the ethical committee of the Institute and written and informed consent was sought from the patients.

### *Inclusion criteria*

Both men and women above 20 years of age were included. The study group consisted of 50 patients with metabolic syndrome (cases) as defined by International Diabetic Federation criteria (as mentioned above). The control group (controls) consisted of 50 obese individuals who did not fulfil the criteria for metabolic syndrome.

### *Exclusion criteria*

- Hypo and hyperthyroidism
- Nephrotic syndrome
- Coronary artery disease
- Pregnancy
- Overt CKD
- Patients on medications for dyslipidemia
- Hypertension and glucose lowering agents.

Both groups were investigated for parameters of metabolic syndrome and renal functions (urine

microalbuminuria, serum creatinine, eGFR). Microalbuminuria and reduced glomerular filtration rate (GFR) are accepted indicators of renal function. The results were analyzed.

All participants completed the consent form and underwent a physical examination. Circumferential measurements of the waist at the level of umbilicus were carried out with the participant standing and rounded to the nearest centimetre. A single blood pressure (BP) measurement was made after 5 min rest, using a calibrated mercury sphygmomanometer. Systolic BP and diastolic BP were recorded as the first and fifth Korotkoff sounds, respectively. Blood samples were drawn after 12 h overnight fast for lipids, glucose, and creatinine.

Besides the routine baseline investigations, all patients underwent urine testing for micro albuminuria using dipstick method. Results were interpreted from colour changes of the dipsticks in comparison to colour codes given with the kit and graded as 0, 1+ and 2+ for convenience. (0 - negative, 1+ - 30 mg/dl and above, 2+ - 100 mg/dl and above). Serum creatinine was measured for all patients and estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease (MDRD) formula.<sup>9</sup> The eGFR values above 120 mL/min/1.73 m<sup>2</sup> were rounded off to 120 mL/min/1.73 m<sup>2</sup>.

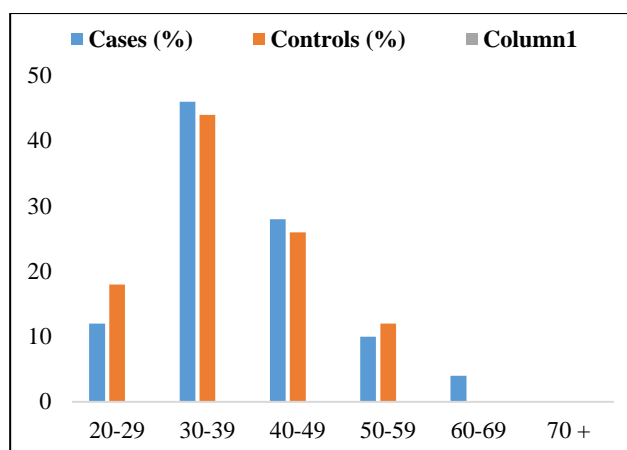
Estimated GFR (eGFR) calculation using modification of diet in renal disease (MDRD) formula-(9) "eGFR = 186 x Serum Creatinine-1.154 x Age-0.203 x (1.212 if Black) x (0.742 if Female) creatinine levels in  $\mu\text{mol/L}$  were converted to mg/dL by dividing them by 88.4. The 32788 number above is equal to  $186 \times 88.41.154$ ". Patients with either eGFR <60 mL/min/1.73 m<sup>2</sup> or positive for urine micro albuminuria (1+ and 2+) were considered as having derangement of renal functions even with normal ultrasonogram findings. Parameters of cases like age, waist circumference, fasting blood sugar, systolic BP, diastolic BP, serum triglycerides, serum HDL levels, serum creatinine, eGFR were correlated individually and compared with those of controls using statistics.

### *Statistical analysis*

It was performed using statistical package for social sciences (SPSS), version 20. The mean, standard deviation, median and ranges were calculated for continuous variables whereas proportion and frequency tables were used to summarize categorical variables. Chi square test was used to test for significance of association between the independent (predictor) and dependent (outcome) variables in categorical variables. P value <0.05 was considered significant.

## RESULTS

A total of 100 individuals were studied. 50 cases and 50 controls were compared as detailed above.



**Figure 1: Age distribution of study population.**

### Age distribution

Mean age in the case group was 37.76 years whereas in control group it was 38.3. Most of the cases were in the age group 30-39 followed by 40-49. The control group also showed a similar distribution as shown in Figure 1.

### Sex distribution

Among cases, 52% were male, while 48% were female. In control group, males comprised 48% while females were 52% (Table 1). There was no significant difference among the groups.

**Table 1: Sex distribution among cases and controls.**

	Male (%)	Female (%)
Cases	26 (52%)	24 (48%)
Controls	24 (48%)	26 (52%)

Baseline characteristics of the two groups are shown in Table 2. As seen in the Table 2 S. creatinine in cases varied from 0.4 to 2.1 mg% with a mean of 1.32 as compared to those in the control group where creatinine varied from 0.1 to 1.10 mg% with a mean of 0.66. Case group had a mean eGFR of 64.46 as compared to that in control group which had a mean of 99.76. Mean value of other parameters like fasting blood sugar, systolic BP and serum triglycerides were more in the cases group as compared to the control group.

**Table 2: Parameters of patients (cases) with metabolic syndrome and controls.**

Parameters	Cases (n = 50)			Controls (n = 50)		
	Mean	Standard deviation	Minimum-maximum	Mean	Standard deviation	Minimum-maximum
Blood urea	30.24	9.93	15-50	31.58	7.13	20-44
Serum creatinine	1.32	0.46	0.4-2.1	0.66	0.276	0.1-1.10
eGFR	64.46	30.53	27.5-120	99.76	22.81	44-124
Age	37.76	9.76	25-65	38.3	8.99	25-59
Waist circumference	90.48	5.6	80-101	87.56	4.7	80-95
FBG	125.22	25.25	85-170	92.04	12.21	70-110
Systolic BP	148.24	12.59	123-170	124.26	8.84	110-140
Diastolic BP	91.5	6.11	80-100	78.72	6.28	70-90
Serum triglycerides	174.52	24.54	123-245	140.60	9.05	110-154
Serum HDL	45.32	10.4	26-62	49.1	7.45	25-60

### Correlation of age with RFT

There was significant correlation between age and S.Creatinine and eGFR values (Table 3). Among the cases with raised serum creatinine (>1mg/dl) and eGFR<60mL/min/1.73 m<sup>2</sup> majority age groups were in 30-39 (49%) and 40-49 (27%) and followed by 50-59 (14%). This was also observed with presence of microalbuminuria. Among patients with altered renal function, there was no difference between males and females. Comparison of renal functions among Cases and Controls: The number of patients having deranged renal functions among cases were comparatively higher than that of controls. After applying Chi-Square tests, the

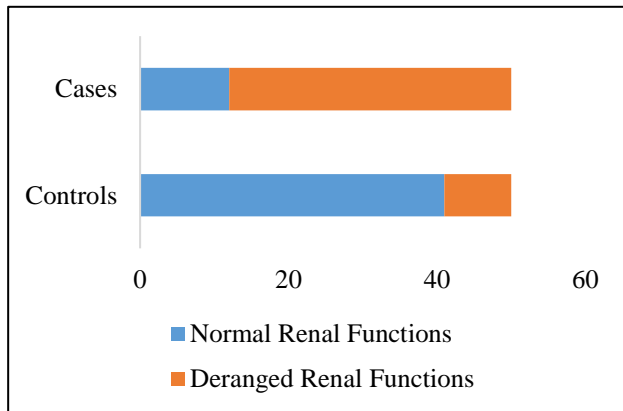
difference was found to be statistically significant. P value <0.005.

**Table 3: Age correlation with eGFR and serum creatinine among cases.**

		Age
Serum creatinine	Coefficient of Correlation	0.468
	p value	0.001
eGFR	Coefficient of Correlation	-0.586
	p value	0.001

There were 38 patients (76%) among the cases (n=50) of metabolic syndrome had deranged renal functions (eGFR

<60 mL/min/1.73m<sup>2</sup> or positive for urine micro albumin excluding USG findings) as compared to 9 patients (18%) among controls (n=50). The difference was statistically significant. P value was 0.001 (Figure 2).



**Figure 2: Comparison of renal functions among cases and controls.**

**Table 4: Renal functions cases versus controls.**

Renal function tests	Cases		Controls	
	Mean	Standard deviation	Mean	Standard deviation
Blood urea (mg %)	30.24	9.94	31.58	7.13
S. Creatinine (mg %)	1.32	0.459	0.66	0.276
eGFR mL/min/1.73 m <sup>2</sup>	64.46	30.53	99.76	22.8

Serum creatinine was raised (> 1 mg/dl) in 37 patients (74%) among cases vs 13 individuals (26%) among controls. (p Value - 0.001). Mean Difference was 0.662 with 95% CI (0.5115, 0.8125) (Table 4). 36 patients (74%) among cases had eGFR <60 mL/min/1.73 m<sup>2</sup> and 5 individuals (10%) among controls had eGFR <60 mL/min/1.73 m<sup>2</sup>. p value was 0.001(<0.05). The mean difference was -35.27 with 95% CI (-45.97,-24.577). 37 patients among cases had positive urine micro albumin and 9 individuals among controls had positive urine micro albumin. After applying Chi-Square test, p-value was 0.001 (<0.05) as seen in Table 5.

**Table 5: Urine for micro albumin among cases and controls.**

	0	1+	2+
Cases	13	26	11
Controls	41	9	0

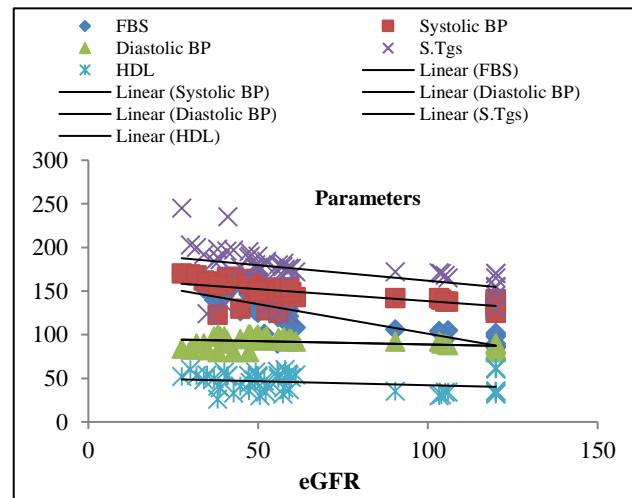
Individual parameters of metabolic syndrome in cases showed correlation with deranged RFT as seen in Table 6 below. Increases in fasting blood sugar values showed significant negative correlation with eGFR (p value =

0.001 and R value was -0.820) and positive correlation with presence of microalbuminuria (p value = 0.001, mean difference 38.13 with 95% CI (23.83, 50.43)).

Systolic BP values also correlated negatively with eGFR (p value = 0.001, R value -0.667) and positively with presence of microalbuminuria [p value = 0.001, mean difference 15.08 with 95% CI (8.09, 22.07)].

High diastolic BP value (> 85 mmHg) was associated significantly with lower eGFR values among cases (P value = 0.006, R value was -0.380). Also, among cases with positive urine microalbumin, 31 had high diastolic BP as against 6 who had normal diastolic BP. P value was 0.003. The mean difference was 5.45 with 95% CI (1.77, 9.13) which was statistically significant. High triglyceride values in cases also showed significant negative correlation with eGFR <60mL/min/1.73 m<sup>2</sup> (p value = 0.001, R value -0.443). There was also positive correlation with presence of microalbuminuria. (p value = 0.036; Mean difference: 16.5 with 95% CI (1.16, 31.84)] which was statistically significant (in correlation charts).

There was no significant correlation of low HDL levels with reduction in eGFR levels (p value = 0.061, R value - 0.267) or with increased microalbuminuria (p value = 0.100).



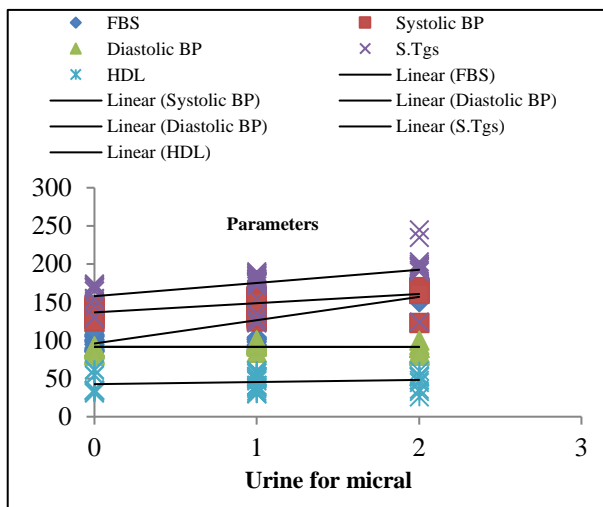
**Figure 3: Correlation chart for EGFR with parameters of metabolic syndrome.**

Figure 3 shows significant negative correlation of eGFR with various parameters of metabolic syndrome like fasting blood glucose (p value 0.001), SBP (p value 0.001) and serum triglycerides (p value 0.001). The figure also shows absence of correlation with serum HDL or DBP.

Significant positive correlation of microalbuminuria was noticed with fasting blood sugar and SBP (p value 0.001) and with DBP (p value 0.005) as seen in Figure 4. There was no correlation with triglyceride and HDL cholesterol values.

**Table 6: Correlation of RFT with various parameters of metabolic syndrome (N = 50).**

Metabolic syndrome parameters	S. Creatinine		e GFR		Microalbuminuria
	Pearson correlation (r)	p value	Pearson correlation (r)	p value	p value
Age	0.467	0.001	-0.586	0.001	-
Waist circumference	0.442	0.001	-0.259	0.069	0.031
Fasting blood glucose	0.919	0.001	-0.820	0.001	0.001
Systolic BP	0.727	0.001	-0.667	0.001	0.001
Diastolic BP	0.268	0.06	-0.381	0.006	0.005
Serum triglycerides	0.561	0.001	-0.443	0.001	0.036
Serum HDL	0.128	0.376	-0.268	0.06	0.1



**Figure 4: Correlation chart for microalbuminuria with parameters of metabolic syndrome.**

**DISCUSSION**

Metabolic syndrome affects approximately 24% of the US adult population; according to the Third National Health and Nutrition Examination Survey (NHANES III) criteria, about 47 million people have metabolic syndrome including 44% of those in the ≥50 year age group.<sup>10</sup>

In Indian population, 33.17% of males and 27.04% of females were identified as having metabolic syndrome.<sup>11</sup>

The association of metabolic syndrome with cardiovascular risk, mortality, type 2 diabetes mellitus, stroke, non-fatty liver disease and gout is well known. However, the association of the metabolic syndrome with chronic kidney disease (CKD) has been emerging in recent times.<sup>12</sup> Studies show that patients with metabolic syndrome have a 2.5-fold higher risk of developing CKD. The risk of microalbuminuria is also increased two-fold. Renal dysfunction becomes apparent long before the appearance of hypertension or diabetes in metabolic syndrome.<sup>12</sup> Although multiple studies have been done to

correlate individual parameters of metabolic syndrome with renal functions, only a few had been done in India.

**Renal functions among cases and controls**

eGFR and presence of microalbuminuria are accepted indicators of renal dysfunction. Presence of microalbuminuria is indicative of early derangement of renal functions. 38(76 %) patients among 50 cases had deranged renal functions (defined by reduced eGFR or presence of microalbuminuria) as compared to 9(18 %) controls. The difference was found to be statistically significant (p value <0.05).

The results were similar to studies done by Chen et al, Kurella et al, Kitiyakara et al, Bonnett et al, Sun et al, Watanabe et al, Ryu S et al, Wang Q et al.<sup>13-20</sup>

Individually also, eGFR and urine for microalbuminuria were found to be deranged significantly in cases as compared to controls. 36 (72%) patients among cases had eGFR <60mL/min/1.73m<sup>2</sup> as compared to 5(10%) individuals among controls which was statistically significant. p value = 0.001. The mean difference was -35.27 with 95% CI (-45.97, -24.577). Similar results were seen in studies done by Chen et al, Kurella et al, Kitiyakara et al, Bonnett et al, Sun et al, Watanabe et al, Ryu S et al, Wang Q et al.<sup>13-20</sup>

The 37 Patients (74%) out of 50 among Cases had urine positive for microalbumin as compared to 9 (18%) individuals out of 50 among controls who were positive for microalbumin which was statistically significant (p value <0.05). Presence of microalbuminuria was used exclusively in studies done by Palaniappan et al, and Bonnet et al who also showed the same association.<sup>16,21</sup>

**Serum creatinine among cases and controls**

Most of the studies done earlier used eGFR and microalbuminuria as parameters to assess renal functions and did not include serum creatinine. In 2004, Chen et al conducted a cross-sectional survey in a nationally representative sample of Chinese adults aged 35-74 years



to study renal functions in patients of metabolic syndrome.<sup>13</sup> Serum creatinine and eGFR were used to assess renal functions. The drawback of eGFR (estimated glomerular filtration rate) was that it was not directly measured GFR. Estimated-GFRs using a serum creatinine-based equation (MDRD) were used to define CKD. The MDRD-equation might have overestimated or underestimated the actual GFR in the Chinese population because it was developed primarily in Caucasian populations in the US. The study faced a similar drawback with the calculation of GFR. To overcome this, serum creatinine was also assessed and correlated.

In present study, the mean serum creatinine of cases was 1.32 as compared to mean serum creatinine of controls which was 0.66, p value was 0.001(<0.05). Mean Difference was 0.662 with 95% CI (0.5115, 0.8125). It was statistically significant. The results were similar to study done by Chen et al.<sup>13</sup>

A prospective study done by Sun et al in Taiwan showed that central obesity, high blood pressure and high triglycerides were considered highly significant in development of CKD among patients of metabolic syndrome.<sup>17</sup> A cross-sectional study among Chinese population carried out by Wang Q et al showed that abdominal obesity and hypertriglyceridemia increase the risk of CKD in metabolic syndrome. The results were similar to this study.<sup>20</sup>

There was a negative correlation and statistical insignificance between Serum HDL levels and eGFR. This result was different from older studies which showed a positive correlation i.e. decrease in serum HDL level corresponding to a fall in eGFR. In 2004, Chen et al showed that metabolic syndrome and its parameters including low serum HDL are important risk factors for CKD and metabolic syndrome is an independent risk factor for CKD.<sup>13</sup> But present group showed borderline significance of serum HDL. This dissimilarity could be due to our comparatively small sample size.

Another cross-sectional study done by Yongqiang Li et al in China among perimenopausal women showed no relationship between CKD and low HDL levels in two different age groups. It also showed no relationship between other parameters of metabolic syndrome and CKD which was not the case in present study.<sup>22</sup>

## CONCLUSION

Metabolic syndrome is a known risk factor for cardiovascular events. It is not widely regarded as a risk factor for chronic kidney disease. Many studies are now demonstrating that all parameters of the metabolic syndrome appear to show adverse correlation with renal function. Many of the studies are from western and Far Eastern populations.

The study showed that metabolic syndrome in Indian population too is associated with CKD. While age, FBS, S.TGL, SBP, LDL-C were all significantly associated with altered renal functions, there was no significant correlation with low HDL values and high DBP values.

Limitations of the study was the small size of the two groups as well as the absence of follow up are major limitations of this study.

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