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Association between Metabolic Syndrome and Chronic Kidney Disease: A Study in South India

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Introduction

Metabolic Syndrome (MetS), known as 'Syndrome X' is a constellation of interrelated risk factors of metabolic origin that increase the risk of atherosclerotic cardiovascular disease. It has been associated with markers of chronic kidney disease such as reduced glomerular filtration rate, proteinuria and/or microalbuminuria, and histological features such as tubular atrophy and interstitial fibrosis [1,2].

Three criteria have been proposed for diagnosis of MetS which include WHO, NCEP-ATP III and IDF criteria (Figure 2).

Out of the three criteria for diagnosis of MetS, the NCEP-ATP III criteria has been deemed useful in clinical setting. The modified NCEP-ATP III criteria take into consideration the phenotypic characters of the Indian population, where the cut off for waist size of men is 90 cm and women is 80 cm.

The etiological role of MetS in Chronic Kidney Disease (CKD) is unclear. Studies on the association of CKD with Mets have been documented in the western population, however there is paucity of literature in the Indian population.

Metabolic syndrome has been associated with derangement of glucose and lipid metabolism in conjunction with hypertension and obesity. Factors that exacerbate these underlying mechanisms include age, genetic makeup and sedentary lifestyle in combination with salty food consumption. An additional risk factor is the prototypical Indian phenotype with high body fat percentage in spite of a low Body Mass Index (BMI) and high waist hip ratio with low lean body mass. Taking this into account a modified diagnostic criterion has been devised specifically for Asians [4].

This study aims to determine the prevalence of metabolic syndrome in CKD patients in a South Indian population, and assess the correlation between the CKD and Metabolic Syndrome using the NCEP-ATP III criteria. We also aim to study the association of demographic details such as age, gender, BMI with CKD and MetS, in an Indian context. Patients with CKD who presented to the Outpatient department at Kasturba Hospital, Manipal, Karnataka, India was recruited, over a period of two months.

Review of Literature

The association of cardiovascular events with MetS has been known for a long time, however its relationship with renal involvement is only currently being studied. The plausible mechanisms which have been documented include insulin resistance and oxidative stress, increased pro-inflammatory cytokine production, increased connective tissue growth and pro-fibrotic factor production, increased micro vascular injury, and renal ischemia [1] (Figure 2).

Table 1. Definitions of metabolic syndrome

	NCEP ATP III (2005 revision)	WHO (1998)	EGIR (1999)	IDF (2005)
Absolutely required	None	Insulin resistance* (IGT, IFG, T2D or other evidence of IR)	Hyperinsulinemia[†] (plasma insulin >75[th] percentile)	Central obesity (waist circumference[‡]): ≥94 cm (M), ≥80 cm (F)
Criteria	Any three of the five criteria below	Insulin resistance or diabetes, plus two of the five criteria below	Hyperinsulinemia, plus two of the four criteria below	Obesity, plus two of the four criteria below
Obesity	Waist circumference: >40 inches (M), >35 inches (F)	Waist/hip ratio: >0.90 (M), >0.85 (F); or BMI >30 kg/m^2	Waist circumference: ≥94 cm (M), ≥80cm (F)	Central obesity already required
Hyperglycemia	Fasting glucose ≥100 mg/dl or Rx	Insulin resistance already required	Insulin resistance already required	Fasting glucose ≥100 mg/dl
Dyslipidemia	TG ≥150 mg/dl or Rx	TG ≥150 mg/dl or HDL-C: <35 mg/dl (M), <39 mg/dl (F)	TG ≥177 mg/dl or HDL-C <39 mg/dl	TG ≥150 mg/dl or Rx
Dyslipidemia (second, separate criteria)	HDL cholesterol: <40 mg/dl (M), <50 mg/dl (F); or Rx			HDL cholesterol: <40 mg/dl (M), <50 mg/dl (F); or Rx
Hypertension	>130 mmHg systolic or >85 mmHg diastolic or Rx	≥140/90 mmHg	≥140/90 mmHg or Rx	>130 mmHg systolic or >85 mmHg diastolic or Rx
Other criteria		Microalbuminuria[†]		

*IGT, impaired glucose tolerance; IFG, impaired fasting glucose; T2D, type 2 diabetes; IR, insulin resistance; other evidence includes euglycemic clamp studies.
[†]Urinary albumin excretion of ≥20 μg/min or albumin-to-creatinine ratio of ≥30 mg/g.
[‡]Reliable only in patients without T2D.
[‡]Criteria for central obesity (waist circumference) are specific for each population; values given are for European men and women.
Rx, pharmacologic treatment.

Figure 1: Different criteria for diagnosis of metabolic syndrome [3].

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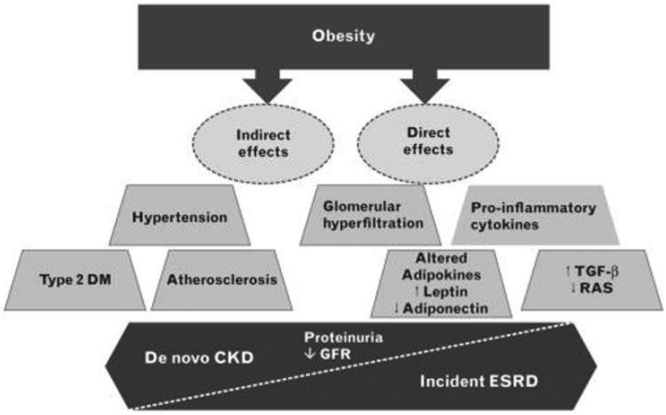

Figure 2: Potential pathways by which obesity leads to the development of chronic kidney disease. CKD: Chronic Kidney Disease; DM: Diabetes Mellitus; ESRD: End-Stage Renal Disease; GFR: Glomerular Filtration Rate; RAS: Renin– Angiotensin– Aldosterone System; TGF-β: Transforming Growth Factor Beta [5].

A recent meta-analysis showed that the different components in metabolic syndrome negatively affect the kidney in different proportions in terms of proteinuria, and their effects are hypertension, hypertriglyceridemia, low HDL, abdominal obesity, and impaired glucose intolerance in decreasing order respectively [6].

A longitudinal analysis by Fox *et al* in the Framingham Offspring Study cohort, with 2585 participants, over a mean follow up of 19 years revealed that new-onset of chronic kidney disease was associated with hypertension, low HDL levels and diabetes [7].

A population-based study in South Korea conducted by Evangelista *et al* revealed that general obesity and abdominal obesity were more prevalent in patients with CKD compared to those without CKD; and that prevalence of obesity was significantly associated with earlier stages of CKD [8].

A study by Bakhshayeshkaram *et al* based in Shiraz, Iran indicated a strong association between CKD and MetS in the Iranian population. This was analyzed by a logistic regression model, to determine the adjusted odds ratios. In their study the adjusted ORs (95% CI) of developing CKD was 1.189 (0.554 - 2.555), 2.025 (0.990 - 4.141) and 4.769 (2.413 - 9.424) as the number of risk factors increased from 1 to ≥ 3. Individuals with hypertension and abdominal obesity had a higher OR of increased susceptibility to CKD in multivariate analysis. The authors recommended that individuals with metabolic risk factors should be detected earlier and undergo multidisciplinary interventions to prevent the development of CKD [9].

A 5-year prospective analysis of the Hong Kong Diabetes Registry by Luk *et al* revealed a multivariable- adjusted Hazard Ratio (HR) of CKD was 1.31 (95% CI 1.12–1.54, $P = 0.001$) for subjects with metabolic syndrome compared with those without metabolic syndrome [10]. Kitiyakara *et al* conducted a cross- sectional study in a South East Asian cohort, with a 12-year follow up which also revealed a positive relationship between presence of metabolic syndrome and development of CKD. In their study, participants with selected combination of risk factors had an 8-to 12-fold higher risk of prevalence of CKD. The OR of CKD prevalence with these combinations was 1.5- to fourfold higher than when these components are considered individually or nearly twofold higher than those with metabolic syndrome by NCEP ATP III definition [11].

Aims and Objectives

The aims and objectives of this study are:

- To determine the prevalence of metabolic syndrome in patients with chronic kidney disease.
- To elucidate association of the stages of CKD with various diagnostic criteria for Metabolic Syndrome
- To correlate non-modifiable parameters such as age and BMI with modified NCEP- ATP III diagnostic criteria
- To study the association of MetS with cardiovascular events.

Material and Methods

Study Design

This is a record based cross sectional study.

Participants

The participants include patients who had been diagnosed with CKD between the age of 30 and 80 years.

Definition of Chronic Kidney Disease

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 the cause [11].

Definition of Metabolic Syndrome

As per NCEP-ATP III criteria for Asians [4]

1. Serum Triglyceride (TG) level >150 mg/dl or specific treatment for this lipid abnormality,
2. Serum High Density Lipoprotein (HDL) cholesterol level <40 mg/dl in men or <50 mg/dl in women or specific treatment for this lipid abnormality,
3. Systolic blood pressure more than 130 mmHg and diastolic blood pressure more than 85 mmHg or use of antihypertensive medication,
4. Fasting plasma glucose level >100 or use of anti-diabetic medication
5. Waist girth >90 cm for men >80 cm for women (modified NCEP- ATP III criteria for Asians) Those fulfilling at least 3 out of 5 criteria were diagnosed with metabolic syndrome.

Sample Size

233 patients were recruited for the study however only 194 patients satisfied the inclusion criteria.

Inclusion Criteria: All patients diagnosed with CKD of both genders, between the ages of 30-80 years.

Exclusion Criteria: All cases of acute glomerulonephritis and acute kidney disease were excluded. All CKD patients below 30 years or above 80 years.

Study Method

All patients who had been diagnosed with CKD were evaluated for Metabolic Syndrome, according to the modified NCEP-ATP III criteria for Asians. The frequency of CKD patients suffering from Metabolic Syndrome and the number of parameters of MetS criteria satisfied (3/5, 4/5 or 5/5) was be noted.

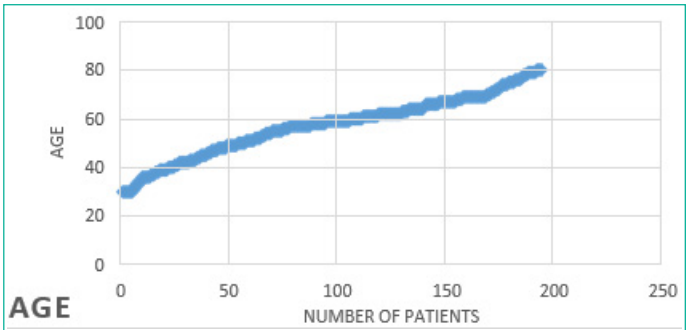

Figure 3: Age distribution.

The association between the number of parameters satisfied and the *stage of* CKD was studied. Other parameters included were history of dialysis and history of cardiovascular events (stroke, Myocardial Infarction). An association of demographic details and MetS with cardiovascular events such as myocardial infarction and stroke and between obesity and CKD was studied.

Data Collection

The data of the subjects with CKD was collected from the medical records at the outpatient clinic in the Department of Nephrology, KH, Manipal.

Procedure

At the time of visit, the subjects' waist-girth measurement was taken after obtaining a written informed consent. The information obtained from the records included age, gender, stage of CKD, history of dialysis, history of diabetes/impaired glucose tolerance, type of diabetic medication, history of hypertension, HDL levels, TG levels and history of cardiovascular events.

Confidentiality: All data was coded and kept confidential.

Statistical tools: Data was entered in Microsoft Excel 2013, and exported to SPSS 16.0 for Windows (SPSSTM Inc., Chicago, IL, USA) for analysis. Descriptive statistics, namely frequencies and percentages, were calculated for categorical data. Continuous variables were analyzed and presented as mean +/- SD. Chi square test was done to study the association between risk factors and the outcome. A p value of <0.05 was considered to be significant. Odds ratio was calculated for risk factors with a 95% Confidence Interval l (CI).

Ethical consideration: The study commenced after obtaining permission from the Institutional Ethics Committee of Kasturba Hospital, Manipal (IEC 448/2019) and CTRI.

Observations and Results

This study was conducted during a period of 2 months from June15 – August 15, 2019. The data of 233 CKD patients was collected on an outpatient basis. After careful evaluation of the medical records, 194 patients were deemed fit for the study due to complete availability of data and fulfillment of the inclusion criteria.

Demographic features of study population

The ages ranged between 30-80 years with a median age of 59 years (Figure 4)

159 males and 35 females were included in the study, the male to female ratio was 4.54:1.

Prevalence of Metabolic syndrome

Prevalence of Metabolic syndrome amongst the CKD patients

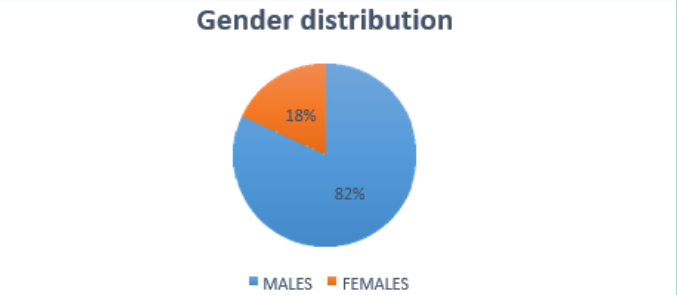

Figure 4 Gender distribution.

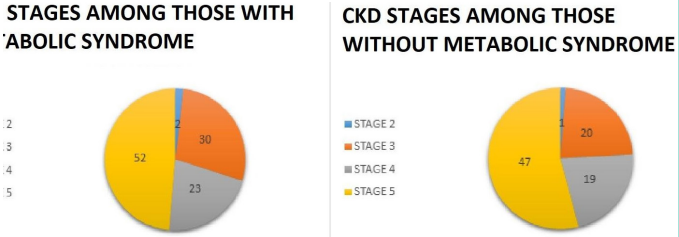

Figure 5: CKD stages among patients with and without MetS.

was 55.2%, with 107 out of 194 patients fulfilling 3 or more of modified NCEP-ATP III Criteria. Out of 194 patients, 99(51%) had stage 5 CKD disease. Out of 107 patients, 1.9% had stage 2 CKD, 28% had Stage 3 CKD and 21.5% had Stage 4 CKD, 48.6% had Stage 5 CKD. Out of 87 patients who did not have MetS, 1.10% had Stage 2 CKD, 23.00% had Stage 3 CKD, 21.8% had stage 4 CKD, and 54% had stage 5 CKD (Figure 6).

Number of patients with CKD and components of MetS

107 patients with CKD were diagnosed to have Metabolic Syndrome as per NCEP-ATP III criteria. Among these, 50 patients (46.73%) satisfied 3 out of 5 components of the criteria for MetS. 87 patients with CKD did not satisfy the MetS criteria. Within the population without Metabolic Syndrome, 45 patients (51.72%) satisfied 2 components for diagnosis of Metabolic Syndrome (Figure 7)

Association and Correlation between MetS components and CKD stages

All (194) patients were categorized into 5 groups based on the number of criteria satisfied for MetS (Figure 8) and the stage of CKD within each group was analyzed, but there was **NO** statistically significant association (p=0.789) Spearman's rho

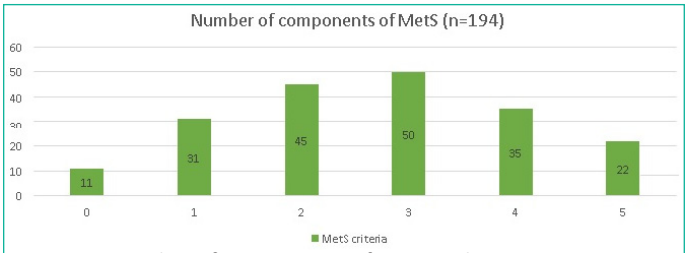

Figure 6: Number of Components of MetS with CKD.

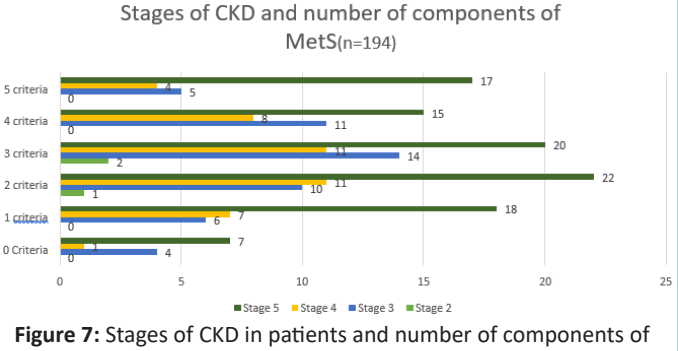

Figure 7: Stages of CKD in patients and number of components of MetS.

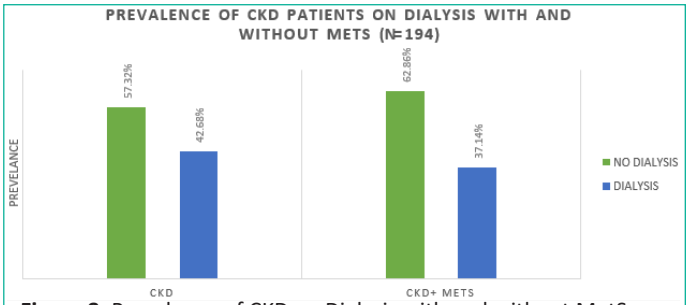

Figure 8: Prevalence of CKD on Dialysis with and without MetS.

correlation coefficient was 0.795. Hence, **NO** significant correlation was established between stages of CKD and MetS criteria.

Prevalence of various components of MetS with CKD

Among 194 patients, hypertension was the most common criteria in majority of the patients (81.96%), followed by abdominal obesity (65.46%) and Diabetes (48.45%). There was **NO** significant gender difference with respect to the MetS criteria (Figure 9).

CKD Patients on Dialysis with and without MetS

A total of 80 patients in the study were on dialysis. Out of which, 37.14% of CKD patients with Metabolic Syndrome were on dialysis, compared to 42.68% of CKD patients without Metabolic Syndrome (Figure 9).

Association between Demographic features, MetS and CKD
All patients were categorized into 3 groups based on age. Group I: 30-45 years, Group II: 45-60, Group III: 60-80.

Variable	Categories		CKD STAGES 2	3	4	5	p value
AGE	Total (n=194)	I	1(2.6%)	8(20.5%)	9(23.1%)	21(53.8%)	0.317
		II	2(2.8%)	20(27.8%)	10(13.9%)	40(55.6%)	
		II	0(0.0%)	22(26.5%)	23(22.7%)	38(45.8%)	
	No MetS (n=87)	I	1(3.4%)	5(17.2%)	5(17.2%)	18(62.1%)	*0.028**
		II	0(0.0%)	10(34.5%)	2(6.9%)	17(58.6%)	
		III	0(0.0%)	5(17.2%)	12(41.4%)	12(41.4%)	
	MetS (n=107)	I	0(0.0%)	3(30.0%)	4(40.0%)	3(30.0%)	0.392
		II	2(4.7%)	10(23.3%)	8(18.6%)	23(53.5%)	
		III	0(0.0%)	17(31.5%)	11(20.4%)	26(48.1%)	
GENDER	Total	M	2(1.3%)	20(25.2%)	37(23.3%)	80(50.3%)	0.619
		F	1(2.9%)	10(28.6%)	5(14.3%)	19(54.3%)	
	MetS	M	2(2.2%)	26(28.9%)	19(21.1%)	43(47.8%)	0.887
		F	0(0.0%)	4(23.5%)	4(23.5%)	9(52.9%)	
	No MetS	M	0(0.0%)	14(20.3%)	18(26.1%)	37(53.6%)	0.054
		F	1(5.6%)	6(33.3%)	1(5.6%)	10(55.6%)	
BMI	Total	I	0(0.0%)	2(18.2%)	0(0.0%)	9(81.8%)	*0.03**
		II	1(1%)	20(20.0%)	19(19%)	60(60%)	
		III	1(1.7%)	22(36.7%)	17(28.3%)	20(33.3%)	
		IV	1(4.3%)	6(26.1%)	6(26.1%)	10(43.5%)	
	MetS	I	0(0.0%)	1(50.0%)	0(0.0%)	1(50.0%)	0.608
		II	1(2.3%)	9(20.5%)	7(15.9%)	27(61.4%)	
		III	1(2.3%)	15(13.4%)	10(23.30%)	17(39.5%)	
		IV	0(0.0%)	5(27.8%)	6(33.3%)	7(38.9%)	
	No MetS	I	0(0.0%)	2(18.2%)	0(0.0%)	9(81.8%)	*<0.001**
		II	0(0.0%)	11(19.6%)	12(21.4%)	33(58.9%)	
		III	0(0.0%)	7(41.2%)	7(41.2%)	3(17.6%)	
		IV	1(20%)	1(20%)	0.00%	3(60%)	

Figure 9: Association of demographic features with CKD and MetS.

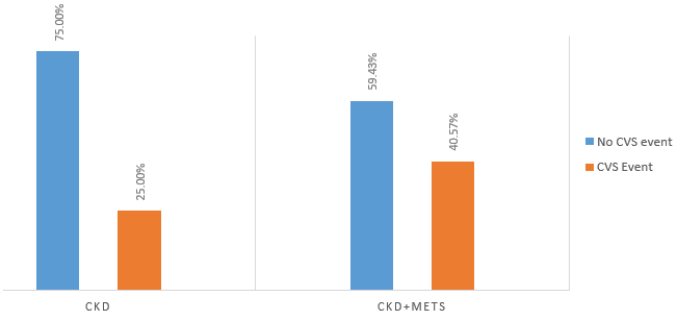

Figure 10: Prevalence of cardiovascular events in CKD patients with and without MetS.

NO significant association was seen between Age and CKD stage (p>0.05). However, a significant association was seen between Age and CKD categories in patients without metabolic syndrome (p=0.028) NO significant association was seen between gender and metabolic syndrome.

The BMI was calculated for each patient, and the patients were categorized into 4 groups as per WHO criteria:

I Underweight: <18.5 II Normal Range: 18.5-24.9 III Overweight: 25.0-29.9 IV Obese: >=30.0

A significant association was seen between BMI and CKD stages in the overall population and the group of patients without MetS (Figure 10).

Association between Cardiovascular events, MetS and CKD

There was a significant association (*p=0.015)* between Cardiovascular events and MetS with CKD (Odds Ratio of 2.195 (1.176-4.097) at 95% CI). The prevalence of cardiovascular events in CKD patients with MetS was 40.75% when compared to patients without MetS (25%) (Figure 11).

Discussion

Metabolic syndrome is a global health concern which is frequently diagnosed at later stages particularly in India, when complications arise. The prevalence of MetS in the Indian population was studied by Harikrishnan *et al* and shown to be 24%, after standardization for age and adjustment for sex and urban-rural distribution in Kerala [12]. In a multiracial study done in the UK by Tillin *et al.,* 29% of South Asian men and 32% of women had MS compared to 18% of white men and 14% of women with South Asians having a 50% to 100% higher prevalence of MetS [13].

In this study, the overall prevalence of metabolic syndrome among the CKD patients was 55.2%, with 107 out of 194 patients fulfilling 3 or more of modified NCEP-ATP III Criteria. A similar study in North Indian in renal transplant patients by Banerjee *et al* revealed a prevalence of MetS in 34% of the patients with CKD [14].

A review of literature showed studies documenting the association between MetS and CKD, however further studies are required to establish the causality. Each component of MetS has been associated with both incidence and progression of CKD and share a complex, bidirectional relationship. [1]. In our study, there was no significant association between MetS and stages of CKD. Within the population diagnosed with MetS as per the NCEP-ATP III criteria, majority of the patients (46.73%) satisfied 3 out of 5 criteria. In the group without MetS, 51.72% satisfied only 2 criteria for diagnosis. Chen *et al*, analyzed 7800 participants with a follow up period of 21 years, found that the risk of CKD increased with the number of MetS components (Odds ratio (OR) of 1.89) in adults with one MetS component to 5.85OR in adults with all five components. The risk of microalbuminuria among adults with MetS was double when compared to adults without MetS. The risk of microalbuminuria also increased in a step-wise fashion with the number of MetS components [15]. A study by Mendy *et al* among African American adults revealed a multivariable adjusted Odds ratio of 2.57, 3.64, 5.85, 6.82, 9.89 of developing CKD with 1, 2, 3, 4 and 5 components of metabolic syndrome respectively [16] In this study, the population included only patients with CKD patients and normal population was not included.

In our study, hypertension, (81.96%), abdominal obesity (65.46%) and diabetes (48.45%) were the most common prevalent components. This is in agreement with the general trend of non-communicable diseases in India, which has the highest incidence of diabetes and hypertension in the world. It is foretold that India will face a catastrophic CKD/End-Stage Renal Disease (ESRD) burden, with 25–40% of its population being at risk [17]. The rising prevalence of abdominal obesity in India also poses a major public health problem, with 30-65% of the adult urban population being overweight or obese [18]. A community based cross-sectional study by Undavalli *et al* revealed a central obesity prevalence of 71.2% within Andhra Pradesh [19]. Various other studies done in the Indian population has revealed a high prevalence of abdominal obesity as compared to general obesity [20–22].

There is paucity of literature regarding association of MetS in CKD patients on dialysis. Alshelleh *et al* noticed a significantly lower prevalence of MetS (34%) among renal transplant patients compared to those on dialysis (55.7%; *P*=0.016) [23]. In a study by Alswat *et al* in Saudi Arabia, a high prevalence of MetS (38.2%) was noted in patients on hemodialysis [24]. However, in our study, there was a low prevalence of MetS among patients on dialysis. (37.14% versus 42.68% without dialysis).

In this study, there was a significant association between increasing BMI and stages of CKD within the total CKD population (p=0.03) and within the population without Metabolic syndrome (p<0.001). In a multiracial population study by Hsu *et al,* they examined the association between BMI and risk of incident ESRD, and noted that patients who were overweight, or had class I,II and extreme obesity (defined as BMI ranges of 25.0–29.9, 30.0–34.9, 35.0–39.9, and ≥40.0kg/ m^2, respectively) had a 1.9, 3.6, 6.1, and 7.1-fold higher risk of developing ESRD when compared with normal weight (BMI 18.0–24.9 kg/m^2) independent of socio-demographics, comorbidities, and laboratory tests, including proteinuria [23] In contrast, a prospective observational study by Brown *et al* showed no effect of BMI on progression of kidney disease [26]. However, there have been documented studies showing the association between BMI and CKD which may be due to the fact that obese people tend to develop diabetes mellitus and hypertension which are risk factors for CKD [27,28]. In the literature, an 'Obesity Paradox' has been described where patients with End-Stage Renal Disease (ESRD) and a higher Body Mass Index (BMI) has been paradoxically associated with better survival [29].

Our study also revealed a significant association (p<0.05) between increasing age and CKD among patients without Metabolic Syndrome. The high prevalence of CKD in the elderly reflects the presence of a variety of different risk factors for CKD such as diabetes and hypertension in older individuals. This may also be due to age-associated decline in kidney function that is not explained by other known risk factors. An important public health implication is the fact that CKD may progress to end stage renal disease rapidly, if appropriate interventions are not taken [30].

There was a significant association (p<0.05) between cardiovascular events and MetS in our study population (Odds ratio of 2.195(1.176-4.097 at 95% CI). Studies have documented the association of MetS with cardiovascular disease and these two features when combined might be associated with the development and progression of CKD. [31] A study by Sagun *et al* revealed 37% of patients with chronic renal failure had three or more major cardiovascular risk factors, and 70% had MetS [32] A noteworthy feature is that, despite the low rates of obesity, there is a high prevalence of diabetes and coronary heart disease among South Asian populations which is commonly known as the 'Asian Indian' or 'South Asian' paradox [33].

To the best of our knowledge, very few studies have examined the prevalence of MetS among CKD patients in the Indian population. Sabanayagam *et al* examined the ethnic variations and the impact of metabolic syndrome components and chronic kidney disease in Singapore. In their study, there was a high prevalence of CKD within Malays. Among Indians, glycemic and the obesity showed a positive association, while the blood pressure had a protective association [34].

Other factors such as type of diet, lifestyle and socio-economic status have been associated with CKD, which was not included in our study. Krop *et al* [35] reported that income <$16,000 compared with income >$35,000 was associated with 2.4-fold increase in CKD. In a case–control study by Plantinga *et al* people with CKD were more likely to come from families of unskilled workers and smoking increase the risk factors [36].

Conclusion

In our study the prevalence of MetS was 55.2% in the CKD population. There was no significant association or correlation between MetS and CKD. This could be due to small sample size. However, there was a statistically significant association between BMI and CKD, and age and CKD. Additionally, there was a high prevalence of risk factors such as hypertension, abdominal obesity and diabetes in this study. It is important to note that the metabolic syndrome constitutes a risk for developing CKD as well as cardiovascular events – as revealed by a statistically significant association between cardiovascular events and metabolic syndrome in our study. Early detection and early modification of lifestyle factors could significantly reduce morbidity and mortality, especially in the ageing Indian population. A multidisciplinary approach is recommended for identifying individuals with metabolic syndrome to reduce the burden chronic kidney disease.

Limitations of the Study

1. There were more males than females in the study.
2. Small sample size and short duration of study.
3. Life style factors were not included in the study.

Summary

1. The Indian population has a higher risk for metabolic syndrome and should be efficiently screened to prevent chronic diseases involving the kidney and heart.
2. The prevalence of Metabolic syndrome among patient with CKD was 55.2%, with almost half (48.6%) with Stage 5 CKD.
3. Hypertension, abdominal obesity and diabetes were the most common NCEP-ATP III criteria in our study population.
4. There was no significant association or correlation between Metabolic Syndrome and CKD.
5. There was a significant association between BMI and CKD, and age and CKD among patients without MetS.

There was a statistically significant increased risk of cardiovascular events in patients with MetS.

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