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RELATION BETWEEN BIOCHEMICAL PROFILE OF METABOLIC SYNDROME AND CHRONIC KIDNEY DISEASE.

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ABSTRACT

Background: The current study provides new and important information regarding the relationship between the metabolic syndrome and risk of CKD in a representative sample of adult population and suggests that prevention and treatment of the metabolic syndrome should be an important priority for reducing the prevalence of CKD and its associated disease burden in adult population. **Aims:** To study the relation between Biochemical Profile of Metabolic syndrome and Chronic Kidney Disease.

Materials and methods: Hospital based observational study conducted in the department of Biochemistry, among the patients who are eligible for metabolic syndrome criteria. Any of the three parameters meeting the inclusion criteria in a patient will be tested for serum creatinine and GFR <60ml/min/1.73m^2 according to MDRD formula.

Results: In our study, prevalence of CKD in Metabolic syndrome is 41.2%, that is very significant, approximately one third of study patients with Metabolic syndrome leading to Chronic Kidney Disease. Diabetes mellitus found have significant association with

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CKD with a p value of 0.006, similarly dyslipidemia had some impact on patients leading to CKD as the TG and HDL as the p values of them are in borderline significant. And finally hypertension found to have a significant association with CKD with a p value of 0.04. Incidentally 22% of the study patients are having Acute Kidney Injury because of various etiologies.

Conclusion: The present study identified a strong, positive, and significant relationship between the metabolic syndrome and risk of CKD in the general adult population. The risk of CKD increased progressively with a higher number of components of the metabolic syndrome. These relationships were independent of potential risk factors for CKD including age, DM, HTN, triglycerides and BMI.

Keywords:

INTRODUCTION

Metabolic syndrome (MetS) is defined by a cluster of interconnected factors that directly increase the risk of coronary heart disease (CHD), other forms of cardiovascular atherosclerotic diseases (CVD), and diabetes mellitus type 2 (DMT2). The term "metabolic" refers to the biochemical processes involved in the body's normal functioning. The term "metabolic syndrome" is used to describe a cluster of conditions including increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels. Recently, other abnormalities such as chronic pro-inflammatory and pro-thrombotic states, non-alcoholic fatty liver disease and sleep apnea have been added to the entity of the syndrome, making its definition even more complex.[1]

Metabolic Syndrome and CKD share a complex, bidirectional relationship. Each component of Metabolic Syndrome has been associated with both CKD incidence and progression. Obesity, Hypertension, Diabetes mellitus and Dyslipidemia is associated with CKD. Possible mechanisms of renal injury and chronic kidney disease in metabolic syndrome insulin resistance, Oxidative stress, Increased pro-inflammatory cytokines (leptin, interleukin6, tumor necrosis factor α), Increased connective tissue growth and/or fibrosis factors (connective tissue growth factor, transforming growth factor β, type lV collagen), Increased glomerular volume and podocyte hypertrophy, Triglyceride- and free-fatty acid induced injury, Increased ischemia and micro-vascular injury (angiotensin II), Hyperuricemia. Metabolic Syndrome is also a higher CVD risk factor at all stages of CKD from early renal insufficiency to end-stage renal disease. CKD however is also a long-term illness, just like Metabolic Syndrome, and often progresses over many years from mild reductions in glomerular filtration rate to more advanced pre-uremic states and eventual renal replacement therapy. [2] Aim of present study is to study the relation between Biochemical Profile of Metabolic syndrome and Chronic Kidney Disease.

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MATERIALS AND METHODS

Study period: September 2018 to august 2019.
Study design: Hospital based observational study
Study population: This study will be conducted in the department of Biochemistry, at Mamata Medical College Khammam among the patients who are eligible for metabolic syndrome criteria.
Inclusion criteria: Age **:** 30 to 70 years, with central obesity i.e. BMI >30kg/m^2, Systemic Blood Pressure more than ≥ 140/90 mmHg **or** on treatment of previously diagnosed hypertension, fasting plasma glucose (FPG) **:** >100 mg/dl (5.6 mmol/L) **or** on treatment for diagnosed type 2 Diabetes Mellitus and with Dyslipidemia
Exclusion criteria: Patients with missing measurements for any component of the metabolic syndrome or renal functions and Pregnant women.
Triglycerides (TG) : ≥150mg/dl
or HDL-C : ≤ 35mg/dl (male)
: ≤ 39mg/dl (female)
ANY OF THE ABOVE THREE PARAMETERS MEETING THE INCLUSION CRITERIA IN A PATIENT WILL BE TESTED FOR SERUM CREATININE and GFR <60ml/min/1.73m^2 according to MDRD formula.

METHOD

After obtaining informed consent, general data regarding age, sex, weight, height, history of hypertension, diabetes, etc. will be noted.

Body Mass Index (BMI) will be calculated by dividing the subject's weight in kilograms by the square of his or her height in meters. The blood pressure will be measured using manual mercury sphygmomanometer. Two recordings will be taken in the sitting position at an interval of 5 minutes. The average of the two readings will be taken as the final measurement.

A 5ml of fasting blood sample will be collected and it will be centrifuged at 3000rpm for 10min and the serum is used for analysis of metabolic syndrome biochemical profile and Serum Creatinine.

Metabolic syndrome will be diagnosed by the presence of three or more of the five criteria of the World Health Organization. **CKD** will be defined according to the Modification of Diet in Renal Disease (MDRD) - eGFR formula.

Data analysis:

Statistical analysis of the data will be performed by using Microsoft Excel and Statistical Package for Social Sciences (SPSS) version 17. Data will be represented in the form of frequencies, percentages and mean ± SD with the help of tables and graphs.

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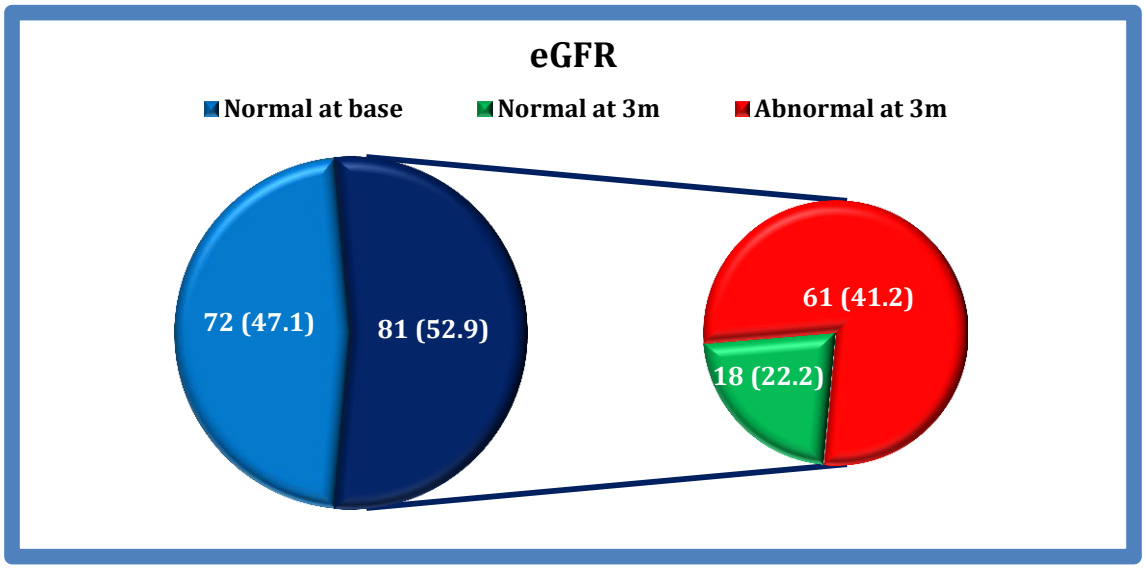
RESULTS

In the present study 153 patients met the criteria formulated at the time of submission.

Figure .1: Pictorial view of Study population eGFR at Base and 3 months



Over the period of approximately two years from September 2018 to august 2019, 153 patients met inclusion criteria, out of 153 patients, 72 patients were having normal eGFR levels at time of entry into the study, 18 patients' eGFR came down to normal levels, suggesting that they were having Acute Kidney Injury, recovered at 3rd month. Finally at the end of 3rd month, eGFR was found to have abnormal (low) levels in 63 patients, prevalence is about 41.2 percent.

Table-1: eGFR relation in to Age.

Age	eGFR		Total
	Normal	Abnormal	
	Count (%)	Count (%)	Count %
31-40	28 (31.1%)	2 (3.2%)	30 (19.6%)
41-50	44 **(48.9%)**	13 (20.6%)	57 (37.3%)
51-60	16 (17.8%)	41 **(65.1%)**	57 (37.3%)

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>60	2 (2.2%)	7 (11.1%)	9 (5.9%)
Total	90 (100.0%)	63 100.0%	153 (100.0%)

Most of the normal patients around 80 %, from 31-40 and 41-50 age groups, out of these around 50% contributed by 41-50years age group.
Out of 63 abnormal eGFR patients, 41 from 51-60years age group, is about 65 percent.

Table-2: eGFR in relation to sex

Sex	**eGFR**				**Total**		**P-value**
	Normal		**Abnormal**				
	Count	**%**	**Count**	**%**	**Count**	**%**	
Female	48	53.3%	30	47.6%	78	51.0%	0.51
Male	42	46.7%	33	52.4%	75	49.0%	
Total	90	100.0%	63	100.0%	153	100.0%	

eGFR by gender wise was not showing any statistical significance.

Table-3: eGFR in relation to Obesity Class

Obesity	**eGFR**				**Total**		**P-value**
	Normal		**Abnormal**				
	Count	**%**	**Count**	**%**	**Count**	**%**	
Class-1	83	92.2%	57	90.5%	140	91.5%	0.77
Class-2	7	7.8%	6	9.5%	13	8.5%	
Total	90	100.0%	63	100.0%	153	100.0%	

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Class-I obesity patients were major participants of the study, but there was no big difference from normal to abnormal eGFR.

Table-4:eGFR in relation to Hypertension

BP	eGFR				Total		P-value
	Normal		Abnormal				
	Count	%	Count	%	Count	%	
Non HTN	20	22.2%	6	9.5%	16	10.5%	0.04
HTN	70	77.8%	57	90.5%	137	89.5%	
Total	90	100.0%	63	100.0%	153	100.0%	

In normal eGFR cases, 77.8% of the study subjects having HTN where as in abnormal eGFR cases, HTN was present in 90.5% of the subjects. It was showing statistically significant (p=0.04).

Table-5; eGFR in relation to Diabetes

FBS >110/ DM	eGFR				Total		P-value
	Normal		Abnormal				
	Count	%	Count	%	Count	%	
Non DM	16	17.7%	2	3.2%	8	5.2%	0.006
DM	74	82.3%	61	96.8%	145	94.8%	
Total	90	100.0%	63	100.0%	153	100.0%	

In normal eGFR cases, 82.3% of the study subjects having DM where as in abnormal eGFR cases, DM was present in 96.8% of the subjects. It was showing statistically significant.

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Table-6: eGFR in relation to Triglycerides

TG	eGFR				Total		P-value
	Normal		Abnormal				
	Count	%	Count	%	Count	%	
Normal	14	15.5%	6	9.5%	20	13.1%	0.28
Abnormal	76	84.5%	57	90.5%	133	86.9%	
Total	90	100.0%	63	100.0%	153	100.0%	

Around 86.9% of the patients were having abnormal Triglycerides fulfilling the inclusion criteria of metabolic syndrome, and one third of them were having CKD, It was also showing statistically significant (0.28).

Table-7: eGFR in relation to HDL

HDL	eGFR				Total		P-value
	Normal		Abnormal				
	Count	%	Count	%	Count	%	
Normal	15	16.7%	15	23.8%	30	19.6%	0.31
Abnormal	75	83.3%	48	76.2%	123	80.4%	
Total	90	100.0%	63	100.0%	153	100.0%	

Approximately 80% of patients were having abnormally low HDL levels in who included in this study, probably statistically HDL level could not determined.

DISCUSSION

Table-8:Risk of CKD in adults with and without the MetS

Study/author	Patients	Study design	Definition of CKD	Results
Chen at al[3] NHANES	6217 US adults	Cross Section	eGFR<60ml/min/1.73m^2	OR for prevalence CKD 2.60 Two components of MetS 2.21

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III				Three components of MetS 3.38 Four components of MetS 4.23 Five components of MetS 5.58Prevalent microalbumuria 1.89 Three components of MetS 1.62 Four components of MetS 2.45 Five components of MetS 3.19
Hoehner et al[4] Inter-Tribal Heart Project	934 Native Americans	Cross Section	Microalbuminuria Alb/Cr ratio of 30–299 mg/g	OR for prevalent CKD One component of MetS 1.80 Two components of MetS 1.80 Three or more components 2.30.
Palaniappan et al[5] NHANES III	5659 Native Americans	Cross Section	Microalbuminuria Alb/Cr ratio of 30–299 mg/g	Microalbuminuria was more common in both Women and men with MetS. OR 2.2 and 4.1, respectively.
Chen et al Inter Asia Study[6]	15,160 Chinese adults	Cross Section	eGFR ,60 mL/min/1.73 m2	OR for CKD 1.64One components of MetS 1.51Two components of MetS 1.50Three components of MetS 2.13Four and five components of MetS 2.72.
Tanaka et al[7]	6,980 Japanese adults	Cross-sectional; hospital-based survey	eGFR ,60 mL/min/1.73 m2or proteinuria (+1 dipstick)	OR of prevalent CKD for those with four metabolic syndrome risk factors compared to those with no metabolic syndrome risk factors was 1.77. (The association was significant in participants, 60 years only).
Chang et al[8]	60921 Korean adults	Retrospective analysis	eGFR ,60 mL/min/1.73 m2or proteinuria (+1 dipstick)	Individuals with MetS had a multivariate adjusted OR of 1.680 for CKD compared with those without MetS.
Ryu et al[9]	10,685	Prospectiv	eGFR ,60	Increased risk of prevalent

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	Korean healthy men	e cohort study;3.8 years follow-up	mL/min/1.73 m2	CKD in individuals with MetS (HR 1.99, 95% CI1.46–2.73).
Sun et al[10]	118,924 Taiwanese	Prospective 3.7 years follow-up	GFR ,60 mL/min/1.73 m2 or proteinuria (+1 dipstick)	Incidences and HRs on CKD increased with the number of MetS components. The multivariable-adjusted HR for CKD associated with MetS was 1.30 (95% CI1.24–1.36).
Thomas et al[11]	30,146 adults	Meta-analysis 11 prospective studies	eGFR ,60 mL/min/1.73 m2and/or Microalbuminuria or proteinuria	Greater CKD risk with than without MetS (OR 1.55, 95% CI1.34–1.80).
Nitya Nand et al[12]	300 adults	Case control	eGFR -60 mL/min/1.73 m2, albumin-Creat ratio in the range of 30 – 300 mg/gm in females & 20 - 200 mg/gm in males	CKD 2 components-0.355, 3 components-1.977, 4 components 2.411 5 components 2.757 microalbuminuria 2 components-0.26, 3 components 1.863, 4 components 2.162 5 components 6.735

Our study was also having prevalence of 41.2 percentages with three metabolic syndrome parameters leading to CKD same as in the previous studies. The prevalence CKD was 15.8, 18.3, 44, 49.1, and 55 % corresponding to one, two, three, four, and five components, respectively in a recent study by Nitya Nand et al from Pandit B. D. Sharma Post-Graduate Institute of Medical Sciences, Rohtak, done in 2015[12,13]. Similar results were found in the Korean population, in a retrospective study of 60,921 healthy adults; prevalence of CKD was greater in those with MetS (11.0% versus 6.3%; *P*,0.001) than those without MetS[8]. This prevalence increased with the number of components of the MetS.

The mean age of the study group was 50 years, ranging from 35 years to 66 years; patients with normal eGFR mean age was 45.5 years with SD of 6.7 percent and patients

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with abnormal eGFR mean age was 54.5 years with SD of 6.2 percent, with significant P value indicating greater likelihood of MS in older age ($p < 0.001$). Probably we can assume that patients identified with metabolic syndrome at an early age, early intervention by physical activity, diet modification and other measures will prevent cardiovascular diseases and CKD. Large number of normal eGFR patients with metabolic syndrome about 80 % from 31-40 and 41-50 age groups, out of which 50 % by 41-50 years age group only. 51-60 years age group was the major contributor of abnormal eGFR and was about 65 percent.

Interestingly 18 patients about 22.2 percent of the patient's serum creatinine / eGFR improved to baseline at 3rd month, indirectly suggesting that there was a high incidence of Acute Kidney Injury by various causes. Our incidence was correlating with major studies and meta-analysis ranging from 12 to 60 % depending on the nature of primary disease severity and place of admission either from the community acquired AKI[14] in wards or ICU, septic and non-septic patients and significant mortality about 40-60 percent. AKI is estimated to occur in up to 15% of hospitalized patients and up to 60% of critically ill patients.[14]

Out study did not show any significant difference between male and female. However, other studies had a female sex predilection was observed in participants with CKD and metabolic syndrome, probably small number of the study could not identify the correlation.[15]

CKD and the MetS which component of the MetS is the main culprit! Probably it is the very difficult question to answer. Since every component of the MetS is a risk factor for the development and progression of CKD, it would be helpful to know which components of the MetS contribute the most to CKD. Epidemiologic studies have demonstrated greater risk for renal dysfunction with specific components of the MetS.

The link between obesity and CKD has been recognized for nearly a century. However, in our study obesity was a prime inclusion criteria, so we could not make any conclusion about obesity. Surprisingly there is little published information on the relationship between renal dysfunction and total or regional body fat. Perhaps one of the strongest epidemiological studies associating obesity (defined by BMI 25 kg/m2) and CKD comes from the Kaiser Permanente database. Hsu et al evaluated over 320,000 members of the Kaiser Permanente healthcare system who volunteered for screening and was followed for 15–35 years. The risk of ESRD increased in a step-wise fashion as BMI rose, even after adjusting for blood pressure, diabetes, smoking, and cardiovascular disease[16].Obesity results in kidney disease beyond just CKD. In a meta-analysis examining the association between obesity and kidney disease, Wang et al reported 60%

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increased risk for any kidney disease including nephrolithiasis, renal cancer, CKD, and ESRD in BMI .30 kg/m2 (relative risk =1.83 [1.57–2.13])[17].

Obesity is not only implicated in the development of CKD but also with a faster progression. Othman et al [18]evaluated influence of obesity on progression of nondiabetic CKD in a retrospective cohort study one hundred twenty-five nondiabetic patients with stage 3 CKD were followed at a single center for 10 years. Higher baseline BMI and younger age were strongly and independently associated with faster CKD progression (fall in eGFR one mL/min/1.73 m2/year) ($R2$=0.122; P, 0.001).

Present study, in normal eGFR cases group, 77.8% of the study subjects having HTN, where as in abnormal eGFR cases, HTN was present in 90.5% of the subjects. It was showing statistically significant (p=0.04). Hypertension alone is a known cause of CKD and proteinuria, typically 500 mg/day. In fact, hypertension is the second leading cause of ESRD. In a study discussed earlier by Rashidiet al[19], controlling for hypertension eliminated the statistical association between MetS and renal disease. This study suggests that hypertension is the key player in the MetS renal disease association; however, these results need to be replicated before a conclusion is drawn.

The synergistic effect of obesity and hypertension on kidney function was examined by Munkhaugen et al[20] who followed 74,986 adults participating in a Norwegian registry with a 20-year follow-up study. They found that pre-hypertension in nonobese patients was not a risk factor for incident kidney disease, whereas it was in obese patients.

In the United States, over 29 million people have diabetes. Of these, 21.0 million are diagnosed and 8.1 million are undiagnosed. In 2013, diabetes led to more than 51,000 new cases of kidney failure and over 247,000 people are currently living with kidney failure resulting from diabetes. Diabetes is characterized by high levels of blood sugar, resulting from insufficient production of insulin or defects in insulin action in the body. Type 2 diabetes (also called noninsulin-dependent diabetes) is far more common than type 1 (insulin-dependent diabetes), accounting for about 90 to 95 percent of the cases of diabetes. Type 2 diabetes is most common in people over 40, but is increasing among younger people including children and adolescents.

In the present study normal eGFR cases, 82.3% of the study subjects having DM where as in abnormal eGFR cases, DM was present in 96.8% of the subjects. It was showing statistically significant (p=0.006). Diabetes is the leading cause of kidney failure, accounting for 44% percent of new cases. Diabetic kidney disease is a type of kidney disease caused by diabetes. Diabetes is the leading cause of kidney disease. About 1 out of 4 adults with diabetes has kidney disease . Present study also highlighting the same, there was a significant number of patients fall in chronic kidney disease group with statistically significance. Having diabetes for a longer time increases the chances that you

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will have kidney damage. If you have diabetes, you are more likely to develop kidney disease if the blood glucose is too high, blood pressure is too high, African Americans, American Indians, and Hispanics/Latinos develop diabetes, kidney disease, and kidney failure at a higher rate than Caucasians and also more likely to develop kidney disease if you have diabetes and smoke, who don't follow your diabetes eating plan, who eat foods high in salt, who are not active, who are overweight have heart disease have a family history of kidney failure[21].

The kidney and the liver are the main sites for insulin clearance, with the kidney removing 50% of peripheral insulin by glomerular filtration and the liver removing approximately 50% during the first portal passage. [22] In addition to glomerular filtration, proximal tubular reabsorption and degradation is responsible for disposal of insulin in the kidney in fact, more than 99% of the filtered insulin is reabsorbed in the proximal tubule and very little insulin is actually excreted in urine which is why the renal clearance of insulin is considerably greater than the GFR. Peritubular insulin uptake increases as renal function deteriorates, and insulin clearance is maintained until the GFR reaches 15-20 ml/min. From this point on, insulin clearance falls rapidly. Therefore, insulin resistance accompanied by hyperinsulinaemia, glucose intolerance and dyslipidaemia, is one of the characteristics of the uraemic (ckd) state.

The presence of insulin resistance in the early stages of CKD suggests that insulin resistance may be a driver, rather than a consequence, of CKD, even in non-diabetic subject. Chen et al[3] have shown a strong, positive, significant, and dose-response relationship between insulin resistance, insulin level and risk of CKD among non-diabetic subjects[21]. Other studies, mostly prospective, have shown that the presence of diabetes is associated with an increased risk of ESRD diabetic and non diabetic origin.

More than 35% of people aged 20 years or older with diabetes have chronic kidney disease. If current trends continue, it is estimated that 1 in 3 U.S. adults will have diabetes in the year 2050 compared to 1 in 10 today.[21]

Around 86.9% of the patients were having abnormal Triglycerides fulfilling the inclusion criteria of metabolic syndrome, and one third of them were having CKD, It was also showing statistically significant (p=0.28) and was same for HDL values as well, more abnormal HDL percentage was representing the normal eGFR (83.3%) than abnormal (76.2%) eGFR. In the Atherosclerosis Risk in Communities Study, reduced HDL cholesterol or elevated triglycerides levels were independently associated with a significantly increased risk for CKD. The adjusted relative risk for the highest versus lowest quartile of triglycerides was 1.65 (95% CI 1.1–2.5; *P*=0.01) and for HDL was 0.47 (95% CI 0.3–0.8; *P*=0.003). Observations in the Modification of Diet in Renal Disease

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Study cohort indicated that low levels of high-density lipoprotein HDL cholesterol predicts faster CKD progression in 840 patients with diverse renal diseases.[23]

LIMITATIONS OF THE STUDY

There are two other major limitations of this study – first, the study is a cross-sectional study; and second, it involves a small sample of subjects.

This highlights for the need of further large scale trials on this subject – particularly as this is an important issue in the current scenario in the developing countries like India where MS and CKD are both increasing at an alarming rate. Also, it needs to be established if timely intervention in these high-risk groups will alter the prevalence of CKD.

CONCLUSION

In conclusion, our study indicates that the metabolic syndrome is a strong and independent risk factor for CKD in general adult population. In addition, there is a graded relationship between the number of the metabolic syndrome components and risk of CKD. These findings warrant future prospective and interventional studies to test the impact of preventing and treating the metabolic syndrome on the risk of CKD.

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