

# Prediction and Risk Factor Analysis of Obesity-related Proteinuria among Individuals with Metabolic Syndrome

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## Abstract

**Objective:** In the present modern era of time, poor and frantic lifestyle has led to an enumerate increase in the number of people with obesity and metabolic syndrome (MS). Epidemiological studies have shown the incidence of chronic kidney disease (CKD) risk factors in individuals with obesity and MS; despite the nonclear evidence on the existing potential risk factors, it became important to reassess existing potential risk factors that are involved in disease progression and its further complications. The strongest risk factor of CKD, albumin-to-creatinine ratio (ACR) recognized as a marker of MS and obesity. This study was carried out to identify the association of obesity (body mass index [BMI]) as a risk factor for albuminuria and to observe the dependence and association with albuminuria of each critical and basic factor of MS. **Design:** We conducted the potential risk factor analysis on 913 subjects, including 398 females and 515 males, from various diabetic hospitals of Vijayawada, Andhra Pradesh from early 2013 to June 2015. The medical records of the patients followed up; the anthropometric measurements and clinical parameters were retrospectively collected. The total subjects were categorized as subjects with and without MS as per National Cholesterol Education Program Adult Treatment Panel (NCEP-ATPIII) and the subjects with BMI more than 30 kg/m<sup>2</sup> were defined as obese according to WHO classification. **Results:** Student's *t* test analysis indicates a significant difference for ACR with mean values of 39.5 ± 44.8 and 18.4 ± 24.3 ( $P < 0.0001$ ) in subjects with MS and without MS, 43.4 ± 48.3 and 36.7 ± 42.5 ( $P < 0.02$ ) in obese and nonobese subjects, respectively. Chi-square analysis showed a significant association ( $P < 0.05$ ) between MS and ACR and correlation analysis manifested significant association ( $P < 0.01$ ) between ACR and FBS, TG, B.P, and Age in subjects with MS. The subjects with high prevalence of albuminuria exhibited significant association with an odds ratio (OR) of 1 (referent) 1.9 (95% CI, 1.34–2.58,  $P = 0.0002$ ), 1.5 (95% CI, 1.11–1.96,  $P = 0.0082$ ) for FBS >110 mg/dL, and TG > 150 mg/dL, respectively. Although the subjects with obesity showed no correlation with albuminuria, the risk for albuminuria was 1.5 times (95%CI 1.03–2.40,  $P = 0.03$ ) higher among obese male subjects compared to obese female subjects. **Conclusion:** Our study strongly supports that albuminuria is highly prevalent among the subjects, with MS showing a significant positive association between obesity (BMI) with albuminuria in males only.

**Keywords:** ACR, BMI, chronic kidney disease, FBS, HDL, metabolic syndrome, TG

## INTRODUCTION

Chronic kidney disease (CKD) has become a major global health problem with an estimated worldwide affected population of 2 million. In this context, early detection of CKD is crucial to prevent the progression of CKD to end-stage renal disease (ESRD). The presence of persistently elevated albuminuria is an early clinical marker of CKD and a predictor for cardiovascular diseases (CVD) and

mortality. The clinical manifestation of CKD includes albuminuria/proteinuria as an important diagnostic tool for primary treatment<sup>[1-3]</sup> and also considered in the definition of the metabolic syndrome (MS) by the World Health Organization.<sup>[4]</sup> The MS is defined as a

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constellation of risk factors including obesity, impaired fasting glucose (FBS >110 mg/dL), increased triglycerides (TG >150 mg/dL), associated with insulin resistance, hypertension (systolic >140 mm Hg), low levels of high-density lipoprotein cholesterol (HDL < 40 mg/dL)<sup>[5]</sup> and chronic inflammation,<sup>[6]</sup> leads to composite metabolic derangements that contribute to CKD and coronary artery disease. As per the prior investigations, the relationship between albuminuria, and MS risk factors percentage of prevalence being reported to be 10%-42% in persons with type II diabetes, 11%-40% in people with hypertension and 5%-10% in those without diabetes, hypertension or cardiovascular disease.<sup>[7-9]</sup> Obesity has been pointed out as one of the critical factors of MS, and the body mass index (BMI) estimate of more than 30 kg/m<sup>2</sup> indicates obesity, and people with MS are at higher risk of many chronic diseases with reduced life expectancy. One of the molecular mechanisms underlying obesity-related CKD is the abnormal or excessive accumulation of fat, characterized by adipocytes hypertrophy. This phenomenon induces hypoxia,<sup>[10]</sup> promoting inflammation and secretion of adipokines such as leptin, which specifically binds to the receptors on glomerulus and show a direct effect on kidney by promoting excessive production of pro-fibrotic transforming growth factor beta (TGF- $\beta$ ) which further enhance the production of extracellular matrix (ECM) components leading to fibrosis.<sup>[11,12]</sup> In obesity, increased adipose storage or inflammation of adipocytes brings about insulin resistance conversely insulin sensitivity reduction by several intracellular mechanisms causing the onset of hyperglycemia facilitating renal fibrosis.<sup>[13]</sup>

In the studies with obesity, the possible existence of a relationship between the roles of obesity executed as BMI in routine clinical practice with kidney dysfunction remains controversial. Weisinger *et al.*<sup>[14]</sup> first reported that massive proteinuria is associated with obesity. Similarly, limited studies have systematically addressed the association between microalbuminuria with obesity or central obesity irrespective of gender and other predisposing conditions. Hoffmann *et al.*<sup>[15]</sup> conversely found that there is no difference in albuminuria levels in lean and obese glucose-tolerant subject's studies.<sup>[16]</sup> However, very fewer studies focused on microalbuminuria, especially in obese nondiabetic, no hypertensive subjects. Our study focused to predict the risk factors of CKD in obesity-associated albuminuria in the south Asian population having unique anthropometric body measurements and to substantiate the clinical practices in most of the hospitals where BMI usually considered as the only clinical parameter to determine obesity.

## MATERIALS AND METHODS

### Study area and population

This study is a cross-sectional analysis carried out in Vijayawada, Krishna District, Andhra Pradesh, India, among subjects aged between 20 and 84 years. The study

was conducted on 913 subjects including 398 females (43.6%) and 515 (56.4%) males during their hospital visit who underwent medical screening at various diabetic hospitals of Vijayawada from early 2013 to June 2015 and have undergone diagnosis. Majority of them had MS. The exclusion criteria of the study were pregnant women with MS and the patients who had other CKDs. The clinical diagnosis reports and anthropometric measurements regarding height and weight were collected with patient consent.

Sample size ( $n$ ) was calculated as follows =  $z^2 p(1-p)/d^2$ . In this study, the sample size for obesity was calculated using prevalence  $P = 6.5\%$ <sup>[17]</sup> and confidence level of 95% and the precision of 0.05, by adding 10% nonresponsive rate. The total sample size was  $n = 103$ . The sample size for obese was 258. Among them, 112 were males and 146 were females. For MS, the sample size was calculated using a 95% confidence level with the margin of error 0.05 and prevalence  $P = 20\%$ <sup>[18]</sup> by adding 10% non-responsive rate, the total sample size should be  $n = 270$ , but a total number of 874 MS subjects included in the study.

### Sampling technique and procedure

#### Laboratory findings

According to the "III Adult Treatment Panel" of the "National Cholesterol Education Program" (NCEP-ATPIII of 2001) principles, MS includes the evaluation of the following risk factors: (1) fasting serum glucose (FBS), (2) TG (triglycerides), and (3) HDL (high-density lipoproteins) with consideration of BMI >30 kg/m<sup>2</sup> and with systolic pressure > 130 mm Hg and diastolic pressure > 90 mm Hg. According to the National Kidney Foundation (NKF) guidelines (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 1997),<sup>[19]</sup> the urinary albumin ( $\mu\text{g/mL}$ ) to creatinine (mg/mL) ratios in an untimed urine specimen is a convenient way to assess albumin excretion. Albuminuria is classified based on severity as normal healthy category ACR <30  $\mu\text{g/mg}$  and unhealthy albuminuria category ACR >30  $\mu\text{g/mg}$ . Among the 913 subjects, 402 (44%) are unhealthy albuminuria subjects and 511 (56%) are healthy albuminuria subjects.

#### Physical examination and clinical data

The anthropometric measurements were carried out as per the hospital standard operating procedures, the height was measured using calibrated height meters with subjects standing bare-footed in erect position placing the feet together and weight measured with the calibrated weighing machine. BMI was calculated as weight in kilograms divided by a square of height in meters. Blood pressure (BP) was measured by trained nurses employing a standard mercury sphygmomanometer, while the subject sit in a chair with feet on the floor and arm reinforced elbow is at around heart level. The average of two readings was used

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for the analysis. All participants' clinical data related to routine laboratory findings were collected from medical records of the respective hospitals.

### Statistical analysis

We performed statistical analysis using the SPSS software package. The results summarized as percentages and as the mean  $\pm$  standard deviation (SD). The Pearson chi-square test and Student's *t* test were used to compare the differences between categorical variables. An appropriate condition among each parameter tested using Spearman's correlation coefficient. A value of  $P < 0.05$  was considered a statistically significant difference. We calculated odds ratios using a 2x2 table.

### Ethical consideration

We conducted this study with the ethical consideration approval got from the institutional review board of

Guntur Medical College and Government General Hospital, Guntur, Andhra Pradesh, India and approved by the Helsinki Declaration. (Application number GMC/IEC/120/2018).

## RESULTS

This cross-sectional study performed on 913 randomly selected individuals with the majority (874) participants having MS. Irrespective of their metabolic condition we categorized the total subjects into three different categories. Each time in this study, the total subjects were categorized individually following presence/absence of MS as with MS (95.7%) and without MS (4.3%), similarly with obesity (28%) and without obesity (72%) and with healthy albuminuria (56%) and unhealthy albuminuria (44%). The mean and SD values of the following risk factors such as anthropometric, BP, lipid profile, and blood

**Table 1: Comparison of baseline characteristics in, without MS and with MS groups, without MA and with MA groups and without obesity and with obesity groups using Student's *t* test**

Risk factor	Without MS ( <i>n</i> = 39)		With MS ( <i>n</i> = 874)		<i>P</i> Value
	Mean	SD	Mean	SD	
BMI	25.57	2.08	28.23	4.64	<0.0001*
FBS	91.00	5.69	147.73	50.79	<0.0001*
ACR	18.43	24.27	39.48	44.76	<0.0001*
TGs	112.72	29.74	174.70	89.91	<0.0001*
HDL	39.28	5.32	40.84	5.65	0.07
BP	125.00	16.37	128.26	17.77	0.22
Age	50.56	13.89	50.38	10.48	0.94

  

Risk factor	Without MA (albumin < 30) ( <i>n</i> = 402)		With MA (albumin > 30) ( <i>n</i> = 511)		<i>P</i> Value
	Mean	SD	Mean	SD	
BMI	27.88	4.31	28.42	4.91	0.07
FBS	138.17	46.76	154.39	54.69	<0.0001*
ACR	12.21	7.86	72.09	48.67	<0.0001*
TGs	169.26	89.32	175.61	88.72	0.28
HDL	40.77	5.69	40.79	5.58	0.95
BP	126.75	16.36	129.87	19.18	<0.0001*
Age	50.17	10.25	50.66	11.12	0.48

  

Risk factor	Without obesity BMI < 30) ( <i>n</i> = 655)		With obesity (BMI > 30) ( <i>n</i> = 258)		<i>P</i> Value
	Mean	SD	Mean	SD	
BMI	25.87	2.58	33.80	3.55	<0.0001*
FBS	145.62	52.21	144.52	47.95	0.76
ACR	36.68	42.47	43.38	38.58	0.02*
T. Gs	173.65	89.52	168.00	87.92	0.10
HDL	41.00	5.70	40.21	5.45	0.056
B. P	127.45	18.15	129.84	16.48	0.06
Age	50.33	10.92	50.55	9.90	0.77

SD = standard deviation, BMI = body mass index, FBS = fasting blood sugar, ACR= albumin creatinine ratio, HDL = high-density lipoproteins, BP = blood pressure

\**P* value significant at <0.05

glucose measures are compared and ascertained [Table 1], similarly correlated with each parameter [Table 2].

Among all baseline characteristics, a significant difference was observed between the mean values of BMI, FBS, ACR, and TG in subjects with the prevalence and absence of MS [Tables 1 and 2] and in subjects with MS, albuminuria (ACR) is highly correlated with the incidence of FBS, TG, BP, and age ( $P < 0.01$ ) [Table 2]. However, the frequency albuminuria is high with the FBS, BP, and TG in the study population and seems to be less associated with obesity [Tables 1 and 2] suggesting the least association between albuminuria and overweight. But we found a significant correlation between ACR with obesity in males ( $P < 0.05$ ) [Tables 3 and 4] emphasizing the sexual dimorphism in adipose tissue distribution and associated comorbidities.

## DISCUSSION

The occurrence and severity of MS are followed by the association of the sum of critical risk factors that include obesity, hypertension, insulin resistance, dyslipidemia,

and albuminuria. According to CJKN studies and NCEP ATP III, the relationship between kidney damage and MS is complex. It is also in debate whether the collective existence of all the risk factors of MS improves CKD beyond that afforded by individual risk factors. However, very fewer studies have been undertaken to incorporate the coexistence of risk factors associated with MS and CKD. The present study results targeted to recognize and correlate the strong integrated relationship of fasting blood glucose, hyper-triglyceridemia, and high systolic BP the three of the five risk factors of MS in association with albuminuria than each independent risk factor.

In this cross-sectional study, we observed a significant difference in albuminuria in obese and nonobese subjects [Table 1], but we observed gender difference in the association of BMI with albuminuria; BMI had a greater association with ACR in males, whereas in females BMI is not associated with ACR [Tables 3 and 4]. Many studies show that there is a strong, linear relationship between obesity and hypertension. Chang *et al.*<sup>[20]</sup> study reported that systolic BP is an independent risk factor of

**Table 2: Correlation analysis of each parameter with baseline parameters in subjects with metabolic syndrome ( $n = 874$ ), with unhealthy ACR ( $n = 402$ ), and with obesity ( $n = 258$ )**

With metabolic syndrome							
Risk factor	BMI	FBS	ACR	TGs	HDL	BP	Age
BMI	1.0	0.281	0.104	0.591	0.111	0.087	0.340
FBS	0.281	1.0	0.000*	0.001*	0.051	0.537	0.031*
ACR	0.104	0.000*	1.0	0.008*	0.939	0.001*	0.002*
T.Gs	0.591	0.001*	0.008*	1.0	0.000*	0.468	0.094
HDL	0.111	0.051	0.939	0.000*	1.0	0.150	0.037*
B.P	0.087	0.537	0.001*	0.468	0.150	1.0	0.000*
Age	0.340	0.031*	0.002*	0.094	0.037*	0.000*	1.0
With unhealthy ACR							
Risk factor	BMI	FBS	ACR	TGs	HDL	BP	Age
BMI	1.0	0.965	0.334	0.472	0.159	0.629	0.459
FBS	0.965	1.0	0.000*	0.010	0.658	0.267	0.189
ACR	0.334	0.000*	1.0	0.002*	0.936	0.020	0.000*
T.Gs	0.472	0.010*	0.002*	1.0	0.000*	0.430	0.080
HDL	0.159	0.658	0.936	0.001*	1.0	0.264	0.422
B.P	0.629	0.267	0.020*	0.430	0.264	1.0	0.000*
Age	0.459	0.189	0.000*	0.080	0.422	0.000*	1.0
With obesity							
Risk factor	BMI	FBS	ACR	TGs	HDL	BP	Age
BMI	1.0	0.501	0.232	0.600	0.854	0.130	0.230
FBS	0.501	1.0	0.018*	0.015*	0.767	0.308	0.043*
ACR	0.232	0.018*	1.0	0.003*	0.586	0.711	0.027*
TGs	0.600	0.015*	0.003*	1.0	0.197	0.759	0.820
HDL	0.854	0.767	0.586	0.197	1.0	0.333	0.193
BP	0.130	0.308	0.711	0.759	0.333	1.0	0.002*
Age	0.230	0.043*	0.027*	0.820	0.193	0.002*	1.0

\*Correlation is significant at  $<0.05$  level (two tailed)

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microalbuminuria in euglycemic normotensive males. Our analysis also confirms this association between obesity and high BP. Yesmin *et al.*<sup>[21]</sup> report shows that there is no microalbuminuria in obese women without diabetes and/or hypertension suggesting in obese women and lean women; urinary albumin excretion was similar. A recent study on Japanese hypertensive patients showed that there were sex-related differences in the associations of insulin resistance and obesity to left ventricular hypertrophy.<sup>[22]</sup> Also Foster *et al.*<sup>[23]</sup> showed that in comparative Framingham heart study microalbuminuria is associated with visceral adipose tissue in men but not in women.

This study reports elucidate that in subjects with MS and unhealthy albuminuria [Table 2], coexistence of three of the five risk factors is strongly associated with the total conditions of the study. Age also shows a positive correlation with albuminuria. With these findings, our data analysis suggests that a gender difference may exist in the association between BMI and albuminuria. The difference might be due to gender-related specifications, such as the role of sex hormones on the inflammatory mechanism that links albuminuria to central obesity or it can be also predicted that the muscle mass in males is more than in females, which can warrant the creatinine levels and gender difference in interpretation.

The gender difference can be partly because of the prevalence of smoking in males, and the absence of

smoking in females. In females, there is a highly significant relationship between anthropometric variables and albuminuria due to potential sex-based divergence in fat distribution pattern and renal outcomes for differential steroid hormone levels. The contradiction may be because of higher upper body adiposity and higher visceral fat for a given BMI in the Asian Indians. The study conducted by Wang *et al.*<sup>[24]</sup> on aboriginal people by receiver operating characteristic (ROC) analysis suggested that measuring body size-related diabetes waist circumference is the best method comparing a few more methods of body size measurement.

### CONCLUSION

This study shows the relationship between obesity and the risk for CKD by gender-specific examination, which was measured clinically in the form of micro/macroalbuminuria that leads to proteinuria. Our findings suggest that BMI has an association with albuminuria in men showing that obesity calculated as BMI is a risk factor for kidney damage in males with a high prevalence of FBS, BP, TG, and age. However the contradictory results with females demonstrate that obesity calculated as BMI is not a high-risk factor for kidney harm in females, due to an account of gender specific variation in distribution of fat indicating men having a relatively more central allocation of fat giving the fact that male obese with hyperglycemia,

**Table 3: Pearson chi-square analysis between risk factors and albuminuria**

	Status of microalbumin				X <sup>2</sup> (df)	P	phi
	Healthy		Unhealthy				
	N	(%)	N	(%)			
Metabolic syndrome (MS)							
Yes	481	55.0	393	45.0	7.26	0.005*	+0.09
No	30	76.9	9	23.1			
Obesity							
Yes	135	52.3	123	47.6	1.92	0.165	+0.05
No	377	57.4	280	42.6			
Obesity in males							
Yes	54	48.2	58	51.7	4.04	0.04*	+0.09
No	232	58.9	162	41.1			

Computed only for a 2 x 2 table

\*Significant at  $P < 0.05$

**Table 4: Risk factors of microalbuminuria in the study population**

Sex	Risk factors	OR (95% CI)	P Value*
Males	BMI > 30 kg/m <sup>2</sup>	1.51(1.033–2.397)	0.03*
Females	BMI > 30 kg/m <sup>2</sup>	0.98(0.65–1.47)	0.93
Both genders	FBS > 110 mg/dL	1.865(1.34–2.58)	0.0002*
Both genders	Triglycerides > 150 mg/dL	1.47(1.105–1.957)	0.0082*
Both genders	HDL < 40 mg/dL	0.99(0.746–1.328)	0.976
Both genders	BP > 130 mm Hg	1.29(0.971–1.71)	0.078

OR = odds ratio

\*Significant at  $P < 0.05$

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hypertension and hypertriglyceridemia are at high risk of developing CKD. The major limitation of this study is that it was conducted by not focusing on dietary patterns of the individuals that might influence the relationship between the severity of obesity and microalbuminuria and ignored alternative methods for the calculation of obesity.

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### Conflicts of interest

There are no conflicts of interest.

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