INTRODUCTION
The metabolic syndrome is a cluster of cardiovascular risk factors associated with obesity.¹ The concept of metabolic syndrome, also known as insulin resistance syndrome, was introduced by Reaven in 1988.² The defining components of the metabolic syndrome are elevation of the following parameters: waist circumference, triglycerides, blood pressure, elevated fasting glucose, Body Mass Index (BMI), 24 hours urinary proteins and creatinine clearance, co-existent risk factors like hypertension and ischemic heart disease was taken. Patients were divided into groups having one to all five metabolic syndrome traits. Progressive increase in the metabolic syndrome traits was compared with decline in creatinine clearance. Pearson correlation test and multiple logistic regression were applied to determine correlation with significance at ‘r’ and ‘p’ ≤0.05.

RESULTS: Out of 104 evaluated female and male patients, 70% had hypertension, ischemic heart disease and a family history of diabetes. While 20% had normal creatinine clearance, 37% had a creatinine clearance between 60-90 ml/min, 19% had a creatinine clearance of 30-59 ml/min, 18% had a creatinine clearance of less than 30 ml/min and 10% were already in stage 5 CKD. The decline in renal function was more severe in subjects evaluated who had a higher number of features of the metabolic syndrome. Age was the only significant determinant of development of CKD (p=0.05).

CONCLUSION: The renal function progressively declined with 3 or more features of the metabolic syndrome.


METHODOLOGY
This cross-sectional descriptive study was performed at Diabetes Clinic, Fauji Foundation Hospital, Rawalpindi.
A total of 104 patients were included in the study who were aged above 35 years and had type-2 diabetes for more than 5 years duration. Information regarding age, gender, duration of diabetes, type of diabetes, treatment taking, complete fasting lipid profile, fasting blood glucose, Body Mass Index (BMI), 24-hour urinary proteins and creatinine clearance and co-existent risk factors like hypertension and ischemic heart disease was noted. Blood pressure was measured using a random-zero sphygmomanometer after the participants had been seated for 5 minutes, and average of two measurements was recorded. Baseline Diabetes was defined as fasting plasma glucose ≥126 mg/dl, self-reported diabetes, or the use of medications for diabetes. According to the definition of the International Diabetes Federation (IDF) panel, the new diagnostic criteria for metabolic syndrome include central obesity (defined as waist circumference ≥94 cm in men or ≥80 cm in women) together with two of the following; triglyceride level of 1.7 mmol/L (150 mg/dL) or higher, low HDL-C level (defined as <1.04 mmol/L [40 mg/dL] in men or <1.29 mmol/L [50 mg/dL] in women), blood pressure of 130/85 mmHg or higher, fasting hyperglycemia (defined as glucose level > 5.6 mmol/L [100 mg/dL] or previous diagnosis of diabetes). In this study, waist-hip ratio with BMI was taken as a marker of obesity because of convenience of sampling and social reasons in taking waist-hip ratio in females. American Association of Clinical Endocrinologists (AACE) clinical criteria for diagnosis of metabolic syndrome includes BMI of 25 kg/m² or higher as one of its diagnostic criteria.

Classification of chronic kidney disease by stage was made according to Kidney Disease Outcome Quality Initiative (KDOQI) clinical practice guidelines for chronic kidney disease. Incident CKD was defined as with or without other signs of kidney damage as an estimated GFR <60 ml/min. Stage 1 disease is defined by a normal GFR (greater than 90 mL/min per 1.73 m²), stage 2 disease is a GFR between 60 to 89 mL/min per 1.73 m², stage 3 disease is a GFR between 30 and 59 mL/min per 1.73 m², stage 4 disease is a GFR between 15 and 29 mL/min per 1.73 m² and stage 5 disease is a GFR of less than 15 mL/min per 1.73 m² or end-stage renal disease. The main outcome variables measured in the study population were creatinine clearance, presence of incident CKD and the number of metabolic syndrome components. The relation of Creatinine Clearance with number of metabolic syndrome components, age and duration of diabetes were studied using Pearson Correlation Coefficient. The relation of increasing metabolic syndrome components to incident CKD was studied using logistic regression analysis.

RESULTS

The study included 104 patients with type-2 diabetes mellitus of more than 5 years duration. Mean age of patients was 54 years ranging from 35 to 77. Twenty-four percent of patients were male and 76% were female with average age of 54 ± 8.6 years. Seventy-two percent of patients were hypertensive. Mean BMI was 29.36 ± 3.7, and 42.3% of patients were obese (28% males and 47% females). Sixty-three percent of patients had elevated triglycerides levels (56.5% males and 66% females) while 68% of patients had low HDL cholesterol levels (44% males and 76% females). In this study population, 79% of patients had 3 or more components of the syndrome. The prevalence of various components were 2.88%, 17.31%, 26.92%, 39.42% and 13.46% for one to five traits respectively. The prevalence of CKD stages were 19.23%, 35.58%, 18.26%, 17.31% and 9.62% respectively for one to stage five CKD.

There was a decline in renal function as evident by decreased creatinine clearance and progression to end stage renal disease with increasing number of metabolic syndrome components (Figure 1). Mean creatinine clearance declined from 97 ± 19 ml/min in patients with single component to 40.3 ± 32 ml/min in patients with all 5 components of metabolic syndrome. Various percentages of patients falling in CKD staging with relation to increasing components of metabolic syndrome components is shown in Figure 2. The Pearson correlation coefficient for creatinine clearance and number of metabolic syndrome component was -0.043, implicating an inverse relation between the two, however, this relation was not statistically significant (p= 0.667). Similarly, age did not have any significant relation to creatinine clearance (Pearson correlation coefficient = -0.018, p=0.858). Duration of diabetes had a significant inverse relation to creatinine clearance (correlation coefficient =-0.332, p=0.001). When the results were adjusted for age, gender and duration of diabetes using logistic regression analysis metabolic
syndrome was not a statistically significant determinant of presence of incident CKD (p=0.308) and age was the only significant determinant of development of CKD (p=0.05) (Table I).

**DISCUSSION**

There is a global increase in prevalence of Diabetes and by 2025 approximately 300 million people will be suffering from diabetes. The greatest increase in percentage is going to be in Asia and underdeveloped nations. Diabetic nephropathy remains the leading cause of End-Stage Renal Disease (ESRD) all over the world as diabetes is a major risk factor for the initiation and progression of CKD. Individuals with evidence of the metabolic syndrome have a substantial risk for developing type-2 diabetes over time and diabetic ESRD is expected to become increasingly prevalent in the future. The World Health Organization (WHO) defined metabolic syndrome as insulin resistance or impaired glucose regulation (impaired fasting glycemia, impaired glucose tolerance, or type-2 diabetes), with two or more of the following: blood pressure of 140/90 mmHg or higher; triglyceride levels of 150 mg/dL (1.7 mmol/L) or higher and HDL-C levels less than 35 mg/dL (0.9 mmol/L) in men and less than 39 mg/dL (1.0 mmol/L) in women; waist-hip ratio greater than 0.90 in men and greater than 0.85 in women or Body Mass Index (BMI; calculated as weight in kilograms divided by the square of height in meters) greater than 30; and microalbuminuria.

The European Group for the study of Insulin Resistance (EGIR) dropped microalbuminuria from the definition of the metabolic syndrome but diabetes and hypertension are both risk factors for CKD. The International Diabetes Federation (IDF) in 2004 defined metabolic syndrome as increased waist circumference plus any two of the following: triglycerides >150 mg/dL (1.7 mmol/L) or treatment for elevated triglycerides, HDL cholesterol <40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women, or treatment for low HDL, systolic blood pressure >130 mmHg, diastolic blood pressure >85 mmHg, or treatment for hypertension, fasting plasma glucose >100 mg/dL (5.6 mmol/L), or previously diagnosed type-2 diabetes.

The Third National Health and Nutrition Examination Survey (NHANES III) showed that compared with those with metabolic syndrome, people with diabetes without metabolic syndrome did not have an increase in the prevalence of Coronary Heart Disease (CHD). Those with metabolic syndrome without diabetes had higher CHD prevalence (13.9%) and those with both metabolic syndrome and diabetes had the highest prevalence of CHD (19.2%) compared with those with neither. Epidemiologic studies have linked the metabolic syndrome with an increased risk of microalbuminuria, an early marker of kidney injury. Presence of metabolic syndrome is an independent predictor of the subsequent development of CKD, and its presence in patients with CKD predicts subsequent development of coronary heart disease and mortality as compared to population without CKD.

Many studies have examined the relationship between the metabolic syndrome and CKD. Hoehner et al. correlated the metabolic syndrome profile and microalbuminuria in a cross-sectional study of American Indians from Wisconsin and Minnesota. After stratification, individuals with three or more metabolic syndrome traits had a 2.3-fold increased odds of having microalbuminuria compared with a control group without the syndrome. Chen et al. extracted data from the Third National Health and Nutrition Examination Survey database, which contains detailed clinical information from more than 6000 subjects. A statistical association was found between metabolic syndrome and microalbuminuria. Chen et al. discovered a significant correlation between number of metabolic syndrome factors and GFR <60 ml/min as observed in this study. Individual components that confer greatest risk were hypertension and hyperglycemia which is not surprising because both factors predispose to CKD pathogenesis and progression.
Chen et al. also found that increased waist circumference significantly correlated with microalbuminuria and GFR decline, suggesting that obesity may be an independent risk for CKD. An association between obesity and the nephrotic syndrome was first recognized years ago. More recently, Iseki et al. showed a statistical association between body mass index and incidence of ESRD in Japanese men, even after adjusting for comorbid risks, such as BP and proteinuria. A large renal pathology study demonstrated that obesity-related glomerulopathy, which is characterized by focal segmental glomerulosclerosis and glomerulomegaly, increased in incidence from 0.2-2% of all biopsy diagnosed during the 15-year period of the study. None of the patients demonstrated a histologic pattern consistent with diabetic nephropathy, the presumed pathology associated with the metabolic syndrome. These studies raise the possibility that obesity, which is a cardinal feature of the metabolic syndrome, may lead to CKD. However, as mentioned earlier, this may be difficult to prove because obesity is also a well-known risk for hypertension and diabetes. In another study, it was found that renal subclinical dysfunction is highly prevalent and is independently associated with classical cardiovascular risk factors and metabolic syndrome. In this study of 842 patients done by Dr. Lea and her fellows, patients with BMI of greater than 30 were taken as marker of obesity instead of waist-hip ratio because of problem in data collection regarding waist-hip ratio, and it was found that 40.6% of the study subjects had a Body Mass Index (BMI) greater than 30. This study concluded that having metabolic syndrome conferred a 38% increased risk for Chronic Kidney Disease (CKD).

Obesity and insulin resistance are prominent features of the metabolic syndrome, and both have been associated with secretion of inflammatory mediators and activation of inflammation-associated signaling pathways. The role of specific mediators in the pathogenesis of the metabolic syndrome, including leptin, IL-6, TNF-, adiponectin, and acylation-stimulating protein, were reviewed by Wisse. Until recently, adipocytes were found to be most likely source of soluble, metabolic syndrome mediators because of their capacity to secrete pro-inflammatory cytokines. However, two groups have published studies implicating macrophages, which infiltrate fat tissue, as the principal site of obesity-related cytokine synthesis. Because many of these cytokines have been suggested to mediate renal disease pathophysiology, it is tempting to speculate that progressive kidney disease could also be regulated by proinflammatory cytokines in the context of the metabolic syndrome. Other potential mechanisms include physical compression of kidney parenchyma by adipose tissue, reduced birth weight and nephron number, enhanced glucocorticoid activity, or altered uric acid metabolism.

**CONCLUSION**

This study showed that the metabolic syndrome was related to renal dysfunction and there was a direct decline in creatinine clearance with increasing components of metabolic syndrome, but a cause-and-effect relationship could not be clearly established. There was an inverse relation for creatinine clearance and number of metabolic syndrome components, however, this relation was not statistically significant. When the results were adjusted for age, gender and duration of diabetes, using logistic regression analysis, metabolic syndrome was not a statistically significant determinant of presence of incident CKD and age was the only significant determinant of development of CKD.

**REFERENCES**


