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Original Research Article

Syndrome X, C-Reactive Protein and Proteinuria in Newly Diagnosed Patients of Type 2 Diabetes Mellitus: A Cross-Sectional Study

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ABSTRACT

Introduction: Diabetes Mellitus (DM) is the commonest metabolic abnormality in the world. Type 2 diabetes, the commonest form of diabetes constitutes nearly 90% of diabetic population in any country. The Syndrome X consists of a constellation of metabolic abnormalities that confer increased risk of cardiovascular disease and diabetes mellitus. Inflammation, as assessed by C-reactive protein (CRP) may be an important precursor of the syndrome X and type 2 diabetes. Syndrome X is a known risk factor for proteinuria in the general population.
Materials and Methods: 100 patients of newly diagnosed type 2 diabetes mellitus in the age group of 25-60 years were included in the study. Patients with Gestational diabetes mellitus were excluded from the study.
Results: Of the 100 patients studied, 58 patients has syndrome X according to the International Diabetes Federation (IDF) criteria. Among the studied subjects 33 males had increased WHR>0.90(Normal <0.90), whereas all the females had WHR>0.85 (Normal <0.85). Mean waist circumference in males with MS was 96.26±1.01as compared to those without syndrome X(85.6±50.57) and mean waist circumference in females with MS was (90.3±40.68) as compared to those without syndrome X(75.63±0.25). Mean serum hs-CRP levels in patients with syndrome X was (6.35±1.07) as compared to those without syndrome X(7.09±1.30). Mean Proteinuria levels in patients with metabolic syndrome was (549.34±68.80) as compared to those without syndrome X (456.74±33.04). The mean Proteinuria level was markedly raised in patients of metabolic syndrome as compared to those without syndrome X. This difference was found to be markedly significant (p <0.01).
Conclusion: In conclusion, considering that Syndrome X is a modifiable risk factor, early detection of syndrome X would be a cost-effective strategy to decrease the prevalence of proteinuria and chronic kidney disease in the general population.
Key words: Diabetes Mellitus, Syndrome X, C-Reactive Protein and Proteinuria.

INTRODUCTION

Diabetes Mellitus is the commonest metabolic abnormality in the world. Type 2 diabetes the commonest form of diabetes constitutes nearly 90% of diabetic population in any country. Prevalence of type 2 diabetes is increasing in most of the countries especially in developing countries.[1]

In most developed countries, diabetes is the fourth or fifth leading cause of death and there is concern that it will become an epidemic in many developing and newly industrialized nations. City dwellers are at especially high risk since

they tend to be less physically active and are more likely to be obese as compared to their rural counterparts. [2]

Heart disease is the leading cause of death for all people with diabetes. [3] Heart disease, coupled with the other long-term complications including kidney, eye, and nerve disease, results in disability, reduced life expectancy, and enormous hearth burdens for virtually every society. [2]

The Syndrome X consists of a constellation of metabolic abnormalities that confer increased risk of cardiovascular disease and diabetes mellitus. In 1988, Reaven introduced the term syndrome X, with insulin resistance as a common denominator for the syndrome. [4] In addition to syndrome X, several other synonyms have been proposed such as deadly quartet, DROP syndrome (dyslipidemia, insulin resistance, obesity, and high blood pressure), multiple metabolic syndrome, and insulin resistance syndrome. [5-7]

The Syndrome X is a multifactorial complex trait that is influenced by both environmental and genetic factors. Mutations and polymorphisms in the genes associated with insulin resistance, adipocyte abnormality, hypertension, lipid abnormalities may underlie the aetiological basis of the metabolic syndrome. The syndrome X prevalence is even higher in diabetes mellitus patients and insulin resistance is believed to be the underlying cause for both type 2 diabetes mellitus and the syndrome X. [8]

The major features of the Syndrome X include central obesity, hypertriglyceridemia, low HDL cholesterol, hyperglycemia, and hypertension.

According to the new International Diabetes Federation (IDF) 2006 definition, for a person to be defined as having the Syndrome X they must have:

- Central Obesity (defined as waist circumference with ethnicity specific values).
- Plus any two of the following four factor:
  - Raised Triglycerides > 150 mg/dl (1.7 mmol/L) or specific treatment for this lipid abnormality.
  - Reduced HDL Cholesterol < 40 mg/dl (1.03 mmol/L) in males, < 50 mg/dl (1.29 mmol/L) in females or specific treatment for this lipid abnormality.
  - Raised Blood pressure- Systolic Blood pressure >130 mmHg or Diastolic Blood pressure > 85 mmHg or treatment of previously diagnosed Hypertension.
  - Raised Fasting Plasma Glucose >100 mg/dl (5.6 mmol/L) or previously diagnosed type 2 diabetes. If above 5.6 mmol/L or 100 mg/dl, oral glucose tolerance test (OGTT) is strongly recommended but is not necessary to define presence of the syndrome.

    (If BMI is > 30 kg/m^2, central obesity can be assumed and waist circumference does not need to be measured.)

The most accepted and unifying hypothesis to describe the pathophysiology of the metabolic syndrome is insulin resistance, caused by an incompletely understood defect in insulin action. The onset of insulin resistance is heralded by postprandial hyperinsulinemia, followed by fasting hyperinsulinemia and, ultimately, hyperglycemia.

C-reactive protein (CRP) is an annular (ring-shaped), pentameric protein found in blood plasma, the levels of which rise in response to inflammation. It is a member of the pentraxin family of proteins. C-reactive protein is an acute-phase protein of hepatic origin that increases following interleukin-6 secretion from macrophages and T cells. Its physiological role is to bind to lysophosphatidylcholine expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate the complement system via the C1Q complex. [9] CRP is synthesized by the liver in response to factors released by macrophages and fat cells (adipocytes). [10]

Inflammation, as assessed by C-reactive protein (CRP), it may be an important precursor of the syndrome X and type 2 diabetes. [11]

Proteinuria is defined as urinary protein excretion of greater than 150 mg per day. Urinary protein excretion in healthy persons varies considerably and may reach proteinuric levels under several circumstances. It occurs when the kidney leaks protein into the urine, in other words, when there is an abnormally high permeability for protein in the glomerulus of the kidney. Proteinuria is common (prevalence rates of 10-48%) and is a well established risk factor for macrovascular diseases in type 2 diabetics.

Proteinuria is considered to be a predictor for cardiovascular disease both among diabetic and non-diabetic subjects. [12] In a study on type 2 diabetic subjects having poor metabolic control a prevalence of renal damage approximates 20% and was associated with components of the syndrome X. [13] The aim of the current study was to investigate the association between Syndrome X, hs-CRP and the risk of proteinuria in newly diagnosed patients of type 2 DM in the Kumaonregion.

MATERIALS AND METHODS

The present study was carried out in the Department of Biochemistry, in association with the Department of Medicine, Government Medical College, Haldwani. 100 patients of newly diagnosed type 2 diabetes mellitus in theage group of 25-60 years, attending the Medicine OPD of GMC, Haldwani, were included in the study Patients with Gestational diabetes mellitus were excluded from the study.

All patients were subjected to detailed history and thorough physical examination.

Anthropometric measurements

Weight: Body weight (in kg) was measured in light clothing and without shoes. The weight was recorded to the nearest kg.

Height: Height was measured without shoes with the subjects standing fully erect on a flat surface and taken to the nearest centimetre.

Body Mass Index (BMI): Body mass index was calculated by the formula- Weight in kg/ (Height in meter).^{2}

Waist circumference: Waist circumference (in centimetre) was measured at midway between the costal margin & iliac crest. Waist circumference was measured at the end of normal expiration.

Hip circumference: Hip circumference (in centimetre) was taken as the largest circumference at the posterior extension of the buttocks (Transtrochantaric).

Waist Hip Ratio (WHR): Was calculated by using the formula - waist circumference÷ hip circumference.

Taking all aseptic precautions, about 5 ml of blood was drawn by veinpuncture from a peripheral vein, with a disposable syringe. All samples were collected in the morning after an overnight fast. Sample for fasting blood glucose, lipid profile was collected in a plain vial. The blood thus collected in clean dry glass tubes was allowed to stand for 30 minutes at room temperature for the retraction of clot. This was then centrifuge at 3000 r.p.m. for 10 minutes to separate the serum. The serum was stored at 4◦C in the refrigerator for analysis.

24hr urine sample for Proteinuria was collected in a clean plastic container. The preservative used was 10% HCL.

The parameters including blood sugar, lipid profile, were analyzed in fully automated Roche/Hitachi Cobas c 501 analyzer.

Estimation of serum hs-CRP was done by using ELISA Micro plate reader (MIOS JUNIOR MERCK).

24 hour urinary protein was estimated by Pyrogallol Red method using semiautomatic analyzer (MERCK Microlab 300)

Statistical Analysis

The data were compiled and entered in MS Excel sheet and the analysis was carried out using the Statistical Package for the Social Sciences (SPSS 19.0.2) program for windows. Unpaired "t" test was used to analyze all the data for statistical significance. Correlation and regression coefficient were also calculated among relevant parameters.

RESULTS

Of the 100 patients studied, 58 patients has syndrome X according to the International Diabetes Federation (IDF) criteria.

Table 1: Age and Sex distribution of patients with syndrome X

Age group (years)	Male		Female		Total	
	No	%	No	%	No	%
25-35	0	0	6	10	6	10
36-45	12	21	13	22	25	43
46-55	8	14	14	24	22	38
56-60	3	5	2	4	5	9
Total	23	40	35	60	58	100

Table 1 Shows the age and sex distribution of patients with syndrome X. 43 % of the patients with syndrome X were in the age group 36-45 years followed by 38% within 46-55 years, 10% 25-35 years and 9% 56-60 years.

Table2: Distribution of patients according to Waist Hip Ratio

WHR	Male (n=43)		Female(n=57)		Total No
	<0.90	>0.90	<0.85	>0.85	
No.	10	33	0	57	100

Table 2 shows the distribution of WHR in the studied subjects. The normal WHR ratio in male is <0.90 and female is <0.85. Among the studied subjects 33 males had increased WHR, whereas all the females had WHR >0.85.

Table3: Waist Circumference in studied subjects (mean±SD).

Variables	Male with MS	Female with MS	Male without MS	Female without MS	Range (cm)
Waist circumference (cm)	96.26±1.01	90.34±0.68	85.65±0.57	75.63±0.25	Male < 90 Female <80

Table 3 shows mean waist circumference in patients with and without syndrome X. Mean waist circumference in males with syndrome X was 96.26±1.01 and mean waist circumference in females with syndrome X was 90.34±0.68.

Table 4: Distribution of patients with syndrome X according to Body Mass Index.

Weight (based on BMI) kg/m^2	Male with MS	%	Female with MS	%	Total no.	%
Overweight (25-29)	16	29	21	37	37	66
Obese (>30)	9	16	10	18	19	34
Total	25	45	31	55	56	100

Table 4 shows the distribution of patients with syndrome X according to body mass index. Out of total subjects with syndrome X 66% were overweight and 34% were obese. Among the male patients, 29% were overweight and 16% were obese. Among the female patients, 37% were overweight and 18% were obese.

Table 5: Serum HDLc, LDLc, VLDLc, and TG levels in studied subjects

Parameters	With MS (n=58)	Without MS (n=42)	*P* value
HDLc (mg/dl)	40.03±1.12	42.51±1.51	NS
LDLc (mg/dl)	114.60±5.01	108.10±6.75	NS
VLDLc (mg/dl)	40.45±2.34	31.10±2.15	*P*<0.007
TG (mg/dl)	256.52±24.92	166.74±13.59	*P*<0.009

Table 5 shows the mean serum HDLc, LDLc, VLDLc and TG levels in patients with syndrome X (40.03±1.12), (114.60±5.01), (40.45±2.34), (256.52± 24.92), and without syndrome X (42.51±1.51), (108.10±6.75), (31.10±2.15), (166.74±13.59), respectively. No significant difference was found in HDLc and LDLc levels in patients with syndrome X as compared to without syndrome X. The mean VLDLc and TG level was markedly raised in patients of syndrome X as compared to without syndrome X. This difference was found to be significant (p <0.007), (p<0.009) respectively.

Table 6: Serum hs-CRP levels in the studied subjects (mean ± SD).

Groups	No. of cases	Hs-CRP(µg/ml)	Range (µg/ml)
With MS	58	6.35±1.07	1-3
Without MS	42	7.09±1.30	

Significance level as compared to without syndrome X: p = NS

Estimation of serum hs-CRP was done in all patients with syndrome X (n=58) and without syndrome X (n=42). The final result was expressed in µg/ml. Table 6 shows the mean serum hs-CRP levels in patients with syndrome X (6.35±1.07) and without syndrome X (7.09±1.30). There was no significant difference between the mean

serum levels of hs-CRP in patients with and without syndrome X.

Table 7: Proteinuria levels in the studied subjects (mean ± SD).

Groups	No. of cases	Proteinuria(mg/24hrs)	Range (mg/24hrs)
With MS	58	549.34±68.80	28-140
Without MS	42	456.74±33.04	

Significance level as compared to without syndrome X: p <0.01

Estimation of Proteinuria was done in all patients with syndrome X (n=58) and without syndrome X (n=42). The final result was expressed in mg/24hrs. Table 7 shows the mean Proteinuria levels in patients with syndrome X (549.34±68.80) and without syndrome X (456.74±33.04). The mean Proteinuria level was markedly raised in patients of syndrome X as compared to without syndrome X. This difference was found to be markedly significant ($p < 0.01$). Proteinuria had significant correlation with WC ($r = 0.34$; $p < 0.05$). Linear relationships were observed between the parameters.

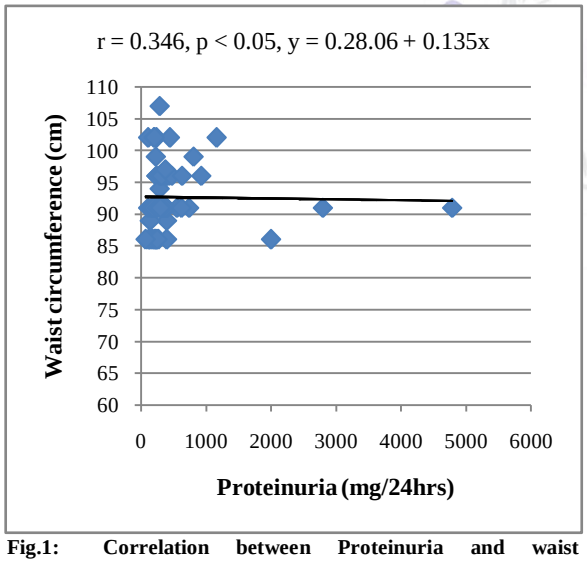

Fig.1: Correlation between Proteinuria and waist circumference levels in patients with syndrome X (n = 58).

DISCUSSION

Syndrome X is a cluster of cardiovascular risk factors. The components of syndrome X are obesity, hypertension, low glucose tolerance and dyslipidemia. Association of other components of metabolic syndrome with diabetes mellitus increases the risk of cardiovascular complications significantly.

Diabetes is the most feared disease because it leads to a variety of complications including end-stage vascular disease, cardiovascular damage and retinal abnormalities. As a consequence, a large burden is put on the National Health System of all countries around the world.

In the present study 100 patients of newly diagnosed type 2 DM attending the Medicine OPD were included. According to the new International Diabetes Federation (IDF) 2006, out of 100 patients studied, 58 patients met the criteria of metabolic syndrome (Table 1). Alshkri and Elmehdawi found that prevalence of metabolic syndrome among type 2 diabetes mellitus patients in Libya was 92% according to NCEP-ATP III criteria and 80.8% according to IDF criteria. [14]

Lin *et al,* found it to be 70% in USA, according to NCEP-ATP III criteria (Lin SX, Pi-Sunyer EX, 2007). Monami *et al*, found in Italy to be 68.4% according to NCEP-ATP III criteria and 73.7% according to IDF criteria. [15]

Our study showed that 60% of the patients of metabolic syndrome were female. There were overall female predominance with metabolic syndrome. In the study of Alshkri and Elmehdawi, out of 99 patients, 61 were female and 38 were males. [14] The results are comparable with the present study.

The International Diabetes Federation (IDF) has adopted different cut offs for waist circumference in different ethnicities; [16] the cut off points for Europids are 94 cm in men and 80 cm in women while those for Chinese, South Asians and Japanese are 90 in men and 80 in women. [17] In our study 67% of the diabetic patients had increased waist circumference, of which 58% met all the criteria for metabolic syndrome.

In our study the mean waist circumference in patients of metabolic syndrome was (96.26±1.01 cm) in males and (90.34±0.68 cm) in females (Table 3). In a study by Oscar H *et al.*, 2009 waist circumference in normal subjects was

(89.016±13.056cm) and in diabetics (102. 656± 11.52 cm), and incidence of metabolic syndrome was 40.6%. [18]

Waist-hip ratio (i.e. the waist circumference divided by the hip circumference) was suggested as an additional measure of body fat distribution. The ratio can be measured more precisely than skin folds, and it provides an index of both subcutaneous and intraabdominal adipose tissue (Bjorntorp, 1987). The suggestion for the use of proxy anthropometric indicators arose from a 12-year follow-up of middle-aged men, which showed that abdominal obesity (measured as waist-hip ratio) was associated with an increased risk of myocardial infarction, stroke and premature death, whereas these diseases were not associated with measures of generalized obesity such as BMI. [19]

In our study WHR was increased in all the females studied (>0.85) while 33% of males had increased WHR (>0.90) (Table 2).

Results of the European Fat Distribution Study (Seidell JC *et al*., 1991) and Paris Prospective Study (Filipovsky J *et al*., 1993) demonstrated importance of abdominal fat and greater WHR in cardiovascular and coronary heart disease mortality. Among Indians too, studies have shown that WHR is an important cardiovascular risk factor and greater levels are associated with multiple risk factors. Gupta R *et al*., 2003 reported that WHR >0.9 in men and >0.8 in women is associated with a significant increase in multiple risk factors. These cut-offs are similar to those suggested by earlier reports of US National Cholesterol Education program (ATP-II) (1994).

Abdominal obesity characterized by high waist circumference is a stronger predictor than generalized obesity defined by elevated Body Mass Index (BMI) of subsequent development of major coronary event, vascular mortality, diabetes and metabolic syndrome. BMI was calculated by the formula weight in kg/ (height in meter) ^{2}. Overweight is defined as a BMI of 25-29 and obese as a BMI >30 (WHO, 1998). It is known that Indians are prone to developing diabetes at a lower BMI in comparison to the western population.

High sensitive C-reactive protein (hsCRP) is an acute phase reactant and a sensitive marker of systemic inflammation has been found to be raised in the conditions like diabetes mellitus, cardiovascular diseases, peripheral vascular disorders. [20,21] Previous studies have proved that type 2 DM is frequently associated with chronic inflammatory state. Thus, chronic inflammation plays an important role in the development and progression of late complications of diabetes. It predicts the mortality in patients with type 2 diabetes mellitus. This emphasizes the utility of estimating hsCRP as cardiometabolic risk factor. [22]

Present study shows serum hs-CRP levels are not significantly elevated in patients of metabolic syndrome (Table 6). A number of studies show that both metabolic syndrome and elevated CRP are associated with increased incidence of cardiovascular events. In the epidemiological studies like West of Scotland Coronary Prevention Study, an 18-year follow up of 14,719 initially healthy American women, and in the Framingham Offspring Study it was shown that metabolic syndrome and CRP are associated with increased cardiovascular morbidity and mortality. [23,24]

Chronic kidney disease (CKD) has become a worldwide public health problem and proteinuria an early marker of CKD. Proteinuria is a common laboratory finding in the general population. Metabolic syndrome, which comprises central obesity, dyslipidemia, high blood pressure (BP), and impaired fasting glucose, is a known risk factor for proteinuria in the general population [25,26] Recently, the increasing prevalence of obesity has affected the increase in metabolic syndrome and glomerulopathy. [27]

Proteinuria levels were found to be higher in patients with metabolic syndrome

than without metabolic syndrome and were found to be significantly elevated ($p<0.01$) in the present study (Table 7). This finding is in agreement with several other finding.

Lucove et al. reported a 1.26-fold increased risk for the development of proteinuria among American Indians with metabolic syndrome. [28] In addition, a close relationship between metabolic syndrome and the development of proteinuria has been reported. Tozawa et al. also reported the effect of metabolic syndrome in a Japanese population. [29] Moreover, similar findings were observed in the general Korean population.

The causal relationship of proteinuria with the components of metabolic syndrome remains unclear. At least two possibilities have to be considered when trying to explain the association of proteinuria with CVD risk in prospective studies. Firstly, the clustering of several risk factors, including obesity, impaired glucose regulation, dyslipidemia and hypertension, may be the primary abnormality leading to endothelial dysfunction.

In present study significant correlation was found between proteinuria and waist circumference (fig. 1). Studies done in US and Japan reported that proteinuria was associated with high Blood pressure and obesity. [30, 31] A study from Nigeria showed that proteinuria is seen in about 37% of newly presenting hypertensive, [32] while in another study from South Africa, the prevalence of proteinuria was significantly higher in hypertensive blacks compared to white, Asian and Indian subjects. [33]

Chen *et al.*, 2004, showed that the risk for being affected by chronic kidney disease was more than twice as high in patients with an increased waist circumference compared to those without, suggesting that obesity may be an independent risk factor for chronic kidney disease. [34]

CONCLUSION

In conclusion, considering that Syndrome X is a modifiable risk factor, early detection of metabolic syndrome would be a cost-effective strategy to decrease the prevalence of proteinuria as well as chronic kidney disease and end-stage renal disease in the general population. This study also suggests that weight reduction among diabetic patients can lead to an improvement of kidney function.

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