RESEARCH ARTICLE

Cystatin C in Patients of Metabolic Syndrome and its Correlation with the Individual Components of Metabolic Syndrome

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Abstract

Aim: To determine serum cystatin C (CysC) levels in metabolic syndrome (MetS)patients and correlation of cystatin C with individual components of MetS.

Materials methods: A cross-sectional study included 100 cases of MetS and 50 controls. One hundred cases were further divided into 3 groups depending upon the number of components of MetS. Anthropometric parameters like height, weight, BMI (body mass index), Waist circumference were measured. Fasting plasma glucose,serum total cholesterol, serum triglycerides, serum HDL (high density lipoprotein), LDL(low density lipoprotein), VLDL (very low density lipoprotein), systolic blood pressure (SBP) and diastolic blood pressure(DBP), creatinine, urea, eGFR (estimated glomerular filtration rate) and CysC were measured in each individual. Correlation of CysC with each component of Mets was studied.

Results: CysC was significantly increased in MetS patients than in controls. Level of serum CysC was increased with an increase in components of MetS. CysC was positively correlated with waist circumference, fasting plasma glucose, triglycerides, SBP, and DBP and negatively correlated with HDL. There was no significant difference in urea, creatinine, and eGFR in studied groups.

Conclusion: CysC is significantly correlated with individual components of MetS.CysC may be used as an early marker of renal dysfunction in MetS patients.

Keywords: Cystatin C, Metabolic syndrome, Renal risk.

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Introduction

The MetS are characterized by central obesity, hypertension, dyslipidemia, and elevated plasma glucose. Dyslipidemia in MetS includes elevated triglycerides and LDL and low HDL concentrations. Insulin resistance and abdominal obesity are the most important underlying risk factors of MetS.[1] The prevalence of the MetS is steadily increasing with the worldwide obesity epidemic.[2] MetS is present in 20–25% of the adult population of world.[3] Prevalence of MetS in Indian population is 29% in women and 23% in men.[4] The MetS is an important risk factor for diabetes mellitus, cardiovascular disease, hyperuricemia, non-alcoholic fatty liver disease, obstructive sleep apnoea, and polycystic ovarian syndrome.[5]

CysC is a non-glycosylated, 120 amino acid and 13 kilodalton protein. It is a member of the family of cysteine protease inhibitors. It is the product of a "housekeeping" gene (CST3 gene), which is located on chromosome 20 at p.11.2. It is produced by nucleated cells at a constant rate. It is freely filtered by glomeruli, because of its small size and basic pH (~ 9.0). After filtration CysC is reabsorbed and catabolized by the proximal tubular epithelial cells. CysC does not return to the bloodstream and is not secreted by renal tubules. So CysC has been suggested to be closer to the "ideal" endogenous marker of GFR.[6-8]

CysC is markedly elevated in patients of MetS, and as the components of MetS increases CysC increases.[9] CysC is strongly associated with abdominal obesity, which may indicate that the association ofCysC levels with MetS are mainly mediated by visceral fat.[10] Hyperglycemia and increased inflammatory factors in MetS lead to increased production of reactive oxygen species (ROS) which increases oxidative stress. Also increase in triglycerides and LDL and decrease in HDL level in MetS may be an effective factor in the development of oxidative damage. Demircan N et al. found that there is an increase in serum CysC in case of oxidative stress.[11]

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Serum creatinine is considered as a specific but not sensitive marker of renal dysfunction. Its level does not increase significantly until the GFR is reduced to less than 50% of its normal value.[12] CysC may be a marker for metabolic syndrome and may identify a certain degree of renal dysfunction even when serum creatinine is within the normal level.[13] And also the levels of serum creatinine is influenced by age, sex, muscle mass, and inflammatory processes while serum CysC level is less affected by these factors.[7]

We investigated the effect on levels of serum CysC in MetS patients and its correlation with individual components of MetS.

Materials and Methods

It was a cross-sectional study carried out in Government Medical College and Hospital, Aurangabad, India during the period from January 2015 to July 2016. After written and informed consent, total 100 cases who met the criteria for MetS defined as per modified National Cholesterol Education Program (NCEP) adult treatment panel (ATP III) between the age group 18–50 years were

selected. The number of cases in each group was not pre-decided, depending upon the number of components of MetS present; these 100 cases were further divided into 3 groups. Group 2 had 30 patients with any 3 components of MetS, group 3 had 38 patients with any 4 components of Mets and group 4 had 32 patients with all 5 components of MetS. Cases of MetS were compared with 50 apparently healthy controls which were included in group 1. The sample size was calculated using open EPI software. Participants in this study were selected on the basis of clinical examination, detailed history, and laboratory investigations. A detailed history of participants including age, sex, and history of any medications and dietary habits was taken. Weight, height, BMI, waist circumference and blood pressure were measured in all participants. Patients with elevated serum creatinine (>1.5 mg/dL), known case of chronic kidney disease and cardiovascular disease, hypothyroidism, Alzheimer's disease were excluded from the study. Patients with H/O (history of) any medication affecting lipid profile, H/O chronic analgesic abuse and chronic glucocorticoid treatment, H/O cigarette smoking, and alcoholism were excluded from the study.

According to National cholesterol education program adult treatment panel III (NCEP ATP III) criteria a case of MetS is defined as having three or more of the following abnormalities.

- Waist circumference >90 cm for men, >80 cm for women (for Asians)
- serum triglycerides >150 mg/dL
- HDL Cholesterol <40 mg/dL in men,<50 mg/dL in women
- Fasting plasma glucose >100mg/dL
- Blood pressure >130/85 mm Hg.[1] Permission of the institutional ethical committee was sought before the study.

Biochemical Assessment

Venous blood samples were collected from all participants in Fluoride (2 cc) and plain bulbs (4 cc) after 10-hour fasting. Serum was separated from plain bulb after 1 hour by centrifugation at 3000 rpm for 10 minutes. Each sample was tested for the following parameters. Quantitative estimation of CysC was done by Latex-Enhanced Immunoturbidimetric Method using commercial kits from AGAPPE diagnostics, total cholesterol was done by cholesterol oxidase-peroxidase method (CHOD-POD), triglycerides were done by lipase/glycerokinase/glycerophosphate oxidase (GPO) method using commercial kits from Accurex diagnostics and HDL was estimated by modified polyvinyl sulfonic acid and polyethylene glycol methyl ether coupled classic precipitation method using commercial kits from ERBA diagnostics on fully automated biochemistry analyzer. Quantitative estimation of plasma glucose was done by glucose oxidase peroxidase (GOD-POD) method, serum urea by Glutamate dehydrogenase(GLDH) - urease method and creatinine by Jaffe's method using commercial kits from ERBA diagnostics on semiautomatic chemistry analyzer. Serum VLDL and LDL were calculated by Friedewalds formula.[14] eGFR was calculated by using modification of diet in renal disease study (MDRD) formula.[5]

Statistical Analysis

The results were analyzed by Graph pad prism software, version 5. The results were interpreted as mean ± standard deviation (SD). One-way analysis of variance (ANNOA test) was applied for comparing between two groups and correlation coefficients were calculated (r value). P value was obtained from ANOVA test and <0.05 was considered statistically significant. Positive and negative r values were estimated to find out the strength of the correlation. These r values were interpreted as follows: r = 0 (no correlation), r = 0–0.3 (poor correlation), r = 0.3–0.7 (considerable correlation) and r = 0.8 or more (strong correlation).

Table 1 represents the demographic characteristic of Group 1, Group 2, Group 3, and Group 4. There was a significant difference in weight, BMI, waist circumference in studied groups.

Table 2 represents CysC and other biochemical parameters in studied groups. There was significant difference inSBP, DBP, fasting plasma glucose, CysC, total cholesterol, triglycerides, HDL, VLDL and LDL in studied groups. The mean value of CysC was significantly higher in cases of MetS than in controls (*p* value <0.005) and it was significantly higher in group 3 as compared to group 2 and in group 4 as compared to group 3 (*p* value <0.005). So as the components of metabolic syndrome, the mean value of CysC increases. There was no significant difference in creatinine, urea, and eGFR.

As per Table 3, CysC was positively correlated with waist circumference, SBP, DBP, fasting plasma glucose and triglycerides (*p* = <0.0001) and negatively correlated with HDL, which were statistically significant.

Discussion

In the present study, we found that serum CysC level was significantly increased in MetS patients, and the level of serum CysC increases with an increase in components of MetS. In our study we found a positive correlation of CysC with waist circumference, it can be explained as the Gene for CysC is highly expressed in preadipocytes, adipocytes, omental and subcutaneous adipose tissue, macrophages, and endothelial cells. Gene expression of CysC and release of CysC by adipose tissue increases two to three fold in obesity. Elevation of CysC represents a compensatory mechanism to reduce cysteine protease cathepsin S. Through cathepsin inhibition CysC might participate in a protective mechanism to reduce adipose tissue mass.[15]

Retnakaran et al. and Vigil et al. in their study found a positive correlation between CysC and body mass index; waist circumference

Table 1: Demographic Characters in studied groups

	Group 1 (n = 50)	*Group 2 (n = 30)*	*Group 3 (n = 38)*	*Group4 (n = 32)*	
Parameter	*Mean ± SD*				*p value*
Age (years)	43.18 ± 5.18	41.13 ± 5.33	42.68 ± 5.92	43.13 ± 5.29	0.385
Weight (kg)	65.06 ± 6.46	77.40 ± 3.95	81.18 ± 4.73	84 ± 4.66	<0.0001*
Height (m)	1.62 ± 0.06	1.60 ± 0.03	1.61 ± 0.04	1.61 ± 0.03	0.314
BMI (kg/m^2)	24.72 ± 2.36	30.11 ± 2.03	31.34 ± 1.90	32.21±1.29	<0.0001*
Waist Circumference (cm)	78.88 ± 5.75	89.73 ± 9.13	97.13 ± 8.37	103.53 ± 4.23	<0.0001*

*highly significant *p* value.

Table 2: Clinical and biochemical parameters in studied groups

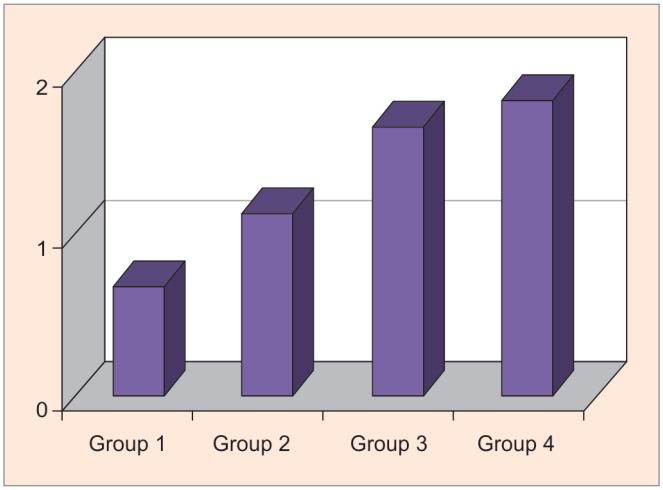
	Group 1 (n = 50)	*Group 2 (n = 30)*	*Group 3 (n = 38)*	*Group 4 (n = 32)*	
Parameter	*Mean ± SD*				*p value*
SBP (mm Hg)	116.6 ± 7.08	126.47 ± 14.51	133.53 ± 11	144.91 ± 6.06	<0.0001*
DBP (mm Hg)	75.36 ± 5.29	80.07 ± 8.92	87.05 ± 7.72	93.75 ± 4.42	<0.0001*
Fasting plasma glucose (mg/dL)	88.7 ± 7.77	124.67 ± 15.63	135.92 ± 23.03	149.34 ± 14.21	<0.0001*
CysC (mg/L)	0.7 ± 0.13	1.15 ± 0.29	1.68 ± 0.19	1.84 ± 0.10	<0.0001*
Total cholesterol (mg/dL)	164.06 ± 13.75	178.6 ± 16.01	189.91 ± 22.43	202.72 ± 27.84	<0.0001*
Triglycerides (mg/dL)	123.26 ± 16.33	161 ± 15.14	185.05 ± 19.03	203.91 ± 35.98	<0.0001*
HDL (mg/dL)	51.04 ± 6.9	46.07 ± 9.57	38.63 ± 9.03	34.75 ± 5.16	<0.0001*
VLDL (mg/dL)	24.22 ± 3.22	31.87 ± 3.17	36.68 ± 3.86	40.56 ± 7.14	<0.0001*
LDL (mg/dL)	88.80 ± 13.36	100.67 ± 18.55	114.66 ± 18.39	127.41 ± 25.44	<0.0001*
Creatinine (mg/dL)	0.78 ± 0.12	0.78 ± 0.11	0.79 ± 0.13	0.81 ± 0.12	0.716
Urea (mg/dL)	28.12 ± 5.68	26.47 ± 6.66	26.45 ± 4.54	27.78 ± 5.92	
eGFR (mL/min/1.73m^2)	100.04 ± 23.94	97.07 ± 13.28	95.61 ± 12.55	92.69 ± 9.87	

*highly significant p value

Table 3: Correlation of CysC with an individual component of MetS in cases

	Group 2		*Group 3*		*Group 4*	
Parameters	*r value*	*p value*	*r value*	*p value*	*r value*	*p value*
Waist circumference (cm)	0.425	< 0.0001*	0.636	< 0.0001*	0.722	< 0.0001*
SBP (mm Hg)	0.312	< 0.0001*	0.336	< 0.0001*	0.356	< 0.0001*
DBP (mm Hg)	0.308	< 0.0001*	0.325	< 0.0001*	0.314	< 0.0001*
Fasting plasma glucose (mg/dL)	0.346	< 0.0001*	0.385	< 0.0001*	0.506	< 0.0001*
Triglycerides (mg/dL)	0.315	< 0.0001*	0.323	< 0.0001*	0.399	< 0.0001*
HDL (mg/dL)	–0.325	< 0.0001*	-0.382	< 0.0001*	–0.509	< 0.0001*

*highly significant p value



Graph 1: Comparison of CysC in studied groups

in MetS patients.[16,17] Deepa et al. in their study found that the serum Cystatin C levels were significantly increased in obese groups.[18]

In the present study positive correlation was seen between CysC and fasting plasma glucose level in MetS patients. CysC may be elevated before the onset of clinical diabetes and CysC is the independent risk factor for hyperglycemia. Increase in CysC may suggest a preclinical stage of renal impairment which develops in parallel with the prediabetic condition. Richard P et al. in their study found that CysC was closely connected with fasting plasma glucose and was associated with progression to prediabetes.[19]

We found the positive correlation of CysC with triglyceridesand negative correlation with HDL. Increase in triglycerides and LDL and decrease in HDL level in MetS may be an effective factor in the development of oxidative damage. This is because high LDL and triglycerides levels increase predisposition to oxidative damage. HDL has antioxidant features and it protects LDL from oxidation. So the increase in CysC in MetS may be due to increased oxidative stress.[11] Nishiyama et al. suggested that oxidative stress induces the synthesis of CysC mRNA and the production of CysC protein. This might be self-defensive cellular responses to oxidative stresses.[20] Kim SY et al. in their study found that serum CysC was positively correlated with triglycerides and negatively correlated with HDL in MetS patients.[21]

In the present study, CysC was positively correlated with SBP and DBP. Elevation in blood pressure promotes damage to the intrarenal vasculature leading to renal ischemia and glomerulosclerosis. The essential hypertensionmight be due to the early variation in kidney function in persons without clinically recognized kidney disease. So this creates a vicious circle of kidney injury and blood pressure deregulation.[22] Peralta CA et al. in their study revealed that SBP and pulse pressure were linearly associated with CysC

concentrations.[22] Kestenbaum et al. found that CysC concentration was independently correlated with blood pressure.[23]

Studies supporting our results

Liua et al. found that CysC concentration was higher in the MetS and Metabolic Disturbance groups than the control group. Compared with Metabolic Disturbance group, the MetS group had significantly higher CysC. As MetS scores rose, serum CysC levels increased. CysC is positively associated with waist circumference, triglycerides, fasting plasma glucose, SBP, and DBP and negatively associated with HDL.[9] Surendar et al. in their study used linear regression analysis to conclude that CysC increases with an increase in metabolic abnormality and CysC is associated with components of MetS.[24]

Obesity, insulin resistance, dyslipidemia, and hypertension, which are components of MetS, individually carry a risk for renal dysfunction. In the case of obesity due to an increase in inflammatory cytokines and compression of renal hilum by increased visceral adipose tissue activates rennin angiotensin aldosterone system.[25] Activation of the renin–angiotensin–aldosterone system promotes glomerulosclerosis.[26] Insulin resistance and compensatory hyperinsulinemia may directly contribute to the development of renal injury by worsening renal hemodynamic through multiple mechanisms. This includes sodium retention,[27] activations of the sympathetic nervous system,[28] decreased Na K-ATPase activity[29] and elevation of glomerular filtration fraction.[30] Oxidation of circulating lipids in extracellular molecules increases the formation of reactive oxygen species,[31] which contributed significantly to glomerulosclerosis.[32] Hashemi et al. in their study found that the serum CysC concentration was significantly increased in the MetS group than the control group and there was no any significant difference in serum creatinine concentration. They concluded that CysC may identify a certain degree of renal dysfunction even when serum creatinine does not exceed the normal level in MetS patients.[33] Servais A et al got that CysC value was significantly higher in MetS patients than in controls independently of serum creatinine level and creatinine clearance.[34] Demircan A et al., Amirrasoul H et al. and Vigil L et al. reported that MetS patients presented with a higher level of serum CysC than controls.[11,13,17]

Our study has certain limitations, like the sample size of our study was relatively small. Selection of a clinic cohort may have increased the number of co morbidities in our study population. This study was a cross-sectional study so the direction of association cannot be ascertained, and no casual interference can be made amongst the factors under consideration. We could not find eGFR in our study group by the direct method.

Conclusion

Serum CysC is significantly correlated with individual components of MetS. CysC showed the strongest positive correlation with waist circumference. Central obesity may be a cause of increased CysC in MetS patients. This study indicates that CysC may be an early marker of renal dysfunction in MetS patients.

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