Section: Biochemistry

Original Research Article

ASSOCIATION OF SERUM HIGH SENSITIVITY C-REACTIVE PROTEIN (HSCRP) AND GAMMA GLUTAMYL TRANSFERASE (GGT) WITH BODY MASS INDEX (BMI), HBA1C AND DYSLIPIDEMIA IN PERSONS WITH METABOLIC SYNDROME

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ABSTRACT

Background: Aim of the study: To evaluate the association of serum high sensitivity C- reactive protein (hsCRP) and Gamma glutamyl transferase (GGT) with Body mass index (BMI), HbA1c and Dyslipidemia in persons with metabolic syndrome.

Materials and Methods: It was a Cross sectional observational study, conducted at SRM Medical College Hospital and Research Centre (TSRMMC&RC) during the period one year (June 2019 to May 2020) . The study participants both males and females of age ≥ 18 years, came for master health check up and those who fulfilled the criteria of metabolic syndrome were included. Persons with history of diabetes mellitus and on antidiabetic medications, known cases of hepatobiliary disorder, Renal disease, patients with acute or Chronic Infectious and inflammatory diseases, malignancy, autoimmune disorders, patients with history of recent trauma or surgery and pregnant individuals were excluded from this study.

Results: Among the study population of metabolic syndrome, 79% belonged to 35-60 years of age group, 13% and 8% belonged to 18-35 years and above 60 years of age respectively. The estimated mean age was 48.1 ± 10.0 years. 59% of participants were males and 42% were females. 85% and 11% of participants were obese and were overweight respectively and remaining 4% belonged to normal BMI (18.5-22.99 kg/m^2). 44% of the study population had normal HbA1c < 5.6 gm%, whereas 56%had elevated HbA1c and mean HbA1c was5.7 which was in the prediabetic (≥ 5.6 - 6.4 gm%) range. About 63% of participants had elevated total Cholesterol concentration. 69%had elevated serum triglycerides concentration. 89% of participants had low serum HDL-C concentration. 16% of participants had elevated serum LDL-C concentration.68% of participants had hsCRP values > 3 mg/ L and 21% had values between 1mg/ L to 3mg/L. Mean hsCRP value was 7.0 mg/ L. Among the 68 participants having CRP value > 3mg/L, majority (56%) were the age group of 35 to 60 years. When we analysed the association of hsCRP with BMI, HbA1C, lipid profiles, there was highly statistically significant positive correlation between hsCRPand BMI, which was in agreement with the well-established biochemical link between the adipocyte metabolism, obesity and systemic inflammation. The positive correlation with HbA1C revealed the interrelationship between hyperglycemic status and chronic, low grade inflammation. statistically significant association of hsCRPwith LDL-C, and statistically significant negative correlation with HDL-C were observed. 87% of study participants had normal GGT and 13% had elevated values. Mean GGT activity was 35.7 U/L. Analysis revealed statistically highly significant association of GGT with alcoholism and smoking status. Though insignificant, a positive correlation between GGT and BMI was observed. When we analysed the association of GGT with HbA1C, GGT showed statistically significant positive correlation with HbA1c. There was a positive correlation between GGT and all cholesterol values except HDL with which it shows negative correlation. But they are not statistically significant.

Conclusion: In the present study, we evaluated the relationship of hs-CRP and insulin resistance with the components of metabolic syndrome in the patients with metabolic syndrome diagnosed by using the criteria of NCET ATP III where, we found a significant elevation of hs-CRP, insulin resistance and components of metabolic syndrome in patients with metabolic syndrome in comparison with healthy controls.

Keywords: Metabolic syndrome, hs-CRP, GGT, HbA1c, Insulin Resistance, BMI.

INTRODUCTION

Metabolic syndrome, a worldwide growing disease,[1] has become a major economic burden (challenge) for the public health system globally. Due to increased urbanization particularly due to changes in eating habits, including increased access to and popularity of processed foods, irregular mealtimes, decreased physical activity, and so on. The prevalence of the metabolic syndrome has been increasing even in developing countries.[2]

Metabolic syndrome is characterized by a combination of interlinked metabolic risk factors such as abdominal obesity, decreased insulin sensitivity, hyperglycemia, elevated blood pressure, hypertriglyceridemia, reduced high density lipoprotein cholesterol in (HDL-C).[3] Adipose tissue dysfunction, insulin resistance, systemic inflammation, oxidative stress, and disruption of the cellular functions in the target tissue are the underlying pathophysiological mechanisms associated with these interconnected risk factors.[4]

Metabolic syndrome increases the risk of cardiovascular diseases (CVD) twofold over a span of 5–10 years, type 2 diabetes mellitus fivefold,[5] and also increases all-cause mortality.[6] Noncommunicable illnesses such as diabetes mellitus, myocardial infarction and obesity are the main causes of about two thirds of deaths all over the world.[7]

Furthermore, people with metabolic syndrome are more vulnerable to other disorders compared to people with no metabolic syndrome, such as bronchial asthma,[8] obstructive sleep apnea syndrome,[9] nonalcoholic steatohepatitis, cholesterol gallstones,[10] polycystic ovarian syndrome.[11] Recently, certain malignancies, such as breast cancer, endometrial, pancreatic, renal, colorectal and prostatic carcinoma, have also been found to be associated with metabolic syndrome.[12]

Identifying individuals with metabolic syndrome in a population otherwise normal is important to recognize people at risk of developing type 2 diabetes mellitus, cardiovascular problems and other conditions associated with metabolic syndrome. If we identify individuals who can benefit from early interventions and even may postpone the disease complications. It has been shown that seemingly stable individual, in the presence of Metabolic syndrome might have biochemical abnormalities.[5] Therefore, it is very helpful to recognize the biomarkers which guide us identifying people with metabolic syndrome in a minimally invasive manner by performing simple blood parameters [1]. Many studies have shown that metabolic syndrome is associated with abnormal levels of acute phase reactants, cytokines, complement factors and other markers of inflammatory signals.[13]

C-reactive protein (CRP), a positive acute-positive phase reactant,[14] a well- established marker of acute and chronic inflammatory status of our body 6 and it was found to be associated with the features of metabolic syndrome. It has been found to be higher in people with impaired glucose tolerance (IGT) and overt type 2 diabetes mellitus compared with those with normal glucose tolerance and considered as an indicator for developing type 2 diabetes mellitus.[15]

Gamma glutamyl transferase (GGT), traditionally, an established marker of hepatobiliary disease and alcohol abuse,[18] is an enzyme located mainly in the liver on the cell membranes. It plays a key role in the extracellular catabolism of glutathione, a potent antioxidant. This raises the amount of reactive oxygen species (ROS) in our body, which play a key role in inflammatory processes and chronic diseases. GGT has therefore been identified as a marker of lipid peroxidation, oxidative stress, and systemic inflammation, which play a key role in the development of insulin resistance and metabolic syndrome pathogenesis. In their study, Ali et al has shown that an association of elevated GGT levels with risk factors for cardiovascular disorders such as diabetes mellitus, high blood pressure, abnormal lipid profiles which are components of metabolic syndrome.[19]

To the best of our knowledge, very few studies have been recorded on the relationship between hs-C Reactive Protein and Gamma Glutamyl Transferase and Metabolic Syndrome components in our region. The participants with normal glycemic status or impaired glucose tolerance, and newly diagnosed type 2 diabetes mellitus during this study only are included. People who are already diagnosed to have diabetes mellitus and on anti-diabetic medications are exempt from this research in order to find out which participants with metabolic syndrome are at risk of developing diabetes mellitus in the future. Recently, it has been discovered that HbA1c can also be used as a biochemical marker to know about the long - term glycemic status of the individual and for the diagnosis of diabetes mellitus.[20]

Since, oxidative stress and systemic inflammation play a major key role in the pathogenesis of obesity-related metabolic disorders such as metabolic syndrome, we have proposed to study hs CRP level (an inflammatory marker) and serum GGT activity (marker of oxidative stress,[21]) in patients with metabolic syndrome in both genders in our area and find out the association with BMI, HbA1c and dyslipidemia which are the key components of metabolic syndrome.

Aim of the Study: To evaluate the association of serum high sensitivity C- reactive protein (hsCRP) and Gamma glutamyl transferase (GGT) with Body mass index (BMI), HbA1c and Dyslipidemia in persons with Metabolic syndrome.

Objectives

1. To estimate serum high sensitivity C- reactive protein (hsCRP) and serum gamma glutamyl transferase (GGT) in participants with metabolic syndrome along with other parameters.
2. To find out the association between serum high sensitivity C- reactive protein, HbA1c %, Body mass index (BMI) and Fasting Lipid profile.
3. To find out the association between serum gamma glutamyl transferase (GGT) Body mass index (BMI), HbA1c and Fasting Lipid profile.

MATERIALS AND METHODS

Study design: Cross sectional observational study

Study centre: Trichy SRM Medical College Hospital and Research Centre: (TSRMMC&RC)

Sample size:100

Duration of the study: One year (June 2019 to May 2020)

Study population

The study participants both males and females of age ≥ 18 years, came for master health check up and those who fulfilled the criteria of metabolic syndrome were included. Persons with history of diabetes mellitus and on antidiabetic medications, known cases of hepatobiliary disorder, Renal disease, patients with acute or Chronic Infectious and inflammatory diseases, Malignancy, Autoimmune disorders, patients with history of recent trauma or surgery and pregnant individuals were excluded from this study.

Ethical approval:

The study was approved by the Institutional Review Board and Institutional Ethical Committee of Trichy SRM Medical College Hospital and Research Centre.

Data collection – History and Anthropometric measurements

Informed written consent was obtained from all the study participants for this research. After registering the patient for this study, the baseline data such as name, age, sex was collected and a brief history of presenting illness, past illness, personal history such as smoking, alcohol consumption, substance abuse and treatment history were taken. Participants were categorised into smokers and non - smokers and drinkers and non - drinkers based on their history.

Anthropometric measurements like Height (cm), Weight (kg), Waist circumference (cm), were measured and body mass index (BMI) was calculated. With the help of stadiometer, height was measured in centimetres and converted to metres. The participants were told to stand upright barefooted, heels held close together with back against the backboard kept vertically and eyes looking forward. Weight in kilograms was measured with the participants standing barefooted and wearing light indoor clothing by an electronic weighing scale on a horizontal surface.

Clinical Examination:

General examination was performed and Pulse rate was noted. Systolic and Diastolic blood pressure (SBP & DBP) were recorded using a standard mercury sphygmomanometer by making the patient seated comfortably for at least minutes of rest at the right arm in the sitting position with the arm at the level of the heart.

Laboratory Measurements

Under strictly aseptic precautions, 5 ml of venous blood was obtained after an overnight fasting for biochemical assessment of plasma glucose, serum lipid profile, serum gamma glutamyl transferase, Serum high sensitivity C Reactive Protein (hs-CRP) in a clot activator tube and glycated haemoglobin (HbA1c) in EDTA tube. Samples were centrifuged immediately and assayed. All parameters were assayed using the fully automated analyser Mindray BS 420. HbA1c was assayed using the fully automated analyser Cobas C 311. The history, anthropometric measurements, clinical findings, investigation reports were entered on a predesigned Proforma.

Diagnosis of the metabolic syndrome

The diagnosis of the metabolic syndrome was done when three or more of the following five factors were present according to the Modified National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol inAdults and Adult Treatment Panel III 2005 (NCEP ATP III), since this criteria has been proven to be more accurate.

- Waist circumference (cm) – Men ≥ 90 cm; Women ≥ 80 cm
- Fasting plasma glucose level - ≥100 mg/dL (Alternative indication – on drugs for hyperglycemia)

- Blood pressure – Systolic ≥ 130 mm or diastolic ≥ 85 mm or already diagnosed and or on drugs for hypertension
- Fasting triglyceride level - >150 mg/dL or on drugs for hypertriglyceridemia

HDL cholesterol level – Males < 40 mg/dL and Females <50 mg/dL or on drugs to normalise HDL cholesterol level.

Biochemical Investigations

Table 1: Estimated parameters

Parameter	Method
Fasting plasma Glucose	Glucose oxidase peroxidase
Glycated haemoglobin (HbA1c)	Turbidimetric Inhibition Immunoassay
Serum Total Cholesterol	Cholesterol oxidase peroxidase
Serum Triglycerides	GPO method- Trinder's reaction
Serum HDL-c	Direct Immuno inhibition method
Serum LDL-c	Selective Direct Single Measurement
Serum high sensitivity C- Reactive Protein	Immunoturbidimetric method
Serum gamma glutamyl transferase (GGT)	Kinetic Photometric Test – according to Szasz / Persijn

Statistical Analysis: Collected data were entered in Microsoft Office Excel and analysed using the software, Software package for social sciences (SPSS), version 21. The results were analysed with the help of descriptive and inferential statistics. Descriptive analysis was done to describe the distribution of age, gender, Body mass index (BMI) and other parameters among the study participants and expressed as percentage (%). For continuous variables, mean and standard deviation were calculated. We have estimated serum high sensitivity c-reactive protein and gamma glutamyl transferase in 100 patients who were fulfilled the criteria of metabolic syndrome. We assessed the association of high sensitivity C-Reactive Protein and Gamma glutamyl transferase with BMI, Glycemic status (HbA1C) and lipid profiles using Chi-Square test. Pearson's correlation was computed to find the correlation between high sensitivity C-Reactive Protein and Gamma glutamyl transferase and other variables like BMI, HbA1c and Lipid profile. A probability (P value) of less than 0.05 was considered as statistically significant.

RESULTS

Table 2: Characteristics of the study population (n = 100)

Parameters		Frequency	Percentage
Age (years)	18 – 35	13	13%
	35- 60	79	79%
	> 60	8	8%
Sex	Male	58	58%
	Female	42	42%
Alcohol intake	Yes	16	16%
	No	84	84%
Smoking	Yes	10	10%
	No	90	90%
Antihypertensive Medication	Yes	18	18%
	No	82	82%
Statins	Yes	3	3%
	No	97	97%
Waist Circumference (WC)	<90	15	15%
	>90	85	85%
Systolic BP (mm Hg)	<130	15	15%
	>130	85	85%
Diastolic BP (mm Hg)	<85	20	20%
	>85	80	80%
Fasting Plasma Glucose (FPG) (mg/dl)	<100	40	40%
	100-125	50	50%
	>125	10	10%

Table 3: Characteristics of the study population (n = 100)

Parameters		**Population n = 100**	**Minimum**	**Maximum**	**Mean**	**Standard Deviation**
BMI (Kg/m^2)						
Normal	**18.5– 22.9**	4	20.6	42.7	29.7	5.2
Over weight	**23-24.9**	11				
Obese	**≥ 25**	85				
HbA1C (gm/dl)						
< 5.6		44				

≥ 5.6 - 6.4	56	4.2	6.3	5.7	0.5
Total Cholesterol (mg/dl)					
<200	63	118	295	193.8	36.7
>200	37				
Triglycerides (mg/dl)					
<150	31	67	299	174.9	58.1
>150	69				
HDL-C (mg/dl)					
<50	89	20	63	40.3	8.6
>50	11				
LDL-C (mg/dl)					
<150	84	66	214	124.7	30.2
>150	16				

Table 2 showed the characteristics of the study participants. All the participants were categorized into three age groups viz. 18-35 years, 36-60 years and >60 years. 79% of the study participantsbelonged to 30-60 years of age group, 13% were 18-35 years of age group and the remainder (8%) came under the group of above 60 years. The mean age was 48.1years and standard deviation was 10.0 years.

59% of study participants were males and 42% were females. Among the 100 study participants, 10% were smokers and 90% were non - smokers. 84% of study participants were non alcoholics and 16 % were alcoholics.

Among the 59% male participants % had waist circumference > 90cm and among the 42% females, % had waist circumference > 80cm.

18% of participants had systolic blood pressure <130 mm Hg and 85% had systolic blood pressure ≥130 mm Hg. 20%of participants had diastolic blood pressure < 85 mm Hg and 80 % haddiastolic blood pressure ≥85 mm Hg.

40% had fasting plasma glucose (FPG) concentration < 100 mg/dl and diagnosed as non- diabetics and 50% had fasting plasma glucose (FPG) concentration 100-125 mg/dl, considered as having impaired fasting glucose tolerance and 10% who were not known cases of type 2 diabetes mellitus, had fasting plasma glucose (FPG) concentration >125 mg/dl at the time of study.

Table 3 showed the distribution of the study participants based on the WHO's BMI classification for Asians, glycemic status of the study participants based on their glycated Haemoglobin (HbA1C) and lipid profile and mean & standard deviation of the parameters based on descriptive statistics.

From the table it is inferred that the mean BMI was 29.7 Kg/m2 and standard deviation was 5.2 Kg/m2. According to the WHO's BMI classification for Asians, majority of the study participants (85%) were obese, 11% were overweight and the remaining 4% were normal.

It is inferred that 44 % of the study participants had normal HbA1c and 56 % had elevated HbA1c (prediabetic state). Mean HbA1c value was 5.7 gm/dl and Minimum was 4.2 5.7 gm/dl and Maximum was 6.3 gm/dl.

From the table, it is inferred that 37 participants had serum total Cholesterol concentration >200 mg/dl. 63 participants had total Cholesterol concentration <200 mg/dl. Mean value was 193.8, minimum value was 118 mg/dland maximum value was 295 mg/dl.

69 participants had serum triglycerides concentration >150 mg/dl. 31 participants had serum triglycerides concentration <150 mg/dl. Mean value was 174.9 mg/dl, minimum value was 67 mg/dland maximum value was 299 mg/dl.

89 participants had serum HDL-C concentration <50mg/dl. 11 participants had serum HDL-C concentration >50mg/dl. Mean value was 40.3mg/dl, minimum value was 20mg/dland maximum value was 63mg/dl.

16 participants had serum LDL-C concentration >150 mg/dl. 84 participants had serum LDL-C concentration <150 mg/dl. Mean value was 124.7 mg/dl, minimum value was 66 mg/dland maximum value was 214 mg/dl.

Table 4: hsCRP &GGT levels in the study participants

Parameters	**Population n = 100**	**Minimum**	**Maximum**	**Mean**	**Standard Deviation**
HSCRP					
<1mg/L	11	0.1	39	7.0	6.3
1-3 mg/L	21				
>3mg/L	68				
GGT (U/L)					
Normal	87	11	214	35.7	6.3
Elevated	13				

This table 4 showed the hsCRP and GGT levels in the study participants. It is inferred that 11% of the study participants had hsCRP values < 3 mg/ L (Low risk), 21% had values between 1mg/ L to 3mg/L (Moderate risk) and 68% had values > 3 mg/ L (High risk). Mean hsCRP value was 7.0 mg/ L minimum hsCRP value was0.1 and maximum mg/ L hsCRP value was 39 mg/ L.

From the above table it is inferred that 87% of study participants had normal GGT and 13% had elevated values. Mean GGT activity was 35.7 U/ L minimum

GGT activity was0.1 and maximum U/ L GGT activity was 39 U/ L.

Table 5: Comparison of hs-CRP levels with Parameters

Parameters		Hs-CRP			Chi-Square test - P value
		<1mg/L (N=11)	1-3 mg/L (N=21)	>3mg/L (N=68)	
Age(years)	18 – 35	1	3	9	0.289
	35- 60	9	14	56	
	> 60	1	4	3	
Sex	Male	5	19	34	*0.003
	Female	6	2	34	
Alcohol	Yes	4	3	9	0.148
	No	7	18	59	
Smoking	Yes	0	4	6	0.198
	No	11	17	62	
Antihypertensive Medication	Yes	3	6	9	0.194
	No	8	15	59	
Statins	Yes	0	0	3	0.483
	No	11	21	65	
BMI (Kg/m^2)	Normal	0	2	2	*0.035
	Overweight	4	2	5	
	Obese	7	17	61	
HBA1C (gm/dl)	<5.6	7	8	29	0.355
	5.7-6.4	4	13	39	
TC (mg/dl)	<200	5	12	46	0.302
	>200	6	9	22	
TGL (mg/dl)	<150	4	3	24	0.176
	>150	7	18	44	
HDL (mg/dl)	<50	9	19	61	0.719
	>50	2	2	7	
LDL (mg/dl)	<150	6	18	60	*0.018
	>150	5	3	8	
GGT (U/L)	Normal	9	19	59	0.783
	Elevated	2	2	9	

P value < 0.05 was taken as statistically significant.

Table 5: Comparison of GGT with the other Parameters

Parameters		GGT		Chi-Square test - P value
		Normal (N=87)	Elevated (N=13)	
Age (years)	18 – 35	10	3	0.306
	35- 60	69	10	
	> 60	8	0	
Sex	Male	48	10	0.138
	Female	39	3	
Alcohol	Yes	7	9	*<0.001
	No	80	4	
Smoking	Yes	6	4	*0.007
	No	81	9	
Antihypertensive Medication	Yes	17	1	0.300
	No	70	12	
Statins	Yes	2	1	0.288
	No	85	12	
BMI (Kg/m^2)	Normal	3	1	0.720
	Overweight	10	1	
	Obese	74	11	
HBA1C (gm/dl)	<5.6	34	10	*0.010
	5.7-6.4	53	3	
TC (mg/dl)	<200	55	8	0.907
	>200	32	5	
TGL (mg/dl)	<150	28	3	0.508
	>150	59	10	
HDL (mg/dl)	<50	76	13	0.174
	>50	11	0	
LDL (mg/dl)	<150	75	9	0.119
	>150	12	4	
Hs-CRP (mg/L)	Low risk	9	2	0.783
	Moderate risk	19	2	
	High risk	59	9	

P value < 0.05 was taken as statistically significant.

Table 5 showed the comparison of hs-CRP levels with variables using the chi-square test. From the table it is inferred that among the 68 participants having CRP value > 3mg/L, majority (56%) were the age group of 35 to 60 years. 34 participants of each gender had CRP levels >3mg/L, 19 male participants had CRP value 1 to 3mg/L compared to 2 female participants with CRP value 1 to 3mg/L and 5males and 6 females had CRP value <1mg/L and it is statistically significant (P value <0.003).

Among the 68 participants having CRP value >3mg/L, 61 were obese, 5 had overweight and 2 had normal weight. 2 normal weight and 2 overweight and 17 obese participants had CRP levels 1 to 3mg/L and 7 obese participants had CRP levels <1mg/L and it is statistically significant (P value <0.035).

Participants with elevated LDL value (<150mg/dl), majority (60) had CRP value >3mg/L, 18 had CRP levels 1 to 3mg/L and 6 had CRP levels <1mg/L compared with participants with normal LDL value (<150mg/dl), 8 had CRP value > 3mg/L, 3 had CRP levels 1 to 3mg/L and 5 had CRP levels <1mg/L and it is statistically significant (P value <0.018).

For other variables HBA1C, Total cholesterol, triglycerides, High density lipoprotein cholesterol) the comparison with CRP levels was not statistically significant.

Table 33 showed the comparison of GGT levels with parameters using the chi-square test. From the table it is inferred that among the 16 participants who had the habit of alcohol intake, 9 participants had elevated GGT levels and among the 84 participants without the habit of alcohol intake, 80 had normal GGT levels and it is statistically significant (p value <0.001). Among the 90 non-smokers 81 had normal GGT levels and among the 10 smokers, 4 had elevated GGT levels and it is statistically significant (p value 0.007).

Among the 56 participants with HBA1C 5.7-6.4 gm/dl, 53 had normal GGT levels and among the 44 participants with HBA1C <5.6 gm/dl, 34 had normal GGT levels and it is statistically significant (p value 0.010).

For other variables (Body mass index, Total cholesterol, triglycerides, High density lipoprotein cholesterol, Low density lipoprotein cholesterol) the comparison with hsCRP levels was not statistically significant.

Table 6: Correlation between hsCRP&GGT with BMI, HBA1C &Lipid profile

Parameters	Hs-CRP		GGT	
	Pearson correlation Coefficient	P value	Pearson correlation coefficient	P value
BMI	0.5512	0.0000	0.0100	0.9212
HBA1C	0.0817	0.4192	0.2332	0.0196
Lipid profile				
TC	-0.1240	0.2191	0.1039	0.3038
TGL	-0.1902	0.0581	0.0589	0.5602
HDL	-0.2394	0.0164	-0.1252	0.2146
LDL	-0.0470	0.6422	0.1594	0.1132

From the table 6 it is inferred that there is positive correlation between hs-CRP and BMI (correlation coefficient is 0.5512). This means that as BMI increases, hs-CRP increases, and it is statistically highly significant as P value is 0.0000. There was positive correlation between hs-CRP and HbA1c (correlation coefficient is 0.0817). This means that as HbA1c increases, hs-CRP level decreases. But it is not statistically significant as P value is 0.4192. Analysis showed a negative correlation between hs-CRP and HDL-C (correlation coefficient is -0.2394) and it is statistically significant as P value is 0.0164.

From the table 34 it is inferred that there is positive correlation between GGT and BMI (correlation coefficient is 0.0100). This means that as BMI increases, GGT increases. But it is statistically not significant as P value is 0.9212.GGT showed statistically significant correlation with HbA1c (P value is 0.0196). There was a positive correlation between GGT and all cholesterol values except HDL with which it shows negative correlation. But these are not statistically significant.

DISCUSSION

In our observational cross-sectional study, we selected the study participants with metabolic syndrome with dyslipidemia without any acute and / or chronic inflammation by enquiring history and measuring height and weight and waist circumference (WC), calculating BMI, and estimating fasting plasma glucose, and lipid profile as per modified NCEP-ATP III criteria among the adults who came for master health check-up in Trichy SRM Medical College Hospital & Research Centre. We estimated HbA1C, high sensitivity C- Reactive Protein (hs-CRP), and Gamma glutamyl transferase (GGT) in the selected participants, who were not known cases of type 2 diabetes mellitus and on antidiabetic medications. We studied the association of high sensitivity C- Reactive Protein (hs-CRP), and Gamma glutamyl transferase (GGT) with BMI, HbA1C, and lipid profile.

In our study, we analysed the age wise distribution status of study participants which showed that majority [79%] belonged to 35-60 years of age group, 13% and 8% belonged to 18-35 years and above 60 years of age group respectively. The estimated mean age was 48.1 ± 10.0 years. Ofer K et. al, in an observational, population -based study stated that the prevalence of metabolic syndrome had been increased with advancing age, and the mean age of the participants was 51.4 years which was consistent with our results. Slagter SN et. alin a study among western European participants andAl-Daghri et. al in the adult Saudic population in their cross-sectional study documented the increased prevalence until 60–69 years of agein both genders and Al-Daghri et. al showed a decline thereafter which were consistent with our study result.[2,3] Song QBet. alin a cross-sectional study among urban Chinese adults documentedlower prevalence in the oldest age group among men (65–74 years).[4] Young people aged 20–29 years showed the least prevalence in a population -based cohorts studied by Scuteri Aet. Al,[5] and this matched with our study findings of low number of participants among the age group 18-35 years (13%). We assessed gender wise distribution of the study participants and 59% of the study participants were males and 42% were females. A cross-sectional study conducted in Japanese men and women by Yamada et al. documented higher prevalence of metabolic syndrome in men than in women similar to our study result. Similar findings of male preponderance had been documented in various studies.[2,3] In a cross-sectional study in urban Chinese adults conducted by Song QBet. al, male preponderance had been observed in study population aged <55 years and higher prevalence inwomen aged ≥55 years.[4] An observational, cohort-based study conducted by Ofer K et. al reported identical prevalence of metabolic syndrome in men and women with differences in their metabolic profile1. Contrary to our results, higher prevalence of metabolic syndrome among women than men had been documented by Harikrishna et al in a community based, cross-sectional study conducted in three districts in Kerala,[7] and lot of other studies.[8,9,10,11,12,13,14]

In our study, though we have selected the participants with metabolic syndrome using waist circumference, we have analysed the association of hs-CRP with BMI. In our study, the mean BMI was 29.7kg/m2 which is above the cut- off point of obesity (≥ 25 kg/m2) according to WHO's BMI classification for Asians. It is inferred from table 30 that majority of the study population (85%) were obese, 11% were overweight and remaining 4% belonged to normal BMI (18.5-22.99 kg/m^2). In an observational, cohort-based study conducted by Ofer K et. al, BMI had been stated as an easy screening tool at the primary care centre. The study had concluded that BMI had a higher negative predict value of 90% even at BMI of 30 kg/m2 to rule out any 3 non obesity criteria in metabolic syndrome and revealed cut off value for BMI to detect metabolic syndrome as 27 kg/m^2 for both genders,[1] which also had been concluded in a cross sectional-study conducted among the european descent by Głuszek S et.al.[15] In a population-based cross-sectional analysis in middle-aged individuals from Indonesia and the Netherlands, Sigit et. al, observed that the most prominent metabolic syndrome component in both populations was hypertension and showed a stable association of BMI and blood pressure after adjustment for waist circumference but a weakened association of waist circumference and blood pressure after adjustment for BMI.[16] Harikrishna et al in a community-based study, conducted in Kerala, documented three and seven fold, higher prevalence of metabolic syndrome in overweight and obese individuals respectively.[7]

In our study, though we have selected the participants with metabolic syndrome using fasting hyperglycemia, we have analysed the association of hs-CRP with HbA1c. Distribution of the study population according to HbA1c was consolidated in Table 30 which showed that 44% of the study population had normal HbA1c < 5.6 gm%, whereas 56%had elevated HbA1c and mean HbA1c was.[5,7] which was in the prediabetic (≥ 5.6 - 6.4 gm%) range. ParkSH et al. in a cross-sectional study reported that prevalence of metabolic syndrome using HbA1c as a criterion has increased to 25.7% compared with fasting hyperglycemia and suggested HbA1c as a good predictor of cardiovascular disorders and ischemic heart disease.[18] Similar to our results, in studies conducted by Millar SR et al,[17] and Kharroubi et al,[16] Mostafa et al,[16] in a United Kingdom cohort, increased number of participants were detected as having pre-diabetes using HbA1c compared with FPG or oral glucose tolerance test (OGTT).

Studies conducted among Asian people by Inoue et al18. and Heianza et al,[19] demonstrated the benefits of combined use of HbA1c and FPG to identify people with type 2 diabetes. Type 2 diabetes has been discovered as having chronic inflammatory state and the components of metabolic syndrome such as obesity, increased triglycerides and decreased HDL-C levels, high systemic blood pressure and insulin resistance have been known as established risk factors for developing diabetes mellitus increasing the risk five-fold.

Previous studies revealed that patients with metabolic syndrome are more susceptible for endothelial dysfunction and vascular diseases such as coronary heart disease and stroke.[22] Dyslipidemiain metabolic syndrome is characterised by the presence of hypertriglyceridemia and low high-density cholesterol (HDL-C) levels (3). Dyslipidemia has been considered as the most prevalent cardiovascular risk factor.[23] In our study, 63 participants had total Cholesterol concentration <200 mg/dl. 69 participants had serum triglycerides concentration >150 mg/dl. 89 participants had serum HDL-C concentration <50mg/dl. 16 participants had serum LDL-C concentration >150 mg/dl.

Metabolic syndrome and its components have been considered as chronic low-grade systemicinflammatory state and characterised by increased secretion of pro-inflammatory cytokines, acute-phase reactant proteins such as C reactive protein, coagulation factors and macrophages.[24,25]

C-reactive protein (CRP), an acute phase reactant protein and a nonspecific marker of systemic inflammation in clinical settings, is synthesised and secreted primarily from hepatic tissue in response to any acute and chronic inflammatory states. Many previous studies have demonstrated the association of hs-CRP levels with metabolic syndrome. In individuals with metabolic syndrome, plasma CRP production from the liver is primarily induced by tumour necrosis factor-α and IL-6 are released into circulation from the activated macrophages, monocytes, located in the inflamed adipocytes.[18] Among variousbiomarkers that reflect inflammation and insulin resistance status in metabolic syndrome, estimation of hs-CRP is a relatively low cost, easily available, standardized assay.[26]

In our study, participants were divided into three subgroups to assess the association of CRP in metabolic syndrome according to American Heart Association definition of risk groups as follows: hs-CRP ≤ 1 mg/L- Low risk, 1 -3 mg/L- moderate risk, and hs-CRP > 3 mg/L - High risk. Majority of participants (68%) had hsCRP values > 3 mg/ L and 21% had values between 1mg/ L to 3mg/L. Mean hsCRP value was 7.0 mg/L. A hospital based cross sectional study conducted by Gowdaiah et al in Bangalore demonstrated a higher mean value of hs-CRP (8.3±1.04 mg/L) in metabolic syndrome patients which was consistent with our result. Contrary to our mean hsCRP value, the mean value of hs- CRP was 1.23±0.03 in a cross-sectional survey study conducted by Jeong H, et al,[27] and median hs-CRP was 0.99 mg/L in a cross-sectional survey study among Chinese population conducted by Sun M et al.[19] The reason for the low CRP concentration could be the nature of the study population as this study was general population based. In our study relatively high mean value of hs- CRP may be due to hospital- based study and the study population does not represent the general population.

Among the 68 participants having CRP value > 3mg/L, majority (56%) were the age group of 35 to 60 years. Similar to our results, in a study conducted by Syauqy et al. majority of the study participants with elevated CRP in metabolic syndrome were 46 to 60 years of age.[20] When we analysed CRP distribution gender wise, 34 participants of each gender had CRP levels >3mg/L, 19 male and 2 female participants had CRP value 1 to 3mg/L and 5males and 6 females had CRP value <1mg/L and it is statistically significant (P value <0.003). It had beenreported that population distribution of CRP had significant ethnic and gender differences in a multi-ethnic, population-based, Dallas Heart Study, conducted by Khera A et al.[31]

When we analysed association of hsCRP with BMI, among the 68 participants having CRP value >3mg/L, majority (61%) were obese, 5 had overweight and 2 had normal weight and it is statistically significant (P value <0.035). It is inferred from table that hs-CRP is positively correlated with BMI (correlation coefficient is 0.5512). This means that as BMI increases, hs-CRP increases, and it is statistically highly significant as P value is 0.0000. Similar to our results, in studies conducted in various parts of India such as a cross sectional study in Ambala conducted by Lamichhane et al,[32] has been reported to have positive correlation with BMI.

Lot of previous studies demonstrated association of CRP with all the components of metabolic syndrome and some studies demonstrated that the levels of CRP were influenced by the presence of the total numbers of metabolic syndrome components and linear increase in CRP values, with increasing numbers of metabolic syndrome components. But in various studies, except adiposity, there were no significant CRP associations or correlations with all the components of metabolic syndrome andno consistent associations of hs-CRP with different components of metabolic syndrome.

In a study conducted in the Chinese population with metabolic syndrome by Sun M et al. found association of hs-CRP with age, Waist circumference, fasting hyperglycemia, low LDL cholesterol level.[21] In a retrospective, cross-sectional study from Korea National Health and Nutrition Examination survey, Jeong H et al demonstrated the association of central obesity, hyperglycaemia, hypertriglyceridaemia, and low HDL with plasma CRP in metabolic syndrome patients but not with hypertension, Total cholesterol and LDL cholesterol. In this study increased CRP concentration had positive association with glycated hemoglobin levels in type 2 diabetic patients and CRP cut-off value for metabolic syndrome was 0.54 mg/L type 2 diabetes was 0.53 mg/L and 0.56 mg/L for hypertriglyceridaemia.

A hospital based cross-sectional study among Saudi patients with metabolic syndrome, conducted by Bahijri SM et al. reported though higher mean values were observed in metabolic syndrome patients, no significant correlation was found between hs-CRP level and HbA1c or BP and dyslipidemia except abdominal obesity in both genders.[22]

In analysis of present study, the results also support that not all the components of metabolic syndrome are associated with hs-CRP. Only obesity (BMI), low HDL-C levels, and an elevated LDL-C level are associated with hs-CRP levels. Analysis showed a positive correlation between hs-CRP and HbA1c (correlation coefficient is 0.0817).

Various previous prospective and epidemiologic studies showed that hs-CRP can be used as an independent predictor of development of type 2 diabetes mellitus and cardiovascular diseases and give more prognostic information than Framingham Risk Score. By causing vascular cells inflammation and injury hs-CRP plays a critical role in atherosclerosis and Cardiovascular diseases.[22,23] Therefore, risk factors of Cardiovascular diseases evaluation and early intervention may decrease mortality rate from Cardiovascular diseases.

In clinical practice, oxidative stress measurement has its limitations. Low levels of reduced glutathione

(GSH), an important powerful antioxidant in human cells were found to be associated with conditions such as type 2 diabetes mellitus and increased microvascular complications. but measurement of GSH levels is not available in clinical practice routinely. Therefore, a more practical biomarker is needed to assess the status of oxidative stress, that is, status of GSH. Previous studies have suggested serum GGT can be used as a biomarker of status of GSH because it plays an important role in GSH recycling and transport in almost all tissues. Though GGT is an established biomarker of excessive alcohol consumption and liver disease, Since the early 2000s lot of studies demonstrated its association with metabolic syndrome, diabetes and car¬diovascular disease and recognised as a biomarker of oxidative stress.[25,38] Several studies reported oxidative stress has an important role in the pathogenesis of metabolic syn¬drome and demonstrated GGT as an oxidative stressbiomarkerand in¬creased risk of metabolic syndrome canbe predicted by the increased activity of GGT in serum.[26,27]

In our study, participants were divided into two subgroups to assess the association of GGT in metabolic syndrome using the reference interval as folllows: Normal - 9- 58 U/L and elevated – >58 U/L. 87% of study participants had normal GGT and 13% had elevated values. Mean GGT activity was 35.7 U/L. Analysis revealed statistically highly significant association with alcoholism (p value <0.001) and smoking status (p value 0.007). Among the 56 participants with HBA1C 5.7-6.4 gm/dl, 53 had normal GGT levels and among the 44 participants with HBA1C <5.6 gm/dl, 34 had normal GGT levels and it is statistically significant (p value 0.010). Analysis showed a positive correlation between GGT and BMI (correlation coefficient is 0.0100). This means that as BMI increases, GGT increases. But it is statistically not significant as P value is 0.9212.GGT showed statistically significant correlation with HbA1c (P value - 0.0196). There was a positive correlation between GGT and all cholesterol values except HDL with which it shows negative correlation. But they are not statistically significant.

Similar to our study, in various studies, significant association of GGT levels with all the components of metabolic syndrome had not been reported. In a cross-sectional study using data from the large-scale population-based Korean Genome and Epidemiology Study (KoGES), Lee MY et al. demonstrated the linearly increased metabolic syndrome prevalence with increasing GGTquartile and the mean GGT level was 37.92±48.20 mg/dL which was similar to the mean value of GGT in our study. Bradley et al. in MESA cohort study demonstrated significant associations between GGT activity and BMI, fasting blood glucose (FBG), fasting insulin, HbA1c and HOMA–IR.

In a retrospective, hospital study conducted by Yoon et al., significantly increased GGT levels were reported with increased number of metabolic syndrome components and significantly higher GGT levels were observed in study participants with abdominal obesity, and hypertriglyceridemia in both genders but not with low HDL levels In a Prospective cohort, Dhananjay Yadav, et al demonstrated the significant association of stepwise increase in baseline GGT levels with the increas¬ed risk of metabolic syndrome (from 13.7% to 27.6%) and the incidence of each metabolic syndrome component.

Correlation of GGT levels with the incidence of NAFLD and MS within the reference intervals in a dose-dependent manner. The relationships of GGT with cardiovascular risk factors include increased age, males, obesity (BMI), alcoholism, smoking, physical inactivity, hypertension, increased fasting glucose, elevated cholesterol and triglycerides, low HDL levels were strong even with normal GGT levels. Reason for this association of GGT with various clinical conditions within the reference range of GGT is currently not well understood.

Though genetic factors involve in the development of obesity and metabolic syndrome, inflammation, oxidative stress and insulin resistance play a critical role in the pathogenesis of metabolic syndrome and its complications such as type 2 diabetes mellitus and cardiovascular diseases. In our present study, though hs-CRP is statistically associated with BMI, HDL-C and LDL-C and GGT is statistically with only HA1c, all the findings suggest a link between oxidative stress, inflammation in obesity, hyperglycemia, dyslipidemia in metabolic syndrome. one of the easily available markers and routinely added in basic blood tests.

Metabolic disorders may be prevented or managed by controlling the low-grade inflammation and oxidative stress by using the strategies such as increased physical activity, drugs include statins, fibrates, aspirin, insulin-sensitizing agents and antioxidants such as β-carotene, vitamin C and glutathione. Because, in addition to normalising the abnormal lipid levels, lipid lowering drugs possess mild anticoagulant and hypotensive actions and angiotensin inhibitors have anti-inflammatory actions apart from the normalising the blood pressure.

CONCLUSION

In our study, we found that hs-CRP is significantly associated with obesity, dyslipidemia and GGT is significantly associated with HbA1c in metabolic syndrome. Though statistically insignificant, hs-CRP is positively associated with HbA1c and GGT is positively associated with BMI, total cholesterol, triglycerides, LDL-c and negatively correlated with HDL-c. Though the levels of hs-CRP and GGT activity in circulation are affected by various factors such as age, gender, alcoholism, smoking and clinical conditions, due to their value as independent metabolic disorders risk predictors, we suggested that these biochemical parameters (hs-CRP and GGT) together may be included in routine screening of people above 35 years of age and monitoring of patients with metabolic syndrome.

Limitations

Because our present study was an observational and cross-sectional study it cannot determine the cause-effect relationship, but it can validate a statistical association.

Hospital based study with small sized sample.

To our knowledge, we excluded people with acute and chronic infection and inflammatory conditions by taking history. But we did not have complete data such as biochemical parameters and/ or radiological evidence to rule out these conditions.

we have only analysed serum CRP as an inflammatory marker and serum GGT as an oxidative marker and not included other related parameters such as IL-6 and uric acid.

We did not perform ultrasonogram abdomen to know whether non-alcoholic liver disease (NAFLD) is present or not as this may influence GGT level.

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