

Relationship of inflammatory markers with metabolic and anthropometric variables in obese individuals

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Abstract

Introduction: It is recognized that obesity is associated with a chronic low-grade inflammation and activation of immune system. Serum sialic acid and C-reactive protein (CRP) are markers of inflammation. **Aims and Objectives:** The aim of our study was to evaluate the serum concentrations of high-sensitivity CRP (hs-CRP) and total sialic acid and the conventional cardiovascular risk factors like lipid parameters, blood pressure and blood glucose in obese subjects and to find the possible correlations between these factors in such patients. **Methodology:** We studied 50 obese subjects and 50 non obese controls, between the age group of 20 and 60 years. Lipid profile, hs- CRP, total sialic acid, fasting blood sugar, body mass index and waist hip ratio were determined in the two groups. Quantitative data of the two groups were expressed as mean and standard deviation and compared by unpaired 't' test. Association between hs - CRP and total sialic acid with the various metabolic and anthropometric variables was assessed by Pearson correlation. A 'p' value less than 0.05 is considered significant. **Results:** Serum total sialic acid and lipid levels were significantly elevated in the obese group compared to the non-obese group ($p < 0.05$). There was significant correlation between hs - CRP and total sialic acid with body mass index, waist hip ratio blood pressure and lipid parameters ($p < 0.05$). **Conclusions:** Our findings suggest that in obesity, there is an association between serum sialic acid and hs- CRP levels with obesity indices, and various conventional cardiovascular risk factors like lipid profile, increased BP and blood sugar, thus contributing to cardiovascular risk.

Key Words: Obesity, inflammatory markers, total sialic acid, C - reactive protein (CRP).

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INTRODUCTION

Obesity is a public health problem affecting countries rich and poor in epidemic proportions. An estimated 500 million adults worldwide are obese. About 1.5 billion are overweight or obese¹. Worldwide obesity has more than

doubled since 1980. In 2014 more than 1.9 billion adults, 18 years and older were overweight. Studies from different parts of India have provided evidence of the rising prevalence of obesity^{2,3}. The ICMR-INDIAB study (Phase I) (2015), showed the prevalence of obesity not only in urban areas, but also in rural areas in India and that the prevalence of abdominal obesity was higher than generalized obesity and urban residents had a higher prevalence of both forms of obesity, that is abdominal as well as general obesity than rural residents⁴. Obesity is a consequence of many factors like increased energy consumption and reduced physical exercise. Obesity and inflammation have been associated with type 2 diabetes, cardiovascular disease, hypertension, stroke and gall bladder disease⁵. Obesity is commonly associated with other metabolic disorders as hyperglycemia and hypertriglyceridaemia, which are well known risk factors

for developing non alcoholic fatty liver disease (NAFLD)⁶. Inflammation is a physiological response of the organism to harmful stimuli, which is necessary to restore homeostasis altered by the diverse stimuli. The normal acute inflammatory response involves the delivery of plasma components and leucocytes to the site of insult and is initiated by tissue - resident macrophages and the mast cells. This leads to production of different types of inflammatory mediators⁷. The activated endothelium allows extravasation of neutrophils and soluble components to the tissue, where they become activated. These activated neutrophils release toxic agents and proteolytic enzymes and thus eliminate the injurious agent. This leads to resolution of inflammation and tissue repair. This is achieved by switching the lipid mediators from proinflammatory to anti inflammatory ones and by the action of tissue resident and newly recruited macrophages⁸. Tissue leucocytes undergo apoptosis, which are then phagocytosed by macrophages which leave the inflammation site by lymphatic drainage. The apoptosis of inflammatory cells is essential for the resolution of inflammation. After engulfing these apoptotic cells, the macrophages release anti-inflammatory signals such as interleukin (IL)-10 and transforming growth factor-beta(TGF- β)⁹. However if these mechanisms fail, the inflammatory process persists and a state of chronic inflammation may arise. It has recently been demonstrated that the chronic inflammation associated with morbid obesity is characterized by a continuous activation of the innate immune system¹⁰. Several chronic diseases involve an inflammatory response characterized by the increase of cytokines and serum concentration of acute - phase reactants such as fibrinogen, C-reactive protein (CRP), complement, serum amyloid A, haptoglobin, sialic acid and low albumin concentrations¹¹. The CRP is a sensitive acute phase reactant and a marker of systemic inflammation, the serum concentration of which increases rapidly in response to a variety of stimuli. It is present in low concentration under normal conditions^{12,13}. C-reactive protein (CRP) is shown to be related to diseases including cardio vascular disease and Type II Diabetes^{14 -17}. The serum sialic acid is a marker of acute phase response. This is because many of the acute phase proteins like haptoglobin, alpha 1- acid glycoprotein, fibrinogen, transferrin, complement, alpha-1 antitrypsin, etc are glycoproteins with sialic acid on the terminal sugar of the oligosaccharide chain. These glycoproteins together explain 70% of the total serum sialic acid concentration¹⁸. It is the most stable acute- phase marker and also a useful indicator of overall acute- phase response. In the same way as CRP, sialic acid has been shown to be associated with cardiovascular disease¹⁹ and type II diabetes²⁰. This

study examines the relationship between inflammatory markers CRP and sialic acid with various metabolic and anthropometric variables in overweight and obese population.

MATERIALS AND METHODS

This was a case control study carried out in the obesity clinic of Government Medical College, Thiruvananthapuram, Kerala. The study was conducted after getting approval from the Institutional ethical committee according to the provisions of Helsinki declaration. A written informed consent was obtained from the participants. The study subjects included 50 obese subjects and 50 non-obese controls between the age group 20 and 60 years. The study groups were grouped as obese and non-obese based on the WHO criteria of obesity in adult Asians²¹. Height and weight were recorded for all subjects. The Body Mass Index (BMI) was calculated from the formula: BMI = Body weight in kg / height in m². Those with a BMI more than 25 were grouped as obese and those with a BMI less than 25 were grouped as non-obese. Subjects with known Diabetes, treated dyslipidaemia, known hypertension, chronic inflammatory conditions, liver disease, malignancy, polycystic ovarian syndrome, pregnant ladies, smokers and alcoholics were excluded from the study. Blood pressure was measured twice using a sphygmomanometer from the right arm of the seated participant after 10 minutes rest. The mean of the 2 readings were taken. Waist and hip circumference were taken. Waist hip ratio was calculated.

Collection of Blood Samples

7ml of venous blood was drawn after 12 hours fast and collected in two tubes. One tube containing sodium fluoride and potassium oxalate for plasma glucose estimation and the other was a plain tube for serum separation. Plasma was separated from the first tube and used for measuring plasma glucose with a commercial kit by GOD-POD method on a fully auto analyzer by Transasia Biomed. The blood in plain tube was allowed to clot to separate serum, which was used to measure fasting lipid profile, total sialic acid and hs-CRP. Total cholesterol, Triglycerides, and HDL cholesterol were measured using commercially procured kits in the fully auto analyzer by Transasia Bio med. LDL- cholesterol was calculated by Frederickson Friedwald formula. LDL cholesterol = Total cholesterol - [HDL cholesterol + Triglycerides/5] Serum hs- CRP levels were measured using a commercial kit from Transasia Biomedicals Ltd., Erba Diagnostics, Mannheim, Germany. hs- CRP was quantitated by particle enhanced turbidimetric immunoassay. Sialic acid was analyzed by thiobarbituric acid assay of Warren²².

Statistical Analysis was performed using SPSS version 22.0. Quantitative data were expressed as mean and standard deviation. Qualitative data were expressed as proportion. Quantitative data for the two groups were compared with unpaired 't' test. Associations between two quantitative variables were analyzed by Pearson correlation. A 'p' value of < 0.05 was considered to be statistically significant.

RESULTS

Table 1 represents the comparison of demographic and biochemical parameters in cases and controls. There was no significant difference of age between the two groups. The mean Body Mass Index (BMI) of cases was $31.2 \pm 3.3 \text{ kg/m}^2$ and that of the controls was $24.6 \pm 2.5 \text{ kg/m}^2$. The mean waist hip ratio (WHR) of cases was 0.93 ± 0.06 and that of controls were 0.82 ± 0.01 . There was a significant difference of the two parameters between the two groups. ($p < 0.001$).

Table 1: Demographic and biochemical parameters in cases and controls

Parameters	Case (N=50)		Control (N=50)		t	p
	Mean	SD	Mean	SD		
Age in years	41.4	10.0	43.0	4.6	1.014	0.313
BMI (kg/m^2)	31.2	3.3	24.6	2.5	11.125	<0.001
Systolic BP (mmHg)	126.6	11.8	121.1	14.2	2.132	0.035
Diastolic BP (mmHg)	83.6	6.7	80.3	7.3	2.390	0.019
Total sialic acid (mg%)	64.5	6.6	57.1	6.3	5.646	<0.001
Total Cholesterol (mg%)	204.8	34.8	189.2	34.1	2.264	0.026
HDL (mg%)	47.4	8.6	48.2	8.8	-.447	0.656
Triglyceride (mg%)	124.18	40.86	102.98	28.3	3.015	0.003
LDL (mg%)	136.26	33.79	119.9	35.23	2.367	0.020
hs-CRP (mg%)	1.41	0.69	1.16	0.52	2.090	0.039
FBS (mg%)	100.8	35.3	83.1	9.6	3.418	0.001
Waist hip ratio	0.93	0.06	0.82	0.01	12.146	<0.001

Abbreviations: BP-blood pressure, HDL-high density lipoprotein, LDL- low density lipoprotein, hs-CRP-Highly sensitive C- reactive protein, FBS- fasting blood sugar.

There was significant difference between systolic and diastolic blood pressure between the two groups ($p < 0.05$). Serum total sialic acid in obese subjects was $64.5 \pm 6.6 \text{ mg}^{\%}$ and that of controls was $57.1 \pm 6.3 \text{ mg}^{\%}$. Increase in total sialic acid was found to be highly significant ($p < 0.001$). Serum hs- CRP levels were (1.41 ± 0.69) mg/L in obese groups and (1.16 ± 0.52) mg/L in the control group. Increase in hs - CRP was found to be statistically significant ($p < 0.05$). There was a significant difference in the total cholesterol, low density lipoprotein, triglycerides ($p < 0.05$) and fasting blood sugar ($p = 0.001$)

between the two groups. There was a significant correlation between total sialic acid and hs- CRP with BMI and waist hip ratio ($p < 0.001$). Total sialic acid was also significantly correlated with systolic and diastolic blood pressure, total cholesterol, LDL cholesterol and fasting blood sugar ($p < 0.001$) and with triglycerides ($p < 0.05$). Total sialic acid was negatively correlated with HDL cholesterol ($p < 0.05$). hs - CRP was significantly correlated with total cholesterol ($p = 0.001$), systolic BP diastolic BP, triglycerides and LDL cholesterol ($p < 0.05$), Table 2. Fig. 1 and 2.

Table 2: Correlation of TSA and hs-CRP with other parameters

Parameters	TSA		Hs_CRP	
	Correlation coefficient (r)	p	Correlation coefficient(r)	p
Age	-.047	0.643	0.089	0.378
BMI	0.521**	<0.001	0.389**	<0.001
Systolic Blood pressure	0.500**	<0.001	0.262**	0.008
Diastolic Blood Pressure	0.568**	<0.001	0.308**	0.002
Total Cholesterol	0.479**	<0.001	0.341**	0.001
HDL	-0.213*	0.033	-0.025	0.805
Triglyceride	0.318**	0.001	0.236*	0.018
LDL	0.428	<0.001	0.226	0.024
FBS	0.341**	0.001	0.151	0.134
Waist hip ratio	0.518**	<0.001	0.347**	<0.001

Abbreviations: HDL-high density lipoprotein, LDL - low density lipoprotein, FBS- fasting blood sugar, TSA - total sialic acid, hs- CRP- high sensitivity C- reactive protein.

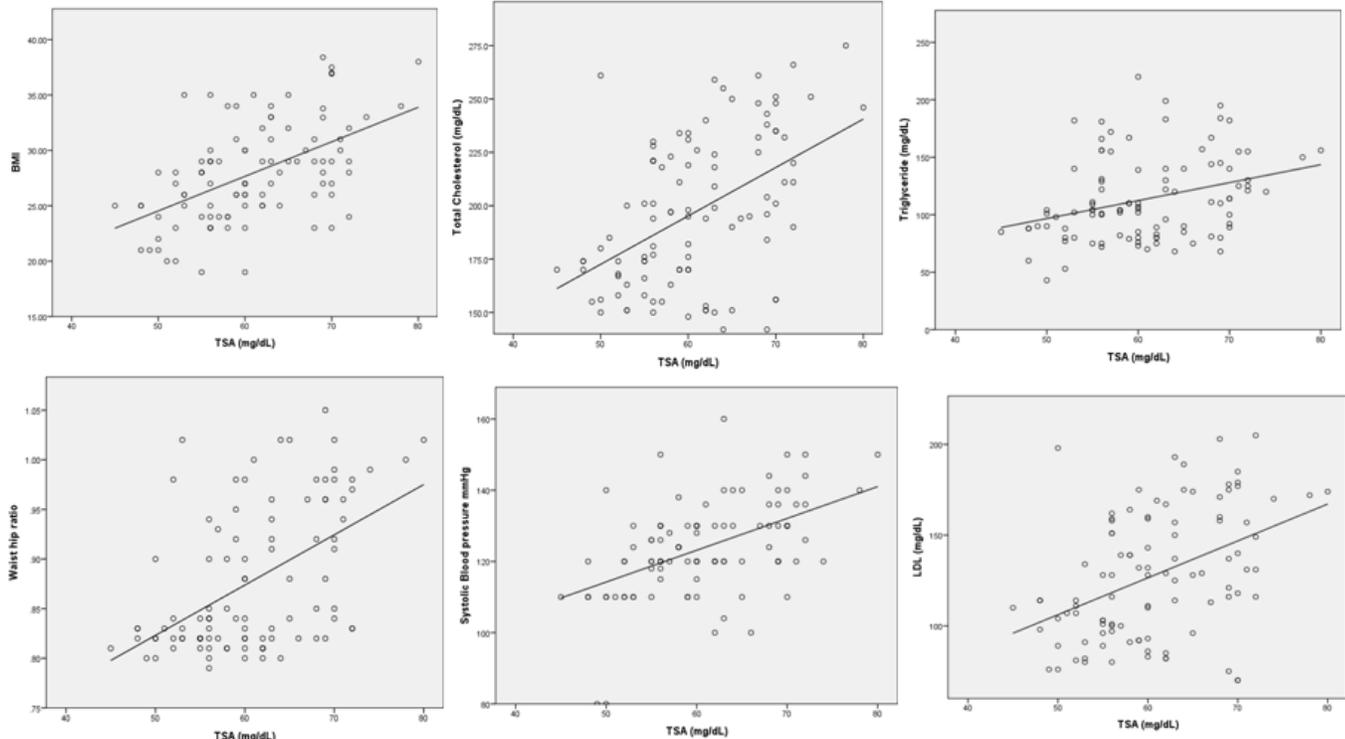


Figure 1: Correlation of total sialic acid with other parameters

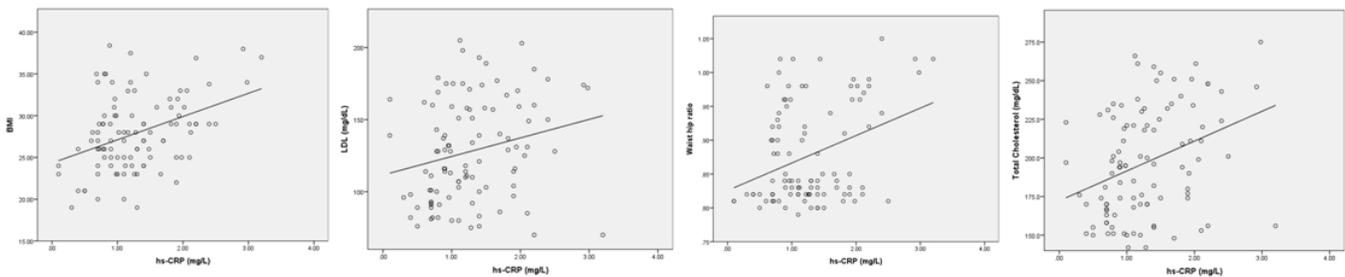


Figure 2: Correlation of hs-CRP with other parameters TSA- total sialic acid

DISCUSSION

Obesity is defined by the American Heart Association (AHA) as a major modifiable risk factor for Coronary Heart Disease. Obesity promotes insulin resistance, hyperinsulinemia, type 2 diabetes, hypertension, hypertriglyceridaemia, low HDL cholesterol, small dense LDL and pro-thrombotic factors. It is associated with an increase in cardiovascular and all cause mortality. Obesity particularly central obesity is the prominent risk factor for insulin resistance and results in type 2 diabetes mellitus and other features of metabolic syndrome such as dyslipidaemia and hypertension [23]. In recent years it has been demonstrated that obesity is associated with a low grade inflammatory process, characterized by increase in circulating levels of pro-inflammatory cytokines and acute-phase proteins like CRP in healthy obese subjects²⁴. In the present study we estimated inflammatory markers

hs - CRP and total sialic acid in obese and non-obese control subjects. Serum hs- CRP levels were significantly elevated in the obese group compared to the control group ($p < 0.05$). This is similar to other studies^[25,26]. There was a very significant increase in serum total sialic acid levels ($p < 0.001$) in the obese group compared to the control group. This is in accordance with the study done by Fh Yerlikaya *et al.*, (2015)²⁷. The reason for this significant increase in total sialic acid may be that sialic acid is a more stable inflammatory marker and therefore may provide a more accurate reflection of an individual's habitual inflammatory status. Sialic acid acts as an integrated marker of a number of acute- phase proteins. Therefore it is a representative of the overall acute phase response, whereas CRP is an acute phase protein released from the liver as part of an inflammatory process²⁸. The studies done by Neiman *et al.*, (2002) and Kannel *et al.*, (1997) prove that obese individuals have significantly

higher serum total cholesterol, triglycerides and LDL values. The results of the present study is comparable with this^[29,30]. Also many studies have shown that obesity is associated with increase in plasma triglycerides³¹. Pearson correlation of total sialic acid and hs- CRP with other parameters shows that both CRP and sialic acid were positively correlated with BMI, systolic and diastolic BP, waist hip ratio, total cholesterol, triglycerides and LDL. This is comparable to other studies^{26,32}. Also recent studies have been confirming the positive association between obesity indices and CRP in women³³. Serum total sialic acid was also associated with other conventional cardiovascular risk factors like increased serum glucose. The results of the correlation between serum total sialic acid and serum lipids may be due in part to sialylation of lipoproteins³². Many apolipoproteins contain sialic acid, which may influence the behavior of the associated lipoproteins. Changes in sialylation of LDL particles have been linked with atherosclerosis³⁴. Increased sialic acid of very low density lipoprotein (VLDL) particles may contribute to hypertriglyceridaemia³⁵ CRP may also have a direct effect on dyslipidaemia by mediating the uptake of LDL by macrophages³⁶. The correlation of sialic acid and hs-CRP with BP and blood sugar shows the association of these inflammatory markers with features of metabolic syndrome²⁸. Thus in the present study there is a significant relationship between inflammation and metabolic disease. It was shown that a potential basis for the initiation of inflammation in obesity is endoplasmic reticulum (ER) stress. Over nutrition and obesity cause ER stress in liver and adipose tissue due to excess lipid accumulation and disturbed energy metabolism. Studies in mice and humans prove that consumption of nutrients may acutely evoke inflammatory responses. Therefore it is thought that the starting signal of inflammation is overfeeding. The process originates in tissues involved in metabolism, which is adipose tissue, liver and muscle which in response of this stimuli trigger the inflammatory response³⁸. It has also been shown that the inflammatory condition which is associated with obesity and overweight plays an important part in the etiology of metabolic syndrome, type 2 diabetes mellitus and cardiovascular disease. Some studies have reported weight loss, through diet is associated with reduction in circulating levels of markers of inflammation and cytokines³⁹. Therefore interventions like dietary modifications, life style changes and weight reduction can be adopted to prevent metabolic syndrome and the related pathological outcomes.

CONCLUSION

Since sialic acid and C-reactive protein are elevated in obese subjects, this supports the view that obesity is in part an inflammatory disorder. Serum TSA and CRP are found to be associated with conventional cardiovascular risk factors including elevated lipid profile and increased BP in obese people, all of which may contribute to the cardiovascular risks in obese people. Acute-phase markers like sialic acid and C-reactive protein are important markers of inflammation and may be useful to study obesity related diseases.

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