Association of serum immunoglobulin M and immunoglobulin G antibody levels with different indicators of metabolic syndrome

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ABSTRACT

Background: Metabolic syndrome (MS) is an assemblage of biochemical derangements of glucose metabolism, dyslipidemia, hypertension, and central obesity allied with implacable low-grade inflammation. **Aims and Objectives:** The current cross-sectional study was conducted to evaluate the levels of serum Immunoglobulin IgM, and IgG concentrations in subjects with and without MS. **Materials and Methods:** The study population included 50 adults with MS as cases confirmed by estimation of serum triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), Fasting Plasma Glucose, waist circumference, and blood pressure. Serum IgM and IgG levels were evaluated in cases and controls (from a healthy population), followed by statistical analysis, with the significance level set at $P<0.05$. **Results:** The comparison of the serum IgM levels between the case and control groups revealed that the level was significantly higher in the former ($P<0.001$) compared to the latter, but no statistically significant difference existed in the IgG values. Correlation analysis showed significant positive correlation of IgM with TG ($\rho = +0.870$, $P<0.001$), waist circumference ($\rho = +0.683$, $P=0.009$) and negative correlation with HDL-C ($\rho = -0.751$, $P<0.001$). A significant positive correlation of IgG with waist circumference ($\rho = +0.889$, $P<0.001$) was derived. Regression analysis affirmed that statistically, TG ($R^2=0.768$), waist circumference ($R^2=0.751$), and HDL-C ($R^2=0.705$) significantly explained the variance in IgM, whereas IgG was related to only waist circumference. **Conclusion:** The present study provides a novel perspective that IgM may be involved in the pathogenesis of MS in a population from eastern India, and the outcome suggests the association between IgM and MS may be through lipid metabolism disorders and obesity.

Key words: Dyslipidemia; Metabolic syndrome; Obesity

INTRODUCTION

Metabolic syndrome (MS), a constellation of biochemical derangements of glucose metabolism, dyslipidemia, hypertension, and central obesity, is a well-recognized risk factor for cardiovascular diseases.[1] Among Indian adults, the prevalence of MS is 30%—more in urban (32%) compared to rural (22%) and tribal (28%) adults.[2]

An important factor contributing to MS is persistent, chronic, low-grade systemic inflammation.[3] Obesity has been recognized as a common pathological process causing the development of MS. India has seen a steep increase in obesity in the last few decades. Visceral fat cells contribute directly to the development of low-grade inflammation as they secrete numerous immune-modulating proinflammatory cytokines. Interleukin (IL)-6 is now considered a co-factor for immunoglobulin (Ig) synthesis and also a common marker of inflammation.[4]

Few epidemiological studies have evaluated the association between Igs and MS in the general population, yielding

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contrasting results.[5,6] The serum IgM concentration was found to be significantly lower in subjects with dyslipidemia.[5] To the contrary, another study reported a positive association between serum IgM concentration and elevated triglyceride (TG) and reduced high-density lipoprotein cholesterol (HDL-C) in male patients.[6] In a study, high serum titers of IgG antibodies to oxidized low-density lipoprotein were found to be associated with MS and smoking.[7] Dyslipidemia was found to be associated with a lower mean serum IgG concentration in a recent study.[8] Moreover, the scarcity of such studies among the local population has compelled us to design this study. It was hypothesized that Igs may be a key molecular link between MS and the systemic inflammatory response induced by obesity. This cross-sectional study aims to evaluate the alteration of serum (IgG and IgM) concentrations in subjects with and without MS and assess any relationship between the Igs and the indicators of MS, including obesity, hypertension, diabetes mellitus (DM), and dyslipidemia estimated by Waist Circumference, Blood pressure, Plasma Glucose, Serum TG, and Serum HDL-C, respectively.

Aims and objectives

The current study was conducted to evaluate the levels of serum IgM, IgG concentrations in subjects with and without metabolic syndrome.

MATERIALS AND METHODS

A hospital-based cross-sectional study was done for 5 months after obtaining approval from the institutional ethics committee. The study population included adults with MS as cases selected from the general medicine outpatient department of the institution. The control group was selected from the accompanying healthy relatives of the patients. Biochemical investigations and result analysis were performed in the department of Biochemistry at the institution.

Following inclusion and exclusion criteria, 50 adults with MS and 50 controls were selected by the method of convenience and after obtaining informed consent.

Inclusion criteria for cases

a. The age of the subjects was >18 years
b. The subjects met the criteria of MS: Three or more of the following as per harmonized guidelines of the national heart, lung, and blood institute of the US American Heart Association and the International Diabetes Federation,[9] which include:
   i. Waist circumference of ≥90 cm in males or ≥80 cm in females—Asian population cutoff for abdominal obesity
   ii. TGs ≥150 mg/dL or receiving drug therapy for hypertriglyceridemia

   iii. HDL-C <40 mg/dL in males or <50 mg/dL in females, or receiving drug therapy for low HDL-C
   iv. Blood pressure ≥130/85 mmHg or receiving drug therapy for hypertension
   v. Fasting plasma glucose ≥110 mg/dL or receiving drug therapy for hyperglycemia.

Exclusion criteria for cases

Subjects with liver diseases, hematological disorders, infections, autoimmune diseases, malignancies, immunodeficiencies, and pregnant mothers were excluded.

Controls were selected after proper consent from healthy individuals without MS as well as any hematological diseases, chronic or active infection, or inflammation.

Ethical considerations

Institutional ethical clearance was obtained as per guidelines from the Helsinki Declaration, 1975, as revised in 1983, and the Indian Council of Medical Research guidelines for human studies. Written and informed consents were obtained from participants as per protocol.

Data collection procedure

Blood was collected from the subjects in plain clot vials and fluoride vials after proper patient preparation. Blood pressure and waist circumference were recorded, along with a clinical history. After centrifugation, serum was harvested for the estimation of Serum IgM, serum IgG, Serum TG, Serum HDL-C, and Fasting Plasma glucose. The data collected was followed by statistical analysis.

Analytes measured

Serum IgM and serum IgG were measured by a solid-phase sandwich enzyme-linked immunosorbent assay (ELISA) from Xema-medica Co., Ltd., using an ELISA Reader and Washer (Tecan Life Sciences). The analytical sensitivity of the assay specified was 0.06 g/L for both IgM and IgG. The manufacturer indicated the following reference intervals for healthy adults: IgM 0.7–3.7 g/L and IgG 9.0–20 g/L.

Serum TG was measured by the glycerol phosphate oxidase method, serum HDL-C by the polyethylene glycol precipitation method, and plasma glucose by the hexokinase method using the Konelab systems pack reagent and Thermo Fisher Scientific Konelab Prime 60i autoanalyzer. All reagents and procedures were pre-validated. Quality control of the Elisa kits and enzymatic methods was monitored through the calibrators and control materials.

Statistical analysis

The data obtained from the above parameters were analyzed for differences between the medians of the serum

IgM and IgG of cases and controls by Mann-Whitney U-test, as the data failed the normality tests. A Spearman correlation analysis between IgM and the components of MS (serum TG, Serum HDL-C, Fasting Plasma Glucose, Waist circumference, and Blood pressure) was performed in the cases. Simple linear regression was done to assess the relationship between the dependent variables Serum IgM and serum IgG and the indicators of MS. All statistical analyses were carried out using the IBM SPSS Statistics 26.0 software with $P<0.05$ as the significance level.

RESULTS

In the current study, 50 MS subjects, including 28 female subjects and 22 male subjects, were evaluated with mean ages of 52.27 and 52.05 years, respectively. The comparison of medians of Serum IgM and Serum IgG between cases and controls by Mann-Whitney U-test as reported in Table 1 revealed that serum IgM levels were much higher (median=5.85 g/L) in the case-MS group ($P<0.001$) compared to the control group (median=1.70 g/L), but no statistically significant difference was found in IgG values, although the median value was lower in the case group. The Box Whisker plot of IgM (g/L) median value in Cases (Median-5.85), Control (Median-1.7) and IgG (g/L) median value difference in Cases (Median-14.85) and Control (Median 15.30) is shown in Figure 1.

The Spearman correlation analysis conducted for Serum IgM, as revealed in Table 2, showed a strong significant positive correlation of serum IgM with serum TG level ($\rho=+0.870$, $P<0.001$), waist circumference ($\rho=+0.683$, $P=0.009$) and a strong negative correlation with serum HDL-C ($\rho=-0.751$, $P<0.001$) thus establishing a positive correlation between serum IgM level and dyslipidemia as well as obesity. There was no significant correlation between serum IgM level, fasting plasma glucose, and both diastolic and systolic blood pressure (SBP). For Serum IgG, a significant positive correlation of serum IgG was detected only with waist circumference ($\rho=+0.889$, $P<0.001$) thus linking serum IgG with obesity. Other indicators did not reveal any significant correlation.

Simple linear regression analysis (Table 2) showed that the variation in Serum IgM (the dependant variable) is very well explained by taking TG ($R^2=0.768$, $\beta=0.864$, $P<0.001$), HDL-C ($R^2=0.705$, $\beta=-0.735$, $P<0.001$), and waist circumference ($R^2=0.751$, $\beta=0.680$, $P=0.011$) into account individually. In the case of Serum IgG (the dependant variable), the regression analysis reflected 74.9% variations taking Waist circumference into account ($R^2=0.749$, $\beta=0.876$, $P<0.001$).

The regression lines were positive for the relation of Serum IgM with TG and Waist Circumference and negative with HDL-C, whereas they were positive for Serum IgG with Waist circumference as in the scatter plots (Figure 2). Thus, the standardized coefficient beta (β) and the regression lines revealed almost similar result as the correlation analysis.

DISCUSSION

IgM is the first antibody produced in an immune response after the initial antigen encounter. It is the

Table 1: Comparison of medians of serum IgM and serum IgG between cases and control				
Analyte tested	Median (Case)	Median (Control)	Mann Whitney U	P-value
Serum IgM (g/L)	5.85	1.70	424	<0.001*
Serum IgG (g/L)	14.850	15.300	1104.000	0.189

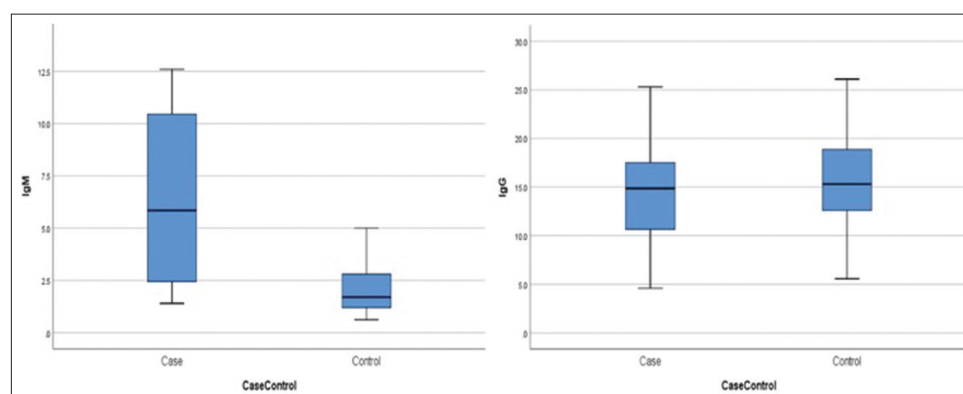*P<0.05 as the significance level, Ig: Immunoglobulin

Figure 1: Box whisker plot of immunoglobulin (Ig)M (g/L) - cases (median-5.85) and control (median-1.7) and IgG (g/L) - cases (median-14.85) and control (median-15.3)

Table 2: Spearman correlation and linear regression (simple linear) analysis of serum IgM, Serum IgG with the indicators of metabolic syndrome

Independent variables	Dependent variable- serum IgM					Dependent variable- serum IgG				
	Spearman correlation		Simple linear regression			Spearman correlation		Simple linear regression		
	Rho (ρ)	P	R²	Standard Coeff. Beta	P-value	Rho (ρ)	P	R²	Standard Coeff. Beta	P-value
TG	+0.870	<0.001*	0.768	+0.864	<0.001*	+0.420	0.088	0.072	+0.393	0.078
HDL-C	−0.751	<0.001*	0.705	−0.735	<0.001*	−0.531	0.098	0.12	−0.511	0.139
WC	+0.683	0.009*	0.751	+0.680	0.011*	+0.889	<0.001*	0.749	+0.876	<0.001*
FBS	+0.239	0.196	0.11	+0.212	0.223	-0.439	0.069	0.032	+0.422	0.082
SBP	+0.332	0.089	0.164	+0.313	0.136	+0.234	0.079	0.043	+0.210	0.095
DBP	+0.384	0.097	0.02	+0.378	0.147	+0.381	0.112	0.022	+0.336	0.213

TG: Serum triglyceride, HDL-C: Serum high-density lipoprotein cholesterol, WC: Waist circumference, FBS: Fasting blood sugar/fasting plasma glucose, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

predominant isotype secreted during T-cell independent immune responses[10] and an important component in autoimmunity.[11] Obesity is a core factor in MS and induces the development of autoimmunity.[12] Thus, IgM may be a major molecular link between MS and the systemic inflammatory response initiated by obesity.[6] In the current study, a statistically significant difference was found in serum IgM levels between the subjects with MS and the normal population, with the former group having a much higher IgM level than the latter. The Tianjin chronic low-grade systemic inflammation and health (TCLSIH) Cohort Study conducted by Song et al. is the first to show that the highest IgM quartile is independently related to the highest prevalence of MS in both males and females.[6]

In the current study, the serum total IgG levels, on the other hand, revealed no such significant result. IgG in human circulation has been suggested to have proatherogenic effects, although the functional effect of alterations in serum concentrations of IgG on atherosclerotic Cardiovascular disease is yet to be understood.[13] The key finding of a study conducted by Lin et al. was that patients with dyslipidemia had IgG concentrations significantly lower than those without dyslipidemia.[7] Gonzalez-Quintela et al. concluded in their study that IgG levels showed no consistent relationship with metabolic abnormalities like obesity and Diabetes.[5] As MS constitutes an array of metabolic defects, IgG level derangements might not be overall linked to MS as found in the current study.

In the present study, the indicators of MS were considered separately as the nominal definition of MS is constantly changing.[14] The first indicator dealt was dyslipidemia which showed a strong and significant positive correlation of IgM with serum TG level and a strong negative correlation with serum HDL-C. Moreover, regression analysis revealed that a statistically significant proportion (76.79% and 70.53%) of the variance for Serum IgM can be explained by serum
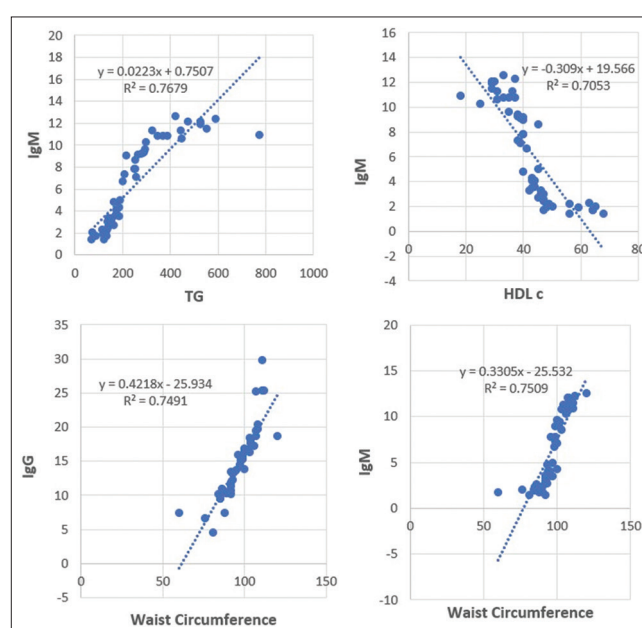

Figure 2: Scatter plots with regression line and R² values of serum immunoglobulin (Ig)M with serum triglyceride, serum high-density lipoprotein cholesterol, waist circumference and serum IgG with waist circumference

TG and HDL-C, respectively, with the trendlines being positive for the former and negative for the latter. The TCLSIH Cohort Study revealed that IgM levels in males were independently and positively related to the prevalence of elevated TG and reduced HDL-C,[6] similar to the current study findings. Recent studies have also suggested that fatty acids activate B cell TLR4 and that this stimulation is a requirement for increased IgM.[15] TG provides the source of fatty acid needed throughout body cells, and both are closely related. Serum fatty acid concentration may help in the interpretation of our observations of the relationships between IgM and MS, TG, or HDL-C. It can therefore be speculated that lipid metabolism disorders may be a key link between serum IgM levels and MS in the population.

In a study, Sadanand and colleagues concluded that abnormal lipid values were statistically associated with anticardiolipin IgM but not IgG concentration in patients with antiphospholipid antibody syndrome.[16] In the current study, correlational as well as regression studies revealed no statistically significant relationship between serum IgG levels and TG or HDL-C levels. Lin et al. found that dyslipidemia was associated with a lower mean serum IgG concentration in their study.[7] Contrariwise, a study by Turkoglu concluded that both serum lipids and Chlamydia pneumoniae IgG levels were raised in acute coronary artery disease patients.[17] In 2016, Khamis et al. reported that patients with higher baseline serum IgG concentrations were associated with experiencing a lower risk of cardiovascular events, especially when attributed to coronary heart disease.[13] Thus, a follow-up study in the current scenario would be best to decide the exact relation between IgG level and the effect of dyslipidemia on the risk of the occurrence of cardiovascular events.

Obesity was the next indicator of MS dealt with in this study, which has increased sharply throughout the world in recent times.[18] The increase in waist circumference (a measurement of obesity) is another crucial indicator of MS, as obesity induces the development of MS. In obesity, many immune cells infiltrate adipose tissue, promoting chronic low-grade inflammation.[19] Furthermore, visceral fat cells, now considered an immune organ, secrete numerous immune-modulating molecules and directly contribute to the development of low-grade inflammation. From the above, obesity triggers autoantibody production and is the most important risk factor for inducing a systemic inflammatory response.[5] The production of proinflammatory adipocytokines like IL-6, a cofactor for Ig synthesis, is increased.[20] This explains the statistically significant positive correlation between IgM and Waist circumference as well as between IgG and Waist circumference. In the current study, regression analysis revealed that statistically, 75.09% of the variance for Serum IgM and 74.91% of the variance for Serum IgG can be explained by Waist circumference, with the regression line being positive. Contrasting results were found in a study done in Spain, where IgG and IgM levels showed no consistent relationship with metabolic abnormalities like obesity and hypertension.[5] The difference in results may be due to differences in the geographical population studied, which needs further exploration.

The next indicator of MS is increased Fasting Plasma glucose, which is one of the diagnostic criteria for DM as per guidelines. In a study, none of the studied Ig concentrations showed a significant association with diagnoses of DM, which is similar to the outcome of the current study.[7] Studies have also reported changes in serum Ig levels among subjects with type 2 diabetes. The pro-inflammatory cytokine IL-6 plays an important role in the mediation of the inflammatory response and the development of microvascular complications in patients with DM.[21] So, elevated levels of IL-6 independently increase the risk of developing type 2 diabetes by diminishing insulin sensitivity. The current study, however, was unable to measure the insulin-resistant state of participants as well as IL6, which would have revealed the exact mechanism of association between DM and MS. Moreover, the extent to which the circulating Igs influence metabolic dysfunction in DM is not fully known, particularly with regard to ethnicity. In the Ghana study, IgM levels were not different in the case and control groups, with results consistent with prior studies and similar to the findings of the current study.[21] Thus, Fasting plasma glucose couldn't explain the variance in IgM or IgG, according to the regression analysis of the present study.

The last but not the least indicator of MS is hypertension. IgG and IgM titres were found to be elevated in essential hypertension in many studies. However, these early studies could not identify the targets of these antibodies, and thus no facts on their exact association with the pathophysiology of hypertension were obtained. In recent times, the most likely explanation for the cause of the raised IgG in hypertension is vascular damage (fragmentation of the internal elastic lamina) induced by the raised BP, resulting in the release of connective tissue components that may become antigenic.[22] In the current study, no significant correlation was found between IgM and Diastolic blood pressure (DBP) or SBP as well as between IgG and DBP or SBP. A regression study also yielded no statistically significant relationship between Serum IgM or IgG and DBP or SBP. In a study, IgM levels showed no consistent relationship with hypertension, but individuals with high blood pressure showed higher IgG.[5] Olsen et al. also demonstrated a pattern of increased IgG, but without any correlation to BP.[23] In that study, untreated and treated patients were not evaluated separately, and the mean values of Ig were highest in the treated patients with normal BP. This may explain the lack of a correlation or any regression relationship, as a reduction of BP with drugs does not necessarily imply a restoration of any possible morphological vascular changes.

In a nutshell, according to the present study, obesity could explain both serum IgM and IgG levels, while dyslipidemia could predict only IgM levels. Chronic inflammation is a key feature of MS, which is a risk factor for cardiovascular events. An increased accumulation of macrophages occurs in obese adipose tissue. Their interactions with endothelial cells, adipocytes, and other immune cells,[24] and the up-regulation of TLR4/nuclear factor-kappa B, the

major signaling pathway,[3] have emerged as key processes in metabolic inflammation.

Almost no study to date has investigated the question of whether serum IgM and serum IgG are related to indicators of MS in the eastern Indian population. The present study provides a novel perspective on the possibility that IgM may be involved in the pathological process of MS in the current population.

Limitations of the study

The present study has two limitations. Firstly, a larger sample size should be undertaken to establish a stronger statistical outcome. Secondly, this is a cross-sectional study which needs more prospective studies in future to assess the association between immunoglobulin levels and risk of cardiovascular events in MS.

CONCLUSION

The present study reveals that IgM may be an important coupling between MS and obesity-induced inflammatory responses in a population from eastern India. The outcome of this study suggests that the association may be due to lipid metabolism disorders and obesity. Further, prospective studies with a large sample size need to be undertaken to establish a causal relationship between Igs and the risk of cardiovascular events in MS in the current population, so that measuring serum Ig may help in earlier identification of MS for apt and prompt intervention.

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