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Relationship between serum levels of immunoglobulins and metabolic syndrome in an adult population: A population study from the TCLSIH cohort study

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Abstract *Background and aims:* Metabolic syndrome (MetS) is a combination of metabolic disorders that increase the risk of developing cardiovascular disease, and inflammation is considered as a pathological basis for MetS. Immunoglobulins (Igs) are the major secretory products of the adaptive immune system. However, no large-scale population study has focused on a possible relationship between Igs and MetS. We designed a cross-sectional study to investigate the relationship between Igs and prevalence of MetS in a large-scale adult population.
Methods and results: A total of 10,289 participants were recruited among residents in Tianjin, China. Metabolic syndrome was defined in accordance with the criteria of the American Heart Association scientific statements of 2009. Serum levels of Igs were determined by immunonephelometry. Multiple logistic regression models were used to assess the relationship between the quintiles of serum levels of Igs and the prevalence of MetS. The overall prevalence of MetS was 36.1%. The mean (standard deviation) values of Igs (IgG, IgE, IgM, and IgA) were 1205.7 (249.3) mg/dL, 93.1 (238.9) IU/mL, 105.7 (57.3) mg/dL, and 236.2 (97.6) mg/dL, respectively. The adjusted odds ratios (95% confidence interval) of MetS for the highest quintile of Igs (IgG, IgE, IgM, and IgA), when compared to the lowest quintile, were 0.81 (0.70, 0.95), 0.97 (0.83, 1.12), 1.13 (0.97, 1.33), and 1.52 (1.30, 1.77), respectively.
Conclusions: This study demonstrated that decreased IgG and increased IgA are independently related to a higher prevalence of MetS. The results indicate that the Igs might be useful predictive factors for MetS in the general adult population.

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Introduction

Metabolic syndrome (MetS), as a set of metabolic disorders, is common in many populations [1,2]. It is related to abdominal obesity, blood lipid disorders, insulin resistance or full-blown diabetes, and an increased risk of developing cardiovascular disease (CVD) [3]. Its worldwide prevalence has increased remarkably during recent decades [1]. In China, the prevalence of MetS has increased sharply, and it reached 21.3% in 2009 [4]. The increasing burden of MetS demonstrates an immediate need to elucidate the mechanisms underlying its pathophysiology to implement preventative strategies.

It has been proven that inflammatory immune response is involved in the pathogenic components of MetS, such as increased blood pressure [5], insulin resistance [6], and dyslipidemia [7], and it is related to the accumulation of visceral fat [8]. Serum immunoglobulins (Igs) are measured routinely in clinical practice because they provide key information about the status of the humoral immune response [9]. An animal study suggested that saturated fatty acids in visceral adipose tissue could increase immunoglobulin M (IgM) levels via stimulation of B cell Toll-like receptor 4(TLR-4). This was because the saturated fatty acids present in the visceral adipose tissue stimulated Toll-like receptor 4 (TLR4) of B cells, thereby causing an increase in the serum IgM level [10]. Several studies showed that mice fed with a high-fat diet demonstrated an increase in the serum immunoglobulin G (IgG) level [11–13]. Moreover, in a population-based study, immunoglobulin E (IgE) was reported to be related to the prevalence of prediabetes and diabetes [14]. From the above studies, we speculated that Igs may be a crucial molecular link between the inflammatory immune response and MetS. A small-scale study (n = 460) addressed the relationship between Igs [including IgG, immunoglobulin A (IgA), and IgM] and metabolic abnormalities [15]. However, there is no study to evaluate the relationship between Igs and MetS in a large-scale general population.

The aim of the present study is to evaluate whether serum Ig levels are related to the prevalence of MetS.

Methods

Participants

Tianjin Chronic Low-grade Systemic Inflammation and Health (TCLSIHealth) Cohort study is a large prospective dynamic cohort study focusing on the relationship between chronic low-grade systemic inflammation and the health status of a population living in Tianjin, China. Full details of the TCLSIHealth Cohort study have been described elsewhere [16]. Briefly, study participants were randomly selected during annual health examinations at health management centers and community management centers of Tianjin, China. The protocol of this study was approved by the institutional review board of Tianjin Medical University, and all participants gave written informed consent before participation in the study. This study conforms to the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines for cross-sectional study.

For this analysis, we chose individuals who participated in the TCLSIHealth Cohort study from 2010 to 2016. During this period, 13,491 participants received health examination, agreed to participate, and provided informed consent for their data to be analyzed. For stringency of the data, we excluded participants with incomplete examinations. We also excluded participants with inflammatory diseases (pharyngitis, tympanitis, nasosinusitis, periodontitis, enteritis, gastritis, etc.) according to the information of inflammatory disease (“yes” or “no”) and recent anti-inflammatory drug use (“yes” or “no”) obtained from the questionnaire (n = 3096), or those with a history of CVD (n = 939) or cancer (n = 1133). Additionally, we excluded participants with white cell cast (WCC) $\geq$ 1.0 μl^{-1} and/or leukocyte count $\geq$ 10 $\times$ 1000 cells/mm^3 (n = 106) [17–20]. Owing to these exclusions, the final cross-sectional study population comprised 10,289 participants.

Assessment of MetS

MetS was defined in accordance with the criteria of the American Heart Association scientific statements of 2009 [21]. Participants were considered to have MetS when they presented three or more of the following components: (1) elevated waist circumference in Chinese individuals ($\geq$85 cm in males; $\geq$80 cm in females), (2) elevated triglycerides (TG) ($\geq$1.7 mmol/L), or drug treatment for elevated TG, (3) reduced high-density lipoprotein–cholesterol (HDL) ($<$1.0 mmol/L in males; $<$1.3 mmol/L in females) or drug treatment for reduced HDL, (4) elevated blood pressure (BP) (SBP $\geq$130 mmHg and/or DBP $\geq$85 mmHg) or antihypertensive drug treatment, and (5) elevated fasting glucose ($\geq$5.56 mmol/L) or drug treatment for elevated glucose.

Serum immunological tests

Serum levels of Igs (IgG, IgE, IgM, and IgA) were determined by immunonephelometry with the automated IMMAGE 800 immunochemistry system (Beckman Coulter, Brea, CA, USA). The detection limit of the assay was IgG 33.3 mg/dL, IgE 5 IU/mL, IgM 4.2 mg/dL, and IgA 6.7 mg/dL, and the measurement range was IgG 33.3–21,600 mg/dL, IgE 5–30,000 IU/mL, IgM 4.2–14,400 mg/dL, and IgA 6.7–25,200 mg/dL. The manufacturer indicates the following reference intervals for healthy adults: IgG 751–1560 mg/dL, IgE $<$ 165 IU/mL, IgM 46–304 mg/dL, and IgA 82–453 mg/dL.

Assessment of other variables

Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Waist circumference was measured at the umbilical level with participants standing and breathing normally. As for lipids, TG and total cholesterol (TC) were

measured by enzymatic methods. Low-density lipoprotein−cholesterol (LDL) was measured by the polyvinyl sulfuric acid precipitation method, and HDL was measured by the chemical precipitation method using appropriate kits on a cobas 8000 analyzer (Roche, Mannheim, Germany). BP was measured twice from the upper right arm using an automatic device (KD598, Andon, Tianjin, China) after 5 min of rest in a seated position, and the mean of these 2 measurements was taken as the BP value. Fasting blood glucose (FBG) was measured by the glucose oxidase method using reagents from Roche Diagnostics on an automatic biochemistry analyzer (Roche cobas 8000 modular analyzer, Mannheim, Germany). CVD was defined as a class of diseases that include coronary artery diseases, stroke, and peripheral arterial disease. Hyperlipidemia was defined as TC $\geq$ 5.17 mmol/l or TG $\geq$ 1.7 mmol/l or LDL $\geq$3.37 mmol/l or history of hyperlipidemia or current use of antihyperlipidemic medications. Type 2 diabetes (T2DM) was defined as an FBG level of $\geq$7 mmol/L or physician-diagnosed diabetes and/or current use of antidiabetic medications. Leukocyte count was assessed with a hematology analyzer XE-2100 (Sysmex, Kobe, Japan). WCC was assessed with an automated urine cell analyzer UF-100™ (Sysmex, Kobe, Japan).

Information of the smoking (and "current smoker") and drinking ("never," "former," and "current drinker") status of the participants was obtained from a questionnaire survey. The questionnaire also assessed sociodemographic variables including gender and age. A detailed personal and family history of physical illness and current medications was noted from "yes" or "no" responses to relevant questions from the questionnaire survey.

Statistical analysis

Data were analyzed using Statistical Analysis System version 9.3 for Windows (SAS Institute, Cary, NC). Descriptive data are presented as the mean (95% confidence interval, CI) for adjusted continuous variables and as percentages for categorical variables. Ig (IgG, IgA, IgM, and IgE) levels of participants were sorted, and any four points that divide an ordered distribution into five parts, each containing one-fifth of the scores, were defined as quintiles of Igs. According to quintiles of Igs, participants were divided into five categories. For analysis, prevalence of MetS was used as a dependent variable and quintiles of IgG, IgE, IgM, and IgA as independent variables. For baseline characteristics analyses, differences between groups with and without MetS were examined using analysis of covariance (ANCOVA) for continuous variables or multiple logistic regression analysis for proportional variables, after adjustment for age and sex. For cross-sectional analysis, we used logistic regression analysis to examine the relationship of the quintiles of IgG, IgE, IgM, and IgA with the prevalence of MetS after adjustment for the covariates age, sex, BMI, smoking status, drinking status, leukocyte count, family history of CVD, hyperlipidemia, and diabetes; the odds ratios (ORs) (95% CI) were also calculated. All tests were two-tailed, and $P < 0.05$ was defined as statistically significant.

Results

The prevalence of MetS was 36.1%. Details of age- and sex-adjusted characteristics of participants with and without MetS are presented in Table 1. The mean (standard deviation) values of age, IgG, IgE, IgM, and IgA were 49.8 (10.8), 1205.7 (249.3) mg/dL, 93.1 (238.9) IU/mL, 105.7 (57.3) mg/dL, and 236.2 (97.6) mg/dL, respectively. Compared with adults without MetS, those with MetS tended to be older and have higher BMI, waist circumference, TC, TG, LDL, SBP, DBP, FBG, leukocyte count, IgE, and IgA and lower levels of HDL (all P values < 0.01). A higher proportion of these participants were males ($P < 0.0001$). Higher proportions were also smokers, drinkers and had a family history of hyperlipidemia and diabetes (all P values $<$ 0.05). However, no significant differences were observed among participants with IgG, IgM, smoking status (ex-smoker), drinking status (everyday drinkers and ex-drinkers), and family history of diseases including CVD (all P values > 0.05).

Table 2 shows the crude and adjusted relationships of quintiles of IgG, IgE, IgM, and IgA with MetS. In the final multivariate models, the ORs (95% CI) of MetS for increasing quintiles of IgG, IgE, IgM, and IgA were 1.00, 0.81 (0.70, 0.93), 0.87 (0.75, 1.01), 0.72 (0.62, 0.84), and 0.81 (0.70, 0.95) (P for trend < 0.01); 1.00, 1.02 (0.88, 1.18), 0.89 (0.77, 1.04), 0.97 (0.83, 1.12), and 0.97 (0.83, 1.12) (P for trend $= 0.88$); 1.00, 1.07 (0.93, 1.23), 1.15 (0.99, 1.33), 1.08 (0.93, 1.25), and 1.13 (0.97, 1.33) (P for trend $= 0.18$); and 1.00, 1.16 (1.00, 1.35), 1.12 (0.96, 1.30), 1.28 (1.10, 1.49), and 1.52 (1.30, 1.77) (P for trend < 0.0001), respectively.

Discussion

In this cross-sectional study, we investigated the relationship between serum levels of Igs and MetS in an adult population. The results showed that a higher prevalence of MetS was related to a decrease in IgG and increase in IgA but not significantly related to IgE and IgM after adjustment for confounding factors.

In the present study, we analyzed extensive potentially confounding factors including age, sex, BMI, WBC counts, etc. The results of population characteristics showed that components of MetS and other factors such as age, BMI, smoking and drinking status, and family history of some diseases showed difference between participants with and without MetS. Moreover, some studies found that age, sex and BMI had prominent influence on the development of MetS and human immune status [15,21,22]. Therefore, we first adjusted for age, sex, and BMI in the analysis. In addition, some genetic factors (family history of diseases including CVD, hyperlipidemia, and diabetes) and leukocyte count were also considered to have an impact on MetS and demic immune status [23−26]. Finally, in view of the interaction effect among Igs, we also adjusted levels of other Igs in our analysis. After adjustment for these confounding factors, the results showed that IgE and IgM were not related to the prevalence of MetS.

Table 1 Age- and sex-adjusted participant characteristics by metabolic syndrome status (n = 10,289)[a].

	Metabolic syndrome status		*P* value[b]
	No	Yes	
No. of subjects	6571	3718	–
Age (y)	47.2 (47.0, 47.5)[c]	51.3 (51.0, 51.7)	<0.0001
Sex (males, %)	50.9	72.4	<0.0001
BMI (kg/m^2)	24.0 (23.9, 24.0)	26.8 (26.7, 26.9)	<0.0001
Waist	82.1 (81.9, 82.3)	90.3 (90.0, 90.5)	<0.0001
TC	5.01 (4.98, 5.03)	5.27 (5.24, 5.31)	<0.0001
TG	1.11 (1.10, 1.12)	2.10 (2.07, 2.13)	<0.0001
LDL	2.94 (2.92, 2.96)	3.04 (3.02, 3.07)	<0.01
HDL	1.45 (1.44, 1.46)	1.17 (1.16, 1.18)	<0.0001
SBP	118.0 (117.7, 118.4)	132.1 (131.6, 132.7)	<0.0001
DBP	75.1 (74.8, 75.3)	83.8 (83.5, 84.2)	<0.0001
FBG	4.89 (4.87, 4.91)	5.71 (5.68, 5.74)	<0.0001
Leukocyte count (× 1000 cells/mm^3)	5.24 (5.22, 5.28)	5.73 (5.69, 5.77)	<0.0001
IgG (mg/dL)	1193.3 (1187.5, 1199.1)	1185.1 (1177.2, 1193.1)	0.11
IgE (IU/mL)	29.3 (28.3, 30.3)	31.5 (30.1, 33.0)	0.01
IgM (mg/dL)	96.6 (95.5, 97.7)	95.1 (93.6, 96.6)	0.12
IgA (mg/dL)	212.9 (210.8, 215.1)	225.3 (222.1, 228.5)	<0.0001
Smoking status (%)			
Smoker	25.9	37.5	<0.01
Ex-smoker	2.29	3.83	0.22
Nonsmoker	71.8	58.7	<0.001
Drinker (%)			
Everyday	1.57	2.51	0.41
Sometimes	45.0	57.6	<0.001
Ex-drinker	1.56	1.30	0.30
Nondrinker	51.9	38.6	<0.0001
Family history of diseases (%)			
CVD	31.4	30.7	0.12
Hyperlipidemia	0.38	0.11	0.04
Diabetes	20.0	22.0	<0.001

[a] BMI, body mass index; TC, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein–cholesterol; HDL, high-density lipoprotein–cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; IgG, immunoglobulin G; IgE immunoglobulin E; IgM, immunoglobulin M; IgA, immunoglobulin A; CVD, cardiovascular disease.
[b] Analysis of variance or logistic regression analysis.
[c] Geometric mean (95% confidence interval) (all such values).

IgG, which is the most abundant Ig secreted by the human body, can reflect demic immune status. Fc-receptors are the receptors of Igs [27], and a previous study suggested that Fc-receptors increased in patients with nascent metabolic syndrome [28]. Thus, it is speculated that IgG may play a role in the development of MetS through its relationship with Fc-receptors. As we did not measure levels of Fc-receptors, further prospective epidemiological studies to investigate the interaction of Fc-receptors and Igs on MetS are needed in the future. Additionally, some of our studies have shown that serum IgG levels were related to the prevalence of diabetes and hypertension among the adult population [29,30]. A population-based cohort study suggested that IgG titers were negatively associated with markers of glucose metabolism [31]. Additionally, an animal study showed that there was a significant relationship between IgG and obesity-associated insulin resistance [13]. As diabetes, obesity, and hypertension are the main components of MetS [3], we speculate that IgG is related to MetS through these components. In the results, IgG was negatively related to the prevalence of MetS. However, a small-sample study (n = 460) in northwestern Spain has shown that there was no significant associations between IgG levels and MetS after adjusting for age and sex [15]. Although the reasons for this discrepancy remain unclear, we speculate that the smaller sample size and differences from confounding factors and race/ethnicity in their study may be the cause for the conflicting results. Further studies are necessary to ensure whether IgG has negative correlation with MetS.

In the current study, the results showed there were no relationships between IgE and MetS. Different from our results, a cross-sectional study demonstrated that IgE levels were positively related to subjects with MetS and T2DM in a small population (n = 340) [32]. Although the exact reasons remain unclear, subjects with different disease conditions may partly explain this discrepancy. Further study is required to clarify it.

Some of our prior studies suggested that IgM was negatively related to hypertension and positively related to T2DM [29,30]. Further, it is reported that obesity is related to anti-inflammatory IgM antibodies [33,34]. However, in the current study, the results showed that IgM was not related to MetS. Similarly, an adult population-based study found that there was no significant relationship between IgM and MetS [15]. Further studies are necessary to investigate whether IgM is related to MetS through large-sample population-based cohort studies.

Table 2 Adjusted relationships of quintiles of serum Ig concentrations with metabolic syndrome (n = 10,289)[a].

	Quintiles of Ig concentrations					*P* for trend[b]
	Level 1	Level 2	Level 3	Level 4	Level 5	
IgG concentration (mg/dL, range)	420.0–1000.0	1010.0–1130.0	1140.0–1240.0	1250.0–1380.0	1390.0–3860.0	–
No. of subjects	2084	2092	1977	1992	2144	–
No. of metabolic syndrome cases	861	745	728	648	736	
Crude	reference	0.79 (0.69, 0.89)[c]	0.83 (0.73, 0.94)	0.69 (0.60, 0.78)	0.74 (0.66, 0.84)	<0.0001
Age-, sex-, and BMI-adjusted	reference	0.82 (0.71, 0.95)	0.91 (0.79, 1.05)	0.77 (0.66, 0.89)	0.90 (0.78, 1.04)	0.13
Multiple adjusted[d]	reference	0.81 (0.70, 0.93)	0.87 (0.75, 1.01)	0.72 (0.62, 0.84)	0.81 (0.70, 0.95)	<0.01
IgE concentration (IU/mL, range)	5.00–7.80	7.81–18.5	18.6–39.9	40.0–104.0	105.0–7380.0	–
No. of subjects	2060	2056	2055	2048	2070	–
No. of metabolic syndrome cases	673	714	709	778	844	–
Crude	reference	1.11 (0.96, 1.25)	1.09 (0.95, 1.24)	1.26 (1.11, 1.44)	1.42 (1.25, 1.61)	<0.0001
Age-, sex-, and BMI-adjusted	reference	1.03 (0.89, 1.19)	0.92 (0.79, 1.07)	1.00 (0.87, 1.16)	1.04 (0.89, 1.20)	0.43
Multiple adjusted[d]	reference	1.02 (0.88, 1.18)	0.89 (0.77, 1.04)	0.97 (0.83, 1.12)	0.97 (0.83, 1.12)	0.88
IgM concentration (mg/dL, range)	4.17–62.2	62.3–83.1	83.2–105.0	106.0–139.0	140.0–1100.0	–
No. of subjects	2059	2060	2028	2049	2093	–
No. of metabolic syndrome cases	867	823	760	677	591	–
Crude	reference	0.92 (0.81, 1.04)	0.82 (0.73, 0.93)	0.68 (0.60, 0.77)	0.54 (0.48, 0.62)	<0.0001
Age-, sex- and BMI-adjusted	reference	1.07 (0.93, 1.23)	1.15 (1.00, 1.33)	1.08 (0.94, 1.26)	1.12 (0.96, 1.31)	0.19
Multiple adjusted[d]	reference	1.07 (0.93, 1.23)	1.15 (0.99, 1.33)	1.08 (0.93, 1.25)	1.13 (0.97, 1.33)	0.18
IgA concentration (mg/dL, range)	0.28–154.0	155.0–199.0	200.0–245.0	246.0–307.0	308.0–1140.0	–
No. of subjects	2075	2047	2047	2062	2058	–
No. of metabolic syndrome	664	728	681	768	877	–
Crude	reference	1.17 (1.03, 1.34)	1.06 (0.93, 1.21)	1.26 (1.11, 1.43)	1.58 (1.39, 1.79)	<0.0001
Age-, sex-, and BMI-adjusted	reference	1.12 (0.97, 1.30)	1.05 (0.90, 1.22)	1.20 (1.03, 1.38)	1.38 (1.19, 1.60)	<0.0001
Multiple adjusted[d]	reference	1.16 (1.00, 1.35)	1.12 (0.96, 1.30)	1.28 (1.10, 1.49)	1.52 (1.30, 1.77)	<0.0001

[a] Igs, immunoglobulins; IgG, immunoglobulin G; BMI, body mass index; IgE, immunoglobulin E; IgM, immunoglobulin M; IgA, immunoglobulin A.
[b] Multiple logistic regression analysis.
[c] Adjusted odds ratios (95% confidence interval) (all such values).
[d] Adjusted for baseline age, sex, body mass index, smoking status, drinking status, leukocyte count, Igs (each other), family history of cardiovascular disease, hypertension, hyperlipidemia, and diabetes.

IgA, which is the principal antibody class in the gastrointestinal secretions that bathe the mucosal surfaces, acts as an important first line of defense [35]. Results from the present study showed that serum levels of IgA were positively related to the prevalence of MetS. It also suggested that obesity and diabetes were associated very strongly with serum IgA [31,36,37]. One of our previous studies indicated that there was a positive relationship between IgA and hypertension [30]. In addition, elevated IgA levels in patients with obesity and metabolic syndrome could be of clinical importance in relation to IgA-related disorders such as IgA nephropathy [38,39]. A small-sample study has shown that IgA levels increased in patients with MetS [15], which was similar to our results. From these results, we speculate that IgA is related to a higher prevalence of MetS through these three components.

It is worth noting that the present study has several strengths. First, this was a recent, large population-based analysis using well-examined data, which strengthens the statistical reliability of the results. Second, we excluded the possibility that MetS is affected by other lifestyle variables that are intrinsically related to the concentration of Igs, such as age, sex, and drinking and smoking status, among others.

Presently, the study also has some limitations, which may cause inconvenience. First, because this is a cross-sectional study, further prospective studies and intervention trials should be undertaken to establish a causal relationship between Igs and MetS. Second, the study population comprised adult Asians, which may minimize confounding from race/ethnicity but limits the generalizability of results to other populations. Third, several inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) and cytokines are also associated with Igs [40,41] and MetS [42,43]. However, as we did not have complete data of hs-CRP and cytokine serum levels, we could not completely exclude the influence of these factors on the associations between Igs and the prevalence of MetS. Further detailed studies are needed to verify this issue.

Conclusions

In conclusion, this is the first report showing that decreased IgG and increased IgA are related to the higher prevalence of MetS in the adult population. These results suggested the Igs might be useful predictive factors for MetS. Further prospective epidemiological studies are needed in the future to investigate the impact of Igs levels on MetS incidence. Ultimately, such information will be crucial in developing novel antibody-based diagnostics for MetS.

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Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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