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Correlation Between Apolipoprotein M and Inflammatory Factors in Obese Patients

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Data Collection B
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Data Interpretation D
Manuscript Preparation E
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Background: The aim of this study was to observe apolipoprotein M (ApoM) level in obese patients and to explore its correlation with inflammatory factors.

Material/Methods: A total number of 96 participants were recruited and divided into 2 groups: the control group (or healthy group) whose participants had normal body weight (n=58), and the obese group with all its participants diagnosed with obesity (n=38). Data on blood pressure, body weight, height, body mass index, diastolic function of brachial artery endothelium, fasting venous blood glucose, blood lipids, plasmatic ApoM, interleukin-6 (IL-6), C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), fasting insulin, and adiponectin levels were collected for both groups.

Results: In the obese group, the levels of plasmatic ApoM, high-density lipoprotein cholesterol (HDL-C), and plasmatic adiponectin were significantly ($p<0.05$) decreased compared to the control group, and the levels of IL-6, TNF-α, CRP, and fasting insulin were significantly increased ($p<0.05$) compared to the control group. For the obese group, plasmatic ApoM level was positively correlated with HDL-C level and negatively correlated with levels of IL-6, TNF-α, CRP, insulin, and insulin resistance index. However, no significant correlations were revealed between plasmatic ApoM and the diastolic function of brachial artery endothelium, adiponectin level, blood pressure, and blood glucose level.

Conclusions: Obese patients showed significantly lower plasmatic ApoM levels than people with normal body weight, and ApoM level showed a strong correlation with CRP, TNF-α, and IL-6 levels, which indicated that ApoM might be regulated by these inflammatory factors.

MeSH Keywords: Anti-Inflammatory Agents • Apolipoproteins • Obesity

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Background

As the incidence of obesity keeps increasing, healthcare problems related to obesity have been among the major challenges that are drawing more and more international attention. High-density lipoprotein cholesterol (HDL-C) level is often detected as decreased in obese patients, but the mechanism is still unclear. Apolipoprotein M (ApoM), a newly identified apolipoprotein, has been reported to play an important role in the metabolism of HDL-C [1,2]. The ApoM gene is located in the MHC-III region of many inflammatory-related genes. Moreover, ApoM and its ligand sphingosine 1-phospate (S1P) exert important anti-inflammatory effects on HDL-C [2], which is a negative acute response protein during infection and inflammation. Additionally, obesity is a chronic inflammatory disease worldwide [3]. The objective of our study was to explore the mechanism by which HDL-C deficiency in blood is correlated with obesity via observing changes in ApoM levels in obese patients, and to explore the correlation between ApoM level and levels of inflammatory factors in the scenario of obesity.

Material and Methods

Objects of study

From April 2015 to January 2016, 112 participants who received physical examination at either Xiangya Hospital or Changsha Central Hospital were recruited in this study. Exclusion criteria were: (1) currently receiving any therapies that might affect the level of compounds in blood; (2) positive for hepatitis B surface antigen, (3) diagnosed with endocrine disorders, including diabetes mellitus (fasting plasma glucose (FPG) ≥7.0 mmol/L, or 2-h postprandial blood glucose ≥11.1 mmol/L), hypothyroidism, polycystic ovary syndrome, and Prader-Willi syndrome; (4) incomplete physical examination or blood biochemical analysis data; and (5) age 65 years and above or 25 years and below. Ninety-six participants were finally enrolled and divided into 2 groups: the control group (or healthy group) whose participants had normal body weight (n=58, aged 30–55 years), and the obese group diagnosed with obesity (n=38, aged 35–53 years). According to the diagnostic standards from the WHO, body mass index (BMI) <25 kg/m^2 was defined as normal, while BMI ≥25 kg/m^2 was defined as obesity. Blood pressure levels of all participants were obtained, and their BMI was calculated based on body weights and heights. Our study was approved by the Ethics Committee of the Xiangya Hospital of Central South University and complied with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from all participants enrolled in the study.

Testing procedures

Fasting venous blood samples of all participants were collected early in the morning. Plasma was extracted as the supernatant from blood samples after centrifugation and preserved at –20°C for plasmatic ApoM concentration measurement. Blood samples obtained from the elbow vein were analyzed via: (1) enzymic method to determine serum triglyceride (TG) and total cholesterol (TC), (2) chemical masking method to detect HDL-C and low-density lipoprotein cholesterol (LDL-C), and (3) immune transmission turbidimetry to determine hypersensitive C-reactive protein (hs-CRP), fasting blood glucose (FBS) level and fasting insulin level. Levels of plasmatic ApoM, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and adiponectin were determined by ELISA with the instruction attached to the kit of ELISA reagents. All measurements and analyses were performed under the supervision of specialized clinical laboratory staffs.

Calculation for insulin resistance index

In our study, insulin resistance index (HOMA-IR) was used to evaluate the extent of insulin resistance, which was calculated by the following formula:

[fasting blood glucose concentration (mmol/L) × fasting insulin concentration (mIU/L)]/22.5.

Determination of endothelium-dependent diastolic function mediated by brachial artery blood flow

According to the method recommended by Celermajer [4] and others, in the morning when the participant did not take any foods or medications, the reactive hyperemia test was performed after the participant's brachial artery diameter (D0) was obtained. When performing the reactive hyperemia test, the sphygmomanometer cuff was placed at the distal end of the chosen artery, inflated to reach a pressure of 300 mmHg, and deflated at the 4th min. Within 60 to 90 s, brachial artery diameter (D1) was measured after the deflation. Endothelium-dependent diastolic function (FMD) mediated by brachial artery blood flow=(D1–D0)/D0×100%.

Statistical analysis

All experimental data are shown in the form of 'mean ± standard deviation (x±s)' and analyzed via SPSS15.0 software. Comparison between mean values of 2 groups were performed with 2-sample *t* test, while one-way ANOVA was used for in-group comparisons. Linear correlation analysis (Pearson correlation coefficient) was used in correlative analyses, with *p*-value lower than 0.05 as the statistical significance threshold for the results.

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Table 1. Basic characteristics of participants according to gender.

Variables	Control group (n=58)			Obese group (n=38)		
	Total (n=58)	Men (n=45)	Women (n=13)	Total (n=38)	Men (n=28)	Women (n=10)
Age (yr)	44.22±8.71	46.42±7.63	42.51±9.04	44.81±5.63	43.55±4.28	45.67±5.88
BMI (kg/m^2)	21.92±2.05	22.03±1.95	20.97±2.17	26.70±3.32*	26.90±4.32	25.90±3.50
Systolic blood pressure (mmHg)	115.67±17.21	117.16±19.87	114.92±15.24	129.81±12.95*	129.17±11.75	128.70±13.78
Diastolic blood pressure (mmHg)	77.53±9.88	75.33±7.54	77.87±8.77	87.24±11.83*	86.19±10.79	87.91±13.75
Blood glucose (mmol/L)	5.17±0.42	5.19±0.52	5.16±0.35	5.57±1.07	5.59±1.71	5.54±1.13
TC (mmol/L)	4.62±0.73	4.57±0.51	4.68±0.81	4.68±0.82	4.69±0.67	4.68±0.67
TG (mmol/L)	1.47±0.53	1.46±0.47	1.47±0.23	1.92±0.74*	1.92±0.76	1.92±0.56
HDL-C (mmol/L)	1.35±0.23	1.35±0.33	1.36±0.24	1.02±0.25*	1.02±0.27	1.02±0.45
LDL-C (mmol/L)	2.61±0.63	2.59±0.55	2.61±0.65	2.79±0.71	2.80±0.50	2.79±0.54
Hs-CRP (mg/L)	1.70±0.36	1.69±0.24	1.70±0.38	3.95±1.04*	3.96±1.02	3.95±1.19
IL-6 (pg/ml)	340.71±87.30	340.01±80.53	339±89.12	470.20±110.23*	472.10±107.83	468.00±108.93
TNF-**a** (ng/ml)	3.48±0.19	3.49±0.20	3.48±0.15	4.97±1.32*	4.97±1.79	4.98±1.05
Adiponectin (mg/L)	9.53±2.89	9.57±2.17	9.52±2.79	5.32±1.13*	5.31±1.05	5.33±1.09
ApoM	12.38±2.03	12.18±2.77	12.53±2.54	9.87±1.54*	9.86±1.51	9.87±1.57
FMD (%)	13.23±1.77	13.17±1.87	13.59±2.94	8.76±1.23*	8.77±1.17	8.75±1.15
Insulin (mIU/L)	5.83±2.01	5.79±3.09	5.89±2.05	8.79±1.52*	8.78±1.86	8.79±1.76
HOMA-IR	1.33±0.34	1.35±0.33	1.32±0.22	2.17±0.58*	2.16±0.76	2.18±0.79

* Compared with control group, $p<0.05$. ApoM – apolipoprotein M; BMI – body mass index; FMD – endothelium-dependent diastolic function; HDL-C – high-density lipoprotein cholesterol; HOMA- IR – insulin resistance index; Hs-CRP – hypersensitive C-reactive protein; IL-6 – interleukin-6; LDL-C – low-density lipoprotein cholesterol; TC – total cholesterol; TG – triglyceride; TNF-α – tumor necrosis factor-α.

Results

As shown in Table 1, no significant differences in age, sex ratio, TC, LDL-C, or blood glucose levels were found between control group and obese group. Compared to the control group, participants in the obese group had significantly higher body mass index, blood pressure, TG, hs-CRP, IL-6, TNF-α, insulin, and HOMA-IR levels, and lower HDL-C, adiponectin, and ApoM levels.

ApoM level and its correlations with BMI, insulin, HOMA-IR, adiponectin, blood pressure, and blood glucose levels

As shown in Table 2, in the obese group, ApoM level was negatively correlated with BMI, insulin level, and HOMA-IR, but was not significantly associated with adiponectin, blood pressure, or blood glucose levels. In the control group, ApoM was negatively correlated with BMI, but was not significantly

Table 2. ApoM level and its correlations with BMI, insulin, HOMA-IR, adiponectin, blood pressure, and blood glucose levels.

Variables	Control group (n=58)	Obese group (n=38)
BMI	–0.53*	–0.57*
Adiponectin	0.07	0.03
Blood pressure	0.02	0.04
Blood glucose	0.11	0.05
Insulin	–0.07	–0.53*
HOMA-IR	–0.03	–0.56*

* Compared with control group, $p<0.05$. ApoM – apolipoprotein M; BMI – body mass index; HOMA- IR – insulin resistance index.

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Table 3. ApoM level and its correlation with blood lipids levels.

Variables	Control group (n=58)	Obese group (n=38)
HDL-C	0.54*	0.57*
TC	0.01	0.03
LDL	0.02	0.03
TG	0.06	0.04

* Compared with control group, $p<0.05$. ApoM – apolipoprotein M; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; TC – total cholesterol; TG – triglyceride.

Table 4. ApoM level and its correlations with hs-CRP, IL-6, TNF-α and FMD levels.

Variables	Control group (n=58)	Obese group (n=38)
Hs-CRP	–0.04	–0.47*
IL-6	–0.07	–0.52*
TNF-α	–0.03	–0.36*
FMD (%)	0.05	0.11

* Compared with control group, $p<0.05$. ApoM – apolipoprotein M; FMD – endothelium-dependent diastolic function; Hs-CRP – hypersensitive C-reactive protein; IL-6 – interleukin-6; TNF-α – tumor necrosis factor-α.

associated with levels of adiponectin, blood pressure, blood glucose, insulin, and HOMA-IR. The correlation between ApoM and the group of BMIs ≥30 kg/m^2 was not analyzed because of the small number of participants (6 people) in that group.

ApoM level and its correlation with blood lipids levels

As shown in Table 3, in the obese group, ApoM level showed a positive correlation with HDL-C level, but no significant correlations with ApoM and TC, LDL-C, or TG levels. In the control group, ApoM levels showed a positive correlation with HDL-C level, but no significant correlations with ApoM and TC, LDL, TG levels.

ApoM level and its correlations with hs-CRP, IL-6, TNF-α, and FMD levels

As shown in Table 4 and Figures 1–3, in the obese group, ApoM level was negatively correlated with hs-CRP, IL-6, and TNF-α levels, but was not significantly correlated with FMD. In the control group, ApoM was not significantly correlated with hs-CRP, IL-6, TNF-α, or FMD levels.

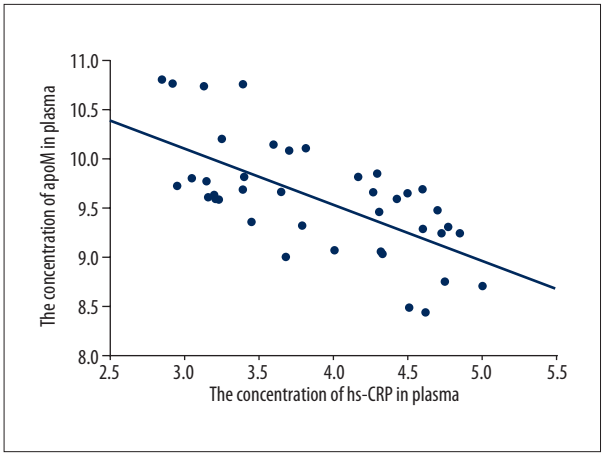

Figure 1. Correlative analysis of ApoM level and hs-CRP level in serum of the obese group.

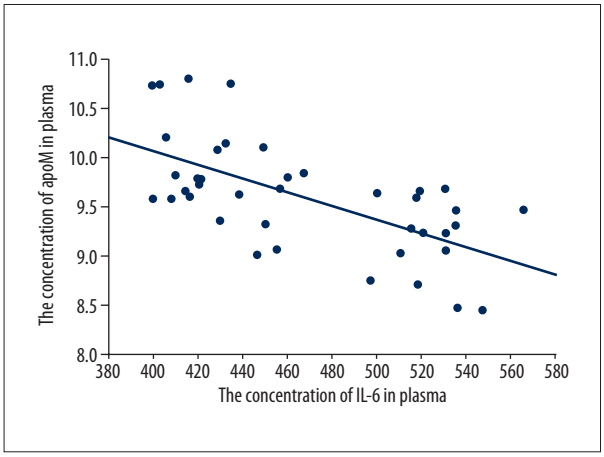

Figure 2. Correlative analysis of ApoM level and IL-6 level in serum of the obese group.

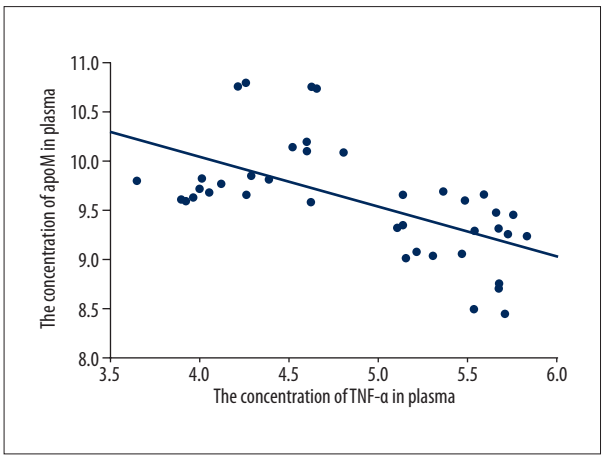

Figure 3. Correlative analysis of ApoM level and TNF-α level in serum of the obese group.

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Discussion

Disorders in lipid metabolism and dyslipidemia, especially the decreased HDL-C level, are commonly seen in obese patients. In our study, the HDL-C level in the obese group was significantly decreased compared to the control group. It has been confirmed by numerus studies that obesity is a chronic inflammatory disease [3], and inflammation might contribute to the decreased HDL-C level and abnormal HDL structure and function [5], but it still remains unclear why HDL-C deficiency in blood is usually found in obese patients. ApoM is a newly discovered apolipoprotein associated with HDL; overexpression of its gene has been shown to result a significant increase in HDL-C level in mouse plasma. Silencing of the ApoM gene can decrease the plasmatic HDL-C level by about 25%, and even cause complete disappearance of pre-β-HDL, which is the primary form of HDL during its maturation. Therefore, ApoM might play an essential role in HDL metabolism [1]. Some other studies also proved that ApoM polymorphism was associated with HDL metabolism in obese patients [2]. Our study showed a significant decline in plasmatic ApoM and HDL-C levels in obese patients, and the plasmatic ApoM level was positively correlated with HDL-C level, which might indicate that, as an important apolipoprotein of HDL, the decreased level of ApoM due to its abnormal metabolism, might contribute in the decreased level of HDL-C in obese patients. However, given the complexity of HDL metabolism, the extent to which ApoM could affect HDL-C levels in obese patients still remains to be determined.

Apart from energy storage, adipose tissue could also have some endocrinal functions [6-8], including the secretion of inflammatory factors like TNF-α and IL-6. Excessive TNF-α and IL-6 could promote hepatic CRP synthesis. These inflammatory factors are involved in the maintenance of numerous physiological functions of the body, including the regulation of insulin, the metabolism of sugar and lipids, and the control of inflammatory responses. Studies showed that the levels of CRP, TNF-α, and IL-6 in the blood were significantly decreased in obese patients [9]. The gene encoding for ApoM is located in the MHc-III region of chromosome 6, in which many other genes are associated with inflammatory responses *in vivo*. The concentration of plasmatic ApoM in patients with sepsis or systemic inflammatory response syndrome is significantly reduced, and the extent of such a decrease in ApoM level could indicate the severity of these diseases [10]. Our study revealed that the levels of CRP, TNF-α, and IL-6 in obese patients were significantly increased and ApoM level was negatively correlated with levels of CRP, TNF-α, and IL-6, which for the first time provides strong evidence that ApoM level is closely involved in inflammation in the scenario of obesity, indicating that ApoM level might be regulated by inflammatory factors.

TNF and IL-1 can reduce ApoM mRNA level in mice *in vivo* [11], and *in vitro* experiments also confirmed that the expression and secretion of ApoM of hepatocytes can be reduced by TNF and IL-1. Lipopolysaccharide can reduce ApoM level in hepatocytes via down-regulating the expression of hepatocyte nuclear factors-1α (HNF-1α), a highly efficient transcription activator for the gene encoding ApoM [12]. Therefore, we speculated that CRP, TNF-α, and IL-6 might regulate the expression of ApoM through the HNF-1α pathway, but this requires further validation. Studies showed that CRP and IL-6 can promote insulin resistance [13,14], which, similar to hyperinsulinemia, could allow insulin to inhibit expression and secretion of ApoM [15]. Adipose tissue is the origin of insulin resistance, and obesity is often accompanied by insulin resistance of cells [16]. Our study showed that insulin sensitivity was significantly lower in obese patients, and ApoM level was negatively correlated with insulin resistance index. Therefore, we speculated that the influence of inflammatory factors on ApoM in obesity might be related to insulin resistance.

Wolfrum [5] and other researchers injected adenovirus expressing recombinant ApoM into LDL receptor-deficient mice fed a high cholesterol diet and found that HDL-C in plasma was increased by 40%, and the average lesion area of atherosclerosis in the aortic root and thoracic aorta was decreased by about 28% and 31%, respectively. This suggested that ApoM could significantly prevent the formation of atherosclerotic lesions due to high cholesterol in LDL receptor-deficient mice. Plasmatic ApoM levels in patients with coronary heart disease were significantly lower than in a control group of healthy people, indicating that ApoM could be used as a biomarker for coronary heart disease [17]. In this study, we investigated the correlation between ApoM and vascular endothelium diastolic function, an early indicator of atherosclerosis, and concluded that vascular endothelial diastolic function in obese patients was decreased but was not significantly correlated with ApoM. Although speculated to have anti-atherosclerotic characteristics, ApoM is still not validated as an early predictor of atherosclerosis. Our study failed to reveal any correlations between ApoM level and adiponectin, blood pressure, or blood glucose levels.

There are certain limitations to this study that deserve mention. Firstly, the sample size of our study is relatively small, which might have affected accuracy of the results. Thus, further research with larger samples is needed to confirm our findings. Secondly, the changes in ApoM and its relationship with inflammatory factors in obese patients after losing weight have not been thoroughly studied. Finally, recent studies show that ApoM is the main carrier of S1P, and many anti-inflammatory and anti-atherosclerotic effects of HDL are achieved by the ApoM-S1P axis [18]. Future studies should focus on the association of S1P, ApoM, and inflammatory factors in obese patients.

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Conclusions

Plasmatic ApoM and HDL-C were both decreased significantly in obese patients, and they were positively correlated, as supported by statistical analysis. The decline of ApoM level might be one of the underlying mechanisms by which HDL-C deficiency in blood occurs with obesity. ApoM level is closely related to CRP, TNF-α, and IL-6 levels, suggesting that ApoM might be regulated by these inflammatory factors.

Conflicts of interest

None.

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