KMJ THE KITAKANTO MEDICAL JOURNAL 2016；66： 1～6

Original

Serum Apolipoprotein M Levels are Correlated with Biomarkers of Coagulation

Kensuke Yoshida[1], Takao Kimura[1], Tomo Shimizu[2], Koichi Sato[3], Tomoyuki Aoki[1], Hiroyuki Sumino[1], Katsuhiko Tsunekawa[1], Osamu Miyazaki[2], Isamu Fukamachi[2], Katsuyuki Nakajima[1], Fumikazu Okajima[3] and Masami Murakami[1]

1 Department of Clinical Laboratory Medicine, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan
2 SEKISUI MEDICAL CO., LTD., 3-3-1 Koyodai, Ryugasaki, Ibaraki 301-0852, Japan
3 Laboratory of Signal Transduction, Institute for Molecular and Cellular Regulation, Gunma University, 3-39-15 Showa-machi, Maebashi, Gunma 371-8511, Japan

Abstract

Background: Apolipoprotein M (ApoM) is bound to high-density lipoprotein (HDL) in plasma, and HDL has anticoagulation effects. However, the association between ApoM and biomarkers of coagulation was unclear. Therefore, we investigated relationships between ApoM and biomarkers of coagulation.

Methods: Serum samples from 233 Japanese participants including with diabetes mellitus, hypertension, dyslipidemia, or healthy controls were analyzed. Serum ApoM levels were measured using Enzyme-Linked Immuno-Sorbent Assay (ELISA).

Results: Analysis of all 233 participants showed that ApoM levels were positively correlated with age ($r=0.284$, $p<0.001$), total cholesterol (TC; $r=0.477$, $p<0.001$), HDL-cholesterol (HDL-C; $r=0.234$, $p<0.001$) and low-density lipoprotein cholesterol (LDL-C; $r=0.331$, $p<0.001$). Higher ApoM levels were correlated with shorter activated partial thromboplastin time (APTT; $r=-0.226$, $p=0.001$) and prothrombin time (PT, %; $r=0.326$, $p<0.001$). Separate analysis of the 115 healthy controls showed that ApoM levels were positively correlated with age, TC, HDL-C and LDL-C, and higher ApoM levels were correlated with shorter PT.

Conclusion: Serum levels of ApoM may influence biomarkers of coagulation.

Article Information

Key words:
apoliporpotein M,
coagulation,
activated partial thromboplastin time,
prothrombin time

Publication history:
Received: December 7, 2015
Revised: December 25, 2015
Accepted: January 5, 2016

Corresponding author:
Takao Kimura, MD, PhD
Department of Clinical Laboratory Medicine, Gunma University Graduate School of Medicine 3-39-15, Showa-machi, Maebashi, Gunma 371-8511, Japan
Tel: +81-27-220-8576
E-mail: tkimura@gunma-u.ac.jp

Introduction

Higher levels of blood lipid have been linked to increased coagulation factors, and shorter activated partial thromboplastin time (APTT) and prothrombin time (PT).[1-5] Fat intake was shown to be associated with increased levels of coagulation factors.[6,7] On the other hand, high-density lipoprotein (HDL) regulates anticoagulation through inactivation of coagulation factors Va and VIIa.[8] HDL-C is inversely related to levels of prothrombin fragment F1+2 and D-dimer.[9] HDL modulates platelet reactivity, coagulation, and endothelial function.[8-11] HDL modulates endothelial function via HDL-associated sphingosine 1-phosphate (S1P)/S1P specific receptors and via apolipoprotein A (apoA)/scavenger receptor class B type I (SR-BI).[12] Apolipoprotein M (ApoM), which is highly associated with HDL, was recently reported to be a major carrier of S1P in plasma.[13] HDL-associated S1P bound to ApoM has a protective effect on the endothelium[14], and an animal study suggested an antiatherosclerotic role for ApoM.[15] Lower levels of ApoM have been observed in patients with critical limb ischemia[16] and lower levels of HDL are associated with higher risk of recurrent venous thromboembolism (VTE).[17] Memon et al.[18] recently reported that the levels of ApoM in recurrent VTE may differ according to gender, and that

lower levels of ApoM may predict VTE recurrence in male patients. Although these reports indicate that HDL-associated ApoM has an antithrombotic effect, the role of ApoM in coagulation remains unclear. In this study, we investigated the possible role of ApoM in modulating coagulation, and examined whether serum ApoM may influence biomarker of coagulation.

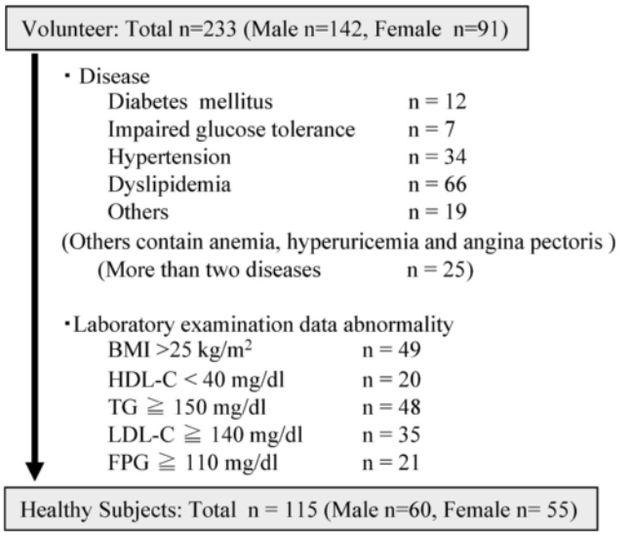

Fig. 1 Selection of healthy controls. Two hundred thirty-three Japanese participants, including participants with diabetes mellitus (n = 19), hypertension (n = 34), or dyslipidemia (n = 66), and healthy control subjects (n = 115) voluntarily enrolled in this study. The 115 healthy controls had no disease or illness, were not taking medicine, had normal laboratory test results for HDL-C (> 40 mg/dl), TG (< 150 mg/dl), LDL-C (< 140 mg/dl), FPG (< 110 mg/dl), and were not obese (BMI < 25 kg/m²).

Material and Methods

1. Study population

The study recruited 233 Japanese participants (mean age; 37.2 ± 15.0). All participants were voluntarily enrolled in the study and included participants with diabetes mellitus (n = 12), impaired glucose tolerance (n=7), hypertension (n = 34), or dyslipidemia (n = 66), and healthy controls (n = 115). Twenty-five participants suffered from diseases more than two. Healthy controls had no disease or illness, were not taking any medicine, and had no abnormal laboratory test results. They were excluded as healthy controls if they had HDL-cholesterol < 40 mg/dl, triglycerides (TG) > 150 mg/dl, low density lipoprotein-cholesterol (LDL-C) > 140 mg/dl, fasting plasma glucose (FPG) > 110 mg/dl, or body mass index (BMI) > 25 kg/m². Finally, 115 participants were chosen as healthy controls (Fig. 1). Characteristics of the entire group of 233 participants (healthy controls and participants with diabetes mellitus, impaired glucose tolerance, hypertension, and dyslipidemia) and the 115 healthy controls are summarized in Table 1A and B, respectively. This study was approved by the Ethics Committee of Gunma University Graduate School of Medicine. Informed consent was obtained from all participants.

2. Clinical examination and laboratory investigations

In the morning after a 12-hour fast, anthropometric measurements were performed and blood samples were collected into three polypropylene tubes for serum and plasma analyses. Blood samples were obtained by antecubital venous puncture using 23 G needles while the participant was seated. Serum samples from all 233 participants were analyzed. Total cholesterol (TC), HDL-C, LDL-C, and TG were measured using a Hitachi LABOSPECT 008 (Hitachi, Tokyo, Japan). PT and APTT were determined using a Sysmex CS-5100 analyzer (Sysmex). PT was described as the percentage of a control value. Serum

Table 1A Characteristics of 233 volunteers including healthy controls, diabetes mellitus, dyslipidemia and hypertension.

Characteristics	Total	Male	Female	*p*
Number (n)	233	142	71	
Age (year)	37.18 ± 14.99	36.11 ± 14.77	38.86 ± 15.27	0.088
Height (cm)	165.93 ± 9.01	171.14 ± 6.5	157.79 ± 5.76	<0.001 *
Weight (kg)	62.39 ± 13.14	69.07 ± 10.93	51.96 ± 8.8	<0.001 *
BMI (kg/m²)	22.51 ± 3.66	23.58 ± 3.55	20.85 ± 3.19	<0.001 *
Apolipoprotein M (mg/ml)	22.97 ± 4.59	22.52 ± 4.68	23.66 ± 4.37	0.031 *
Total cholesterol (mg/dl)	198.24 ± 37.51	193.77 ± 36.1	205.21 ± 38.8	0.013 *
HDL-C (mg/dl)	59.96 ± 14.1	55.49 ± 13.3	66.93 ± 12.43	<0.001 *
LDL-C (mg/dl)	111.88 ± 33.73	111.1 ± 34.22	113.1 ± 33.1	0.329
LDL-C/HDL-C ratio	2.01 ± 0.87	2.15 ± 0.89	1.79 ± 0.79	0.001 *
Triglycerides (mg/dl)	103.99 ± 82.18	115.37 ± 93.7	86.23 ± 55.93	0.002 *
Non-HDL-C (mg/dl)	138.28 ± 38.77	138.28 ± 37.66	138.27 ± 40.67	0.499
Prothrombin time (%)	101.79 ± 10.83	100.21 ± 10.8	104.26 ± 10.47	0.002 *
APTT (sec)	32.28 ± 3.36	31.69 ± 3.3	33.2 ± 3.24	<0.001 *
Fibrinogen (mg/dl)	246.73 ± 56.9	237.96 ± 55.73	260.42 ± 56.29	0.002 *

APTT: activated partial thromboplastin time. Value are mean ± SD.* Statistical significance ($p < 0.05$).

Table 1B Characteristics of 115 healthy controls.

Characteristics	Total	Male	Female	*p*
Number (n)	115	60	55	
Age (year)	28.43 ± 8.65	26.48 ± 6.53	30.56 ± 10.12	0.006 *
Height (cm)	166.25 ± 9.42	173.44 ± 5.6	158.42 ± 5.77	<0.001 *
Weight (kg)	57.21 ± 9.64	64.58 ± 6.37	49.17 ± 5.07	<0.001 *
BMI (kg/m²)	20.55 ± 1.77	21.45 ± 1.63	19.57 ± 1.35	<0.001 *
Apolipoprotein M (μg/ml)	21.92 ± 4.28	21.13 ± 4.16	22.78 ± 4.28	0.02 *
Total Cholesterol (mg/dl)	185.43 ± 29.74	180.65 ± 27.37	190.65 ± 31.55	0.037 *
HDL-C (mg/dl)	66.38 ± 10.64	62.57 ± 10	70.55 ± 9.79	<0.001 *
LDL-C (mg/dl)	98.37 ± 24.52	96.98 ± 23.72	99.89 ± 25.5	0.265
LDL-C/HDL-C ratio	1.52 ± 0.44	1.59 ± 0.47	1.43 ± 0.4	0.026 *
Triglycerides (mg/dl)	67.36 ± 26.28	73.5 ± 29.65	60.65 ± 20.23	0.004 *
Non-HDL-C (mg/dl)	119.05 ± 26.71	118.08 ± 25.68	120.11 ± 27.99	0.344
Prothrombin time (%)	98.94 ± 10.86	96.63 ± 10.81	101.45 ± 10.45	0.008 *
APTT (sec)	33.23 ± 3.28	32.54 ± 3.22	33.99 ± 3.19	0.008 *
Fibrinogen (mg/dl)	229.65 ± 46.37	221.17 ± 47.54	238.91 ± 43.62	0.02 *

APTT: activated partial thromboplastin time. Value are mean±SD.* Statistical significance ($p < 0.05$).

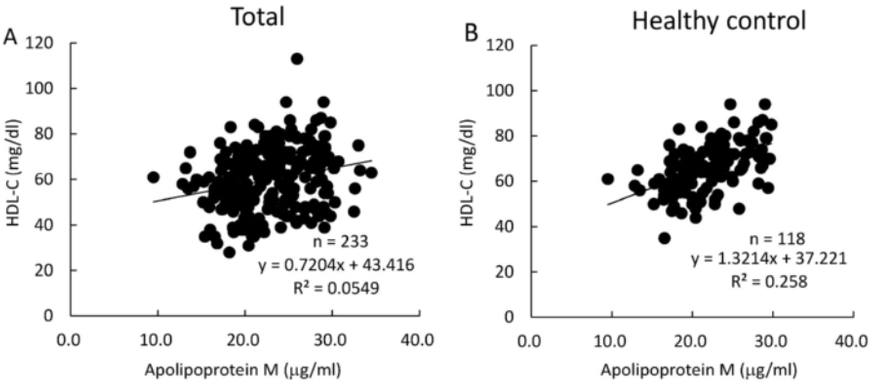

Fig. 2 Correlations of serum apolipoprotein M (ApoM) concentration with high density lipoprotein cholesterol (HDL-C) concentration in all participants and healthy controls. Serum ApoM concentration was positively correlated with HDL-C concentration (A) and in all participants. Serum ApoM concentration was positively correlated with HDL-C concentration (B) in healthy controls.

ApoM levels were determined using sandwich Enzyme-Linked Immuno-Sorbent Assay (ELISA). BMI was calculated as weight (kg)/(height (m)×height (m)).

3. Statistical analysis

Data are expressed as means±standard deviation (SD). Simple regression analysis was used to assess the relationship between serum apoM concentration and the various factors. All probability values are two-tailed. A value of $p < 0.05$ was accepted as indicating statistical significance.

Results

1. Results for all 233 participants, including healthy participants, and those with diabetes mellitus, dyslipidemia, and hypertension

The physical characteristics and laboratory findings for all 233 participants, including healthy controls and participants with diabetes mellitus, impaired glucose tolerance, dyslipidemia, or hypertension, are shown in Table 1A. Height, weight, BMI, LDL-C/HDL-C ratio, and TG of male participants were significantly higher compared with those of female participants. Conversely, ApoM levels, TC, HDL-C, PT (%), APTT, and fibrinogen levels of male participants were significantly lower compared with those of female participants. Nine of 66 subjects with dyslipidemia were treated by lipid lowering therapy, 6 subjects were treated by statin, 2 subjects were treated by ezetimibe and one subject was treated by fibrate. Six subjects treated by statin and one subject treated by ezetimibe showed normal levels of TC, HDL-C, LDL-C and TG, however, other 2 subjects showed higher levels of TG.

Single linear regression analysis of serum ApoM and physical and biochemical parameters among all participants, including healthy controls, is shown in Table 2A. Among all participants (male and female), serum ApoM levels were positively correlated with age ($r = 0.284$, $p < 0.001$), but not with height, weight, or BMI. Serum ApoM levels were also positively correlated with lipid-related parameters TC ($r = 0.477$, $p < 0.001$), HDL-C ($r = 0.234$, $p < 0.001$), LDL-C ($r = 0.331$, $p <$

Table 2A A single liner regression analysis of serum apolipoprotein M and the various factors among 233 volunteers including healthy controls, diabetes mellitus, dyslipidemia and hypertension.

Analyte	Total		Male		Female	
	r	*p*	*r*	*p*	*r*	*p*
Age (year)	0.284	<0.001 *	0.247	0.003 *	0.325	0.002 *
Height (cm)	−0.119	0.069	−0.035	0.681	−0.069	0.516
Weight (kg)	−0.066	0.318	0.076	0.371	−0.112	0.289
BMI (kg/m²)	−0.024	0.712	0.088	0.298	−0.103	0.333
Total cholesterol (mg/dl)	0.477	<0.001 *	0.506	<0.001 *	0.412	<0.001 *
HDL-C (mg/dl)	0.234	<0.001 *	0.185	0.028 *	0.24	0.022 *
LDL-C (mg/dl)	0.331	<0.001 *	0.36	<0.001 *	0.279	0.007 *
LDL-C/HDL-C ratio	0.107	0.102	0.154	0.067	0.099	0.349
Triglycerides (mg/dl)	0.122	0.062	0.111	0.187	0.257	0.014 *
Non-HDL-C (mg/dl)	0.377	<0.001 *	0.419	<0.001 *	0.319	0.002 *
Prothrombin time (%)	0.326	<0.001 *	0.323	<0.001 *	0.292	0.005 *
APTT (sec)	−0.226	0.001 *	−0.339	<0.001 *	−0.128	0.226
Fibrinogen (mg/dl)	0.106	0.106	0.044	0.601	0.153	0.148

APTT: activated partial thromboplastin time.* Statistical significance ($p < 0.05$). Shaded columns: $p < 0.05$

Table 2B A single liner regression analysis of serum apolipoprotein M and the various factors among 115 healthy controls.

Analyte	Total		Male		Female	
	r	*p*	*r*	*p*	*r*	*p*
Age (year)	0.277	0.003 *	−0.016	0.904	0.427	0.001 *
Height (cm)	−0.141	0.132	0.052	0.693	−0.01	0.942
Weight (kg)	−0.134	0.153	0.111	0.4	−0.066	0.634
BMI (kg/m²)	−0.097	0.304	0.089	0.499	−0.097	0.479
Total cholesterol (mg/dl)	0.428	<0.001 *	0.39	0.002 *	0.428	0.001 *
HDL-C (mg/dl)	0.478	<0.001 *	0.377	0.003 *	0.521	<0.001 *
LDL-C (mg/dl)	0.249	0.007 *	0.256	0.048 *	0.229	0.093
LDL-C/HDL-C ratio	−0.024	0.8	0.036	0.786	−0.019	0.889
Triglycerides (mg/dl)	0.074	0.435	0.099	0.452	0.177	0.196
Non-HDL-C (mg/dl)	0.286	0.002 *	0.269	0.038 *	0.3	0.026 *
Prothrombin time (%)	0.22	0.018 *	0.107	0.414	0.27	0.046 *
APTT (sec)	−0.145	0.122	−0.344	0.007 *	−0.039	0.775
Fibrinogen (mg/dl)	0.101	0.282	−0.019	0.888	0.166	0.227

APTT: activated partial thromboplastin time.* Statistical significance ($p < 0.05$). Shaded columns: $p < 0.05$

0.001), but not with TG. Higher ApoM levels were associated with shorter PT ($r = 0.326$, $p < 0.001$) and APTT ($r = -0.226$, $p < 0.001$). Serum ApoM levels were positively correlated with TG only among female participants (Table 2A). Figure 2 showed that serum ApoM concentration was positively correlated with HDL-C concentration (Fig. 2A) in all participants. These results suggest that serum ApoM levels may differ according to gender and that ApoM levels reflected and/or influenced coagulation in all participants, including those with diabetes mellitus, dyslipidemia, or hypertension, and healthy controls.

Single linear regression analysis of lipid parameters and biomarkers of coagulation among all participants, including healthy controls, is shown in Table 3A. Higher TC levels were correlated with higher levels of fibrinogen and shorter APTT and PT. Similar results were found for LDL-C and TG. Higher levels of LDL-C were correlated with higher levels of fibrinogen and shorter APTT. Higher TG levels were correlated with higher fibrinogen levels, shorter APTT and PT. Conversely, higher levels of HDL-C were correlated with lower levels of fibrinogen and longer APTT. These results suggest that in all participants, including those with diabetes mellitus, hypertension, or dyslipidemia, and healthy participants, TC, LDL-C, and TG simultaneously influenced coagulation, and that HDL-C inhibited the coagulation cascade.

2. Results for the 115 healthy controls

The physical characteristics and laboratory findings for the 115 healthy controls are shown in Table 1B. Height, weight, BMI, LDL-C/HDL-C ratio, and TG of male healthy controls were significantly higher compared with those of female healthy controls. ApoM, TC, HDL-C, and age of male healthy controls were significantly lower compared with those of female healthy controls. Coagulation markers such as PT,

Table 3A A single liner regression analysis of lipid parameters and biomarkers of coagulation among 233 volunteers including healthy controls, diabetes mellitus, dyslipidemia and hypertension.

Analyte	TC		HDL-C		LDL-C		Triglycerides	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Prothrombin time (%)	0.19	0.004 *	-0.003	0.962	0.115	0.08	0.262	<0.001 *
APTT (sec)	−0.226	0.001 *	0.166	0.011 *	−0.23	<0.001 *	−0.305	<0.001 *
Fibrinogen (mg/dl)	0.287	<0.001 *	−0.151	0.021 *	0.285	<0.001 *	0.156	0.017 *

APTT: activated partial thromboplastin time * Statistical significance ($p < 0.05$). Shaded columns: $p < 0.05$

Table 3B A single liner regression analysis of lipid parameters and biomarkers of coagulation among 115 healtyhy controls.

Analyte	TC		HDL-C		LDL-C		Triglycerides	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Prothrombin time (%)	0.111	0.237	0.154	0.1	0.047	0.616	0.126	0.181
APTT (sec)	−0.182	0.052	0.074	0.432	−0.232	0.013 *	−0.232	0.012 *
Fibrinogen (mg/dl)	0.104	0.269	0.019	0.844	0.089	0.342	0.053	0.574

APTT: activated partial thromboplastin time * Statistical significance ($p < 0.05$). Shaded columns: $p < 0.05$

APTT, and fibrinogen levels of male healthy controls were significantly lower compared with those of female healthy controls.

Single linear regression analysis of ApoM and physical and biochemical parameters among the 115 healthy controls is shown in Table 2B. Serum ApoM levels were positively correlated with TC, HDL-C, LDL-C, and non-HDL-C. Higher ApoM levels were correlated with shorter PT. For male healthy controls only, higher ApoM levels were correlated with shorter APTT. For female healthy controls only, ApoM levels positively correlated with age, and higher ApoM levels correlated with shorter PT. These results suggest that serum ApoM levels reflected and/or influenced the activity of coagulation in healthy controls.

Single linear regression analysis of lipid parameters and biomarkers of coagulation among the 115 healthy controls is shown in Table 3B. No association was found between TC and biomarkers of coagulation. Higher values of LDL-C were correlated with shorter APTT. Higher TG levels were correlated with shorter APTT. Figure 2 showed that serum ApoM concentration was positively correlated with HDL-C concentration (Fig. 2B) in healthy controls.

Discussion

This study demonstrated that serum ApoM levels were positively related to biomarkers for coagulation in a group of Japanese subjects including patients with diabetes mellitus, hypertension, or dyslipidemia, and healthy controls. These findings were unexpected results. In plasma, ApoM is mainly bound to HDL.[13,19–21] HDL regulates anticoagulation through inactivation of coagulation factors Va and VIIa.[8] HDL-C is inversely related to levels of prothrombin fragment F1+2 and D-dimer.[9] Expectedly, the positive correlation between ApoM levels and HDL-C levels identified in line with previous findings,[13,19–21] and HDL-C levels were related to coagulation, higher levels of HDL-C correlated with lower fibrinogen levels and longer APTT. These findings suggest that HDL-C influenced anticoagulation activity. However, higher serum ApoM levels were correlated with shorter values of PT and APTT. These results could be partially explained by the close correlation serum ApoM levels and lipid parameters. Previous reports demonstrated that close correlations between ApoM levels and lipid parameters.[19–21] In this study we confirmed that serum ApoM levels were positively correlated with HDL-C, TC and LDL-C in line with previous reports.[19–21] When all 233 participants were included in the analysis, TC and LDL-C levels were positively correlated with fibrinogen levels, and were correlated with shorter APTT, and higher TC levels were correlated with shorter PT. These results agree with those reported in previous studies. Higher levels of blood lipid have been linked to increased coagulation factors, and shorter PT and APTT.[1–5] Fat intake was shown to be associated with increased levels of coagulation factors.[6,7] These previous findings suggest that higher levels of blood lipid are linked to increased coagulation activity. Statin treatment decreases blood lipid levels and hypercoagulability.[22–24] On the other hand, Kappelle et al reported that plasma ApoM was lowered by statin treatment.[25] Statin-induced decrease in ApoM and a positive correlation between ApoM and LDL-C observed in their study were partly explained by the hypothesis that high plasma ApoM was linked with slow turnover of plasma LDL receptor,[26,27] and that plasma clearance of ApoM was influenced by LDL receptor-mediated clearance of apoB-containing particles.[26,27] As well as serum TC and LDL-C levels, higher serum ApoM levels were correlated with shorter PT and APTT when all 233 participants were included in the analysis. In the healthy controls, ApoM levels were correlated with shorter PT. Higher ApoM levels were correlated with shorter APTT in male participants, but not in female participants. These results suggest that ApoM levels influenced coagulation in participants with metabolic disorders and/or hypertension and in healthy controls, and that influence of

ApoM in coagulation cascade may differ according to gender. Serum levels of ApoM, TC, LDL–C, and TG were positively related to biomarkers of coagulation, whereas HDL–C was inversely related to coagulation. These previous reports and the present results suggest that modulation of ApoM is a potential therapeutic target for thrombogenic diseases.

In conclusion, serum ApoM levels were correlated with biomarkers of coagulation. Further study is needed to clarify the physiological role of ApoM in coagulation.

Limitations

This study was a cross-sectional study with a relatively small number participants performed in a single unit. A prospective study including larger participants is necessary to confirm the physiological role of ApoM in coagulation.

Disclosure Statement

There was no conflict of interest that has affected the results of this study. The institutional ethics committee approved this study.

References

1. Branchi A, Rovellini A, Sommariva D, et al. Effect of three fibrate derivatives and of two HMG–CoA reductase inhibitors on plasma fibrinogen level in patients with primary hypercholesterolemia. Thromb Haemost 1993; 70: 241-243.
2. Chan P, Tomlinsoin B, Tsai CW, et al. Thrombophilia in patients with hypercholesterolemia. Metabolism 1996; 45: 966-969.
3. Chan P, Huang TY, Shieh SM, et al. Thrombophilia in patients with hypertriglyceridemia. J Thromb Thrombolysis 1997; 4: 425-429.
4. Kim JA, Kim JE, Song SH, et al. Influence of blood lipids on global coagulation test results. Ann Lab Med 2015; 35: 15-21.
5. Kim SY, Kim JE, Kim HK, et al. Influence of coagulation and anticoagulant factors on global coagulation assays in healthy adults. Am J Clin Pathol 2013; 139: 370-379.
6. Bowman R, Joosen AM, Welch AA, et al. Factor VII, blood lipids and fat intake: gene-nutrient interaction and risk of coronary heart disease with the factor VII R353Q polymorphism. Eur J Clin Nutr 2009; 63: 771-777.
7. Silveira A. Postprandial triglycerides and blood coagulation. Exp Clin Endocrinol Diabetes 2001; 109: S527-532.
8. van der Stoep M, Korporaal SJ, Van Eck M. High-density lipoprotein as a modulator of platelet and coagulation responses. Cardiovasc Res. 2014; 103: 362-371.
9. Ząbczyk M, Hońdo L, Krzek M, et al. High-density cholesterol and apolipoprotein AI as modifiers of plasma fibrin clot properties in apparently healthy individuals. Blood Coagul Fibrinolysis 2013; 24: 50-54.
10. Naqvi TZ, Shah PK, Ivey PA, et al. Evidence that high-density lipoprotein cholesterol is an independent predictor of acute platelet-dependent thrombus formation. Am J Cardiol 1999; 84: 1011-1017.
11. Mineo C1, Deguchi H, Griffin JH, et al. Endothelial and antithrombotic actions of HDL. Circ Res 2006; 98: 1352-1364.
12. Okajima F, Sato K, Kimura T. Anti-atherogenic actions of high-density lipoprotein through sphingosine 1-phosphate receptors and scavenger receptor class B type I. Endocr J 2009; 56: 317-334.
13. Christoffersen C, Nielsen LB. Apolipoprotein M: bridging HDL and endothelial function. Curr Opin Lipidol 2013; 24: 295-300.
14. Christoffersen C, Obinata H, Kumaraswamy SB, et al. Endothelium-protective sphingosine-1-phosphate provided by HDL-associated apolipoprotein M. Proc Natl Acad Sci U S A 2011; 108: 9613-9618.
15. Christoffersen C, Jauhiainen M, Moser M, et al. Effect of apolipoprotein M on high density lipoprotein metabolism and atherosclerosis in low density lipoprotein receptor knock-out mice. J Biol Chem 2008; 283: 1839-1847.
16. Ahnstrom J, Gottsater A, Lindblad B, et al. Plasma concentrations of apolipoproteins A-I, B, and M in patients with critical limb ischemia. Clin Biochem 2010; 43: 599-603.
17. Eichinger S, Pecheniuk NM, Hron G, et al. High density lipoprotein and the risk of recurrent venous thromboembolism. Circulation 2007; 115: 1609-1614.
18. Memon AA, Sundquist J, Zöller B, et al. Apolipoprotein M and the risk of unprovoked recurrent venous thromboembolism. Thromb Res 2014; 133: 322-326.
19. Karuna R, Park R, Othman A, et al. Plasma levels of sphingosine-1-phosphate and apolipoprotein M in patients with monogenic disorders of HDL metabolism. Atherosclerosis 2011; 219: 855-863.
20. Axler O, Ahnström J, Dahlbäck B. An ELISA for apolipoprotein M reveals a strong correlation to total cholesterol in human plasma. J Lipid Res 2007; 48: 1772-1780.
21. Karlsson H, Lindqvist H, Tagesson C, et al. Characterization of apolipoprotein M isoforms in low-density lipoprotein. J Proteome Res 2006; 5: 2685-2690.
22. Martin JF, Kristensen SD, Mathur A, et al. The causal role of megakaryocyte-platelet hyperactivity in acute coronary syndromes. Nat Rev Cardiol 2012; 9: 658-670.
23. Undas A, Brummel-Ziedins KE, Mann KG. Statins and blood coagulation. Arterioscler Thromb Vasc Biol 2005; 25: 287-294.
24. Mayer J, Eller T, Brauer P, et al. Effects of long-term treatment with lovastatin on the clotting system and blood platelets. Ann Hematol 1992; 64: 196-201.
25. Kappelle PJ, Ahnström J, Dikkeschei BD, et al. Plasma apolipoprotein M responses to statin and fibrate administration in type 2 diabetes mellitus. Atherosclerosis 2010; 213: 247-250.
26. Christoffersen C, Pedersen TX, Gordts PL, et al. Opposing effects of apolipoprotein m on catabolism of apolipoprotein B-containing lipoproteins and atherosclerosis. Circ Res 2010; 106: 1624-1634.
27. Christoffersen C, Benn M, Christensen PM, et al. The plasma concentration of HDL-associated apoM is influenced by LDL receptor-mediated clearance of apoB-containing particles. J Lipid Res 2012; 53: 2198-2204.