HORMONES 2016, 15(1):99-105

Research paper

The relationship between retinol-binding protein 4 and apolipoprotein B-containing lipoproteins is attenuated in patients with very high serum triglycerides: A pilot study

Georgios A. Christou,[1] Constantinos C. Tellis,[2] Moses S. Elisaf,[3] Alexandros D. Tselepis,[2] Dimitrios N. Kiortsis[1]

[1]Laboratory of Physiology, Medical School, [2]Laboratory of Biochemistry, Department of Chemistry, [3]Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece

ABSTRACT

OBJECTIVE: The investigation of the association between retinol-binding protein 4 (RBP_4) and lipoproteins in subjects with hypertriglyceridemia. DESIGN: Forty-six obese or overweight hypertriglyceridemic patients were studied at baseline and 20 of them underwent a hypocaloric low-fat diet for 3 months. RESULTS: Plasma RBP_4 levels were positively correlated with serum triglycerides (TG) in the subgroup of patients with TG <200 mg/dL (r=0.453, p=0.039) and negatively correlated with TG in patients with TG ≥200 mg/dL (r=-0.487, p=0.019). In the subgroup with TG <200 mg/ dL, subjects with circulating RBP_4 above the median 46 mg/L had higher levels of intermediate density lipoprotein-cholesterol (IDL-C), low-density lipoprotein-cholesterol (LDL-C) and apolipoprotein B (ApoB), while these differences were absent in patients with TG ≥200 mg/dL. The associations of percentage changes of circulating RBP_4 with the percentage changes of LDL-C, very low-density lipoprotein-cholesterol (VLDL-C) and ApoB were positive after the first month and 3 months of diet for patients with baseline TG <200 mg/dL, while no correlations existed for patients with TG ≥200 mg/dL. CONCLUSIONS: The positive association between circulating RBP_4 and ApoB-containing lipoproteins in a steady metabolic state, as well as during a hypocaloric diet, appears to be attenuated in patients with very high TG.

Key words: Apolipoprotein B, Diet, Obesity, Retinol-binding protein 4, Triglycerides

INTRODUCTION

Retinol-binding protein 4 (RBP_4), a transport protein for vitamin A, is synthesized mainly by the hepatocytes and secondly by the adipose tissue.[1] Plasma RBP_4 levels are upregulated in insulin resistant states associated with obesity, while RBP_4 also induces insulin resistance.[1,2] Furthermore, elevated circulating RBP_4 has been associated with the development of cardiovascular disease.[3-6] Circulating RBP_4 has been shown to be positively correlated with serum triglycerides (TG)

Address for correspondence:
Dimitrios N Kiortsis, MD, PhD, Professor of Physiology, Laboratory of Physiology, Medical School, University of Ioannina, 45110 Ioannina, Greece; Tel.: +30 2651007551, Fax: +30 2651007850, E-mail: dkiorts@cc.uoi.gr

Received: 05-12-2015, Accepted: 22-02-2016

and low-density lipoprotein-cholesterol (LDL-C) and negatively with high-density lipoprotein-cholesterol (HDL-C).[1,7] Among these associations the strongest and the most consistently reported has been the association with TG.[1,8] Moreover, serum RBP_4 levels have been shown to increase TG in mice.[9] These data indicate that RBP_4 are possibly associated with TG metabolism. In the present study we investigated the association of RBP_4 with various lipid parameters in subjects with obesity-related hypertriglyceridemia at baseline and during dietary intervention.

MATERIALS AND METHODS

Subjects

In the present study 46 subjects were recruited. They attended the obesity outpatient clinic of the University of Ioannina, Greece. Inclusion criteria were: body mass index (BMI) ≥27 Kg/m^2 and hypertriglyceridemia (TG ≥150 mg/dL). Exclusion criteria were: age less than 18 years old, pregnancy, breastfeeding, kidney disease, liver disease, gastrointestinal disease, malignancy, any endocrine disorder or metabolic disease other than obesity or type 2 diabetes mellitus (T2DM), alteration of body weight (BW) by up to 5% of the initial BW during the last 3 months, any state of stress or systemic inflammation, taking any one of the following drugs within 3 weeks before the start of the study: hypolipidemic agents, antidiabetics, drugs for weight loss, β-blockers or thiazides. Diagnosis of T2DM was reasonably excluded by asking medical history and assessing the values of fasting serum glucose and HbA1c.

Among the total population, 20 participants underwent a hypocaloric low-fat diet for 3 months. A dietician, taking into account each patient's basal energy requirements and on an estimation of the subject's typical activity level, prescribed an individualized low-fat diet promoting a 500 to 1000 kcal reduction in daily energy intake. The administered diets consisted of a mean of 1471±382 kcal/day (ranging from 1085 to 2000 kcal/day depending on the initial BW). The daily distribution of nutrients during the study was as follows: carbohydrates 52.4±3.5%, fat 27.8±2.6% (monounsaturated 15.4±1.7%, polyunsaturated 7.3±1.2% and saturated fatty acids 5.1±1.0%) and protein 19.8±1.2%. There were no differences in diet composition between the study groups. At the end of the 3-month period, the patients were consuming significantly less carbohydrates and saturated fatty acids as well as more monounsaturated fatty acids and n-3 polyunsaturated fatty acids compared with their baseline diet. All patients were asked to attend the clinic monthly during the treatment in order to assess diet compliance.

Anthropometric measurements and collection of venous blood samples, after an overnight fast of at least 12 h, were performed at baseline, after 1 month and after 3 months of treatment. Plasma samples were stored at -80 °C until analysis.

Measurement of RBP_4

Plasma RBP_4 was analyzed using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (ALPCO DIAGNOSTICS), following the manufacturer's instructions, as previously described.[10]

LDL subclass analysis

LDL subclass analysis was performed electrophoretically by use of high-resolution 3% polyacrylamide gel tubes and the Lipoprint LDL System (Quantimetrix, Redondo Beach, CA), as we have previously described.[10] After electrophoresis, very low-density lipoprotein (VLDL) remained at the origin [retention factor (Rf) = 0.0], HDL migrated to the front (Rf=1.0). In between, several bands can be detected: MID bands C, B, and A, which correspond mainly to intermediate-density lipoprotein (IDL), as well as up to 7 LDL bands. The LDL-1 and LDL-2 bands correspond to large buoyant LDL particles, whereas bands LDL-3 to LDL-7 correspond to sdLDL particles. A detailed description of the methods used for the measurement of LDL subclasses can be found in an expert consensus document of the "European panel on LDL subclasses".[11]

Routine biochemical measurements

Total serum cholesterol (TC), HDL-C and TG were measured by enzymatic methods, as previously described.[10,12] Non-HDL-cholesterol was calculated as TC-HDL-C. Serum apolipoprotein (Apo) A-I and ApoB levels were measured with a Behring Holding GmbH analyzer (Liederbach, Germany).

Serum Creatinine (Cr) levels were determined by

standard laboratory methods. The Modification of Diet in Renal Disease (MDRD) formula was used for the estimation of glomerular filtration rate (eGFR).[13] Body surface area (BSA) was calculated by body weight (BW) and height (H) using the Du Bois formula: $BSA = 0.007184 \times BW^{0.425} \times H^{0.725}$ (BSA is in m^2, BW is in kg, and H is in cm).[14]

Statistical analysis

All statistical analyses were performed using the SPSS 16.0 statistical package for Windows (SPSS Inc., 1989-2007). The Kolmogorov-Smirnov test was used to verify the normality of the distributions of the parameters of interest. Normally distributed data were expressed as means±SD. Parameters with skewed distribution were reported as median (range). The paired t-test, independent t-test and Pearson's correlation analysis were performed for normally distributed parameters, whereas the Mann-Whitney U test and Spearman's correlation analysis were performed for non-normally distributed parameters. Linear regression analysis was used for the assessment of the relationship between circulating RBP_4 and lipid parameters after adjustment for gender and cGFR. A two-tailed p value <0.05 was considered significant.

RESULTS

Baseline

Participants were 50±14 years old (24 males and 22 females) and their BMI was 36.5±7.3 Kg/m^2. Plasma RBP_4 levels were higher in males compared with females (54.7±14.2 mg/L vs 42.2±13.6 mg/L, p=0.005). Circulating RBP_4 was positively correlated with Cr (r = 0.367, p = 0.014). Although circulating RBP_4 was not correlated with eGFR, it was negatively correlated with corrected GFR for BSA (cGFR) (r=-0.311, p=0.040).

Plasma RBP_4 levels were not correlated with TG in all patients. Circulating RBP_4 was positively correlated with TG in the subgroup of patients with TG <200 mg/dL (r=0.453, p=0.039) and negatively correlated with TG in the subgroup of patients with TG ≥200 mg/dL (r=-0.487, p=0.019).

Table 1 shows the values of circulating lipoproteins in the subgroups of patients with plasma RBP_4 levels below or above the median 46 mg/L in all patients as well as in subjects with TG < or ≥200 mg/ dL. In all patients, subjects with circulating RBP_4 above the median 46 mg/L had higher levels of IDL-C, LDL-C, nonHDL-C and ApoB and lower levels of ApoE compared with subjects with circulating RBP_4 below 46 mg/L. There was a tendency for higher levels of TC and VLDL-C in subjects with circulating RBP_4 above 46 mg/L.

In the subgroup of patients with TG <200 mg/ dL, subjects with circulating RBP_4 above 46 mg/L had higher levels of IDL-C, LDL-C and nonHDL-C and lower levels of Lp(a) compared with subjects with circulating RBP_4 below 46 mg/L. There was a tendency for higher levels of ApoB in subjects with circulating RBP_4 above 46 mg/L. Linear regression analysis showed that plasma RBP_4 levels were positively correlated with VLDL-C after adjustment for gender and cGFR (β=1.779, p=0.013).

In the subgroup of patients with TG ≥200 mg/ dL, subjects with serum RBP_4 levels above 46 mg/L had lower levels of TG, sdLDL-C and ApoE compared with subjects with circulating RBP_4 below 46 mg/L.

Dietary treatment

BMI was significantly decreased from baseline (36.2±5.7 Kg/m^2) after first month (35.7±4.6 Kg/m^2, p <0.001), as well as after 3 months of diet (34.9±5.1 Kg/m^2, p <0.001). Circulating RBP_4 decreased after 3 months of diet (from 51.9±13.8 to 45.7±14.7, p=0.03). Table 2 shows the associations between the percentage change of plasma RBP_4 levels after 1 month of treatment and the percentage changes of IDL-C, LDL-C, VLDL-C, sdLDL-C and ApoB in the total of subjects who underwent dietary treatment and in the subgroups of patients with baseline TG above or below 200 mg/dL. Table 3 shows similar data to Table 2 regarding the 3 months of diet. The associations of percentage changes of circulating RBP_4 with the percentage changes of IDL-C, LDL-C, VLDL-C, sdLDL-C and ApoB were positive over the first month and 3 months of diet for patients with baseline TG <200 mg/dL, while no correlations existed for patients with baseline TG ≥200 mg/dL, except for IDL-C during first month and sdLDL-C for 3 months.

Table 1. The comparison of lipid parameters between subjects with circulating RBP_4 below and above the median 46 mg/L, in all patients and in the subgroups with serum triglycerides (TG) < or ≥ 200 mg/ dL

	All patients (n=46)			TG <200 mg/ dL (n=22)			TG ≥200 mg/ dL (n=24)		
	RBP_4 <46 mg/L (n=22)	RBP_4 ≥46 mg/L (n=24)	p	RBP_4 <46 mg/L (n=12)	RBP_4 ≥46 mg/L (n=10)	p	RBP_4 <46 mg/L (n=10)	RBP_4 ≥46 mg/L (n=14)	p
TC (mg/dL)	239 ± 28	259 ± 39	0.059	235 ± 27	256 ± 26	0.135	243 ± 30	260 ± 46	0,483
TG (mg/dL)	235 ± 100	227 ± 56	0.697	162 ± 18	171 ± 21	0.473	323 ± 86	262 ± 41	0.049
HDL-C (mg/dL)	45 ± 9	45 ± 7	0.688	47 ± 9	44 ± 7	0,734	41 ± 7	45 ± 7	0,343
IDL-C (mg/dL)	51 ± 10	62 ± 14	0.010	55 ± 10	69 ± 12	0.043	48 ± 9	57 ± 13	0.180
LDL-C (mg/dL)	132 ± 15	149 ± 28	0.028	127 ± 14	154 ± 21	0.043	136 ± 16	147 ± 32	0.582
VLDL-C (mg/dL)	52 ± 10	59 ± 12	0.102	50 ± 4	54 ± 6	0.282	54 ± 12	62 ± 14	0.346
sdLDL-C (mg/dL)	19 ± 11	14 ± 8	0.147	10 ± 7	10 ± 8	0.950	25 ± 10	16 ± 7	0.025
nonHDL-C (mg/dL)	185 ± 23	208 ± 34	0.037	188 ± 21	212 ± 23	0.031	202 ± 26	215 ± 41	0.648
ApoA-I (mg/dL)	141 ± 17	137 ± 16	0.320	141 ± 16	132 ± 15	0.310	142 ± 19	139 ± 17	0.693
ApoB (mg/dL)	114 ± 24	131 ± 31	0.049	113 ± 19	127 ± 18	0.075	115 ± 30	134 ± 38	0.483
ApoE (mg/L)	63 ± 21	51 ± 11	0.037	50 ± 11	47 ± 11	0.456	76 ± 22	54 ± 10	0.022
Lp(a) (mg/dL)	8.40 (2.44-69.90)	4.45 (2.44-32.00)	0.257	8.80 (2.44-69.90)	4.70 (2.44-7.70)	0.042	2.97 (2.44-50.60)	4.20 (2.44-32.00)	0.661

Data are means ± SD for normally distributed variables or median (range) for non-normal variables.
TC: total cholesterol; TG: triglycerides; HDL-C: high density lipoprotein-cholesterol, IDL-C: intermediate-density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol; VLDL-C: very low density lipoprotein-cholesterol; sdLDL-C: small dense LDL-cholesterol; nonHDL-C: non-HDL-cholesterol; ApoA-I: apolipoprotein A-I; ApoB: apolipoprotein B; ApoE: apolipoprotein E; Lp(a): lipoprotein(a)
The p value refers to the comparison of the lipid parameters between subjects with serum RBP4 levels below and above 46 mg/L, after performing the independent t-test for normally distributed parameters and Mann–Whitney U test for non-normally distributed parameters.

Table 2. Correlations between percentage change of plasma RBP4 levels over one month of diet and percentage changes of TG, LDL-C, IDL-C, VLDL-C, sdLDL-C and ApoB

	All patients (n=20)		TG <200 mg/dL (n=10)		TG ≥200 mg/dL (n=10)	
	r	p	r	p	r	p
% change of IDL-C	0.296	0.265	0.500	0.207	0.095	0.823
% change of LDL-C	0.290	0.276	0.786	0.021	- 0.685	0.061
% change of VLDL-C	0.441	0.087	0.976	< 0.001	- 0.238	0.570
% change of sdLDL-C	0.447	0.083	0.898	0.002	- 0.024	0.955
% change of ApoB	0.493	0.045	0.667	0.049	0.110	0.796

TG: triglycerides; IDL-C: intermediate-density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol; VLDL-C: very low density lipoprotein-cholesterol; sdLDL-C: small dense LDL-cholesterol; ApoB: apolipoprotein B.

DISCUSSION

The present study showed that the association between circulating RBP_4 and TG was characterized by a biphasic mode, being positive for TG <200 mg/dL and negative for TG ≥200 mg/dL. Moreover, the positive association between RBP_4 and ApoB-containing lipoproteins in a steady metabolic state, as well as during the hypocaloric low-fat diet, was found to be attenuated in subjects with TG ≥200 mg/dL.

The relationship between RBP_4 and ApoB-containing lipoproteins

The current study demonstrated that circulating RBP_4 was positively correlated with serum levels of the ApoB-containing lipoproteins LDL-C, IDL-C and

Table 3. Correlations between percentage change of plasma RBP4 levels over 3 months of diet and percentage changes of TG, LDL-C, IDL-C, VLDL-C, sdLDL-C and ApoB

	All patients (n=20)		TG <200 mg/dL (n=10)		TG ≥200 mg/dL (n=10)	
	r	p	r	p	r	p
% change of IDL-C	-0.117	0.654	0.783	0.013	-0.429	0.289
% change of LDL-C	0.708	0.001	0.967	<0.001	0.619	0.102
% change of VLDL-C	0.570	0.017	0.760	0.018	- 0.190	0.651
% change of sdLDL-C	0.872	<0.001	0.908	0.001	0.790	0.020
% change of ApoB	0.635	0.005	0.782	0.008	0.405	0.320

TG: triglycerides; IDL-C: intermediate-density lipoprotein-cholesterol; LDL-C: low density lipoprotein-cholesterol; VLDL-C: very low density lipoprotein-cholesterol; sdLDL-C: small dense LDL-cholesterol; ApoB: apolipoprotein B.

VLDL-C. Importantly, this relationship was shown not only at baseline but also during a hypocaloric low-fat diet. Indeed, our study group has demonstrated that circulating RBP_4 is possibly associated more consistently and strongly with the metabolism of the ApoB-containing lipoproteins than the metabolism of the ApoA-I-containing lipoprotein HDL.[1,10] RBP_4 has been found to induce not only the enhancement of hepatic production of ApoB-containing lipoproteins but also the decrease in catabolism of ApoB-containing lipoproteins through the downregulation of the LDL receptor.[15] To our knowledge, the association between circulating RBP_4 and IDL-C has not previously been investigated.

The relationship between RBP_4 and TG in patients with TG <200 mg/dL

The positive association between circulating RBP_4 and TG has consistently been reported in studies investigating subjects with variable TG levels, including normal as well as high TG levels.[7,8] This relationship is possibly causal since treatment with RNA oligonucleotide against RBP_4 was shown to reduce TG levels in mice.[9] Vergès et al found that circulating RBP_4 in patients with T2DM was negatively correlated with indirect VLDL-apoB fractional catabolic rate (FCR), which represents the VLDL delipidation toward IDL, while there was no significant association with direct VLDL-apoB FCR, which reflects the direct VLDL removal from plasma through receptor-mediated particle uptake.[16]

The relationship of RBP_4 with lipoproteins in patients with TG ≥200 mg/dL

The negative association between circulating RBP_4 and TG in patients with TG ≥200 mg/dL of the current study was accompanied by the dissociation between circulating RBP_4 and ApoB-containing lipoproteins. A possible explanation for these data is the downregulation of plasma RBP_4 levels in patients with TG ≥200 mg/dL. Further studies are needed to confirm these findings and elucidate the underlying mechanisms. The dissociation between circulating RBP_4 and ApoB-containing lipoproteins in patients with considerable hypertriglyceridemia that was found in the present study implies that the adverse impact of RBP_4 on lipoprotein metabolism may be important only in patients without considerable hypertriglyceridemia. In this context, it is prudent to evaluate the effects of RBP_4 on lipoprotein metabolism only in patients without considerable hypertriglyceridemia, at least in initial studies.

The negative relationship between circulating RBP_4 and serum ApoE levels in patients with TG ≥200 mg/dL of the current study may be explained by the high serum levels of ApoE, which is carried by remnants of triglyceride-rich lipoproteins in subjects with hypertriglyceridemia.[17] The relationship between RBP_4 and ApoE has not been investigated in any previous study.

Study strengths and limitations

Strengths of this study include the investigation for the first time of the relationship of RBP_4 with lipoproteins in patients who had exclusively hypertriglyceridemia and not in mixed populations with variable TG levels. Secondly, taking into account the many factors that influence circulating RBP_4, including renal or liver impairment and drugs affect-

ing metabolism, the present study excluded patients with all these conditions.[1] However, an important limitation of the majority of studies investigating RBP_4 was that they did not take into account all these factors. Thirdly, the current study applied a direct measurement of all ApoB-containing lipoproteins through lipoprotein electrophoresis. However, most of the studies investigating the relationship between RBP_4 and LDL-C assessed LDL-C by its indirect calculation using the Friedewald equation [LDL-C = TC - (HDL-C + TG/5)], which is less accurate than the direct measurement of LDL-C, especially in subjects with considerable hypertriglyceridemia, as is the case in the present study.[18] Moreover, LDL-C calculated through the Friedewald equation represents a crude estimation of the sum of directly measured LDL-C and IDL-C and thus it is not a highly accurate estimation of true LDL-C.

The results of the present study should be interpreted in light of some limitations. Firstly, the number of patients was not large enough, thus decreasing the statistical power of the study to detect significant associations of circulating RBP_4 with serum lipoprotein levels. Therefore, taking into account the small number of study participants, firm conclusions cannot be drawn regarding the relationship between circulating RBP_4 and ApoB-containing lipoproteins in subjects with hypertriglyceridemia. Secondly, the relationships between RBP_4 and lipoproteins that were found in the current study cannot confirm the existence of causal mechanisms underlying these associations.

In conclusion, the present study showed that circulating RBP_4 was positively correlated with serum levels of ApoB-containing lipoproteins in a steady metabolic state, as well as during a hypocaloric low-fat diet in overweight or obese patients with hypertriglyceridemia. This relationship appears to be attenuated in patients with TG $\geq$200 mg/dL. Further well designed studies with a greater number of patients are needed to confirm these results and elucidate the underlying mechanisms.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

1. Christou GA, Tselepis AD, Kiortsis DN, 2012 The metabolic role of retinol binding protein 4: an update. Horm Metab Res 44: 6-14.
2. Yang Q, Graham TE, Mody N, et al, 2005 Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. Nature 436: 356-362.
3. Sun Q, Kiernan UA, Shi L, et al, 2013 Plasma retinol-binding protein 4 (RBP4) levels and risk of coronary heart disease: a prospective analysis among women in the nurses' health study. Circulation 127: 1938-1947.
4. Lambadiari V, Kadoglou NP, Stasinos V, et al. 2014 Serum levels of retinol-binding protein-4 are associated with the presence and severity of coronary artery disease. Cardiovasc Diabetol 13: 121.
5. Liu Y, Wang D, Chen H, Xia M, 2015 Circulating retinol binding protein 4 is associated with coronary lesion severity of patients with coronary artery disease. Atherosclerosis 238: 45-51.
6. Wan K, Zhao J, Deng Y, et al, 2014 A genetic polymorphism in RBP4 is associated with coronary artery disease. Int J Mol Sci 15: 22309-22319.
7. Klöting N, Graham TE, Berndt J, et al, 2007 Serum retinol-binding protein is more highly expressed in visceral than in subcutaneous adipose tissue and is a marker of intra-abdominal fat mass. Cell Metab 6: 79-87.
8. Ingelsson E, Sundström J, Melhus H, et al, 2009 Circulating retinol-binding protein 4, cardiovascular risk factors and prevalent cardiovascular disease in elderly. Atherosclerosis 206: 239-244.
9. Tan Y, Sun LQ, Kamal MA, Wang X, Seale JP, Qu X, 2011 Suppression of retinol-binding protein 4 with RNA oligonucleotide prevents high-fat diet-induced metabolic syndrome and non-alcoholic fatty liver disease in mice. Biochim Biophys Acta 1811: 1045-1053.
10. Christou GA, Tellis CC, Elisaf MS, Tselepis AD, Kiortsis DN, 2012 The changes in plasma retinol-binding protein 4 levels are associated with those of the apolipoprotein B-containing lipoproteins during dietary and drug treatment. Angiology 63: 67-75.
11. Mikhailidis DP, Elisaf M, Rizzo M, 2011 European panel on low density lipoprotein (LDL) subclasses: a statement on the pathophysiology, atherogenicity and clinical significance of LDL subclasses. Curr Vasc Pharmacol 9: 533-571.
12. Christou GA, Tellis KC, Elisaf MC, Tselepis AD, Kiortsis DN, 2012 High density lipoprotein is positively correlated with the changes in circulating total adiponectin and high molecular weight adiponectin during dietary and fenofibrate treatment. Hormones (Athens) 11: 178-188.
13. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D, 1999 A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction

equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 130: 461-470.
14. Du Bois D, Du Bois EF, 1989 A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition 5: 303-311.
15. Liu Y, Chen H, Wang J, Zhou W, Sun R, Xia M, 2015 Elevated retinol binding protein 4 induces apolipoprotein B production and associates with hypertriglyceridemia. J Clin Endocrinol Metab 100: E720-728.
16. Vergès B, Guiu B, Cercueil JP, et al, 2012 Retinol-binding protein 4 is an independent factor associated with triglycerides and a determinant of very low-density lipoprotein-apolipoprotein B100 catabolism in type 2 diabetes mellitus. Arterioscler Thromb Vasc Biol 32: 3050-3057.
17. Mahley RW, Ji ZS, 1999 Remnant lipoprotein metabolism: key pathways involving cell-surface heparan sulfate proteoglycans and apolipoprotein E. J Lipid Res 40: 1-16.
18. Friedewald WT, Levy RI, Fredrickson DS, 1972 Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18: 499-502.