Postprandial Hyperlipidemia and Remnant Lipoproteins

Daisaku Masuda¹ and Shizuya Yamashita¹, ², ³

¹Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
²Rinku General Medical Center, Osaka, Japan
³Department of Community Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

Fasting hypertriglyceridemia is positively associated with the morbidity of coronary heart disease (CHD), and postprandial (non-fasting) hypertriglyceridemia is also correlated with the risk status for CHD, which is related to the increase in chylomicron (CM) remnant lipoproteins produced from the intestine. CM remnant particles, as well as oxidized low density lipoprotein (LDL) or very low density lipoprotein (VLDL) remnants, are highly atherogenic and act by enhancing systemic inflammation, platelet activation, coagulation, thrombus formation, and macrophage foam cell formation. The cholesterol levels of remnant lipoproteins significantly correlate with small, dense LDL; impaired glucose tolerance (IGT) and CHD prevalence. We have developed an assay of apolipoprotein (apo)B-48 levels to evaluate the accumulation of CM remnants. Fasting apoB-48 levels correlate with the morbidity of postprandial hypertriglyceridemia, obesity, type III hyperlipoproteinemia, the metabolic syndrome, hypothyroidism, chronic kidney disease, and IGT. Fasting apoB-48 levels also correlate with carotid intima-media thickening and CHD prevalence, and a high apoB-48 level is a significant predictor of CHD risk, independent of the fasting TG level. Diet interventions, such as dietary fibers, polyphenols, medium-chain fatty acids, diacylglycerol, and long-chain n-3 polyunsaturated fatty acids (PUFA), ameliorate postprandial hypertriglyceridemia, moreover, drugs for dyslipidemia (n-3 PUFA, statins, fibrates or ezetimibe) and diabetes concerning incretins (dipeptidyl-peptidase IV inhibitor or glucagon like peptide-1 analogue) may improve postprandial hypertriglyceridemia. Since the accumulation of CM remnants correlates to impaired lipid and glucose metabolism and atherosclerotic cardiovascular events, further studies are required to investigate the characteristics, physiological activities, and functions of CM remnants for the development of new interventions to reduce atherogenicity.

Key words: Hypertriglyceridemia, Postprandial hypertriglyceridemia, Remnant lipoproteins, Chylomicron remnants, Apolipoprotein B-48, Atherosclerosis

Copyright©2017 Japan Atherosclerosis Society
This article is distributed under the terms of the latest version of CC BY-NC-SA defined by the Creative Commons Attribution License.

1. Fasting and Postprandial Hypertriglyceridemia

In Japan, the morbidity and mortality of atherosclerotic cardiovascular diseases (ASCVD), including coronary heart disease (CHD) and stroke have gradually increased in recent decades. Intensive intervention against hypercholesterolemia or hyper low-density lipoprotein (LDL)-cholesterolemia using statins improves the primary and secondary prevention of CHD events, however the complete suppression of CHD events has not yet been accomplished. Recently, the importance of controlling “residual risk factors” for CHD has been emphasized, and hypertriglyceridemia (≥150 mg/dL) and hypo high-density lipoprotein (HDL)-cholesterolemia (<40 mg/dL) have both been investigated in basic and clinical research settings to determine a possible method for the prevention of ASCVD¹, ²). As fasting triglyceride (TG) levels at the registration increased (<100, 100-149, 150-199, 200-499, and ≥500 mg/dL) the age- and sex-adjusted hazard ratio (HR) for adjusted all-cause mortality worsened (1.06, 1.16, 1.29, and 1.28 compared with <100 mg/dL, respectively)³). A systematic review and meta-analysis of 35 observational studies revealed that fasting hypertriglyceridemia is significantly associated with cardiovascular death (odds ratios (OR) 1.80; 95% confidence interval (CI) 1.31-2.49), cardiovascular events...
(OR, 1.37; 95% CI, 1.23-1.53) and myocardial infarction (OR, 1.31; 95% CI, 1.15-1.49)4. Moreover, on a background of statin treatment after ACS, fasting triglycerides are related to the risk of CHD death, non-fatal myocardial infarction, stroke, and unstable angina in models adjusted for classic CHD risk factors5. The Japan Atherosclerosis Society Guidelines 2012 suggest that if a subject with hypertriglyceridemia (fasting TG level ≥ 150 mg/dL) is defined as high risk for ASCVD (especially CHD) by an annual medical checkup, he or she should be encouraged to receive secondary checkups and medical intervention6. However, fasting TG levels may vary by the lipid content and the consumption time of the patient’s meal, and the fasting TG level is not always positively correlated with atherogenicity. The slightly elevated TG levels that are observed in patients with impaired glucose tolerance (IGT) or the metabolic syndrome (MetS) are highly atherogenic, whereas the severely high TG levels that are observed in patients with primary chylomicronemia or lipoprotein lipase (LPL) deficiency are rarely atherogenic. Therefore, measurement of the fasting TG level is not always sufficient for evaluating individual ASCVD risks, thus the exact analysis of impaired lipoprotein metabolism, is required.

In contrast, many studies have revealed that postprandial (non-fasting) hypertriglyceridemia is likely to reflect the risk for ASCVD. Iso et al. showed the positive correlation between the incidence of CHD (myocardial infarctions, angina pectoris events, and sudden cardiac deaths) and non-fasting TG levels in a 15.5-year prospective observation, in which the multivariate relative risk of CHD associated with a 1 mmol/L increase in TG level was 1.29 (95% CI: 1.09-1.53; p < 0.01) for men and 1.42 (1.15-1.75; p < 0.01) for women independent of total cholesterol levels7. Nordestgaard et al. also showed that non-fasting TG levels are correlated with the morbidity of CHD8 and ischemic stroke9 in a prospective cohort study (Copenhagen City Heart Study). However, there has been no standardized reference value for postprandial TG levels to define postprandial hypertriglyceridemia as a risk factor for ASCVD events. In 2016, the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine published a joint consensus statement recommending the routine use of non-fasting blood samples for assessing plasma lipid profiles10, based on the epidemiological data that there was no clinically significant difference between LDL-C and non-HDL-C levels in both the fasting and the postprandial state. Since maximal mean changes in TG levels at 1-6 h after habitual meals are stable (+ 26 mg/dL), they suggest that the cut-off for abnormal postprandial TG levels should be >2 mmol/L (175 mg/dL) and point out the usefulness of measuring non-fasting lipid levels in usual clinical settings10. For the future, the cut-off value of the non-fasting TG level based upon the prospective study in a larger population is strongly recommended for the purpose of evaluating ASCVD risks with high sensitivity.

2. Metabolism of Remnant Lipoproteins

In patients with hypertriglyceridemia, the TG-rich lipoproteins (TRLs) mainly increase during fasting and the postprandial state. TRLs are metabolized in exogenous and endogenous pathways. The exogenous pathway distributes the lipids that are absorbed by the intestine after a meal to the peripheral tissue using chylomicron (CM) particles during the postprandial state. In the intestines, CM particles are synthesized by apoB-48, apoA-1, TG, and cholesterol ester (CE) in enterocytes during the fasting state, which are expanded by lipid-enriched foods, and secreted into the intestinal lymphatic trunks11, 12. TGs that are contained in CM particles are released into the bloodstream and apoC-2 and apoE and are metabolized by apoC-2 activated LPLs. CM particles are referred to as smaller CM remnant particles that are rich in CE and poorer in TG that CM. The liver takes up CM remnant particles, predominantly via the LDL receptor with apoE acting as the ligand or by LDL receptor-related protein 1 (LRP1) with the cooperation of heparan sulfate proteoglycans (HSPG)13-15. On the other hand, the endogenous pathway distributes the lipids that are stored in the liver to the peripheral tissues by very low-density lipoproteins (VLDL) during the fasting state. A VLDL particle is synthesized with apoB-100, TG, and CE in hepatocytes and produced throughout the day, which are then metabolized into smaller VLDL remnants and intermediate-density lipoproteins (IDL) by LPL and further metabolized to LDLs by hepatic lipase. LDLs are absorbed by the liver or peripheral tissues. The apoB gene encodes both the apoB-48 and apoB-100 proteins. One apoB-48 protein is contained within one CM particle up to liver uptake, and one apoB-100 protein is also contained within one VLDL particle up to liver uptake. The apoB-100 protein consists of 4563 amino acids and the apoB48 protein is generated when a stop codon (UAA) at residue 2153 is created by the RNA editing of the apobec-1 protein16.

3. Atherogenicity of Remnant Lipoproteins and Chylomicron Remnants

Remnant lipoproteins exist in the systemic bloodstream continuously and their atherogenicity has been
investigated in many studies. Using histological examinations in rabbits, the accumulation of remnant lipoproteins within the arterial wall was observed in the rabbits with diet-induced or heritable hypercholesterolemia, as well as the accumulation of LDLs. Many basic and clinical experiments have proven that remnant lipoproteins directly and indirectly correlate to the enhancement of atherogenicity, since they enhance systemic inflammation and platelet activation, coagulation, and thrombus formation by the induction of plasminogen activator inhibitor-1 (PAI-1); they induce the proliferation of smooth muscle cells (SMC) via epidermal growth factor (EGF) receptor transactivation; they up-regulate intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and tissue factor (TF); they increase the adhesion of monocyte cells to endothelial cells; and they stimulate the transmigration of monocytes into the sub-endothelial space by up-regulating monocyte chemoattractant protein-1 (MCP-1) expression. Besides these changes, remnant lipoproteins can directly penetrate the arterial wall, infiltrate the sub-endothelial space, and accelerate macrophage foam cell formation.

It is unclear whether or how much intestine-derived CM remnants are involved in the formation of atherosclerotic plaque. The simultaneous perfusion of both apoB-48-containing lipoproteins and apoB-100-containing lipoproteins at equivalent concentrations in normal rabbits induced the accumulation of apoB-48-containing lipoproteins within the subendothelial space of the carotid artery twice as much as apoB-100-containing lipoproteins. In human carotid and femoral endarterectomy samples, the quantity of apoB-48 proteins were similar to that of apoB-100 proteins, and apoB-48/apoB-100 ratio was much higher than predicted based on the relative plasma concentration. The contribution of intestine-derived CM remnants to atherosclerosis may be significant, and many investigations have revealed that the atherogenicity of CM remnants is the same as remnant lipoproteins. As shown in Fig. 1, CM remnants also enhance systemic inflammation (release in interleukin-1β) and platelet activation by the induction of PAI-1; they induce SMC proliferation via early growth response factor-1 (Egr-1); they stimulate the apoptosis of endothelial cells; they up-regulate CD40 expression, which is associated with the expression of matrix metalloproteinase chymokines, cytokines, and adhesion molecules via B-cell differentiation; they up-regulate MCP-1 expression; and they enhance the cellular cholesterol content. These adverse effects of CM remnants support the instability and progression of atherosclerotic plaque. Fujioka et al. showed that 40% of the cellular uptake of CM remnants is mediated by the LDL receptor, 20% is by the LDL receptor-related protein (LRP) or other LDL receptor family, and the rest is by unknown receptors. Some researchers have reported that apoB-48 receptors may uptake CM remnants and may contribute to foam cell formation, however very few studies have investigated this, therefore the function of the apoB-48 receptor remains unclear. Taken together, the accumulation of CM remnants is highly atherogenic, as well as the accumulation of VLDL remnants, and quantitative evaluation methods of CM remnants are required.

4. Quantitative Evaluation of Remnant Lipoproteins

Postprandial hypertriglyceridemia is principally due to the overproduction and/or decreased catabolism of TRLs or remnants, thus a measurement system for the quantitative evaluation of atherogenic remnant lipoproteins is necessary. Thus, a method for evaluating the cholesterol concentration of remnant lipoproteins was developed, which is known as Remnant-Like Particles-Cholesterol (RLP-C). The RLP-C method measures the cholesterol content of isolated fractions from human sera using both anti-apoA-1 and anti-apoB-100 monoclonal antibodies. In patients with type III hyperlipoproteinemia (HL) the genetic defective receptor-binding function of apoE (mainly apoE2/E2 phenotype) causes the decreased clearance of remnant lipoproteins. RLP-C levels are significantly higher than other types of hyperlipoproteinemia. The accumulation of remnant lipoproteins is related to IGT, which may exacerbate atherosclerosis, and RLP-C and RLP-TG levels are elevated in subjects with type 2 diabetes mellitus (DM) and IGT; and postprandial increases in RLP-C or RLP-TG levels are significantly higher in hyperinsulinemic diabetic patients. Funada et al. found that both fasting and postprandial RLP-C levels were higher in the high homeostasis model assessment of the insulin resistance (HOMA-IR) group than in the normal HOMA-IR group. The accumulation of remnant lipoproteins is also related to the accumulation of small, dense LDL [sLDL, small in diameter (25.5 nm) and high in density because it is rich in TG content] or hypo-HDL-cholesterolemia. SdLDL particles, which are generated by the hydrolysis of large VLDL particles by the regulation of the cholesteryl ester transport protein (CETP), have a low affinity for binding the LDL receptor so that they are continuously maintained within the bloodstream, and easily infiltrated into the arterial wall, and thus con-
clearly demonstrated that patients in the highest tertile of RLP-C levels (≥ 5.1 mg/dL) had a higher occurrence of CHD events than those with the lowest tertile (≤ 3.3 mg/dL), even though their LDL-C levels were less than 100 mg/dL57). Another method for evaluating the cholesterol concentration of remnant lipoproteins was developed, which is known as Remnant Lipoprotein-Cholesterol (RemL-C)58). The RLP-C method can measure the cholesterol and TG contents of isolated fractions, however it lacks the specificity of remnant lipoproteins because the anti-apoB-100 antibody cannot recognize apoE-rich VLDLs or TG-rich CMs59). In Japan, Kugiyama et al.

Fig. 1. Chylomicron remnants are accumulated in many metabolic disorders and contributes to the progression of atherosclerotic plaque.

Many metabolic disorders that correlate the hypertriglyceridemia, postprandial hypertriglyceridemia, type III hyperlipidemia, the metabolic syndrome, diabetes mellitus, impaired glucose tolerance, chronic kidney disease, are related to the accumulation of chylomicron remnants and high apolipoprotein(apo)B-48 concentrations. Chylomicron remnants in sera can directly penetrate into the arterial wall and infiltrate the sub-endothelial space. They enhance systemic inflammation, induce platelet activation, the proliferation of smooth muscle cells, the adhesion of the monocyte, apoptosis of endothelial cells and macrophage foam cell formation. These changes induce the instability and progression of atherosclerotic plaque. High apoB-48 concentrations correlate with the thickening of carotid arteries and the prevalence of coronary artery stenosis.
bilized and degraded by a surfactant and phospholipase-D and separated from other lipoproteins with higher specificity than RLP-C60. The RemL-C assay has a significantly positive correlation with the RLP-C assay and the cholesterol in IDL fractions in healthy subjects61. The RemL-C method is used for examining the accumulation of remnant lipoproteins precisely in patients with chronic kidney disease (CKD), impaired cholesterol absorption, and any status of CHD in patients with DM62. The RemL-C level is used for examining the link between remnant lipoproteins and coronary plaque vulnerability, and high serum RemL-C levels are correlated with high necrotic and low fibrotic components of coronary plaque in patients with stable angina and the RemL-C/TG ratio correlates with the high lipid components of coronary plaque63. The measurement of RemL-C level may be useful in annual health examinations of women for detecting large artery atherosclerosis64. Taken together, the measurement of the cholesterol levels of remnant lipoproteins is useful for analyzing the risk status in subjects with the accumulation of remnant lipoproteins.

5. Apolipoprotein B-48 Concentration and Metabolic Disorders

Zilversmit proposed over three decades ago that CM remnants in a postprandial state may be related to the development of atherosclerosis65. However, there has been controversy whether postprandial hypertriglyceridemia is due to the increase in the TRLs of the endogenous pathway or that of the exogenous pathway. Karpe et al. supposed that the delipidation process of VLDL is halted during the postprandial state, thus leading to the prolonged residence of VLDL remnants in the bloodstream (91%–96% of all TG-rich lipoproteins)66, 67. In contrast, Cohn et al. reported that the postprandial TG increase is predominantly (approximately 80%) due to an increase in CM remnants68. The polyacrylamide gradient gel electrophoresis with the scanning of protein mass or the measurement of retinal palmitate used in these studies is not suitable for the accurate and independent analysis of CM remnants. An appropriate measuring method for the evaluation of CM remnants has long been desired.

One particle of CM remnant contains one apoB-48 molecule, therefore we developed an anti-apoB-48 monoclonal antibody69, an enzyme-linked immunosorbent assay (ELISA) for measuring apoB-48 concentration 70, and a chemiluminescent enzyme immunoassay (CLEIA) for use on a fully automated analyzer system71. We reported the accumulation of CM remnants in many metabolic disorders and ASCVD by measuring the apoB-48 level in many clinical trials for a long time. (see Fig. 1). The upper reference limit was estimated to be 5.7 µg/mL and the reference interval was 0.74–5.65 µg/mL among 332 patients with normolipidemia72. The postprandial levels of apoB-48, TG, RLP-C, and RLP-TG significantly increased after the intake of a high-fat meal, however there was no postprandial increase in apoB-100 and LDL-C levels73. These results strongly support that the postprandial increase in CM remnants is the main cause of postprandial hypertriglyceridemia. Fasting apoB-48 levels are significantly correlated with the incremental area under the curve (AUC) of TG after the intake of a high-fat meal, thus the fasting apoB-48 value is a strong and sensitive marker for postprandial hypertriglyceridemia. Fasting apoB-48 levels were significantly higher in men than in women (mean ± SD, 3.8 ± 3.3 vs. 2.4 ± 1.9 µg/mL, p < 0.001); in obese subjects (BMI ≥ 25 kg/m²) than in non-obese subjects (BMI < 25 kg/m²) (4.4 ± 3.7 vs. 2.8 ± 2.4 µg/mL, p < 0.001); and in subjects with MetS than in those without MetS (6.5 ± 4.3 vs 3.0 ± 2.6 µg/mL, p < 0.001)72. ApoB-48 levels positively correlate with the number of abnormal factors of dyslipidemia (hyper LDL-cholesterolemia, hypertriglyceridemia, or hypo HDL-cholesterolemia) and the number of risk factors for MetS72. Kinoshita et al. also showed that fasting apoB-48 levels are significantly higher in males than females (geometric mean; 1.92 vs. 1.69 µg/mL; p < 0.001) and significantly higher in subjects with MetS than those without MetS74. In clinical settings, HL patients are promptly treated with lipid-lowering agents without the diagnosis of the underlying cause. We confirmed that the apoB-48 to TG ratio is significantly higher in patients with type III HL than other types of dyslipidemia before and after medical treatments (after medical treatments; AUC-ROC value, 0.895; cut-off value, 0.110)70, 75. High apoB-48 levels are also observed in subjects with clinical and subclinical hypothyroidism, and it was suggested that hypothyroidism might correlate with the accumulation of remnant lipoproteins76. Proteinuria and a reduced estimated glomerular filtration rate (eGFR) are independent risk factors for renal dysfunction and ASCVD events in CKD patients, and we found that log-apoB-48 and log-apoB-48/TG levels are significantly higher in subjects with both low eGFR (< 60 mL/min/1.73 m²) and proteinuria (≥ 1+ by urine dipstick) than those with high eGFR and without proteinuria, which imply that an increased accumulation of CM remnants contributes to an increased risk of ASCVD events in CKD patients77. Similar to CKD patients, Hayashi et al. also showed that apoB-48 levels gradually increased as
renal dysfunction worsened to end-stage renal disease (ESRD) in patients with diabetic nephropathy who were receiving hemodialysis. In patients with IGT and DM, the impaired metabolism of CM remnants is assumed. Using an animal model of insulin resistance (fluctose-fed hamster), Guo et al. showed that the overproduction of CM particles occurs during insulin-resistant states, which may cause both fasting and postprandial dyslipidemia. During the fasting state, apoB-48 is mostly secreted on VLDL-, LDL-, and denser HDL-sized lipoprotein particles, and a major proportion of CM particles is assembled and secreted as highly dense, HDL-sized lipoprotein particles. These changes are suggested to be due to the up-regulation of intestinal enterocyte de novo lipogenesis.

6. Apolipoprotein B-48 Concentration and Atherosclerotic Cardiovascular Diseases

Similar to RLP-C or RemL-C, fasting apoB-48 levels correlate with IMT of the carotid artery, and the morbidity of CHD has been investigated. First, we determined the association between the fasting apoB-48 level and max-IMT of the carotid artery and determined independent predictors of max-IMT by multiple regression analysis. Subjects who took their annual health check were enrolled after the exclusion of subjects with systolic blood pressure ≥ 140 mmHg, intake of antihypertensive or antihyperlipidemic drugs, or age > 65 years. We postulated that apoB-48 values may correlate with max-IMT in all subjects, however there was no correlation. Alternatively, a significant correlation between the fasting apoB-48 level and max-IMT in all subjects, however there was no correlation. Consequently, a high apoB-48 level is a useful marker for evaluating the residual risk factor for CHD, which has the possibility to be replaced by the classic coronary risk factor, hypertriglyceridemia.

7. Interventional Therapy for Postprandial Hypertriglyceridemia

7.1 Diet Intervention

Dyslipidemia should be treated with lifestyle modification and diet therapy, as well as drug intervention. Certain functional foods are useful for improving postprandial hypertriglyceridemia.

Dietary fibers: food containing dietary fiber slows the absorption of lipids in the intestine. Oat bran, wheat fiber, or wheat germ decrease the postprandial TG response, and wheat fiber reduces the TG contents of CM.

Polyphenols: the effect of polyphenol is mainly assessed as the antioxidant capacity or the counter effect for oxidative stress, on the other hand, the intake of polyphenols improves fasting and postprandial TG levels as well as reduces oxidative stress and lowers CHD risk.

Medium-chain fatty acids (MCFA): MCFA are composed of 8–10 carbon atoms, and are absorbed in the intestine and transported directly into the liver via the portal vein, thus the postprandial TG response is reduced since they are not absorbed as a component of CM, such as long-chain triacylglycerols (LCT). Medium-chain triacylglycerol suppresses body fat accumulation compared with LCT, which is caused by the rapid clearance by beta-oxidation and diet-induced thermogenesis.

Diacylglycerol (DAG): as summarized by Yanai and Tada et al., DAG is effective in reducing postprandial hypertriglyceridemia. Dietary TAG is hydrolyzed to 2-monoacylglycerol (MAG) and FFA, and these two molecules are incorporated into CM promptly via the 2-MAG pathway. In contrast, dietary DAG is hydrolyzed to 1-MAG subsequently to glycerol and FFA, and TG is synthesized via the glycerol-3-phosphate (G3P) pathway which is less active than the 2-MAG pathway, thus resulting in slower re-acylation to TAG. A 1,3-DAG lowers the postprandial increase of TG and remnant lipoproteins in subjects with insulin-resistance, which is partially due to the increased clearance of DAG-incorporated CM via LPL-mediated lipolysis and hepatic uptake. The
long-term consumption of DG-rich oil significantly decreases visceral and subcutaneous fat areas and hepatic fat content in humans\(^9\) and atherosclerotic plaque in diabetic apoE-deficient mice\(^9\).

Long-chain n-3 polyunsaturated fatty acids (PUFA): fish oils, which are a rich source of the long-chain n-3 PUFA, eicosapentaenoic (EPA), and docosahexaenoic (DHA) acids, decrease apoB-100- and apoB-48-conating TRLs by decreasing their production rate\(^9\). The intake of n-6 PUFA also decreases VLDL by up-regulating their lipolysis and uptake by the liver. The intake of saturated fatty-acids with increased palmitic acid is associated with decreased postprandial lipemia\(^9\). In both acute and chronic (for 25 days) dietary fat loads, n-3 PUFA and n-6 PUFA diets reduce CM and non-CM retinyl palmitate (RP) levels\(^9\).

7.2 Drug Intervention

Drugs for dyslipidemia and insulin resistance are supposed to be effective for improving postprandial hypertriglyceridemia. Drugs for dyslipidemia (n-3 PUFA, statins, fibrates or ezetimibe) and those for DM-related incretins (dipeptidyl-peptidase IV inhibitor or glucagon like peptide-1 analogue) have possibilities for improving postprandial hypertriglyceridemia.

n-3 PUFA includes eicosapentaenoic acid, EPA and/or docosahexaenoic acid, and DHA includes long chain n-3 PUFA, which reduce the postprandial levels of CM-C and VLDL-apoB-48 in overweight/obese individuals\(^9\) and improve endothelial dysfunction after the cookie test\(^9\). The JELIS trial, which was operated in Japan, revealed that a high dose of EPA (1800 mg/day) improves the primary (\(-17\%\)) and secondary (\(-23\%\)) prevention of CHD\(^9\). In a sub-analysis of the JELIS trial, EPA was more effective for the primary prevention of CHD (\(-53\%\)) in subjects with hypertriglyceridemia (\(\geq 150\) mg/dL) and hypo-HDL cholesterol (\(< 40\) mg/dL), which suggests that EPA may be especially beneficial in patients with increased accumulation of remnant lipoproteins\(^9\).

To the contrary, there is little data describing the effect of DHA on postprandial hypertriglyceridemia, although high-fat meals rich in EPA plus DHA suppress postprandial TG increase but that rich in DHA only does not\(^9\). Instead, the oxidative stress marker, plasma 8-isoprostane F2\(\alpha\), is increased by the addition of EPA plus DHA but reduced by the addition of DHA only\(^9\), thus further investigation for the antiatherogenic effect of DHA is needed.

Statins: statins, which are mainly used for hypercholesterolemia, may improve postprandial hypertriglyceridemia. We found that atorvastatin decreased the fasting levels of TG (\(-56\%\)), RLP-C (\(-73\%\)), RLP-TG (\(-65\%\)), and apoB-48 (\(-43\%\)) as well as total cholesterol (\(-52\%\)) and apoB-100 (\(-52\%\)) in patients with type III HL (\(p<0.01\))\(^9\). Parhofer et al. showed that atorvastatin significantly decreased the postprandial increase of TG and CM\(^9\). Pitavastatin attenuates postprandial TG increase, abolishes the decrease in postprandial FMD by improving postprandial endothelial dysfunction\(^9\), and suppresses the postprandial increase of oxidative stress (urine 8-OHdG)\(^9\).

Fibrates: fibrates are the representative drug for hypertriglyceridemia. In subjects with hypertriglyceridemia and MetS, fenofibrate reduced postprandial increases VLDL, LDL, and remnant lipoproteins as well as oxidized fatty acids, soluble VCAM-1, and soluble ICAM-1, which indicate that fenofibrate might improve postprandial free fatty acid oxidation and inflammatory responses\(^9\). Sabine et al. found that fenofibrate reduces the postprandial increase of small CM remnants effectively in patients with mixed hyperlipidemia\(^9\). We found that a fenofibrate markedly suppressed the postprandial TG and apoB-48 response by suppressing CM production from the intestines, using an animal model of postprandial hypertriglyceridemia, CD36 knockout (KO) mice\(^9\). A bezafibrate was associated with a small but significant risk reduction in mortality (HR 0.90; 95 % CI 0.82-0.98, \(p=0.026\)) in patients with hypertriglyceridemia (TG \(\geq 200\) mg/dL) in the BIP trial\(^9\). However, the FIELD trial showed that a fenofibrate did not significantly reduce CHD events in diabetic patients\(^9\), and the ACCORD Lipid trial also showed that a fenofibrate in combination with simvastatin did not reduce CHD events in diabetic patients\(^9\). On the other hand, when DM patients with hypertriglyceridemia (\(\geq 204\) mg/dL) and hypo-HDL-cholesterolemia (\(< 34\) mg/ dL) were selected as study subjects, the combination of fenofibrate with simvastatin reduced CHD events significantly (12.37% vs 17.32%, \(p<0.05\)), which suggests that fibrates might be effective for preventing CHD events in patients with accumulated remnant lipoproteins and must be used for these patients selectively.

Ezetimibe: the intestinal cholesterol transporter inhibitor, ezetimibe, improves postprandial hypertriglyceridemia in patients with type IIb hyperlipidaemia\(^9\), obesity, and MetS\(^9\). We found that ezetimibe significantly reduced the postprandial increase in TG, apoB-48, and RemL-C levels in addition to a decrease in CM particles\(^9\). Ezetimibe dramatically reduced the postprandial TG content in CM and CM remnant-sized particles in both wild-type mice fed a high-fat diet and CD36KO mice fed a normal chow diet, which is due to reduced intestinal CM production and low expressions of FATP4 and apoB\(^9\). In clinical studies, ezetimibe in combination with statins improved
postprandial hypertriglyceridemia in obese patients with MetS\textsuperscript{116}) in combination with the improvement of endothelial function\textsuperscript{116}), and these effects were also observed in normal healthy volunteers\textsuperscript{117}). In a crossover trial, ezetimibe improved postprandial hypertriglyceridemia but did not improve postprandial hyperglycaemia\textsuperscript{118}). Recently, the IMPROVE-IT trial proved that the combined use of ezetimibe with simvastatin reduces cardiovascular outcomes in patients with an acute coronary syndrome (HR, 0.936; 95% CI, 0.89–0.99; \( p = 0.016 \)) in addition to a decrease in fasting LDL-C and TG levels\textsuperscript{119}). In a subgroup analysis of this trial, the reduction in CV outcome was significantly higher in patients with DM than in those without DM, which suggests that ezetimibe therapy is suitable for patients with an increase in remnant lipoproteins for CV risk reduction.

DPP-4 inhibitors and GLP-1 agonist: as previously described, IGT is often complicated with the accumulation of remnant lipoproteins and vice versa. Sitagliptin reduces the postprandial increase in apoB-100, apoB-48, TG, VLDL-C, FFAs, and glucose levels by ameliorating the endogenous and exogenous pathways in diabetic patients\textsuperscript{120}). Vildagliptin therapy also suppresses postprandial hypertriglyceridemia, which was intended to be a reduction in the postprandial increase of CM remnants\textsuperscript{121, 122}). A glucagon-like peptide 1 (GLP-1) analogue is now used to decrease fasting blood sugar by activating incretin, and its receptor is essential for CM synthesis and secretion in hamsters and mice\textsuperscript{123}). The GLP-1 analogue, liraglutide, suppresses postprandial TG and apoB-48 elevations after a fat-rich meal in diabetic patients without any difference in postprandial FFAs levels and gastric emptying rate\textsuperscript{124}). Another report showed that gastric emptying was delayed and FFAs levels were low\textsuperscript{125}), however the mechanism of improving postprandial hypertriglyceridemia is controversial. Mega trials of the DPP-4 inhibitors saxagliptin (SAVOR-TIMI 53)\textsuperscript{126}), alogliptin (EXAMINE)\textsuperscript{127}), and sitagliptin (TECOS)\textsuperscript{128}) did not improve cardiovascular outcomes in diabetic patients, however a recent study showed that liraglutide significantly decreased CV related death (HR, 0.87; 95% CI, 0.78–0.97; \( p < 0.001 \) for noninferiority; \( p = 0.01 \) for superiority) in patients with type 2 DM and high cardiovascular risk\textsuperscript{129}). There is a possibility that DPP4 inhibitors and GLP-1 administration may reduce the cardiovascular risk in patients with DM and the accumulation of remnant lipoproteins. Further studies are needed to improve postprandial hypertriglyceridemia in drugs for DM-related incretins.

8. Conclusion

The accumulation of remnant lipoproteins, especially intestine-derived chylomicron remnants, is related to impaired lipid and glucose metabolism and ASCVD events. High apoB-48 levels may be a useful biomarker for the evaluation of atherogenicity compared with previous biomarkers such as hypertriglyceridemia. If we can detect the risk for ASCVD events more precisely by measuring apoB-48 levels, the morbidity and mortality of ASCVD could be reduced. Moreover, postprandial hypertriglyceridemia is easily improved by weight loss, physical exercise, and diet intervention. ApoB-48 levels may also be useful for evaluating lifestyle modifications or drug therapies and improving residual risks. One recent new drug for DM, the sodium/glucose cotransporter-2 (SGLT2) inhibitor, effects weight loss\textsuperscript{130, 131}), improves congestion or edema\textsuperscript{132}), and may improve the CV outcome, however further studies are necessary to determine its effect on postprandial hypertriglyceridemia. Investigation into the atherogenicity of CM remnants is very difficult because the selective isolation of CM remnants has historically been impossible. Kinoshita et al. created a specific monoclonal antibody against apoB48 and isolated apoB48-containing lipoproteins\textsuperscript{133}). The characteristics, physiological activities, and functions of CM remnants should be examined to acquire a new paradigm of interventions for the reduction of atherogenicity.

Acknowledgement

We thank Kaori Hizu-Shioyama, Risa Wada, Ayami Saga, and Kyoko Ozawa for their excellent administrative and technical assistance. We also thank Airi Urase for the excellent drawing of schematic figure. DM wrote the manuscript and YS reviewed the manuscript. This work was supported by Japan Society for the Promotion of Science (JSPS) KAKENHI Grant Number 15K01713, Grant-in-Aid for Scientific Research (C).

Conflict of Interest

Shizuya Yamashita and Daisaku Masuda received research funds from Ono Pharmaceutical Company Co Ltd., Kowa Pharmaceutical Company Ltd., Sanwa Kagaku Kenkyusho Co.Ltd., Astrazeneca K.K., Nippon Boehringer Ingelheim and MSD K.K. Fuji-Rebio Company shared the cost of measuring the apoB-48 levels as part of a joint research study with Shizuya Yamashita and Daisaku Masuda.
Abbreviations

apo: apolipoprotein
ASCVD: atherosclerotic cardiovascular disease
AUC: area under the curve
CHD: coronary heart disease
CI: confidence interval
CLEIA: chemiluminescence enzyme immunoassay
CM: chylomicron
eGFR: estimated glomerular filtration rate
ELISA: enzyme-linked immunosorbent assay
HDL: high-density lipoprotein
HOMA-IR: homeostatic model assessment of insulin resistance
HR; hazard ratio
HSPG: heparan sulfate proteoglycan
IDL: intermediate-density lipoprotein
LDL: low density lipoprotein
LPL: lipoprotein lipase
LRP: LDL receptor-related protein
MetS: metabolic syndrome
OR: odds ratios
PUFA: polyunsaturated fatty acids
RemL-C: Remnant Lipoprotein-Cholesterol
RemP-C: Remnant Protein-Cholesterol
TC: total cholesterol
TG: triglyceride
VLDL: very low density lipoprotein

References

1) Goldberg IJ, Eckel RH, McPherson R. Triglycerides and heart disease: still a hypothesis? Arterioscler Thromb Vasc Biol. 2011; 31: 1716-1725
2) Hirata A, Okamura T, Sugiyama D, Kudoh K, Kado A, Fujiiyoshi A, Miura K, Okuda N, Okubito T, Okayama A, Ŭeshima H; NIPPON DATA90 Research Group. The Relationship between Very High Levels of Serum High-Density Lipoprotein Cholesterol and Cause-Specific Mortality in a 20-Year Follow-Up Study of Japanese General Population. J Atheroscler Thromb. 2016; 23: 800-809
3) Klempfner R, Erez A, Sagit B-Z, Goldenberg I, Fisman E, Kopel E, Shlomo N, Israel A, Tenenbaum A. Elevated Triglyceride Level Is Independently Associated With Increased All-Cause Mortality in Patients With Established Coronary Heart Disease: Twenty-Two-Year Follow-Up of the Bezafibrate Infarction Prevention Study and Registry. Circ Cardiovasc Qual Outcomes. 2016; 9: 100-108
4) Murad MH, Hazem A, Coto-Yglesias F, Dzyubak S, Gupta S, Bancos I, Lane MA, Erwin PJ, Berglund L, Elraiyah T, Montori VM. The association of hypertriglyceridemia with cardiovascular events and pancreatitis: a systematic review and meta-analysis. BMC Endocr Disord. 2012; 12: 2
5) Schwartz GG, Abt M, Bao W, DeMicco D, Kallend D, Miller M, Mundl H, Olsson AG. Fasting Triglycerides Predict Recurrent Ischemic Events in Patients With Acute Coronary Syndrome Treated With Statins. J Am Coll Cardiol. 2015; 65: 2267-2275
6) Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi S, Egusa G, Hiro T, Hirobe K, Iida M, Kihara S, Kinoshita M, Maruyama C, Ohta T, Okamura T, Yamashita S, Yokode M, Yokote K; Japan Atherosclerosis Society. Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan -2012 version. J Atheroscler Thromb. 2013; 20: 517-523
7) Iso H, Naito Y, Sato S, Kitamura A, Okamura T, Sankai T, Shimamoto T, Iida M, Komachi Y. Serum triglycerides and risk of coronary heart disease among Japanese men and women. Am J Epidemiol. 2001; 153: 490-499
8) Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. JAMA. 2007; 298: 299-308
9) Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides and risk of ischemic stroke in the general population. JAMA. 2008; 300: 2142-2152
10) Nordestgaard BG, Langsted A, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and the risk of coronary heart disease: still a hypothesis ? Arterioscler Thromb Vasc Biol. 2011; 31: 1716-1725
11) Imai K, Fainaru M, Havel R. Composition of proteins of mesenteric lymph chylomicrons in the rat and alterations produced upon exposure of chylomicrons to blood serum and serum proteins. J Lipid Res. 1978; 19: 712-722
12) Mahmoud Hussain M. A proposed model for the assembly of chylomicrons. Atherosclerosis. 2000; 148: 1-15
13) Fujikata Y, Ishikawa Y. Remnant lipoproteins as strong key particles to atherogenesis. J Atheroscler Thromb. 2009; 16: 145-154
14) Cooper AD. Hepatic uptake of chylomicron remnants. J Lipid Res. 1997; 38: 2173-2192
15) Mahley RW, Huang Y. Atherogenic remnant lipoproteins: role for proteoglycans in trapping, transferring, and internalizing. J Clin Invest. 2007; 117: 94-98
16) Teng BB, Ochsner S, Zhang Q, Soman K V, Lau PP, Chan L. Mutational analysis of apolipoprotein B mRNA editing enzyme (APOBEC1). structure-function relationships of RNA editing and dimerization. J Lipid Res. 1999; 40: 623-635
17) Daugherty A, Lange LG, Sobel BE, Schonfeld G. Aortic accumulation and plasma clearance of beta-VLDL and
HDL: effects of diet-induced hypercholesterolemia in rabbits. J Lipid Res. 1985; 26: 955-963

18) Proctor SD, Mamo JCL. Intimal retention of cholesterol derived from apolipoprotein B100- and apolipoprotein B48-containing lipoproteins in carotid arteries of Watanabe heritable hyperlipidemic rabbits. Arterioscler Thromb Vasc Biol. 2003; 23: 1595-1600

19) Mohrscladt M, Weverling-Rijnsburger A, de Man F, Stoeken D, Sturk A, Smelt A, et al. Hyperlipoproteinemia affects cytokine production in whole blood samples ex vivo. The influence of lipid-lowering therapy. Atherosclerosis. 2000; 148: 413-419

20) Eriksson P, Nilsson L, Karpe F, Hamsten A. Very-Low-Density Lipoprotein Response Element in the Promoter Region of the Human Plasminogen Activator Inhibitor-1 Gene Implicated in the Impaired Fibrinolysis of Hypertriglyceridemia. Arterioscler Thromb Vasc Biol. 1998; 18: 20-26

21) Kawakami A, Tanaka A, Nakano T, Saniabadi A, Numano F. Stimulation of arterial smooth muscle cell proliferation by remnant lipoprotein particles isolated by immuno-affinity chromatography with anti-apolipoprotein A-I and anti-apolipoprotein B-100. Horm Metab Res. 2001; 33: 67-72

22) Kawakami A, Tanaka A, Chiba T, Nakajima K, Shimokado K, Yoshida M. Remnant Lipoprotein-Induced Smooth Muscle Cell Proliferation Involves Epidermal Growth Factor Receptor Transactivation. Circulation. 2003; 108: 2679-2688

23) Zhao, D Letterman, J Schreiber B. beta-Migrating very low density lipoprotein (beta VLDL) activates smooth muscle cell mitogen-activated protein (MAP) kinase via G protein-coupled receptor-mediated transactivation of the epidermal growth factor (EGF) receptor: effect of MAP kinase activation on beta VLDL plus EGF-induced cell proliferation. J Biol Chem. 2001; 276: 30579-30588

24) Doi H, Kugiyama K, Oka H, Sugiyama S, Ogata N, Koide SL, Nakamura SL, Yasue H. Remnant lipoproteins induce proatherothrombogenic molecules in endothelial cells through a redox-sensitive mechanism. Circulation. 2000; 102: 670-676

25) Kawakami A, Tanaka A, Nakajima K, Shimokado K, Yoshida M. Atorvastatin attenuates remnant lipoprotein-induced monocyte adhesion to vascular endothelium under flow conditions. Circ Res. 2002; 91: 263-271

26) Maeno Y, Kashiwagi A, Nishio Y, Takahara N, Kikkawa R. IDL can stimulate atherogenic gene expression in cultured human vascular endothelial cells. Diabetes Res Clin Pr. 2000; 48: 127-138

27) Park SY, Lee JH, Kim YK, Kim CD, Rhim BY, Lee WS, Hong KW. Cilostazol prevents remnant lipoprotein particle-induced monocyte adhesion to endothelial cells by suppression of adhesion molecules and monocyte chemotactant protein-1 expression via lectin-like receptor for oxidized low-density lipoprotein receptor activation. J Pharmacol Exp Ther. 2005; 312: 1241-1248

28) Wilhelm MG, Cooper AD. Induction of atherosclerosis by human chylomicron remnants: a hypothesis. J Atheroscler Thromb. 2003; 10: 132-139

29) Pitas RE, Innerarity TL, Mahley RW. Foam cells in explants of atherosclerotic rabbit aortas have receptors for beta-very low density lipoproteins and modified low density lipoproteins. Arteriosclerosis. 1983; 3: 2-12

30) Pal S, Semorine K, Watts GF, Mamo J. Identification of lipoproteins of intestinal origin in human atherosclerotic plaque. Clin Chem Lab Med. 2003; 41: 792-795

31) Okumura T, Fujioka Y, Morimoto S, Masai M, Sakoda T, Tsujino T, Kashiwamura S, Okamura H, Ohyanagi M. Chylomicron remnants stimulate release of interleukin-1beta by THP-1 cells. J Atheroscler Thromb. 2006; 13: 38-45

32) Morimoto S, Fujioka Y, Hosoi H, Okumura T, Masai M, Sakoda T, Tsujino T, Ohyanagi M, Iwasaki T. The renin-angiotensin system is involved in the production of plasminogen activator inhibitor type 1 by cultured endothelial cells in response to chylomicron remnants. Hypertens Res. 2003; 26: 315-323

33) Takahashi Y, Fujioka Y, Takahashi T, Domoto K, Takahashi A, Taniguchi T, et al. Chylomicron remnants regulate early growth response factor-1 in vascular smooth muscle cells. Life Sci. 2005; 77: 670-682

34) Kawasaki S, Taniguchi T, Fujioka Y, Takahashi A, Takahashi T, Domoto K, Taguchi M, Ishikawa Y, Yokoyama M. Chylomicron remnant induces apoptosis in vascular endothelial cells. Ann New York Acad Sci. 2000; 902: 336-341

35) Kamemura K, Fujioka Y, Takaishi H, Takahashi A, Taniguchi T, Ishikawa Y, Yokoyama M. Chylomicron remnants upregulate CD40 expression via the ERK pathway and a redox-sensitive mechanism in THP-1 cells. Atherosclerosis. 2006; 187: 257-264

36) Domoto K, Taniguchi T, Takaishi H, Takahashi T, Fujioka Y, Takahashi A, Ishikawa Y, Yokoyama M. Chylomicron remnants induce monocyte chemoattractant protein-1 expression via p38 MAPK activation in vascular smooth muscle cells. Atherosclerosis. 2003; 171: 193-200

37) Florén CH, Albers JJ, Bierman EL. Uptake of chylomicron remnants causes cholesterol accumulation in cultured human arterial smooth muscle cells. Biochim Biophys Acta. 1981; 663: 336-349

38) Fujioka Y, Cooper AD, Fong LG. Multiple processes are involved in the uptake of chylomicron remnants by mouse peritoneal macrophages. J Lipid Res. 1998; 39: 2339-2349

39) Brown M, Ramprasad MP, Umeda PK, Tanaka A, Kobayashi Y, Watanabe T, Shimoyama H, Kuo WL, Li R, Song R, Bradley WA, Gianuturo SH. A macrophage receptor for apolipoprotein B48: cloning, expression, and atherosclerosis. Proc Natl Acad Sci USA. 2000; 97: 7488-7493

40) Bermudez B, Lopez S, Varela LM, Ortega A, Pacheco YM, Moreira W, Moreno-Luna R, Abia R, Muriana FJ. Triglyceride-Rich Lipoprotein Regulates APOB48 Receptor Gene Expression in Human THP-1 Monocytes and Macrophages. J Nutr. 2012; 142: 227-232

41) Kawakami A, Tani M, Chiba T, Yui K, Shinosaki S, Nakajima K, Tanaka A, Shimokado K, Yoshida M. Atorvastatin inhibits remnant lipoprotein-induced macrophage foam cell formation through apoB48 receptor-dependent mechanism. Arterioscler Thromb Vasc Biol. 2005; 25: 424-429

42) Chan DC, Pang J, Romic G, Watts GF. Postprandial hypertriglyceridemia and cardiovascular disease: current
and future therapies. Curr Atheroscler Rep. 2013; 15: 309

43) Nakajima K, Saito T, Tamura A, Suzuki M, Nakano T, Adachi M, Tanaka A, Tada N, Nakamura H, Campos E. Cholesterol in remnant-like lipoproteins in human serum using monoclonal anti apo B-100 and anti apo A-I immunofluorescence stained gels. Clin Chim Acta. 1993; 223: 53-71

44) Devaraj S, Vega G, Lange R, Grundy SM, Jialal I. Remnant-like particle cholesterol levels in patients with dysbetalipoproteinemia or coronary artery disease. Am J Med. 1998; 104: 445-450

45) Eto M, Saito M, Nakata H, Iwashima Y, Watanabe K, Nakajima K, Saito T, Tamura A, Suzuki M, Nakano T, Imke C, Rodriguez BL, Grove JS, McNamara JR, Waslien C, Katz AR, Willcox B, Yano K, Curb JD. Are remnant-like particles independent predictors of coronary heart disease incidence? The Honolulu heart study. Arterioscler Thromb Vasc Biol. 2005; 25: 1718-1722

46) Watanabe N, Taniguchi T, Taketoh H, Kitagawa Y, Funada JI, Sekiya M, Otani T, Watanabe K, Sato M, Tanaka A. Postprandial hyperlipidemia and atherosclerosis. Curr Atheroscler Rep. 2013; 15: 309

47) Nakada Y, Kurosawa H, Tohyma J-I, Inoue Y, Ikewaki K. Increased Remnant Lipoprotein in Patients with Coronary Artery Disease—Evaluation Utilizing a Newly Developed Remnant Assay. Remnant Lipoproteins Cholesterol Homogenous Assay (RemL-C). J Atheroscler Thromb. 2007; 14: 56-64

48) Yoshida H, Kurosawa H, Hiroi Y, Inoue Y, Ikewaki K, Abe I, Saikawa S, Domitsu K, Ito K, Yanai H, Tada N. Characteristic comparison of triglyceride-rich remnant lipoprotein measurement between a new homogeneous assay (RemL-C) and a conventional immunoseparation method (RCL-P). Lipids Health Dis. 2008; 7: 18

49) Sonoda M, Sato T, Inoue Y, Ikewaki K, Abe I, Saikawa S, Domitsu K, Ito K, Yanai H, Tada N. Characteristic comparison of triglyceride-rich remnant lipoprotein measurement between a new homogeneous assay (RemL-C) and a conventional immunoseparation method (RCL-P). Lipids Health Dis. 2008; 7: 18

50) Nakada Y, Kurosawa H, Tohyma J-I, Inoue Y, Ikewaki K. Increased Remnant Lipoprotein in Patients with Coronary Artery Disease—Evaluation Utilizing a Newly Developed Remnant Assay. Remnant Lipoproteins Cholesterol Homogenous Assay (RemL-C). J Atheroscler Thromb. 2007; 14: 56-64

51) Matsuo N, Matsuoka T, Onishi S, Yamamoto H, Kato A, Makino Y, Kihara S. Impact of Remnant Lipoprotein on Coronary Plaque Components. J Atheroscler Thromb. 2015; 22: 783-795

52) Taguchi M, Ishigami M, Nishida M, Moriyama T, Yamashita S, Yamamura T. Remnant lipoprotein-cholesterol is a predictive biomarker for large artery atherosclerosis in apparently healthy women: usefulness as a parameter for annual health examinations. Ann Clin Biochem. 2011; 48: 332-327

53) Zilverstn DB. Atherogenesis: a postprandial phenomenon. Circulation. 1979; 60: 473-485

54) Carpe F, Hellénius ML, Hamsten A. Differences in postprandial concentrations of very-low-density lipoprotein and chylomicron remnants between normotriglyceridemic and hypertriglyceridemic men with and without coronary heart disease. Metabolism. 1999; 48: 301-307

55) Carpe F. Postprandial lipoprotein metabolism and atherosclerosis. J Intern Med. 1999; 246: 341-355

56) Cohn JS, Marcoux C, Davignon J. Detection, quantification, and characterization of potentially atherogenic triglyceride-rich remnant lipoproteins. Arterioscler Thromb Vasc Biol. 1999; 19: 2474-2486

57) Uchida Y, Kuroko Y, Ito S. Establishment of monoclonal antibody against human Apo B-48 and measurement of
Apo B-48 in serum by ELISA method. J Clin Lab Anal. 1998; 12: 289-292

70) Sakai N, Uchida Y, Ohashi K, Hibiye T, Saika Y, Tomari Y, Kihara S, Hiraoka H, Nakamura T, Ito S, Yamashita S, Matsuzawa Y. Measurement of fasting serum apo-B48 levels in normolipidemic and hyperlipidemic subjects by ELISA. J Lipid Res. 2003; 44: 1256-1262

71) Hanada H, Mugii S, Okubo M, Maeda I, Kuwayama K, Hidaka Y, Kitazume-Taneike R, Yamashita T, Kawase R, Nakaoka H, Inagaki M, Yuasa-Kawase M, Nakatani K, Tsubakio-Yamamoto K, Masuda D, Ohama T, Matsuyama A, Ishigami M, Nishida M, Komuro I, Yamashita S. Establishment of chemiluminescence enzyme immunoassay for apolipoprotein B-48 and its clinical applications for evaluation of impaired chylomicron remnant metabolism. Clin Chim Acta. 2012; 413: 160-165

72) Masuda D, Nishida M, Arai T, Hanada H, Yoshida H, Yamauchi-Takahara K, Moriyama T, Tada N, Yamashita S. Reference Interval for the Apolipoprotein B-48 Concentration in Healthy Japanese Individuals. J Atheroscler Thromb. 2014; 21: 618-627

73) Masuda D, Sakai N, Sugimoto T, Kitazume-Taneike R, Yamashita T, Kawase R, Nakaoka H, Inagaki M, Nakatani K, Yuasa-Kawase M, Tsubakio-Yamamoto K, Ohama T, Nakagawa-Toyama Y, Nishida M, Ishigami M, Masuda Y, Matsuyama A, Komuro I, Yamashita S. Fasting serum apolipoprotein B-48 can be a marker of postprandial hyperlipidemia. J Atheroscler Thromb. 2011; 18: 1062-1070

74) Kinoshita M, Ohnishi H, Maeda T, Yoshimura N, Takeoka Y, Yasuda D, Kusano J, Mashimo Y, Saito S, Shimamoto K, Teramoto T. Increased serum apolipoprotein B48 concentration in patients with metabolic syndrome. J Atheroscler Thromb. 2009; 16: 517-522

75) Yuasa-Kawase M, Masuda D, Kitazume-Taneike R, Yamashita T, Kawase R, Nakaoka H, Inagaki M, Nakatani K, Tsubakio-Yamamoto K, Ohama T, Toyama-Nakagawa Y, Nishida M, Ishigami M, Saito M, Eto M, Matsuyama A, Komuro I, Yamashita S. Apolipoprotein B-48 to triglyceride ratio is a novel and useful marker for detection of type III hyperlipidemia after antihyperlipidemic intervention. J Atheroscler Thromb. 2012; 19: 862-871

76) Mugii S, Hanada H, Takeoka K, Hidaka Y, Masuda D, Ohama T, Toyama Y, Yamashita S. Clinical significance of apolipoprotein B-48 (apoB-48) in patients with thyroid disease. Rinsho Byori. 2009; 57: 1058-1063

77) Okubo M, Hanada H, Matsui M, Hidaka Y, Masuda D, Sakata Y, Yamashita S. Serum apolipoprotein B-48 concentration is associated with a reduced estimated glomerular filtration rate and increased proteinuria. J Atheroscler Thromb. 2014; 21: 974-982

78) Hayashi T, Hirano T, Taira T, Tokuno A, Morii Y, Koba S, Adachi M. Remarkable increase of apolipoprotein B48 level in diabetic patients with end-stage renal disease. Atherosclerosis. 2008; 197: 154-158

79) Guo Q, Avramoglu RK, Adeli K, Kohen Avramoglu R, Adeli K. Intestinal assembly and secretion of highly dense/lipid-poor apolipoprotein B48-containing lipoprotein particles in the fasting state: evidence for induction by insulin resistance and exogenous fatty acids. Metabo-

lism. 2005; 54: 689-697

80) Haidari M, Leung N, Mahbub F, Uffelman KD, Kohen-Avramoglu R, Lewis GF, Adeli K. Fasting and postprandial overproduction of intestinally derived lipoproteins in an animal model of insulin resistance. Evidence that chronic fructose feeding in the hamster is accompanied by enhanced intestinal de novo lipogenesis and ApoB48-containing lipoprotein overproduction. J Biol Chem. 2002; 277: 31646-31655

81) Nakatani K, Sugimoto T, Masuda D, Okano R, Oya T, Monden Y, Yamashita T, Kawase R, Nakaoka H, Inagaki M, Yuasa-Kawase M, Tsubakio-Yamamoto K, Ohama T, Nishida M, Ishigami M, Komuro I, Yamashita S. Serum apolipoprotein B-48 levels are correlated with carotid intima-media thickness in subjects with normal serum triglyceride levels. Atherosclerosis. 2011; 218: 226-232

82) Masuda D, Sugimoto T, Tsuji K-I, Inagaki M, Nakatani K, Yuasa-Kawase M, Tsubakio-Yamamoto K, Ohama T, Nishida M, Ishigami M, Kawamoto T, Matsuyama A, Sakai N, Komuro I, Yamashita S.. Correlation of fasting serum apolipoprotein B-48 with coronary artery disease prevalence. Éur J Clin Invest. 2012; 42: 992-999

83) Mori K, Ishida T, Yasuda T, Monguchi T, Sasaki M, Kondo K, Hasokawa M, Nakajima H, Haraguchi Y, Sun L, Shinohara M, Toh R, Nishimura K, Hirata K. Fasting serum concentration of apolipoprotein B48 represents residual risks in patients with new-onset and chronic coronary artery disease. Clin Chim Acta. 2013; 421: 51-56

84) Cara L, Dubois C, Borel P, Armand M, Senft M, Portugal H, Pauli AM, Bernard PM, Lairon D. Effects of oat bran, rice bran, wheat fiber, and wheat germ on postprandial lipemia in healthy adults. Am J Clin Nutr. 1992; 55: 81-88

85) Annuzzi G, Bozzetto L, Costabile G, Giacco R, Mangione A, Anniballi G, Vitale M, Vetrani C, Cipriano P, Della Corte G, Pasanisi F, Riccardi G, Rivellese AA.. Diets naturally rich in polyphenols improve fasting and postprandial dyslipidemia and reduce oxidative stress: a randomized controlled trial. Am J Clin Nutr. 2014; 99: 463-471

86) Hooper L, Kay C, Abdelhamid A, Kroon PA, Cohn JS, Rimm EB, Cassidy A. Effects of chocolate, cocoa, and flavan-3-ols on cardiovascular health: a systematic review and meta-analysis of randomized trials. Am J Clin Nutr. 2012; 95: 740-751

87) Aoyama T, Nosaka N, Kasai M. Research on the nutritional characteristics of medium-chain fatty acids. J Med Invest. 2007; 54: 385-388

88) Yanai H, Tomono Y, Ito K, Furutani N, Yoshida H, Tada N. Diacylglycerol oil for the metabolic syndrome. Nutr J. 2007; 6: 43

89) Maki KC, Mustad V, Dickdin MR, Geohas J. Postprandial metabolism with 1,3-diacylglycerol oil versus equivalent intakes of long-chain and medium-chain triacylglycerol oils. Nutrition. 2009; 25: 627-633

90) Takase H, Shoji K, Hase T, Tokimitsu I. Effect of diacylglycerol on postprandial lipid metabolism in non-diabetic subjects with and without insulin resistance. Atherosclerosis. 2005; 180: 197-204

91) Yasunaga K, Saito S, Zhang Y, Hernandez-Ono A, Ginsberg HN. Effects of triacylglycerol and diacylglycerol oils
on blood clearance, tissue uptake, and hepatic apolipo-
protein B secretion in mice. J Lipid Res. 2007; 48: 1108-1121
92) Nagao T, Watanabe H, Goto N, Onizawa K, Taguchi H, 
Matsuo N, Yasukawa T, Tsushima R, Shimasaki H, Ita-
kura H. Dietary diacylglycerol suppresses accumulation 
of body fat compared to triacylglycerol in men in a dou-
ble-blind controlled trial. J Nutr. 2000; 130: 792-797
93) Fuji A, Allen TJ, Nestel PJ. A 1,3-diacylglycerol-rich oil 
duces less atherosclerosis and lowers plasma cholesterol 
in diabetic apoE-deficient mice. Atherosclerosis. 2007; 193: 55-61
94) Ooi EM, Lichtenstein AH, Millar JS, Diffenderfer MR, 
Lamon-Faya S, Rasmussen H, Wely FK, Barrett PH, Schaefer EJ. Effects of Therapeutic Lifestyle Change 
diets high and low in dietary fish-derived FAs on lipoprotein metabolism in middle-aged and elderly subjects. 
J Lipid Res. 2012; 53: 1958-1967
95) Ooi EMM, Watts GF, Ng TWK, Barrett PHR. Effect of dietary 
Fatty acids on human lipoprotein metabolism: a 
comprehensive update. Nutrients. 2015; 7: 4416-4425
96) Weintraub MS, Zechner R, Brown A, Eisenberg S, Bres-
low JL. Dietary polyunsaturated fats of the ω-6 and 
ω-3 series reduce postprandial lipoprotein levels. 
Chronic and acute effects of fat saturation on postpran-
dial lipoprotein metabolism. J Clin Invest. 1988; 82: 
1884-1893
97) Miyoshi T, Noda Y, Ohno Y, Sugiyma H, Oe H, Nakam-
ura K, Kohno K, Ito H. Omega-3 fatty acids improve 
postprandial lipemia and associated endothelial dysfunc-
tion in healthy individuals - a randomized cross-over 
trial. Biomed Pharmacother. 2014; 68: 1071-1077
98) Matsuzaki M, Yokoyama M, Saito Y, Origasa H, Ishi-
kawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita 
T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shi-
rato K, Matsuzawa Y; JELIS Investigators. Incremental 
effects of eicosapentaenoic acid on cardiovascular events 
in statin-treated patients with coronary artery disease. 
Circ J. 2009; 73: 1283-1290
99) Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, 
Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Ita-
kura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shi-
mada K, Shirato K; Japan EPA lipid intervention study 
(JELIS) Investigators. Effects of eicosapentaenoic acid 
on major coronary events in hypercholesterolaemic 
patients (JELIS): a randomised open-label, blinded end-
point analysis. Lancet. 2007; 369: 1090-1098
100) Saito Y, Yokoyama M, Origasa H, Matsuzaki M, Matsu-
zawa Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Ita-
kura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shi-
mada K, Shirato K; JELIS Investigators, Japan. Effects of 
EPA on coronary artery disease in hypercholesterolemic 
patients with multiple risk factors: Sub-analysis of pri-
mary prevention cases from the Japan EPA Lipid Inter-
vention Study (JELIS). Atherosclerosis. 2008; 200: 135-
140
101) Purcell R, Latham SH, Botham KHM, Hall WL, 
Wheeler-Jones CPD. High-fat meals rich in EPA plus 
DHA compared with DHA only have differential effects 
on postprandial lipemia and plasma 8-isoprostane F2α 
concentrations relative to a control high-oleic acid meal: 
A randomized controlled trial. Am J Clin Nutr. 2014;
100: 1019-1028
102) Ishigami M, Yamashita S, Sakai N, Hirano K, Hiraoka 
H, Nakamura T, Matsuzawa Y. Atorvastatin markedly 
improves type III hyperlipoproteinemia in association 
with reduction of both exogenous and endogenous apo-
liprotein B-containing lipoproteins. Atherosclerosis. 
2003; 168: 359-366
103) Parhofer KG, Laubach E, Barrett PHR. Effect of ator-
vasatin on postprandial lipoprotein metabolism in hyper-
triglyceridemic patients. J Lipid Res. 2003; 44: 1192-1198
104) Nagashima H, Endo M. Pitavastatin prevents postpran-
dial endothelial dysfunction via reduction of the serum 
triglyceride level in obese male subjects. Heart Vessels. 
2011; 26: 428-434
105) Arao K, Yasu T, Umemoto T, Jinbo S, Ikeda N, Ueda S, 
Kawakami M, Momomura S. Effects of pitavastatin on 
fasting and postprandial endothelial function and blood 
rheology in patients with stable coronary artery disease. 
Circ J. 2009; 73: 1523-1530
106) Rosenson RS, Wolff DA, Huskin AL, Helenowski IB, 
Rademaker AW. Fenofibrate therapy ameliorates fasting 
and postprandial lipoproteinemia, oxidative stress, and 
the inflammatory response in subjects with hypertriglyc-
eridemia and the metabolic syndrome. Diabetes Care. 
2007; 30: 1945-1951
107) Sabine W, Lilli W, Katrin G, Jutta D, Claus L. Chylomi-
cron remnants of various sizes are lowered more effec-
tively by fenofibrate than by atorvastatin in patients with 
combined hyperlipidemia. Atherosclerosis. 2003; 171: 
369-377
108) Sandoval JC, Nakagawa-Toyama Y, Masuda D, Tochino 
Y, Nakaoka H, Kawase R, Yuasa-Kawase M, Nakatani K, 
Inagaki M, Tsukabio-Yamamoto K, Ohama T, Nishida 
M, Ishigami M, Komuro I, Yamashita S. Fenofibrate 
reduces postprandial hypertriglyceridemia in CD36 
knockout mice. J Atheroscler Thromb. 2010; 17: 610-618
109) Masuda D, Hirano K, Oku H, Sandoval JC, Kawase R, 
Yuasa-Kawase M, Yamashita Y, Takada M, Tsukabio-
Yamamoto K, Tochino Y, Koseki M, Matsuura F, Nishida 
M, Kawamoto T, Ishigami M, Hori M, Shimomura I, 
Yamashita S. Chylomicron remnants are increased in 
the postprandial state in CD36 deficiency. J Lipid Res. 
2009; 50: 999-1011
110) Arbel Y, Klemplner R, Erez A, Goldenberg I, Benzekry 
S, Shlomo N, Fisman EZ, Tenenbaum A; BIP Study 
Group. Bezafibrate for the treatment of dyslipidemia in 
patients with coronary artery disease: 20-year mortality 
follow-up of the BIP randomized control trial. Cardi-
vasc Diabetol. 2016; 15: 11
111) Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen 
MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, 
Kesäniemi YA, Sullivan D, Hunt D, Colman P, d’Emden 
M, Whiting M, Ehnholm C, Laakso M; FIELD study 
investigators. Effects of long-term fenofibrate therapy on 
cardiovascular events in 9795 people with type 2 dia-
abetes mellitus (the FIELD study): randomised controlled 
trial. Lancet. 2005; 366: 1849-1861
112) ACCORD Study Group, Ginsberg HN, Elam MB, 
Lovato LC, Crouse JR 3rd, Leiter LA, Linz P, Friedewald 
WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH,
113) Masuda D, Nakagawa-Toyama Y, Nakatani K, Inagaki M, Tsubakio-Yamamoto K, Sandoval JC, Ohama T, Nishida M, Ishigami M, Yamashita S. Ezetimibe improves postprandial hyperlipidaemia in patients with type IIb hyperlipidaemia. Eur J Clin Invest. 2009; 39: 689-698

114) Hajer GR, Dallinga-Thie GM, van Vark - van der Zee LC, Visseren FLJ. The effect of statin alone or in combination with ezetimibe on postprandial lipoprotein composition in obese metabolic syndrome patients. Atherosclerosis. 2009; 202: 216-224

115) Sandoval JC, Nakagawa-Toyama Y, Masuda D, Tochino Y, Nakaoka H, Kawase R, Yuasa-Kawase M, Nakatani K, Inagaki M, Tsubakio-Yamamoto K, Ohama T, Matsuyama A, Nishida M, Ishigami M, Komuro I, Yamashita S. Molecular mechanisms of ezetimibe-induced attenuation of postprandial hypertriglyceridemia. J Atheroscler Thromb. 2010; 17: 914-924

116) Westerink J, Deanfield JE, Imholz BP, Spiering W, Basart DC, Coll B, Kastelein JJ, Visseren FL. High-dose statin monotherapy versus low-dose statin/ezetimibe combination on fasting and postprandial lipids and endothelial function in obese patients with the metabolic syndrome: The PANACEA study. Atherosclerosis. 2013; 227: 118-124

117) Yuno K, Nakamura K, Miyoshi T, Enko K, Kohno K, Morita H, Kusano KF, Ito H. Ezetimibe improves postprandial hyperlipemia and its induced endothelial dysfunction. Atherosclerosis. 2011; 217: 486-491

118) Kikuchi K, Nezu U, Inazumi K, Miyazaki T, Ono K, Shirakawa J, Sato K, Koike H, Wakasugi T, Sato M, Kawakami C, Watanabe S, Yamakawa T, Terauchi Y. Double-blind randomized clinical trial of the effects of ezetimibe on postprandial hyperlipidemia and hyperglycaemia. J Atheroscler Thromb. 2012; 19: 1093-1101

119) Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators. Ezetimibe added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015; 372: 2387-2397

120) Tremblay AJ, Lamarche B, Deacon CF, Weissagal SJ, Couture P. Effect of sitagliptin therapy on postprandial lipoprotein levels in patients with type 2 diabetes. Diabetes Obes Metab. 2011; 13: 366-373

121) Boschmann M, Engeli S, Dobberstein K, Budziarek P, Strauss A, Boehnke J, Sweep FC, Luft FC, He Y, Foley JE, Jordan J. Dipeptidyl-peptidase-IV inhibition augments postprandial lipid mobilization and oxidation in type 2 diabetic patients. J Clin Endocrinol Metab. 2009; 94: 846-852

122) Matkainen N, Mänttäri S, Schweizer A, Ulvestad A, Mills D, Dunning BE, Foley JE, Taskinen MR. Vildagliptin therapy reduces postprandial intestinal triglyceride-rich lipoprotein particles in patients with type 2 diabetes. Diabetologia. 2006; 49: 2049-2057

123) Hsieh J, Longuet C, Baker CL, Qin B, Federico LM, Drucker DJ, Adeli K. The glucagon-like peptide 1 receptor is essential for postprandial lipoprotein synthesis and secretion in hamsters and mice. Diabetologia. 2010; 53: 552-561

124) Hermansen K, Bakdal TA, Düring M, Pietraszek A, Mortensen LS, Jørgensen H, Flint A. Liraglutide suppresses postprandial triglyceride and apolipoprotein B48 elevations after a fat-rich meal in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled, cross-over trial. Diabetes Obes Metab. 2013; 15: 1040-1048

125) Meier JJ, Getzmann A, Götz O, Gallwitz B, Holst JJ, Schmidt WE, Nauck MA. Glucagon-like peptide 1 abolishes the postprandial rise in triglyceride concentrations and lowers levels of non-esterified fatty acids in humans. Diabetologia. 2006; 49: 452-458

126) Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederick R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013; 369: 1317-1326

127) White WB, Cannon CP, Heller SR, Nissen SE, Bergestal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013; 369: 1327-1335

128) Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F, Peterson ED, Holman RR; TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015; 373: 232-242

129) Marso SP, Daniels FR, Kristensen P, Mann JF, Nissen SE, Pocock S, Poore SR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016; 375: 311-322

130) Kaku K, Watada H, Iwamoto Y, Utsunomiya K, Terauchi Y, Tobe K, Tanizawa Y, Araki E, Ueda M, Suganami H, Watanabe D; Tofogliflozin 003 Study Group. Efficacy and safety of monotherapy with the novel sodium/glucose cotransporter-2 inhibitor tofogliflozin in Japanese patients with type 2 diabetes mellitus: a combined Phase 2 and 3 randomized, placebo-controlled, double-blind, parallel-group comparative study. Cardiovasc Diabetol. 2014; 13: 65

131) Li J, Ma J, Li H, Mansfield TA, T'joen CL, Iqbal N, Ptaszynska A, List JF. Dapagliflozin as monotherapy in drug-naive Asian patients with type 2 diabetes mellitus: a randomized, blinded, prospective phase III study. Clin Ther. 2014; 36: 84-100

132) Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki
E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015; 373: 2117-2128

Yoshimura N, Kinoshita M, Teramoto T. Isolation and characterization of apolipoprotein B48-containing lipoproteins with a monoclonal antibody against apolipoprotein B48. J Atheroscler Thromb. 2009; 16: 740-747