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Review

Postprandial Hyperlipidemia and Remnant Lipoproteins

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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

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 ASCVD[1, 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

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(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, nonfatal myocardial infarction, stroke, and unstable angina in models adjusted for classic CHD risk factors[5]. 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 intervention[6]. 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 levels[7]. Nordestgaard *et al*. also showed that non-fasting TG levels are correlated with the morbidity of CHD[8] and ischemic stroke[9] 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 profiles[10], 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 settings[10]. 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 trunks[11, 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 protein[16].

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[13]. 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[17, 18]. Many basic and clinical experiments have proven that remnant lipoproteins directly and indirectly correlate to the enhancement of atherogenicity, since they enhance systemic inflammation[19] and platelet activation, coagulation, and thrombus formation by the induction of plasminogen activator inhibitor-1 (PAI-1)[20]; they induce the proliferation of smooth muscle cells (SMC)[21] via epidermal growth factor (EGF) receptor transactivation[22, 23]; they up-regulate intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and tissue factor (TF)[24]; they increase the adhesion of monocyte cells to endothelial cells[25]; and they stimulate the transmigration of monocytes into the sub-endothelial space by up-regulating monocyte chemoattractant protein-1 (MCP-1) expression[26, 27]. Besides these changes, remnant lipoproteins can directly penetrate the arterial wall, infiltrate the sub-endothelial space, and accelerate macrophage foam cell formation[28, 29].

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[18]. 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 (1/100-200 in the fasting concentration)[30]. 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[13]. As shown in **Fig. 1**, CM remnants also enhance systemic inflammation (release in interleukin-1β)[31] and platelet activation by the induction of PAI-1[32]; they induce SMC proliferation via early growth response factor-1 (Egr-1)[33]; they stimulate the apoptosis of endothelial cells[34]; they up-regulate CD40 expression, which is associated with the expression of matrix metalloproteinase chemokines, cytokines, and adhesion molecules via B-cell differentiation[35]; they up-regulate MCP-1 expression[36]; and they enhance the cellular cholesterol content[37]. 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[38]. 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[39-41]. 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[42], 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)[43]. 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[43]. 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[44, 45]. 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[46]; and postprandial increases in RLP-C or RLP-TG levels are significantly higher in hyperinsulinemic diabetic patients[47, 48]. 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[49]. The accumulation of remnant lipoproteins is also related to the accumulation of small, dense LDL [sdLDL, small in diameter ($\leqq$25.5 nm) and high in density because it is rich in TG content][50] or hypo-HDL-cholesterolemia[13, 51]. 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-

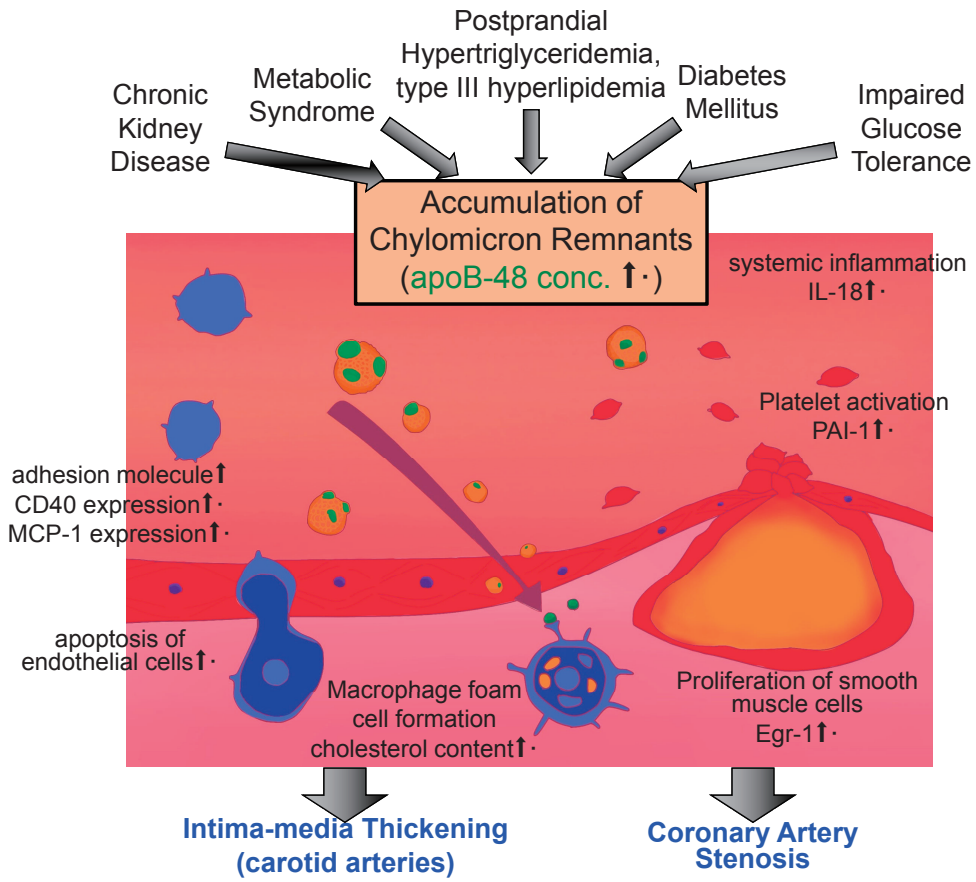

Fig. 1. Chylomicron remnants are accumulated in many metabolic disorders and contributes to the progression of atherosclerotic plaque

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.

tribute to the development of atherosclerotic plaque. Clinically, the increased cholesterol levels of sdLDL fractions correlate the frequency of CHD[52, 53]. High sdLDL levels are observed in patients whose remnant lipoproteins are elevated, such as in metabolic syndrome patients or in patients with abnormal glucose metabolism[54]. The clustering of high remnant lipoproteins, high sdLDL, and hypo-HDL-cholesterolemia may strongly induce atherosclerotic plaque formation and enhance the morbidity of ASCVD. RLP-C levels correlate with an increase in the intima-media thickness (IMT) of the carotid artery[55] and the morbidity of CHD[44], which is independent of hypertriglyceridemia, hyper LDL-cholesterolemia, or hypo HDL-choelsterolemia[56]. In Japan, Kugiyama *et al.* 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/dL[57].

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 any type of lipoproteins properly such as apoE-rich VLDLs or TG-rich CMs[59]. In the RemL-C method, CM remnants and VLDL remnants are directly solu-

bilized and degraded by a surfactant and phospholipase-D and separated from other lipoproteins with higher specificity than RLP-C[60]. The RemL-C assay has a significantly positive correlation with the RLP-C assay and the cholesterol in IDL fractions in healthy subjects[61]. 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 DM[62]. 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 plaque[63]. The measurement of RemL-C level may be useful in annual health examinations of woman for detecting large artery atherosclerosis[64]. 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 atherosclerosis[65]. 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 remnants[68]. 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 antibody[69], 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 system[71]. 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 normolipidemia[72]. 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 levels[73]. 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/m^2) than in non-obese subjects (BMI < 25 kg/m^2) (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 MetS[72]. 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 MetS[74]. 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 lipoproteins[76]. 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 m^2) 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 patients[77]. 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[78]. 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[79]. 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[79]. These changes are suggested to be due to the up-regulation of intestinal enterocyte *de novo* lipogenesis[80].

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[81, 82]. 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[81]. 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 them was observed in the subjects with 100≤ TG <150 mg/dL, which is treated as the normal TG level in Japanese Guidelines[6]. This result indicates the possibility that the cut-off level of hypertriglyceridemia (150≤TG mg/dL) does not necessarily reflect atherogenicity of the carotid artery and the fasting apoB-48 level might be a stronger marker for atherogenicity than the TG level. Moreover, fasting apoB-48 levels correlate with the prevalence of coronary artery stenosis[82]. The serum apoB-48 level is significantly higher in subjects with coronary artery stenosis (n=96) than age-, sex-, and body mass index (BMI)-matched subjects without overt coronary artery stenosis (n=67) (6.9±2.6 vs. 3.9±2.4 μg/mL, $p<0.0001$) among subjects who received a coronary angiography and did not take any lipid-lowering drugs. The fasting apoB-48 level has the most significant correlation with the existence of CHD and the clustering of high fasting apoB-48 levels (>4.34 μg/mL) and other coronary risk factors increase the prevalence of CHD. Mori *et al*. showed that after adjusting for classic ASCVD risk factors, the apoB-48 level was higher in new-onset and chronic CAD patients than in those without CAD ($p<0.001$), which is an independent predictor of coronary risk in new-onset and chronic CAD, and correlated with a new lesion progression after the prior percutaneous coronary intervention (PCI)[83]. 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[6]. 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[84].

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[85] and lowers CHD risk[86].

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[87].

Diacylglycerol(DAG): as summarized by Yanai and Tada *et al*., DAG is effective in reducing postprandial hypertriglyceridemia[88]. 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[88]. A 1,3-DAG lowers the postprandial increase of TG and remnant lipoproteins in subjects with insulin-resistance[89, 90], which is partially due to the increased clearance of DAG-incorporated CM via LPL-mediated lipolysis and hepatic uptake[91]. The

long-term consumption of DG-rich oil significantly decreases visceral and subcutaneous fat areas and hepatic fat content in humans[92] and atherosclerotic plaque in diabetic apoE-deficient mice[93].

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-conatining TRLs by decreasing their production rate[94]. 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[95]. 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[96].

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 docoxahexaenoic 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[85] and improve endothelial dysfunction after the cookie test[97]. 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[98, 99]. In a subanalysis of the JELIS trial, EPA was more effective for the primary prevention of CHD (−53%) in subjects with hypertriglyceridemia (≧150 mg/dL) and hypo-HDL cholesterolemia (<40 mg/dL), which suggests that EPA may be especially beneficial in patients with increased accumulation of remnant lipoproteins[100]. 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[101]. Instead, the oxidative stress marker, plasma 8-isoprostane F2α, is increased by the addition of EPA plus DHA but reduced by the addition of DHA only[101], 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 ($p<0.01$)[102]. Parhofer *et al.* showed that atorvastatin significantly decreased the postprandial increase of TG and CM[103]. Pitavastatin attenuates postprandial TG increase, abolishes the decrease in postprandial FMD by improving postprandial endothelial dysfunction[104], and suppresses the postprandial increase of oxidative stress (urine 8-OHdG)[105].

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[106]. Sabine *et al.* found that fenofibrate reduces the postprandial increase of small CM remnants effectively in patients with mixed hyperlipidemia[107]. 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 postprandail hypertriglyceridemia, CD36 knockout (KO) mice[108, 109]. 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 ≥200 mg/dL) in the BIP trial[110]. However, the FIELD trial showed that a fenofibrate did not significantly reduce CHD events in diabetic patients[111], and the ACCORD Lipid trial also showed that a fenofibrate in combination with simvastatins did not reduce CHD events in diabetic patients[112]. On the other hand, when DM patients with hypertriglyceridemia (≧204 mg/dL) and hypo-HDL-cholesterolemia (<34 mg/dL) were selected as study subjects, the combination of fenobibrate 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[113], obesity, and MetS[114]. 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[113]. 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[115]. In clinical studies, ezetimibe in combination with statins improved

postprandial hypertriglyceridemia in obese patients with MetS[116] in combination with the improvement of endothelial function[116], and these effects were also observed in normal healthy volunteers[117]. In a crossover trial, ezetimibe improved postprandial hypertriglyceridemia but did not improve postprandial hyperglycaemia[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[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[120]. Vildagliptin therapy also suppresses postprandial hypertriglyceridemia, which was intended to be a reduction in the postprandial increase of CM remnants[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[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[124]. Another report showed that gastric emptying was delayed and FFAs levels were low[125], however the mechanism of improving postprandial hypertriglyceridemia is controversial. Mega trials of the DPP-4 inhibitors saxagliptin (SAVOR-TIMI 53)[126], alogliptin (EXAMINE)[127], and sitagliptin (TECOS)[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[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[130, 131], improves congestion or edema[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[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.

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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., Astrazeneka 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: an 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
IGT: impaired glucose tolerance
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
RLP-C: Remnant-Like Particles-Cholesterol
TC: total cholesterol
TG: triglyceride
VLDL: very low density lipoprotein

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