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Table 1. Prevalence of type IIb dyslipidemia in 3 Japanese cohorts: NIPPON DATA90, Serum Lipid Survey in 2000, and Hisayama study

	NIPPON DATA90		Serum Lipid Survey		Hisayama Study	
	men	women	men	women	men	women
n	485	592	168	67	149	172
prevalence (%)	13.8	12.1	8.8	5.0	10.8	9.4
mean age ± SD	51.0 ± 12.3	58.9 ± 11.4	47.8 ± 10.1	57.9 ± 11.2	56 ± 11	62 ± 10
BMI	25.0 ± 2.9	24.5 ± 3.1	25.3 ± 2.8	24.9 ± 3.4	24.7 ± 2.5	24.6 ± 3.8
SBP (mmHg)	140.4 ± 17.7	143.3 ± 20.3	129.8 ± 19.7	128.0 ± 18.3	140.3 ± 18.0	138.7 ± 23.0
DBP (mmHg)	87.1 ± 11.5	84.2 ± 12.1	81.1 ± 12.6	77.70 ± 11.0	85.6 ± 10.6	81.0 ± 13.3
HbA1c (%)	5.2 ± 1.0	5.3 ± 1.1	5.1 ± 0.9	5.2 ± 0.8	5.3 ± 0.9	5.4 ± 0.9
T-Cho (mg/dL)	249.0 ± 27.5	254.7 ± 30.9	252.1 ± 24.2	255.5 ± 31.0	246.1 ± 32.2	248.5 ± 34.1
TG (mg/dL)	269.7 ± 150.9	235.8 ± 104.4	272.5 ± 221.2	190.3 ± 48.4	288.9 ± 223.6	214.0 ± 95.7
HDL-c (mg/dL)	44.4 ± 13.1	44.8 ± 13.0	47.0 ± 10.1	53.1 ± 11.3	53.2 ± 11.5	57.0 ± 12.8
LDL-c (mg/dL)	150.7 ± 34.0	158.8 ± 32.4	163.3 ± 20.8	164.4 ± 24.7	135.1 ± 50.3	148.8 ± 34.6
non-HDL-c (mg/dL)	204.6 ± 29.0	206.0 ± 33.0	205.1 ± 23.3	202.5 ± 27.8	192.9 ± 33.0	191.6 ± 35.1
diabetes (%)	13.0	15.0	3.6	9.0	34.9	25.0
hypertension (%)	60.0	65.5	10.7	25.4	57.7	51.7
metabolic syndrome (%)	38.6	33.5	32.7	14.9	51.7	30.8
smoking (%)	68.0	6.6	55.4	7.5	44.3	9.3
coronary artery disease (%)	2.5	4.2	3.6	3.0	2.0	1.2
stroke (%)	1.7	2.0	1.2	0.0	2.0	1.2

ides. In Japan, hypercholesterolemia and hypertriglyceridemia are defined as LDL cholesterol ≥ 140 mg/dL and triglycerides ≥ 150 mg/dL, respectively[1]. Type IIb dyslipidemia is frequently associated with type 2 diabetes mellitus, metabolic syndrome, and chronic kidney disease (CKD)[2-4]. Among primary dyslipidemia, familial combined hyperlipidemia (FCHL) often shows this type of dyslipidemia[5]. Type IIb dyslipidemia is also associated with the development of small, dense LDL, low high-density lipoprotein (HDL) cholesterolemia along with high triglycerides and LDL cholesterol. These features of small, dense LDL, low HDL cholesterolemia, high triglycerides are called the atherogenic lipid triad, implying their role in atherogenesis.

Although many lines of evidence indicate that LDL cholesterol is an important risk factor for cardiovascular disease (CVD)[6], it is still controversial whether plasma triglyceride levels are associated with the development of cardiovascular disease; however, recent reports have shown that plasma triglyceride levels are an independent risk for coronary artery disease (CAD)[7-10]. In addition, non-fasting triglyceride levels have been shown to be associated with CAD and stroke[11, 12]. In spite of the accumulating evidence against LDL cholesterol and triglycerides, few reports have addressed the effect of type IIb dyslipidemia on cardiovascular disease. Therefore, considering that elevated LDL cholesterol and triglyceride along with an increase of atherogenic lipoproteins, such as small, dense LDL and remnants, are found in type IIb dyslipidemia, and that this type of dyslipidemia is often associated with type 2 diabetes, metabolic syndrome, CKD, and FCHL, we should recognize that type IIb dyslipidemia is a high-risk condition for CVD and should establish a guideline for its management.

Epidemiology of Type IIb Dyslipidemia

To show the prevalence of type IIb dyslipidemia in the Japanese population, we studied the prevalence of type IIb dyslipidemia in three Japanese cohorts (NIPPON DATA90, Serum Lipid Survey in 2000, and the Hisayama study). NIPPON DATA90 is a cohort study of the National Survey on Circulatory Disorders of Japan, including the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged (NIPPON DATA)[13]. Baseline surveys of this cohort were performed in 1990. The Serum Lipid Level Survey 2000 was designed to produce representative data of serum lipid levels in the civilian Japanese population in 2000[14]. The total number of this cohort is 12,839. The Hisayama study is a cohort study that started in 1961 in a small town near Fukuoka[15]. **Table 1** shows

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Table 2. Prevalence of type IIb dyslipidemia in each age group in the Serum Lipid Survey in 2000

age	30-39		40-49		50-59		60-69		70-79	
gender	men	women	men	women	men	women	men	women	men	women
prevalence (%)	9.73	1.54	9.21	2.31	9.36	8.24	6.99	11.01	5.49	6.41

the prevalence in three different cohorts: NIPPON DATA90, Serum Lipid Survey in 2000, and Hisayama study (from The Research Committee report for Primary Hyperlipidemia, Research on Measures against Intractable Diseases by the Ministry of Health, Labor, and Welfare in 2007, http://mhlw-grants.niph.go.jp/niph/search/NIDD00.do). The prevalence of type IIb dyslipidemia in men was 8.8 to 13.8%, and 5.0 to 12.1% in women. In all cohorts, the prevalence of type IIb dyslipidemia was higher in men than in women. The mean age at onset of type IIb dyslipidemia was higher in women than in men in all cohorts, indicating that women tend to develop type IIb dyslipidemia after menopause. In terms of the comorbidities, 3.6 to 34.9% of men had type 2 diabetes, while 9.0 to 25.0% of women had type 2 diabetes, showing no significant difference between men and women in the three cohorts; however, the prevalence of metabolic syndrome in type IIb dyslipidemia was higher in men (32.7 to 51.7%) than in women (14.9 to 33.5%).

Table 2 shows the prevalence of type IIb dyslipidemia in each age group of men and women according to the data from the Serum Lipid Survey in 2000. In men, the prevalence of type IIb dyslipidemia was approximately 20%, similar from their 30s to 50s, while in women, the prevalence was increased from their 50s. In their 60s, the prevalence was higher in women than in men.

Familial Combined Hyperlipidemia (FCHL)

FCHL, the most common genetic dyslipidemia in man, affects 1%-2% of the population and occurs in 10%-20% of premature myocardial-infarction survivors[16, 17]. It is believed that the primary metabolic defect in FCHL leads to hepatic overproduction of very-low-density lipoprotein (VLDL), resulting in elevated plasma cholesterol and triglyceride levels; type II b dyslipidemia. The existence of small, dense LDL particles is another characteristic feature of FCHL, and the combination of small, dense LDL with increased triglycerides and apolipoprotein B (apoB) concentrations and reduced HDL cholesterol levels is termed "atherogenic lipid triad". This atherogenic lipid triad is independently associated with an increased risk for CAD[18]. Moreover, it has been suggested that hyper-apoB, defined as an increased apoB:LDL cholesterol (apoB:LDL-C) ratio, reflects the presence of FCHL in affected individuals. Delayed clearance of triglyceride-rich remnant particles, such as intermediate density lipoproteins (IDL) and chylomicron remnants, leads to an increased residence time of these atherogenic particles within the circulation[16]. These changes also contribute to the insulin resistance often accompanying FCHL. FCHL shares considerable phenotypic overlap with type 2 diabetes as well as with metabolic syndrome, and therapeutic lifestyle change is effective to decrease LDL cholesterol and triglycerides in FCHL patients.

FCHL was first postulated to segregate as an autosomal dominant trait[19], but there is increasing evidence that it is an oligogenic disorder with a complex pattern of inheritance[20, 21]. FCHL family members exhibit varying degrees of dyslipidemia with either isolated high triglycerides, LDL cholesterol, or both, which is another feature of FCHL. Several candidate genes have been reported, such as upstream stimulatory factor 1 (USF1)[21], apoA5[22], Retinoid X receptor-γ[23], hepatic lipase[24], and so forth.

The diagnostic criteria for FCHL in Japan are as follows:

1) Increased levels of LDL cholesterol $\geq$140 mg/dL and/or triglycerides $\geq$150 mg/dL (mainly type IIb dyslipidemia, but sometimes type IIa or IV dyslipidemia)

2) ApoB/LDL cholesterol ratio $>$1.0 and/or presence of small, dense LDL (LDL particle size $<$25.5 nm)

3) Rule out familial hypercholesterolemia and secondary dyslipidemia, such as dyslipidemia accompanied with type 2 diabetes

4) Family history of dyslipidemia, such as IIa, IIb, or IV 1)-4): definite FCHL, 1)-3): probable FCHL

Management of Type IIb Dyslipidemia

Treatment Goals

On the basis of large outcome trials with statins and epidemiological data, the Japan Atherosclerosis Society[25] guideline for the diagnosis and prevention

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Table 3. LDL-Cholesterol and non-HDL-Cholesterol Goals for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories[24]

treatment	risk category		goals (mg/dL)		
		coronary risk factors other than LDL-C	primary LDL-C	secondary non-HDL-C	HDL-C
Primary prevention improving lifestyle as the first line, followed by drug therapy	I (low)	0	<160	<190	≥40
	II (intermediate)	1-2	<140	<170	
	III (high)	3 or more	<120	<150	
Secondary prevention improving lifestyle and drug therapy	past history of CAD		<100	<130	

of atherosclerosis cardiovascular diseases for the Japanese population recommends reducing LDL cholesterol to a goal according to the number of coronary risks in patients with dyslipidemia[6]. Therefore, the same goals should be applied to the patients with type IIb dyslipidemia. In terms of the treatment goals for triglycerides, the guideline recommends reducing them to <150 mg/dL. In spite of the recommended goal for triglycerides, there is no clear consensus on the benefits of targeting hypertriglyceridemia. Because type IIb dyslipidemia is associated with atherogenic lipoprotein particles, such as remnants, IDL, small, dense LDL, and non-HDL cholesterol levels are considered as secondary targets after the goal for LDL cholesterol is achieved (**Table 3**)[26, 27]. Non-HDL cholesterol is calculated by subtracting HDL cholesterol from total cholesterol. It thus includes not only cholesterol from lipoprotein (a), LDL cholesterol, and IDL- cholesterol, which are traditionally included in the LDL cholesterol values calculated by the Friedewald formula, but also cholesterol from potentially atherogenic triglyceride-rich lipoproteins, such as VLDL remnants. Non-HDL cholesterol also has advantages, because fasting or additional tests are not required for the calculation. Several studies have reported that the level of non-HDL cholesterol is a better indicator of future cardiovascular events than LDL cholesterol[28, 29]. According to previous studies, the goal for non-HDL cholesterol is set at 30 mg/dL higher than that for LDL cholesterol. HDL cholesterol levels >40 mg/dL are the tertiary goal. Among all the lipid parameters, triglycerides are most responsive to lifestyle interventions such as diet and exercise; therefore, for the management of type IIb dyslipidemia we should begin with therapeutic lifestyle changes and should treat type 2 diabetes, metabolic syndrome, and CKD when dyslipidemia is caused by these disorders. We should also treat hypothyroidism or other disorders in cases of secondary dyslipidemia.

Therapeutic Lifestyle Changes

Therapeutic lifestyle changes, including those to diet and exercise, constitute the cornerstone of management in patients with type IIb dyslipidemia. Restriction of dietary cholesterol (less than 300 mg/day) and saturated fat, and increasing dietary fiber and plant sterols can lower LDL cholesterol, and restriction of alcohol, sugar, saturated fat and high intake of omega-3 fatty acids can reduce serum triglycerides[30]. Because weight reduction can further lower LDL cholesterol and triglycerides and raise HDL cholesterol levels, maximal improvement in dyslipidemia should be attempted with lifestyle intervention before prescribing lipid-lowering medications. For example, the total calorie intake should be approximately 30 kcal x standard body weight (kg) and fat intake should be 25 to 35% of the total calorie intake in type IIb dyslipidemia[31, 32].

Exercise, primarily aerobic exercise such as walking, is effective for the improvement of dyslipidemia. Appropriate daily exercise should be performed for 30 min or longer per day and more than 3 times per week. In obese patients, more daily exercise should be recommended; however, there is a risk of musculoskeletal injuries during exercise, particularly if the person is not used to exercise or has knee joint pain or back pain; therefore, consideration should be given to the physical fitness of the patient. In terms of the exercise intensity, 11 to 13 according to Borg's scale for the rating of perceived exertion is recommended. The details of therapeutic lifestyle changes are described in the JAS guideline[33].

Drug Therapy

Statin Monotherapy

A number of clinical trials have demonstrated that event reduction occurred in patients who had elevated triglycerides as well as LDL cholesterol levels, although all these studies were not specifically

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designed to examine the effect of statins in type IIb dyslipidemia. Stronger statins, such as atorvastatin, pitavastatin, and rosuvastatin can lower LDL cholesterol more than so-called standard statins, such as pravastatin, simvastatin, and fluvastatin. Greater triglyceride-lowering effects can be obtained by stronger statins; therefore, if the target LDL and non-HDL cholesterol goals are not achieved by standard statins, changing to stronger statins is a reasonable option.

Many studies have been performed to show the effect of statins on cardiovascular disease. In the primary prevention West of Scotland Coronary Prevention Study, for example, CAD event reduction with pravastatin was 29% in hypercholesterolemic men with triglyceride below the median of 148 mg/dL and 32% in those with triglycerides at or above the median[34]. In a post hoc analysis of the Scandinavian Simvastatin Survival Study, the hypercholesterolemic patients in the highest quartile for triglycerides (>159 mg/dL) and the lowest quartile for HDL cholesterol (<39 mg/dL) had the greatest event reduction (52%) by simvastatin treatment[35]. In the CARDS trial, atorvastatin caused a significant event reduction in the subgroup of triglycerides >150 mg/dL, but not in the group of triglycerides <150 mg/dL[36], while the Prospective Pravastatin Pooling Project showed a non-significant event reduction in the subgroup of triglycerides >220 mg/dL[37]. Overall, meta-analysis by Cholesterol Treatment Trialist showed a significant event reduction by statins in patients with triglycerides 124-178 mg/dL and >178 mg/dL[38]; therefore, statin monotherapy is recommended as the first-line therapy in patients with type IIb dyslipidemia.

Fibrate Monotherapy

Fibrates can reduce triglycerides by 20% to 50% and increase HDL cholesterol by 10% to 35%. Their effect on LDL cholesterol is variable, yet fibrates can increase the size of LDL particles. Although the clinical data on fibrate therapy are less consistent than those on statins, post-hoc analyses of fibrate trials have demonstrated the greatest clinical benefit in patients with combined dyslipidemia. In the Helsinki Heart Study, cardiac events were reduced by 34% with gemfibrozil, yet in the high-risk subgroup defined by triglycerides >205 mg/dL and LDL cholesterol/HDL cholesterol ratio >5, cardiac events were reduced by 71% with gemfibrozil[39]. Similarly, in the Bezafibrate Infarction Prevention (BIP) study, the subgroup with triglycerides ≥200 mg/dL had a significant 39.5% reduction in cardiac events, compared with a nonsignificant 7.3% reduction in the study overall[40]. In these trials, LDL cholesterol was reduced only modestly, whereas triglycerides were decreased by 35% and 21%, respectively, and HDL cholesterol was increased by 8% and 18%, respectively.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study reported a nonsignificant 11% reduction in the primary endpoint of coronary heart disease (CHD) events in type 2 diabetics treated with fenofibrate (200 mg daily) compared with those on a placebo; however, a significant reduction in total cardiovascular events was achieved with fenofibrate therapy[41]. Consistent with other fibrate trials, the highest risk and greatest benefits of fenofibrate were seen among those with marked hypertriglyceridemia >203 mg/dL[42]. In the FIELD trial, fenofibrate was shown to decrease diabetic microangiopathy, such as nephropathy and retinopathy[43, 44]; however, there was no benefit of fibrates for all-cause mortality, cardiovascular mortality, sudden death, or stroke.

Therefore, fibrate monotherapy is recommended for patients with type IIb dyslipidemia, especially diabetic patients with microangiopathy. If target LDL cholesterol and non-HDL cholesterol goals are not achieved combination with ezetimibe, probucol, or statin would be optional.

Niacin Monotherapy

Niacin can favorably modify all major lipid fractions. It is the only lipid-lowering agent that decreases lipoprotein (a), and is the most effective in increasing HDL cholesterol. Niacin can reduce LDL cholesterol by 5% to 25%, reduce triglycerides by 20% to 50%, and increase HDL cholesterol by 15% to 35%; therefore, niacin monotherapy is a reasonable option for type IIb dyslipidemia.

In the Coronary Drug Project, conducted in patients with previous myocardial infarction, niacin therapy at a dose of 3 g per day decreased total cholesterol by 10% and triglycerides by 26% compared with a placebo, and it decreased recurrent nonfatal myocardial infarction by 27%[43].

However, these data were obtained by the once-daily extended-release formula of niacin, which has improved tolerability and hepatic safety compared with the regular formula. Unfortunately, the once-daily formula of niacin is not available in Japan. Further, Japanese patients are generally less tolerable to niacin than Caucasians, and the maximum dose of niacin is 1.5 g per day. Hepatic toxicity, glucose intolerance, and an increase in uric acid should be carefully monitored when niacin is used to treat patients with type IIb dyslipidemia.

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Ezetimibe

Ezetimibe is a new option in the management of type IIb dyslipidemia as monotherapy or in combination. Ezetimibe is a selective cholesterol absorption inhibitor that preferentially blocks the absorption of cholesterol, while not affecting triglycerides and fat-soluble vitamins[44]. Although it has produced fair reductions in LDL cholesterol as monotherapy (on average 18%), it has also some favorable effects on triglycerides (−17%) and HDL cholesterol (+17%) in combined dyslipidemia. It also has important complementary effects in combination with statins and fibrates[45, 46]. Ezetimibe added to statin therapy provided an additional 25% reduction in LDL cholesterol and 11% reduction in triglycerides compared with a placebo. Recent studies showed that ezetimibe could ameliorate fatty liver and postprandial hyperlipidemia[47, 48]; therefore, ezetimibe can be recommended for type IIb dyslipidemic patients with fatty liver or postprandial hyperlipidemia.

Statin-Fibrate Combination Therapy

Statin-fibrate combination has been shown to provide benefits in patients with type IIb dyslipidemia. Several trials have examined the safety and efficacy of combination therapy with statins and fibrates. In a study of 389 patients with familial combined hyperlipidemia randomized to receive pravastatin 20 mg plus gemfibrozil 1,200 mg, or simvastatin 20 mg plus gemfibrozil 1,200 mg, LDL cholesterol was decreased by 35% and 39%, triglycerides was decreased by 48% and 54%, and HDL cholesterol was increased by 14% and 25%, respectively[49]. In a more recent study conducted in 120 patients with type 2 diabetes mellitus and combined hyperlipidemia, the combination of atorvastatin 20 mg and fenofibrate 200 mg decreased LDL cholesterol by 46%, triglycerides by 50%, and increased HDL cholesterol by 22%[50]. The Fluvastatin Alone and in Combination Treatment (FACT) study was a multicenter, prospective, double-blind study of 333 patients with CAD and combined dyslipidemia. The combination of fluvastatin 40 mg plus bezafibrate 400 mg was very effective for all lipid parameters, decreasing LDL cholesterol by 24% and triglycerides by 38% and increasing HDL cholesterol by 22%[51].

Action to Control Cardiovascular Risk in Diabetes (ACCORD) was designed to address the effect of add-on therapy of fenofibrate to simvastatin in type 2 diabetes patients; however, the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, as compared with simvastatin alone[52]. Therefore, the routine use of combination therapy with fenofibrate and simvastatin to reduce cardiovascular risk in the majority of high-risk patients with type 2 diabetes is not recommended. In subgroup analysis of the ACCORD trial, patients with high triglycerides (>204 mg/dL) and low HDL cholesterol (<34 mg/dL) had a significant event reduction by fenofibrate; thus this combination regimen is only recommended in type IIb dyslipidemia with low HDL cholesterolemia.

Thus, in spite of its powerful lipid-lowering effects, combination therapy with statins and fibrates requires careful selection and monitoring of patients. Because of the potential increased risk for myopathy with the statin-fibrate combination, patients with muscle symptoms may be advised to halt therapy immediately. If creatinine kinase is markedly elevated, assessment of renal function and serum potassium is required along with increased fluid intake to prevent acute renal failure associated with rhabdomyolysis.

Statin-Niacin Combination

The combination of statins with niacin can be an option because both have excellent outcomes of improving cardiovascular disease. In a review of 9 clinical trials of combination therapy with statins plus niacin, LDL cholesterol was reduced by 25% to 57% and HDL cholesterol was increased by 13% to 36%[53]. Fluvastatin 20 mg per day plus niacin 3 g per day has been reported to reduce lipoprotein (a) levels by 37%[54], and pravastatin 20 mg per day plus niacin 3 g per day was reported to decrease levels of small, dense LDL by 43%[55].

Combination therapy was also studied in the HDL-Atherosclerosis Treatment Study, in which simvastatin plus niacin significantly reduced the risk for a composite cardiovascular endpoint by 90% compared with a placebo[56]. Further, patients with coronary disease, normal LDL cholesterol levels, and low HDL cholesterol levels were treated with simvastatin plus niacin for three years. As a result, the rate of major clinical events was 90% lower in the combination group than in the placebo group. Further, the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) study is on-going to investigate the effect of combination therapy of niacin and statin on cardiovascular event reduction; however, as described for niacin monotherapy, treatment with niacin should proceed with caution.

Statin-Eicosapentaenoic Acid Combination Therapy

Epidemiological and clinical evidence has consis-

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tently demonstrated the triglyceride-lowering effect of eicosapentaenoic acid (EPA)[57]. At doses of 1.8 g per day, EPA reduces triglyceride levels by approximately 20%. The triglyceride-lowering effect is believed to be primarily the result of a reduction in hepatic triglyceride synthesis and hence diminished secretion of triglyceride-rich lipoproteins from the liver into the circulation. Observational and clinical trial data suggest that omega-3 fatty acid can reduce the risk of CAD-related death and reduce nonfatal coronary events[58-60].

Few intervention studies have reported the combination of statin and EPA. The Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS) was designed to study the effects of EPA on major coronary events in patients with hypercholesterolemia[61]. A total of 18,645 patients were randomized to receive either 1.8 g EPA plus statin or statin alone. A 19% relative reduction of the primary endpoint of major coronary events was shown in the study conducted in Japan. The mean triglyceride levels were 154 mg/dL in the EPA plus statin arm and 153 mg/dL in the statin arm, indicating that this study cohort included a significant number of patients with type IIb dyslipidemia. In this study, triglyceride levels were significantly decreased by 9% from baseline in the EPA group and by 4% in controls ($p<0.0001$ between groups). A greatest reduction of coronary events by EPA was found in secondary prevention; however, the OMEGA study did not support the effect of omega-3 fatty acids on cardiovascular events in secondary prevention[62]. Therefore, the potential of omega-3 fatty acids may vary, depending on individual clinical conditions. Currently, the JAS guideline recommends adding EPA for statin-treated high-risk patients and statin-EPA combination would be an option for patients with type IIb dyslipidemia.

Conclusions

Type IIb dyslipidemia is often associated with type 2 diabetes, metabolic syndrome, CKD, and FCHL, and atherogenic lipoproteins, such as small, dense LDL, remnants, and IDL; therefore, patients with this type of dyslipidemia have a high risk for CAD and need risk management, including hypertension, diabetes, and so forth. Data from prospective epidemiological as well as interventional studies indicate that a significant proportion of high-risk patients may benefit not only from LDL cholesterol lowering, but also from treatment of other lipid parameters, such as non-HDL cholesterol, triglycerides, and HDL cholesterol. Achievement of LDL cholesterol and non-HDL cholesterol targets in patients with type IIb dyslipidemia sometimes requires either higher doses of statins or increased use of combination therapy. Optimal management requires a targeted strategy to correct the underlying lipid abnormalities to reduce the risk for CAD events, while minimizing adverse effects. Future clinical trials are needed to determine both the risks and benefits of monotherapy versus combination regimens for the treatment of patients with type IIb dyslipidemia.

Conflict of Interest

Dr. Arai has received unrestricted grants from Otsuka Pharmaceutical Co., Ltd., received honoraria from MSD, and is an advisor of Kowa Pharmaceutical Co. Ltd. Dr. Ishibashi has received unrestricted grants from Takeda Pharmaceutical Co. Ltd. and is an advisor of Kowa Pharmaceutical Co. Ltd. Dr. Oikawa has received unrestricted grants from Daiichi-Sankyo Co. Ltd. Dr. Harada-Shiba has received unrestricted grants from MSD. Dr. Yamashita has received unrestricted grants from MSD, Otsuka Pharmaceutical Co., Ltd., Astellas Pharma Inc., and JT, collaborative research grants from Shionogi & Co., Ltd., Otsuka Pharmaceutical Co., Ltd., and National Institute of of Biomedical Innovation, honoraria for lectures from MSD, Bayer Yakuhin, Ltd., and Kowa Pharmaceutical Co., Ltd., and is an advisory of Skylight Biotech Co. Dr. Eto is an advisor of MSD. The other authors declare that they have no conflict of interest.

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Special Report

Diagnosis and Management of Type I and Type V Hyperlipoproteinemia

Takanari Gotoda[1], Koji Shirai[2], Takao Ohta[3], Junji Kobayashi[4], Shinji Yokoyama[5, 17], Shinichi Oikawa[6], Hideaki Bujo[7], Shun Ishibashi[8], Hidenori Arai[9], Shizuya Yamashita[10], Mariko Harada-Shiba[11], Masaaki Eto[12], Toshio Hayashi[13], Hirohito Sone[14], Hiroaki Suzuki[15] and Nobuhiro Yamada[16]: The Research Committee for Primary Hyperlipidemia, Research on Measures against Intractable Diseases by the Ministry of Health, Labour and Welfare in Japan

[1]Department of Clinical and Molecular Epidemiology, 22nd Century Medical and Research Center, University of Tokyo Hospital, Tokyo, Japan
[2]Internal Medicine, Sakura Hospital, School of Medicine, Toho University, Chiba, Japan
[3]Department of Child Health and Welfare (Pediatrics), Faculty of Medicine, University of the Ryukyus, Okinawa, Japan
[4]Department of Lipidology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan
[5]Department of Biochemistry, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan
[6]Division of Endocrinology and Metabolism, Department of Medicine, Nippon Medical School, Tokyo, Japan
[7]Department of Genome Research and Clinical Application, Chiba University Graduate School of Medicine, Chiba, Japan
[8]Division of Endocrinology and Metabolism, Diabetes Center, Department of Medicine, Jichi Medical University Graduate School of Medicine, Tochigi, Japan
[9]Department of Human Health Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan
[10]Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
[11]Department of Molecular Innovation in Lipidology, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan
[12]School of Pharmaceutical Sciences, Ohu University and Department of Medicine, Ohu University Hospital, Fukushima, Japan
[13]Department of Geriatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan
[14]Department of Internal Medicine, University of Tsukuba Institute of Clinical Medicine, Ibaraki, Japan
[15]Department of Endocrinology and Metabolism, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Ibaraki, Japan
[16]University of Tsukuba, Ibaraki, Japan
[17]Food and Nutritional Sciences, College of Biosciences and Biotechnology, Chubu University, Aichi, Japan

Both type I and type V hyperlipoproteinemia are characterized by severe hypertriglyceridemia due to an increase in chylomicrons. Type I hyperlipoproteinemia is caused by a decisive abnormality of the lipoprotein lipase (LPL)- apolipoprotein C-II system, whereas the cause of type V hyperlipoproteinemia is more complicated and more closely related to acquired environmental factors. Since the relationship of hypertriglyceridemia with atherosclerosis is not as clear as that of hypercholesterolemia, and since type I and V hyperlipoproteinemia are relatively rare, few guidelines for their diagnosis and treatment have been established; however, type I and V hyperlipoproteinemia are clinically important as underlying disorders of acute pancreatitis, and appropriate management is necessary to prevent or treat such complications. Against such a background, here we propose guidelines primarily concerning the diagnosis and management of type I and V hyperlipoproteinemia in Japanese.

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Key words; Chylomicronemia, Gene mutation, Hyperlipidemia, Lipase, Triglyceridemia

Address for correspondence: Takanari Gotoda, Department of Clinical and Molecular Epidemiology, 22nd Century Medical and Research Center, University of Tokyo Hospital, Hongo 7-3-1, Bunkyo-ku, 113-8655 Tokyo, Japan
E-mail: gotoda-tky@umin.ac.jp
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Background

According to Fredrickson's classification of hyperlipoproteinemia (WHO classification), type I and V hyperlipoproteinemia (hyperlipidemia) are characterized by an increase in chylomicrons alone and an

increase in very low-density lipoprotein (VLDL) in addition to chylomicrons, respectively[1]. Type I hyperlipoproteinemia is a clinical condition showing the severest hypertriglyceridemia and is classically represented by two rare genetic disorders, i.e., familial lipoprotein lipase (LPL) deficiency (MIM 238600) and familial apolipoprotein C-II deficiency (MIM 207750)[2]. Even rarer conditions such as familial inhibitor of lipoprotein lipase (MIM 118830) and the presence of autoantibodies also cause type I hyperlipoproteinemia[3, 4]. More recently, patients with mutations in two additional genes have also been reported to manifest primary type I hyperlipoproteinemia, i.e., genes for glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1 (GPIHBP1) (MIM 612757) and for lipase maturation factor 1 (LMF1) (MIM 611761)[5, 6]. Since LPL is an insulin-dependent enzyme, diabetic lipemia observed in insulin-deficient conditions such as type 1 diabetes is well-known as secondary type I hyperlipoproteinemia. Therefore, type I hyperlipoproteinemia is caused by a decisive abnormality of either LPL, which is a rate-limiting enzyme involved in the hydrolysis of triglyceride (TG)-rich lipoproteins such as chylomicrons and VLDL, or apolipoprotein C-II, a cofactor necessary for the expression of LPL activity.

The cause of type V hyperlipoproteinemia is more complicated, and more miscellaneous clinical conditions are considered to belong to this category. It rarely shows familial occurrence, but its inheritance pattern is variable; therefore, type V hyperlipoproteinemia is usually considered to be triggered by acquired environmental factors in individuals with some congenital susceptibility to altered TG metabolism (genetic factors). While the involved environmental factors vary, involvement of heavy drinking, type 2 diabetes, hormonal therapy using steroids and estrogen, and drugs such as diuretics and β-blockers are frequently observed[7].

Many guidelines concerning the diagnosis and treatment of hypercholesterolemia have been formulated[8], and outstanding results of clinical intervention using lipid-lowering drugs, particularly statins, have been reported by large-scale clinical studies. On the other hand, since the relationship of hypertriglyceridemia with atherosclerosis is not as clear as that of hypercholesterolemia, and since type I and type V hyperlipoproteinemia, in particular, are relatively rare, few guidelines for their diagnosis and treatment have been established either in Japan or abroad; however, diagnostic criteria for primary hyperchylomicronemia were issued in the 1988 report by the Study Group on Primary Hyperlipidemia of the Ministry of Health and Welfare (Group leader: Seiichiro Tarui)[9]. Type I and V hyperlipoproteinemia are important as underlying disorders of acute pancreatitis, which is often lethal, and appropriate management, including restriction of fat intake, is necessary to prevent or treat such complications. Against such a background, the Study Group on Primary Hyperlipidemia of the Ministry of Health, Labour and Welfare (Group leader: Nobuhiro Yamada) proposes guidelines primarily concerning the diagnosis and management of type I and V hyperlipoproteinemia in Japanese.

Characteristics of Hyperchylomicronemia

The half-life of chylomicrons is about 5 minutes, and no chylomicron is observed in the plasma of normotriglyceridemic to moderately hypertriglyceridemic individuals after 12-hour fasting. Chylomicrons are considered to appear in fasting plasma in those with a serum TG level of about 1,000-2,000 mg/dl or above, and physical symptoms usually occur above this level ($\geq$ 2,000 mg/dl); therefore, there is a strict viewpoint defining hyperchylomicronemia as a serum TG level of 2,000 mg/dl or above accompanied by characteristic complaints or findings. However, caution is necessary, because there are patients showing no clinical symptom even at a serum TG level of 20,000-30,000 mg/dl, even though they are rare. From a clinical standpoint, it must be explained to the patient that there is risk of pancreatitis when the TG level is 1,000 mg/dl or higher even on casual sampling. This may also apply to neonates whose blood sampling after a long period of fasting is usually difficult. It must also be remembered in clinical laboratory testing that a marked increase in the serum TG level often affects the measurement system, causing apparently low serum amylase, hemoglobin, and electrolyte levels (e.g., sodium appears to be reduced by about 2-4 mEq/l with every 1,000 mg/dl increase in the TG). In particular, acute pancreatitis secondary to hypertriglyceridemia must not be misdiagnosed due to apparently low serum amylase.

Type I Hyperlipoproteinemia

A) Familial Lipoprotein Lipase (LPL) Deficiency

a) Concept and Definition

LPL is an enzyme that hydrolyzes TG of lipoprotein particles in blood, and its abnormal activity underlies type I hyperlipoproteinemia in many cases and type V hyperlipoproteinemia in some. Familial LPL deficiency is a rare monogenic disorder that exhibits the severest hyperchylomicronemia. It was first docu-

mented in 1932 in a boy born to a family with a history of consanguineous marriage[10], and the underlying abnormality was demonstrated to be a congenital defect of LPL activity, the rate-limiting enzyme of chylomicron hydrolysis, by Havel *et al.* in 1960[11]. Following the classification of familial hypercholesterolemia, it has been proposed to classify this disease as a class I defect causing complete loss of LPL protein, a class II defect characterized by the production of catalytically inactive protein, and a class III defect characterized by the production of inactive protein lacking affinity to heparan sulfate[12].

b) Etiology

The disease is caused by an abnormality of the human LPL gene, and the patients are homozygotes (including so-called compound heterozygotes) who have inherited LPL gene abnormalities from both parents in an autosomal recessive pattern with penetrance of 100%. The human LPL gene is located on the short arm of chromosome 8 (8p22), is about 35 kb in length, contains 10 exons, and codes for an enzyme protein consisting of 448 amino acids[13-15].

c) Clinical Symptoms

This disease is a relatively rare autosomal recessive disorder, and more than 30 families with this condition have been reported in Japan. The frequency of the occurrence of homozygous patients is estimated to be 1 in every 500,000 to 1 million people. Many patients have a family history of consanguineous marriage, and since patients exhibit chylous serum due to hyperchylomicronemia from early childhood and abdominal pain due to pancreatitis after the intake of fat, the disease is frequently diagnosed during the suckling period or early childhood. In females, the detection of hyperchylomicronemia during pregnancy may lead to the diagnosis. Attacks of abdominal pain due to acute pancreatitis following hyperchylomicronemia are often mistaken for acute abdomen, and the patient may undergo unnecessary laparotomy. While some patients acquire a dietary habit to avoid the intake of fat and suffer growth impairment, some show no marked attack of abdominal pain until adulthood, with consequent overlooking of the disease. It is the primary disease to be differentially diagnosed in a patient with persistent abdominal pain accompanied by hypertriglyceridemia[2].

Hyperchylomicronemia itself is also a major clinical finding, and the serum TG level reaches about 1,500 to even 20,000 mg/dl or more. The presence of chylomicrons can be confirmed by a simple method, i.e., the appearance of a top white cream layer in serum after standing at 4℃ for 24 hours or mild centrifugation. In typical cases, the lower layer is clear and transparent, reflecting an increase in chylomicrons alone. The possibility of LPL deficiency is high if the serum TG level is 1,500 mg/dl or higher, and the serum total cholesterol level is about 1/10 the serum TG level or lower. All other clinical findings are due to the marked increase in chylomicrons. First, eruptive xanthomas, which appear when the serum TG level increases to 2,000 mg/dl or above, are noted in about half of the patients, particularly on the extensor sides of the limbs, buttocks, and shoulders. They appear in association with changes in the serum TG level and disappear gradually over several weeks to a few months. When the serum TG level increases above 4,000 mg/dl, lipemia retinalis, in which the retinal vessels appear whitish pink due to chylous serum on funduscopy, appears, but vision is not impaired. Among other findings, hepatosplenomegaly due to the infiltration of macrophage foam cells that have phagocytozed lipids in the extravascular space, is observed, with hepatomegaly being frequent, but these changes are reversible and are rapidly improved (within 1 week) with correction of the serum lipid levels; however, the most serious complication is acute pancreatitis, and it must be managed carefully as it may be a prognostic determinant. From a clinical viewpoint, the possibility of acute pancreatitis must be explained to the patient if the TG level is 1,000 mg/dl or higher even on casual sampling. Dyspnea and neurological symptoms such as dementia, depression, and memory disorders have been reported as complications of this disorder.

As mentioned above, a major prognostic determinant of homozygous familial LPL deficiency is acute pancreatitis, which is often lethal. LPL deficiency has long been considered not to be closely related to atherosclerosis in humans, because no marked atherosclerotic lesion was noted at the autopsy of several homozygous patients with LPL deficiency who died due to acute pancreatitis. However, detailed research has reported that heterozygotes, which are considered to occur in 1 in every 500 individuals, usually show no marked abnormality in the lipid level but are likely to exhibit hypertriglyceridemia when they develop diabetes or are exposed to burdens such as severe obesity, excessive drinking, and pregnancy[16, 17]. There have also been reports of the frequent occurrence in heterozygotes of familial combined hyperlipidemia (FCHL)[12] and monogenic familial hypertriglyceridemia[16], which are common hyperlipidemia related to atherosclerosis; however, it remains controversial whether homozygotes with LPL gene abnormality are likely to develop atherosclerosis. A Canadian group

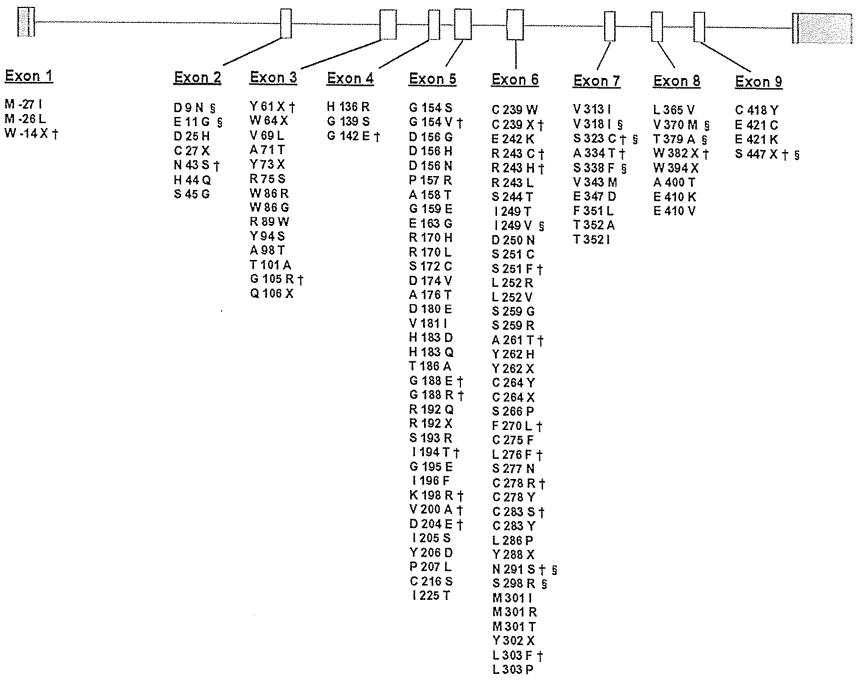

Fig. 1. Missense and nonsense mutations in the human lipoprotein lipase (LPL) gene

Each number indicates the position of affected amino acids, with +1 corresponding to the first amino acid of the mature human LPL protein.
†Mutations identified in Japanese patients with familial LPL deficiency.
§Mutations or polymorphisms not necessarily underlie LPL deficiency.

that followed-up 4 patients with LPL deficiency over 14-30 years reported that coronary angiography established atherosclerotic lesions in all patients before the age of 55 years[18], but studies on homozygotes in Japan[19, 20] both reported no advanced atherosclerotic lesion in those Japanese patients.

d) Diagnosis

Since LPL is anchored by binding with heparan sulfate on the surface of capillary endothelial cells, it appears markedly in the circulation by intravenous injection of heparin; therefore, the diagnosis is usually made by measuring plasma LPL activity and/or protein level 10 minutes after intravenous injection of heparin (10-50 U/kg). LPL protein is also present in plasma before heparin injection, but is markedly reduced or undetectable in patients with LPL null mutation (class I defect). LPL accounts for about 1/3 of the total lipase activity in plasma after heparin injection, and most of the remaining lipase activity is due to hepatic triglyceride lipase (HTGL), so diagnosis of this disorder is impossible by simple measurement of the total lipase activity. Anti-LPL and anti-HTGL antibodies are necessary for the differential measurement of LPL activities, but there is also a method to inactivate LPL using protamine sulfate or 1 M NaCl. Although this technique requires a stable synthetic substrate as well as skill and experience, measurement kits for research use are presently being marketed. Also, if either macrophages derived from peripheral blood monocytes or adipose tissue can be used as samples, differentiation from HTGL becomes unnecessary. If changes in the LPL protein level are involved, the immunological protein assay is effective and there have been a few reports on the use of ELISA in Japan[21-23], which has been adopted as a general clinical laboratory test[21]. If the LPL activity is markedly reduced, and if the concentration of apolipoprotein C-II, a critical cofactor of LPL, is normal or elevated, the diagnosis of this condition would be considered definite. Naturally, close inquiry into the familial history is often very helpful. While very rare cases with an LPL inhibitor or autoantibody are known, they can be eventually excluded by examining whether the patient's serum inhibits LPL activity in the serum of a normal control.

A diagnosis based on the LPL gene level is also widely practiced. To date, at least 163 gene mutations[2, 24, 25], including 35 in Japan alone[26], have been

Table 1. Mutations resulting from deletion/insertion or occurring at splice sites/promoter regions of the human lipoprotein lipase (LPL) gene

Deletion mutation	**Insertion mutation**	**Splice site mutation**
small deletions	*small deletions*	IVS1 ds +1 G>C
Gln(−12) Ter (del 2bp)	ins CC in 5'UTR (+14–+15)	IVS1 as −4–−2 (del 3bp)
Thr18Ter (del 11bp)	Glu35Ter (ins A)	IVS2 ds +1 G>A†
Val69Ter (del 2bp)	ins 5bp in exon 3	IVS2 as −1 G>A
Ala70Ter (del 4bp)	Lys312Ter (ins C)	IVS3 as −6 C>T†§
Lys102Ter (del 5bp)	Thr361Ter (ins A)	IVS6 as −3 C>A
Asn120Ter (del 4bp)		IVS8 ds +2 T>C†
Ser172Ter (del 1bp)	*gross insertion*	
Gly209Ter (del 1bp)	ins 2kb (exon6–IVS6)	**Promoter region mutation**
Ala221Ter (del 1bp)†		T(−93)G§
Arg243Ter (del 1bp)†	**Insertion-deletion (Indel) mutation**	G(−53)C§
Ser251Ter (del 2bp)	*small indels*	T(−39)C§
Asn291Ter (del 1bp)†	Ala70Ter (del 4bp + ins 2bp)	
Leu353Ter (del 2bp)	Thr101Ter (del 1bp + ins 6bp)	
del Ser396-Pro397 (del 6bp)	Ser193Arg + Ile194Thr (del 5bp + ins 5bp)	
gross deletions	*gross indels*	
del 54kb (5' upstream–IVS1)†	del 2.3kb inc. exon2 + ins 150bp *Alu* element†	
del 6kb (IVS2–IVS5)		
del 2.1kb (IVS7–IVS8)		
del (exon8–exon10)		

†Mutations identified in Japanese patients with familial LPL deficiency
§Mutations or polymorphisms not necessarily underlying LPL deficiency
Abbreviations: Ter, termination of codon; del, deletion; IVS, intervening sequence; UTR, untranslated region; ins, insertion; ds, donor splice site; as, acceptor splice site

identified and reported worldwide (**Fig. 1** and **Table 1**). Mutations are reportedly identified in 97% of patients, nearly 70% of which are missense mutations involving amino acid substitutions[25] that are highly concentrated in exons 5 and 6 that code for the catalytic center of LPL (**Fig. 1**); therefore, these exons should be examined first in the gene-based diagnosis of unknown mutations. Many of the amino acid substitutions cause a decrease in lipophilicity of the α-helix or β-sheet region. Other known mutations include nonsense mutations, frame-shift mutations due to insertion or deletion of a few bases, gross rearrangements due to insertion or deletion of a large DNA fragment, and splicing mutations due to mutations at splice donor or acceptor sites (**Table 1**). Since decisive mutations such as those above have been identified in most patients of European ancestry, patients who develop this disorder due to changes in the LPL gene expression levels caused by abnormality of a promoter region etc. are considered to be very rare[2]; however, since several Japanese patients are reported to be devoid of any such decisive mutations, it seems worth investigating the other region of the LPL gene in such cases.

In Japan, at least 35 mutations have been reported. In particular, as nonsense mutations in exon 3 (Y61X) and exon 8 (W382X)[27] and a single-base deletion in exon 5 (A221Ter (del 1bp))[28] have been identified in multiple families of Japanese patients, these mutations are considered to be distributed relatively widely in the LPL gene of Japanese. On the other hand, S447X, which is considered to be a gain-of-function polymorphism, has been shown to reduce TG and increase HDL-cholesterol[29].

While LPL gene mutations are relatively rare, their diagnosis is considered clinically important because of the severity of the disorders they cause. Examination of a few relatively frequent mutations has already been incorporated into routine clinical laboratory tests. Also, screening for 22 known mutations can be conducted simultaneously using the LPL gene test employing the invader method reported[30], and similar attempts are expected to make high throughput screening possible.

e) Treatment

The most problematic complication of this dis-

order is acute pancreatitis, and treatments are carried out to prevent the occurrence or progression of pancreatitis. The basic treatment is restriction of fat intake, i.e., restricting dietary fat intake to 20 g/day or less or to 15% or less of the total energy intake, to maintain the postprandial TG level at a maximum of 1,500 mg/dl or less[2]. Infants are given milk containing medium chain triglycerides (MCTs), which enter the circulation without being incorporated into chylomicrons, and defatted milk. MCTs can also be used for cooking. In the 2nd or 3rd trimesters of pregnancy, fat intake restriction up to 2 g/day has been reported not to affect neonates[2]. Acute pancreatitis is treated by fasting and low-calorie infusion, and the intravenous infusion of lipid preparations or high-calorie infusion should be avoided. This disorder barely responds to anti-hyperlipidemic drugs, but the use of fibrates should be considered in adults showing an increase also in VLDL. The effectiveness of gene therapy has been demonstrated experimentally in various animal models[31].

B) Familial Apolipoprotein C-II Deficiency

a) Concept and Definition

Apolipoprotein C-II is present primarily as a component of chylomicrons, VLDL, and HDL, and it functions on the surface of TG-rich lipoproteins as a cofactor necessary for full activation of LPL; therefore, congenital defect of this molecule causes an autosomal recessive disease that manifests marked type I or type V hyperlipoproteinemia similar to familial LPL deficiency. The first case, reported in 1978, was a 58-year-old man who had repeated episodes of acute pancreatitis accompanied by hyperchylomicronemia. The condition was not alleviated by insulin therapy for complicating diabetes, and the disease was identified incidentally as it markedly responded to transfusion performed as symptomatic therapy for anemia[32]. Similarly to LPL deficiency, consanguineous marriage is often observed in the patient's familial history, but the prevalence of this disorder is estimated to be even lower than that of LPL deficiency, and only about 20 families with this disease have been reported worldwide since it was discovered in Canada[32] and Japan[33] in the 1970s.

b) Etiology

The disease is caused by abnormality of the human apolipoprotein C-II gene and occurs in homozygotes who have inherited an abnormal apolipoprotein C-II allele from both parents (including so-called compound heterozygotes). It is inherited in an autosomal recessive pattern with penetrance of 100%. The human apolipoprotein C-II gene is located on the short arm of chromosome 19 (19q13.2), contains 4 exons, and codes for a protein with a molecular weight of 8,800, consisting of 79 amino acids[34, 35].

c) Clinical Symptoms

Since all clinical symptoms are secondary to hyperchylomicronemia, they are nearly identical to those of LPL deficiency described above; however, as the activation of LPL is partially independent of apolipoprotein C-II, clinical symptoms are often slightly milder, and, consequently, the diagnosis of the disease is often made later than LPL deficiency. As the patients tend not to be subjected to strict fat restriction from early childhood, which is more common in LPL deficiency, the incidence of acute pancreatitis has been reported to be higher in adult patients[32, 36], and hyperchylomicronemia is more often accompanied by a high VLDL level. In heterozygotes, apolipoprotein C-II is present in blood at about 50% of the normal level, and no abnormality is usually observed in the serum lipid levels, including TG.

d) Diagnosis

The diagnosis is based on demonstration of the selective absence of, or a marked decrease in, apolipoprotein C-II on clinically practical laboratory tests of serum apolipoproteins as well as clinical symptoms resembling those of LPL deficiency. The diagnosis is further supported by the presence of familial consanguinity. If LPL activity can be measured, reduced LPL activity in the patient's serum can be promptly recovered by the addition of normal human serum or purified apolipoprotein C-II. This phenomenon was also noted in the first reported Canadian patient, in whom hypertriglyceridemia was markedly improved (reduced from 1,750 to 196 mg/dl) immediately after transfusion for the treatment of anemia[32]. Another measurement method using cow's milk, which contains LPL but lacks apolipoprotein C-II, is also known.

Many families known to have this disorder have been analyzed at the gene level, and a wide variety of mutations of the apolipoprotein C-II gene have been identified, including 3 reported in Japanese patients[37-39]. Differently from LPL deficiency, apolipoprotein C-II is completely absent in many patients with this disorder due to splicing or nonsense mutation of the apolipoprotein C-II gene, but there are rare cases in which a low level of apolipoprotein C-II with a structural defect in the activation of LPL is detectable in the blood of patients. Concerning other apolipoproteins, apolipoprotein C-III and E are increased, and A-I, A-II, and B are reduced, reflecting an increase in chylomicrons and decreases in LDL and HDL.

e) Treatment

The objective of treatment for this disorder is to prevent the occurrence or exacerbation of pancreatitis, so it is treated similarly to LPL deficiency. A major difference from LPL deficiency is that serum TG can be reduced rapidly by the transfusion of normal plasma upon emergencies such as acute pancreatitis.

C) Patients Showing Inhibitors of or Autoantibodies to LPL

Families showing inhibitors of LPL in blood have been reported, and this trait is considered to be inherited in an autosomal dominant pattern[3]; therefore, in such patients, LPL activity is reportedly deficient only in blood and is normal in tissues.

Also, Kihara *et al.* noted symptoms resembling those of LPL deficiency in a young Japanese female with a history of ITP and Graves' disease, and reported the presence of an IgA autoantibody that reacts with both LPL and HTGL in her serum[4].

D) Patients with a Mutation in the Gene for GPIHBP1 or LMF1

GPIHBP1 is a capillary endothelial protein that provides a platform for LPL-mediated hydrolysis of chylomicrons, and LMF1 plays a critical role in the maturation of lipases including LPL. Recently, a few patients with mutations in these genes have also been reported to manifest type I hyperlipoproteinemia[5, 6].

Type Ⅴ Hyperlipoproteinemia

According to Fredrickson's classification (WHO classification), type V hyperlipoproteinemia is defined as hyperlipoproteinemia accompanied by an increase in VLDL as well as chylomicrons. In contrast to the fact that type I hyperlipoproteinemia is mostly categorized as a condition caused by congenital abnormality of the LPL-apolipoprotein C-Ⅱ system or a secondary abnormality due to marked deficiency of insulin action, type V hyperlipoproteinemia is considered to be a category that includes a wide range of pathological conditions having both congenital (genetic) and acquired (environmental) aspects and exhibiting moderate to marked hypertriglyceridemia. Indeed, upon close investigation of the patients' families, some members have been found to be hypertriglyceridemic, while many patients are associated with secondary factors such as diabetes and drinking. Since type V hyperlipoproteinemia is much more prevalent than type I, clinically encountered hyperchylomicronemia is more often type V hyperlipoproteinemia. It is difficult to accurately estimate the prevalence of type V hyperlipoproteinemia in the general population, but a survey of about 40,000 people by the Lipid Research Clinic reported the frequency of individuals with a plasma TG level of 2,000 mg/dl or higher to be about 0.018%[2]. Chylomicrons may also be observed in the blood in type Ⅲ hyperlipoproteinemia due to the inhibition of chylomicron catabolism.

Although there have been only a limited number of studies in Japan, Murase *et al.* reported the results of the evaluation of 120 Japanese with a serum TG level ≥ 1,000 mg/dl (22 type I and 98 type V patients)[7, 40]. A history of acute pancreatitis was observed in about 17% of these patients, demonstrating that hyperlipidemia is frequently complicated by pancreatitis also in Japanese, in whom the fat intake is lower than in Western people, and stressing the importance of its prevention and management. According to the cause of type I hyperlipoproteinemia, familial LPL deficiency was noted in 11, familial apolipoprotein C-Ⅱ deficiency in 3, and secondary type I hyperlipoproteinemia such as diabetic lipemia in 8 (**Table 2**). Of the patients with type V hyperlipoproteinemia, the presence of underlying diseases or contributing factors such as diabetes and drinking was confirmed in about 2/3 but not in the remaining 1/3. Many of the latter patients reportedly usually show type Ⅳ hyperlipoproteinemia and have hypertriglyceridemia in the familial history.

Among congenital (genetic) abnormalities that underlie type V hyperlipoproteinemia, (1) familial combined hyperlipidemia (FCHL), which is accompanied by increased apolipoprotein B and VLDL synthesis and usually shows type Ⅱb or Ⅳ hyperlipoproteinemia, (2) monogenic familial hypertriglyceridemia accompanied by increased TG synthesis and exhibiting type Ⅳ hyperlipoproteinemia, and (3) heterozygosity of LPL gene abnormalities or abnormal expression of the LPL gene are considered important (**Fig. 2**). Such genetic abnormalities are considered to be present in a few percent of the general population and usually cause type Ⅳ hyperlipoproteinemia, some of which is considered to change to type V under the influence of environmental factors. Recently, apolipoprotein A-V was shown to strengthen the interaction between apolipoprotein C-Ⅱ and LPL, suggesting that familial apolipoprotein A-V deficiency causes hyperchylomicronemia[41]. There have also been many reports that abnormalities of apolipoprotein E (E2 or E4) are involved in the pathogenesis of type V hyperlipoproteinemia[42].

While homozygous LPL deficiency can be easily diagnosed, heterozygous LPL deficiency is difficult to detect, because its phenotype may be very mild type Ⅳ hyperlipoproteinemia alone or completely asymp-

Table 2. Classification of hyperchylomicronemia according to the cause derived from data on 120 Japanese patients with a serum TG level of 1,000 mg/dL or more

		Number of patients	(males/females)
A. Hyperchylomicronemia due to abnormalities of the LPL-apolipoprotein C-II system for hydrolysis of chylomicrons			
Primary hyperchylomicronemia			
Familial LPL deficiency		11	(4/7)
Familial apolipoprotein C-II deficiency		3	(3/0)
Secondary hyperchylomicronemia			
Diabetic lipemia		6	(4/2)
Hyperlipidemia due to acromegaly		2	(0/2)
B. Type V hyperlipoproteinemia of unknown cause or underlying disorders			
Cause unknown (idiopathic)		33	(29/4)
Underlying disorders			
Complicated by diabetes (drinking: none-light)		18	(15/3)
Heavy drinking†	Non-diabetic	29	(22/7)
	Diabetic	11	(11/0)
Others§		7	

†Heavy drinking: habitual drinking of 60 g/day or more of ethanol
§2: von Gierke disease, 1: Nelson syndrome, 1: Weber-Christian disease, 1: diabetes due to L-asparaginase, 2: suspect of an LPL inhibitor
Cited from reference no. 40) Murase T: Guidelines for the Diagnosis and Treatment of Hyperlipidemia. (Bunkodo) 2005, pp 100 (in Japanese)

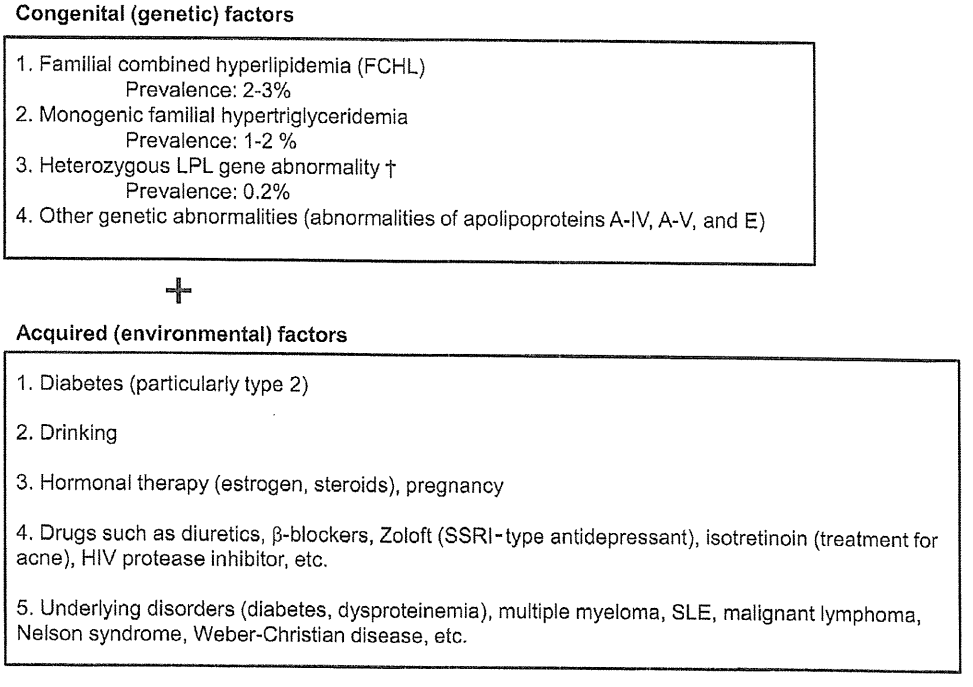

Fig. 2. Etiological factors underlying primary type V hyperlipoproteinemia

†Reported to be present in 10% of people in Western countries, but no mutation was noted in 100 Japanese subjects with a TG level of 400-1,000 mg/dl examined by Arai *et al.*[45].

Table 3. Diagnostic criteria for primary hyperchylomicronemia (draft)

Primary hyperchylomicronemia

The presence of chylomicrons in the serum confirmed after fasting for 12 hours or longer (note) is called hyperchylomicronemia, which is classified into the following 4 types.

Usually, the possibility of this disorder is high when the serum triglyceride level exceeds 1,000 mg/dl.

Note: The presence of chylomicrons can be confirmed by the appearrance of a supernatant cream layer after allowing serum to stand for 24 hours or longer at 4℃. The detection of chylomicrons by ultracentrifugation or electrophoresis (agarose or polyacrylamide gel) also contributes to the diagnosis.

1. Familial lipoprotein lipase (LPL) deficiency

(1) The absence of LPL activity in postheparin plasma, adipose tissue, or macrophages.
(2) Being a homozygote with a causative LPL gene mutation on both alleles.
(3) The presence of apolipoprotein C-II.
(4) The presence of clinical symptoms due to hyperchylomicronemia (acute pancreatitis, eruptive xanthoma, lipemia retinalis, hepatosplenomegaly).
(5) The presence of consanguinity in the familial history.
(6) A marked decrease in LPL protein mass measured by ELISA for LPL.

Definitively diagnosed if (1) or (2) is established, and provisionally diagnosed if (3) is concurrent with (4), (5), or (6).

2. Familial apolipoprotein C-II deficiency

(1) The absence of plasma (serum) apolipoprotein C-II.
(2) Being a homozygote with a causative apolipoprotein C-II gene mutation on both alleles.
(3) The appearance of activity after the addition of apolipoprotein C-II or plasma from a normal subject.
(4) The presence of clinical symptoms due to hyperchylomicronemia (acute pancreatitis, eruptive xanthoma, lipemia retinalis, hepatosplenomegaly).
(5) The presence of consanguinity in the familial history.

Definitively diagnosed if (1) or (2) is established, and provisionally diagnosed if (3) is concurrent with (4) or (5).

3. Primary type V hyperlipoproteinemia

(1) Demonstration of an increase in VLDL in addition to hyperchylomicronemia.
(2) The absence of LPL deficiency, apolipoprotein C-II deficiency, or apolipoprotein E abnormality.

Definitively diagnosed if both (1) and (2) are fulfilled.

4. Idiopathic hyperchylomicronemia

Hyperchylomicronemia not in agreement with 1, 2, or 3 above.

For example, cases suggestive of the presence of an LPL inhibitor or autoantibody have been reported. More recently, a few cases of mutations in the gene for GPIHBP1 or LMF1 have also been reported to manifest primary hyperchylomicronemia.

tomatic. In such heterozygotes, type IV-V hyperlipoproteinemia is often triggered by pregnancy, diabetes, obesity, and excessive alcohol intake. Also, there are patients with low LPL activity in families with common hyperlipidemia such as FCHL and familial hypertriglyceridemia, and the possible involvement of LPL gene abnormalities is attracting attention as a background of these disorders. Such abnormalities include abnormal LPL gene expression. Indeed, the possibility that a single nucleotide polymorphism in the promoter region, which impairs the binding of transcription factor Oct-1 and reduces transcription activity to 15% or less, is related to FCHL and ischemic heart disease has been suggested[43]. Reports from Western countries include a study in which LPL gene abnormalities were observed in 10% of patients with type V hyperlipoproteinemia[44], but Arai *et al.* found no LPL gene mutations in any of 100 Japanese subjects with a serum TG level of 400-1,000 mg/dl examined[45].

Generally, poor control of blood glucose in diabetic patients is the most frequent acquired stressor, but drinking, estrogen, steroids, pregnancy, Zoloft (selective serotonin reuptake inhibitor type antidepressant), isotretinoin (treatment for acne), diuretics, β-blockers, HIV protease inhibitors, dysproteinemia, multiple myeloma, SLE, malignant lymphoma, etc., have also been reported. Since all clinical symptoms that accompany hypertriglyceridemia are also reversible in type V hyperlipoproteinemia, fundamental treatment involves reducing the TG level. If there are strong genetic fac-

tors such as in FCHL and homozygous familial hypertriglyceridemia, strict restriction of fat intake, such as in type I hyperlipoproteinemia, may be necessary. Since acquired environmental factors are usually present in type V hyperlipoproteinemia, they must be eliminated first. Among lipid-lowering drugs, fibrates, nicotinic acid, and strong statins are indicated, but caution against possible exacerbation of the glucose tolerance is necessary in the treatment of diabetic patients with nicotinic acid. Also, as marked weight control in obese patients may induce severe hypertriglyceridemia and acute pancreatitis associated with rebound of the body weight, this risk must be considered.

Proposal of Diagnostic Criteria for Primary Hyperchylomicronemia (Draft)

Lastly, against the background described above, provisional diagnostic criteria for primary hyperchylomicronemia are presented (**Table 3**). Items related to genetic diagnosis, which has become possible, and those related to clinical symptoms and familial history have been added to the diagnostic criteria proposed by the Tarui Group[9]. Since no such diagnostic criteria or management guidelines have been established anywhere in the world, further discussion and rigorous evaluation are needed.

Conflict of Interest

Dr. Oikawa has received unrestricted grants from Daiichi-Sankyo Co. Ltd. Dr. Ishibashi has received unrestricted grants from Takeda Pharmaceutical Co. Ltd. and is an advisor of Kowa Pharmaceutical Co. Ltd. Dr. Arai has received unrestricted grants from Otsuka Pharmaceutical Co., Ltd., received honoraria from MSD, and is an advisor of Kowa Pharmaceutical Co. Ltd. Dr. Yamashita has received unrestricted grants from MSD, Otsuka Pharmaceutical Co., Ltd., Astellas Pharma Inc., and JT, collaborative research grants from Shionogi & Co., Ltd., Otsuka Pharmaceutical Co., Ltd., and National Institute of of Biomedical Innovation, honoraria for lectures from MSD, Bayer Yakuhin, Ltd., and Kowa Pharmaceutical Co.,Ltd., and is an advisory of Skylight Biotech Co. Dr. Harada-Shiba has received unrestricted grants from MSD. Dr. Eto is an advisor of MSD. The other authors declare that they have no conflict of interest.

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