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Review

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Current Diagnosis and Management of Primary Chylomicronemia

Hiroaki Okazaki[1], Takanari Gotoda[2], Masatsune Ogura[3], Shun Ishibashi[4], Kyoko Inagaki[5], Hiroyuki Daida[6], Toshio Hayashi[7], Mika Hori[8], Daisaku Masuda[9], Kota Matsuki[10], Shinji Yokoyama[11] and Mariko Harada-Shiba[12] on behalf of the Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Disease of the Ministry of Health, Labour and Welfare of Japan[†]

[1]Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[2]Department of Metabolic Biochemistry, Faculty of Medicine, Kyorin University, Tokyo, Japan
[3]Department of Molecular Innovation in Lipidology, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan
[4]Division of Endocrinology and Metabolism, Department of Internal Medicine, School of Medicine, Jichi Medical University, Tochigi, Japan
[5]Division of Diabetes, Endocrinology, and Metabolism, Department of Medicine, Nippon Medical School, Tokyo, Japan
[6]Faculty of Health Science, Juntendo University, Juntendo University Graduate School of Medicine, Tokyo, Japan
[7]School of Health Sciences, Nagoya University Graduate School of Medicine, Nagoya, Japan
[8]Department of Endocrinology, Research Institute of Environmental Medicine, Nagoya University, Nagoya, Japan
[9]Department of Cardiology, Health Care Center, Rinku Innovation Center for Wellness Care and Activities (RICWA), Rinku General Medical Center, Osaka, Japan
[10]Department of Endocrinology and Metabolism, Hirosaki University Graduate School of Medicine, Hirosaki, Japan
[11]Institute for Biological Functions, Chubu University, Aichi, Japan
[12]Department of Molecular Pathogenesis, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan

[†]**The Committee on Primary Dyslipidemia under the Research Program on Rare and Intractable Disease of the Ministry of Health, Labour and Welfare of Japan:** Mariko Harada-Shiba (Department of Molecular Pathogenesis, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan), Shun Ishibashi (Division of Endocrinology and Metabolism, Department of Internal Medicine, School of Medicine, Jichi Medical University, Tochigi, Japan), Shinji Yokoyama (Institute for Biological Functions, Chubu University, Aichi, Japan), Hitoshi Shimano (Department of Internal Medicine (Endocrinology and Metabolism), Faculty of Medicine University of Tsukuba, Tsukuba, Japan), Koutaro Yokote (Department of Endocrinology, Hematology and Gerontology, Chiba University Graduate School of Medicine, Chiba, Japan), Hideaki Bujo (Department of Clinical-Laboratory and Experimental-Research Medicine, Toho University Sakura Medical Center, Chiba, Japan), Shizuya Yamashita (Rinku General Medical Center, Osaka, Japan), Kazuhisa Tsukamoto (Department of Internal Medicine, Teikyo University, Tokyo, Japan), Toshio Hayashi (School of Health Sciences, Nagoya University Graduate School of Medicine, Nagoya, Japan), Katsunori Ikewaki (Division of Neurology, Anti-Aging, and Vascular Medicine, Department of Internal Medicine, National Defense Medical College, Saitama, Japan), Takanari Gotoda (Department of Metabolic Biochemistry, Faculty of Medicine, Kyorin University, Tokyo, Japan), Kazushige Dobashi (Department of Pediatrics, School of Medicine, University of Yamanashi, Yamanashi, Japan), Yoshihiro Miyamoto (Open Innovation Center, National Cerebral and Cardiovascular Center, Osaka, Japan), Misa Takegami (Department of Preventive Medicine and Epidemiology, National Cerebral and Cardiovascular Center, Osaka, Japan), Yoshiki Sekijima (Department of Medicine (Neurology & Rheumatology), Shinshu University School of Medicine, Matsumoto, Japan), Yasushi Ishigaki (Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Iwate Medical University, Iwate, Japan), Hiroaki Okazaki (Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan), Atsushi Nohara (Ishikawa Prefectural Central Hospital, Kanazawa, Japan), Shingo Koyama (Division of Neurology and Clinical Neuroscience, Department of Internal Medicine III, Yamagata University Faculty of Medicine, Yamagata, Japan), Kyoko Inagaki (Division of Diabetes, Endocrinology, and Metabolism, Department of Medicine, Nippon Medical School, Tokyo, Japan), Koh Ono (Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan), Masahiro Koseki (Division of Cardiovascular Medicine, Department of Medicine, Osaka University Graduate School of Medicine, Osaka, Japan), Hiroyuki Daida (Faculty of Health Science, Juntendo University, Juntendo University Graduate School of Medicine, Tokyo, Japan), Manabu Takahashi (Division of Endocrinology and Metabolism, Department of Internal Medicine, Jichi Medical University, Tochigi, Japan), Kimitoshi Nakamura (Department of Pediatrics, Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan), Takashi Miida (Department of Clinical Laboratory Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan), Masa-aki Kawashiri (Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kanazawa University, Kanazawa, Japan), Tetsuo Minamino (Department of Cardiorenal and Cerebrovascular Medicine, Faculty of Medicine, Kagawa University, Kagawa, Japan), Sachiko Okazaki (Division for Health Service Promotion, The University of Tokyo, Tokyo, Japan), Hayato Tada (Department of Cardiovascular Medicine, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan), Jun Wada (Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University

Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan), Masatsune Ogura (Division of Lipid Metabolism, Department of Molecular Innovation in Lipidology, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan), Hirotoshi Ohmura (Department of Cardiovascular Medicine, School of Medicine, Juntendo University, Tokyo, Japan), Mika Hori (Department of Endocrinology, Research Institute of Environmental Medicine, Nagoya University, Nagoya, Japan), Kota Matsuki (Department of Endocrinology and Metabolism, Hirosaki University Graduate School of Medicine, Hirosaki, Japan), Masashi Yamamoto (Department of Endocrinology, Hematology and Gerontology, Chiba University Graduate School of Medicine, Chiba, Japan), Yasuo Takeuchi (Division of Nephrology, Kitasato University School of Medicine, Kanagawa, Japan), Atsuko Nakatsuka (Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan), Daisaku Masuda (Department of Cardiology, Health Care Center, Rinku Innovation Center for Wellness Care and Activities (RICWA), Rinku General Medical Center, Osaka, Japan), Satoshi Hirayama (Department of Clinical Laboratory Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan), Masayuki Kuroda (Center for Advanced Medicine, Chiba University Hospital, Chiba University, Chiba, Japan), Takashi Yamaguchi (Center of Diabetes, Endocrinology and Metabolism, Toho University Sakura Medical Center, Chiba, Japan), Takeyoshi Murano (Clinical Laboratory Program, Faculty of Science, Toho University, Chiba, Japan).

Primary chylomicronemia (PCM) is a rare and intractable disease characterized by marked accumulation of chylomicrons in plasma. The levels of plasma triglycerides (TGs) typically range from 1,000 - 15,000 mg/dL or higher.

PCM is caused by defects in the lipoprotein lipase (LPL) pathway due to genetic mutations, autoantibodies, or unidentified causes. The monogenic type is typically inherited as an autosomal recessive trait with loss-of-function mutations in LPL pathway genes (*LPL*, *LMF1*, *GPIHBP1*, *APOC2*, and *APOA5*). Secondary/environmental factors (diabetes, alcohol intake, pregnancy, etc.) often exacerbate hypertriglyceridemia (HTG).

The signs, symptoms, and complications of chylomicronemia include eruptive xanthomas, lipemia retinalis, hepatosplenomegaly, and acute pancreatitis with onset as early as in infancy. Acute pancreatitis can be fatal and recurrent episodes of abdominal pain may lead to dietary fat intolerance and failure to thrive.

The main goal of treatment is to prevent acute pancreatitis by reducing plasma TG levels to at least less than 500-1,000 mg/dL. However, current TG-lowering medications are generally ineffective for PCM. The only other treatment options are modulation of secondary/environmental factors. Most patients need strict dietary fat restriction, which is often difficult to maintain and likely affects their quality of life.

Timely diagnosis is critical for the best prognosis with currently available management, but PCM is often misdiagnosed and undertreated. The aim of this review is firstly to summarize the pathogenesis, signs, symptoms, diagnosis, and management of PCM, and secondly to propose simple diagnostic criteria that can be readily translated into general clinical practice to improve the diagnostic rate of PCM. In fact, these criteria are currently used to define eligibility to receive social support from the Japanese government for PCM as a rare and intractable disease.

Nevertheless, further research to unravel the molecular pathogenesis and develop effective therapeutic modalities is warranted. Nationwide registry research on PCM is currently ongoing in Japan with the aim of better understanding the disease burden as well as the unmet needs of this life-threatening disease with poor therapeutic options.

Key words: **Chylomicronemia, Triglyceride, Pancreatitis, Diagnostic criteria, Treatment guide**

1. Definition of Chylomicronemia

Chylomicrons (CMs) are intestine-derived lipoproteins that transport dietary fat to peripheral tissues[1]. CMs are usually quickly cleared from plasma after an overnight fast. The hallmark of chylomicronemia is persistent elevation of CMs in the fasting state (>12h). Plasma triglyceride (TG) levels

Address for correspondence: Hiroaki Okazaki, Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113–8655, Japan E-mail: hokazaki-tky@umin.ac.jp

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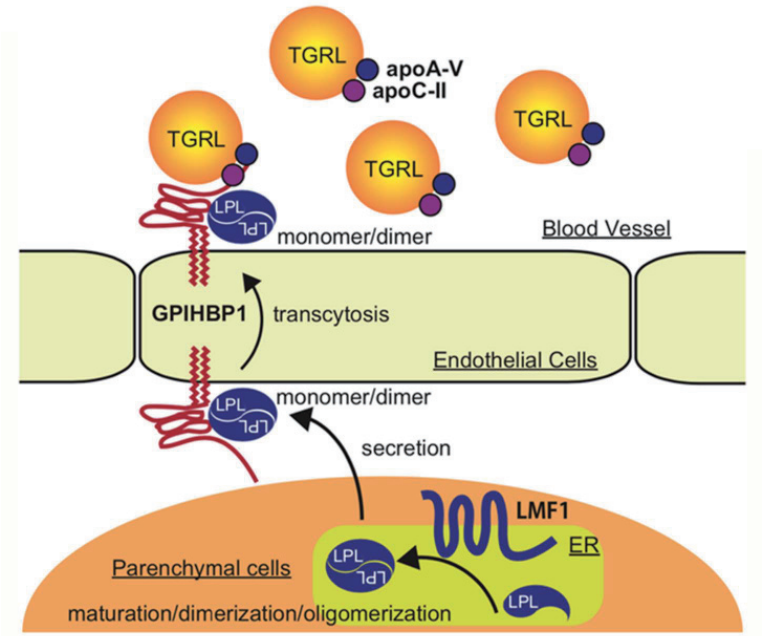

Fig. 1. Molecular basis of primary chylomicronemia

Lipoprotein lipase (LPL) hydrolyzes triglycerides (TGs) in TG-rich lipoproteins (TGRLs), such as very low-density lipoproteins (VLDLs) and chylomicrons (CMs) to liberate free fatty acids (FFAs), which are utilized by peripheral tissues (e.g., muscle, heart, and adipose tissues). Activity of LPL is regulated by a quaternary structure (monomer/dimer/oligomer) as well as by multiple LPL-pathway proteins[210-212]. LMF1 is required for the synthesis of LPL in parenchymal cells of these peripheral tissues. GPIHBP1 is a transmembrane protein that tethers LPL on the endothelial cell surface to provide a platform for TG hydrolysis. GPIHBP1 captures LPL in the subendothelial (interstitial) space of peripheral tissues, transports LPL from the subendothelial surface to the luminal surface of endothelial cells by transcytosis, and anchors LPL on the luminal surface facing the bloodstream to facilitate lipolysis. For the hydrolytic activity of LPL, two apolipoproteins, apoC-II and apoA-V, are required. ApoC-II is necessary for the enzymatic activity of LPL. ApoA-V primarily enhances the interaction between TGRL and LPL by forming TGRL-apoA-V-GPIHBP1-LPL complex via its dual binding affinity to TGRL and GPIHBP1. Defects in LPL pathway proteins (LPL, LMF1, GPIHBP1, apoC-II, apoA-V) due to genetic mutations or autoantibodies cause primary chylomicronemia (PCM). LPL activity can be measured after releasing LPL from the luminal surface into the circulation by i.v. injection with heparin.
Abbreviations: apoA-V, apolipoprotein A-V; apoC-II, apolipoprotein C-II; GPIHBP-1, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; LMF1, lipase maturation factor 1.

in chylomicronemia typically range from 1,000 to 15,000 mg/dL or higher[2]. As CMs start to accumulate in plasma when TG levels increase to more than 500 - 1,000 mg/dL[1], it is practical to screen and suspect chylomicronemia if plasma TGs >1,000 mg/dL[2, 3].

2. Metabolism of Chylomicrons

CMs are produced by the intestine after a meal and secreted into the circulation[1]. Their synthesis requires apoB-48 protein, which is transcribed from the edited mRNA of *APOB*, and microsomal triglyceride transfer protein (MTTP), which incorporates dietary TGs into CMs. More than 90% of lipids in CMs are TGs (derived from dietary fatty acids and TGs), which are hydrolyzed by lipoprotein lipase (LPL) on the endothelial cell surface of peripheral tissues (muscle, heart, adipose tissue, etc.) to liberate free fatty acids (FFAs). FFAs are used as an energy source in peripheral tissues, or stored as TGs in adipose tissues, or re-esterified and secreted as very low-density lipoprotein (VLDL)-TG by the liver. CMs are converted to CM remnants after TG hydrolysis by LPL and then cleared from plasma through endocytosis mainly by the liver.

3. Molecular Basis of Chylomicronemia

Plasma levels of CMs are affected by primary factors as well as secondary factors[2, 4, 5]. Primary factors consist of defects in the proteins that metabolize CMs, such as LPL and its related proteins (apolipoprotein(apo)C-II, apoA-V, glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1 (GPIHBP1), lipase maturation factor 1 (LMF1)) **(Fig. 1)**. Secondary factors include conditions that impair CM metabolism, such as poor control of diabetes, excessive alcohol intake, and pregnancy. In primary chylomicronemia (PCM), chylomicronemia usually persists even after

management of secondary factors. PCM is caused by defects in LPL pathway genes (*LPL*, *APOC2*, *APOA5*, *GPIHBP1*, *LMF1*) due to genetic mutations or presence of autoantibodies against LPL pathway proteins (GPIHBP1, LPL, and apoC-II)[6-9].

4. Complications of Chylomicronemia

Chylomicronemia is a risk factor for acute pancreatitis[10]. Although the underlying mechanisms are not fully understood, the widely accepted hypothesis is that an excess of FFAs derived from lipolysis of chylomicron-TG by pancreatic lipase damages pancreatic acinar cells or endothelial cells of pancreatic capillaries, leading to activation of inflammatory processes[11]. In addition, high levels of plasma CM may increase the viscosity of pancreatic microcirculation and impair pancreatic blood flow, further exacerbating inflammation. Genetic predisposition may also contribute to the pathogenesis[12].

Based on this hypothesis, it is generally believed that chylomicronemia per se induces pancreatitis and, therefore, reducing plasma CM levels should lower the risk of pancreatitis[10]. The widely accepted treatment goal is to reduce plasma TG levels to at least less than 1,000 mg/dL[2, 4, 5, 12-14].

5. Primary Factors of Chylomicronemia

Five genes (*LPL*, *LMF1*, *GPIHBP1*, *APOC2*, *APOA5*) have been identified as the causative genes of monogenic chylomicronemia **(Fig. 1)**[4, 5]. All of them are required for the normal function of LPL. Homozygous, compound heterozygous, or double heterozygous loss-of-function mutations of these LPL pathway genes usually cause monogenic chylomicronemia with an autosomal recessive mode of inheritance[15]. Heterozygous mutations or pathological variants in HTG-susceptible genes, including those for hepatic lipase (HL) and apolipoprotein E, may also predispose to chylomicronemia[3, 5, 16-18].

Loss-of-function mutations in LPL-pathway genes have been identified in only less than 30-40% of patients suspected of monogenic chylomicronemia[19, 20]. In some cases, autoantibodies against LPL pathway proteins can cause PCM. Additional genetic factors or unknown causes may also underlie PCM.

•***LPL*** (LPL deficiency, OMIM: 238600): *LPL* is the most common causative gene of monogenic chylomicronemia. More than 220 pathogenic variants in *LPL* have been described (missense, nonsense, splicing variants, insertion/deletion of nucleotide(s), deletion/duplication/insertion/rearrangement of exon(s))[2, 4, 15, 20-22]. A list of mutations in *LPL* has been comprehensively summarized in exon-intron diagrams by Rabacchi C *et al.* and Rodrigues R *et al.*[20, 22]. LPL activity is usually tested in post-heparin plasma taken 10-15 min after iv. heparin injection (10-60 IU/kg body weight)[4, 23].

•***LMF1*** (LMF1 deficiency, OMIM: 246650): *LMF1* encodes LMF1, a transmembrane chaperone protein of parenchymal cells (muscle, adipose tissues, etc.). LMF1 is localized to the endoplasmic reticulum and is required for proper synthesis and secretion of LPL and HL. In addition to nonsense mutations that were originally reported, several other mutations, including missense loss-of-function mutations, have been identified in *LMF1*[24-29].

•***GPIHBP1*** (GPIHBP1 deficiency, OMIM: 615947): *GPIHBP1* encodes GPIHBP1, a transmembrane protein that tethers LPL on the endothelial cell surface to provide a platform for TG hydrolysis[30, 31]. GPIHBP1 captures LPL in the subendothelial (interstitial) space of peripheral tissues (skeletal muscles, heart, adipose tissues, etc.), transports LPL from the subendothelial surface to the luminal surface of endothelial cells by transcytosis, and anchors LPL on the luminal surface facing the bloodstream to facilitate lipolysis. So far, at least 23 pathogenic mutations in *GPIHBP1* have been reported in severe HTG patients, including those causing total GPIHBP1 deficiency[21, 32-36]. Mutations in *GPIHBP1* are comprehensively summarized in the exon-intron diagram by Rabacchi *et al.*[35]. GPIHBP1 deficiency may be differentiated from LPL deficiency in that LPL activity or protein in post-heparin plasma is not totally lacking in GPIHBP1 deficiency[37].

•***APOC2*** (apoC-II deficiency, OMIM: 207750): *APOC2* encodes apoC-II, a co-factor required for LPL activity. *APOC2* is the second most common causative gene of monogenic chylomicronemia. At least 24 mutations have been reported worldwide[2, 4, 5, 38-41], and are comprehensively summarized in the exon-intron diagram by Wolska *et al.*[41]. In some cases, plasma levels of apoC-II have been severely decreased but are detected with apparently normal electrophoretic patterns (so-called hypoapoC-II)[42-45]. In apoC-II deficiency, symptoms often develop at an older age (13-60 years) than in LPL deficiency[1, 4]. As apoC-II deficient patients tend to be subjected to strict fat restriction at an older age, they may have poorer dietary adherence and more frequent episodes of acute pancreatitis in adulthood than LPL deficient patients, often accompanied by high VLDL levels[2].

•***APOA5*** (apoA-V deficiency, OMIM: 144650): *APOA5* encodes apoA-V, a co-factor of LPL that enhances interaction between LPL and TG-rich lipoproteins (TGRLs)[46, 47]. ApoA-V has dual binding

affinity for both TGRL and GPIHBP1, thereby forming the TGRL-apoA-V-GPIHBP1-LPL complex to facilitate lipolysis[31, 48, 49]. So far, at least 21 mutations in *APOA5* have been reported, which are comprehensively summarized in exon-intron diagrams by Albers *et al.*[50-53]. In most cases, severe HTG develops later in life due to the combinatorial effects of primary (genetic) and secondary factors (aging, diabetes, pregnancy, HIV therapy, etc.)[53]. The underlying molecular mechanisms of apoA-V deficient HTG in terms of gene-environmental interactions has only begun to be elucidated[54, 55].

•**Autoantibodies against LPL pathway proteins**: Autoimmune chylomicronemia due to autoantibodies against LPL pathway proteins (GPIHBP1, LPL, apoC-II) has been reported[6-9]. Autoimmune chylomicronemia may be complicated by other autoimmune diseases and be ameliorated by steroid or immune-suppressive therapy.

6. Secondary Factors of Chylomicronemia

The following factors have been reported to induce chylomicronemia[3-5, 13, 35, 56-61]. Among them, excess alcohol consumption and diabetes mellitus are the two most common factors associated with severe HTG[18, 62, 63].

Pregnancy is another important factor that can induce chylomicronemia. Hormonal changes during pregnancy result in hyperlipidemia even in healthy subjects, as a physiological response to ensure nutrient supply to the fetus[64-66]. Plasma TG levels progressively increase in healthy subjects by 2- to 4-fold[67], and markedly increase in subjects with PCM[68-74]. Pregnancy increases TGRL (VLDL) production and decreases TGRL clearance[75-78].

•**Lifestyle-related factors**: Dietary factors such as excessive alcohol intake, high-fat diet, high-carbohydrate diet rich in fructose and other simple sugars. Less exercise and excessive intake of total calories, particularly in subjects who are overweight, have metabolic syndrome, or diabetes mellitus.

•**Pathophysiological conditions**: Pregnancy, obesity, metabolic syndrome, anorexia nervosa, glucose intolerance, diabetes mellitus with insulin resistance or insulin deficiency, endocrine diseases such as hypothyroidism, acromegaly, Cushing's syndrome, Nelson's syndrome, glycogen storage diseases, amyloidosis, renal disease (nephrotic syndrome, proteinuria, uremia, glomerulonephritis, etc.), liver disease, autoimmune disorders, lipodystrophies, Weber-Christian disease, multiple myeloma, paraproteinemia, and lymphoproliferative disorders, etc.

•**Medications**: Glucocorticoids, oral estrogens (contraceptives, postmenopausal replacement therapies), clomiphene, tamoxifen, exogenous testosterone; retinoids such as isotretinoin, bexarotene; immunosuppressants and anticancer drugs such as sirolimus, cyclosporine A, tacrolimus, capecitabine, cyclophosphamide, asparaginase; antihypertensives such as thiazides, loop diuretics, non-selective β -blockers; bile acid-sequestrants; antiviral drugs such as entecavir, ritonavir and other antiretroviral protease inhibitors; second-generation antipsychotics (atypical antipsychotics), such as dozapine, clozapine, olanzapine, risperidone, quetiapine; antidepressants such as mirtazapine, venlafaxine; selective serotonin reuptake inhibitors (sertraline, etc.); anticonvulsants, such as valproate; anesthetic drugs, such as propofol.

7. Classification of Chylomicronemia

Chylomicronemia was formerly classified as type 1 and 5 hyperlipoproteinemia (HLP) in the Fredrickson classification (WHO classification)[5, 79], where increased plasma lipoproteins are CM for type 1 and CM+VLDL for type 5 HLP. However, differentiation of type 1 and type 5 HLP is often difficult because of considerable overlaps in phenotypes and genetic backgrounds[3, 5, 17].

Differentiation of monogenic from polygenic chylomicronemia is also difficult[80]. Even when monogenic chylomicronemia is suspected, causative mutations have been identified in less than 30-40%[19, 20].

For practical reasons, we prefer to use the term PCM, which is defined as a condition with persistent elevation of TG >1,000 mg/dL even after management of secondary factors. The term familial chylomicronemia syndrome (FCS) is not used here, as monogenic chylomicronemia is typically autosomal recessive, and most cases are sporadic, without a family history. The term "familial" may confuse both patients and doctors, and may lead to underdiagnosis[3, 81].

8. Prevalence of Chylomicronemia

The prevalence of severe HTG (TG >10 mmol/L (885 mg/dL)) is estimated at ~1 in 600 in North America[5]. In a population of 440,240 subjects in the US, severe HTG (886-2,000 mg/dL) and very severe HTG (>2,000 mg/dL) were observed in 0.15% and 0.014%, respectively[36].

The monogenic type of chylomicronemia is very rare and its frequency is estimated at 1 to 2 per million in the general population[1, 4, 5]. The most common causative gene is *LPL*, followed by other LPL pathway

genes (*APOC2*, *GPIHBP1*, *APOA5*, and *LMF1*)[5, 15, 53].

Severe HTG is more often due to polygenic causes[3, 82]. Dron *et al.* reported that the etiology of severe HTG (TG >10 mmol/L (885 mg/dL)) is monogenic in 1.1%, polygenic in 46%, and genetically unidentified in the rest of cases[83]. Another study identified monogenic causes in 0.96% of patients with very severe HTG (TG >20 mmol/L (1770 mg/dL)) recorded at least once during regular medical care[22].

9. Prevalence of HTG-Induced Acute Pancreatitis

Regardless of the underlying etiology of HTG, the risk of acute pancreatitis increases as TG levels increase, particularly when they exceed 1,000 - 2,000 mg/dL[84].

HTG is the third leading cause (5-38%) of acute pancreatitis after alcohol and gallstones[1, 12, 85-87]. HTG is the leading cause (25~50%) of acute pancreatitis during pregnancy[12, 74, 88], which is most often seen in the third trimester (19%, 26%, 53% in the 1st, 2nd, and 3rd trimester, and 2% in postpartum period)[89]. The frequency of HTG-induced acute pancreatitis in pregnancy is estimated as 1 in 1000-12,000 pregnancies[14, 73, 74].

Risk of acute pancreatitis increases by ~4% for every 100 mg/dL increase in plasma TG[56, 84, 87, 90, 91]. According to the 2010 Endocrine Society guidelines, HTG can be classified into mild HTG (150-199 mg/dL), moderate HTG (200-999 mg/dL), severe HTG (sHTG, 1000-1999 mg/dL), or very severe HTG (vsHTG, >2000 mg/dL). The prevalence of pancreatitis in sHTG and vsHTG is about 10% and 20%, respectively[5, 13, 14, 87, 92].

Clinically, it remains difficult to predict if a HTG patient will develop acute pancreatitis or not. Some patients do not develop acute pancreatitis even at TG levels higher than 30,000 mg/dL[1, 2]. Conversely, patients can develop acute pancreatitis at TG levels of 5-10 mmol/L (442-885 mg/dL)[93]. The underlying etiology of monogenic chylomicronemia seems to confer a potent risk of acute pancreatitis[53, 94-96]. Compared to normolipidemic individuals, the risk of acute pancreatitis increased by 16-fold, 56-fold, and 361-fold in HTG (5-9 mmol/L (442-796 mg/dL)) without LPL deficiency, HTG (>9 mmol/L (796 mg/dL)) without LPL deficiency, and HTG (>9 mmol/L (796 mg/dL)) with LPL deficiency (genetically-confirmed), respectively[94]. Greater cumulative exposure of HTG to the pancreas due to genetic causes may impose higher pancreatitis risk[53, 94-97](See **sections 12 and 16(B)** for other suggested risk factors of acute pancreatitis among HTG subjects).

10. Signs, Symptoms, and Complications of Chylomicronemia

Depending on the severity of the mutation, signs, symptoms, and complications of chylomicronemia may manifest as early as in infancy, in childhood, or later in life[4, 95].

•**Abdominal pain, fat intolerance, failure to thrive**: Abdominal pain affects ~60% of monogenic chylomicronemia patients and can be mild to incapacitating[4, 95, 96]. Recurrent episodes of abdominal pain may lead to dietary fat intolerance and failure to thrive. Body weight may be lower because of restricted food intake.

•**Pancreatitis**: Acute pancreatitis can be severe, recurrent, and life-threatening[1, 4, 95]. Acute pancreatitis may lead to chronic pancreatitis and diabetes. Irrespective of its etiology, severe HTG should be carefully monitored for the possible complications of pancreatitis. Compared to polygenic chylomicronemia, monogenic chylomicronemia is associated with a higher risk of acute pancreatitis and tends to manifest severe phenotypes[86, 94, 95]. According to a survey of lipidologists, ~67% of monogenic patients were hospitalized for acute pancreatitis vs. ~14% of polygenic patients[95, 96]. It should be noted that high levels of plasma TG may interfere with assays of plasma pancreatic enzymes (lipase, amylase), resulting in falsely low levels[2, 98-100]. HTG-induced acute pancreatitis should not be misdiagnosed due to apparently low serum levels of pancreatic enzymes.

•**Lipemic plasma**: Lipemic plasma (milky-looking plasma) is characterized by a creamy CM layer floating above the bottom layer, after leaving serum standing overnight in a refrigerator (the "refrigerator" test)[1]. In type 5 HLP, the bottom layer contains VLDLs and has a lactescent appearance. In type 1 HLP, the bottom layer is clear without apparent VLDL accumulation. Type 1 HLP is more frequently observed than type 5 in monogenic chylomicronemia[19]. (See reference by Yuan G *et al.* for a photograph of lipemic plasma[56].)

•**Eruptive xanthomas**: Eruptive xanthomas affect 10-50% of the monogenic type[95, 96]. They appear when plasma TG levels increase to more than 2,000 mg/dL as yellow papules on the skin of the trunk, buttocks, and extremities (extensor surfaces of the arms and knees) as a result of TG uptake by macrophages (see references by Nayak KR *et al.* and Yuan G *et al.* for photographs)[2, 4, 56, 101]. Along with reduction in plasma TG levels, they gradually

Table 1. Diagnostic criteria for primary chylomicronemia

A. Entry Criterion:
A1 and A2 with exclusion of differential diagnosis in E
A1) Plasma TG level ≧1,000 mg/dL (after fasting for 12 hours or longer)
A2) Presence of chylomicrons in serum (from appearance of supernatant cream layer after allowing serum to stand for 24 hours or longer at 4℃, ultracentrifugation, or electrophoresis (agarose gel, polyacrylamide gel, or HPLC))
B. Clinical manifestations (major (B1-B4) and minor (B5, B6))
B1) Recurrent episodes of abdominal pain and/or acute pancreatitis
B2) Eruptive xanthomas
B3) Lipemia retinalis
B4) Hepatomegaly and/or splenomegaly
B5) Dyspnea
B6) Neurological symptoms (cognitive impairment, memory impairment, depression, etc.)
C. Laboratory findings
C1) LPL activity and/or protein in post heparin plasma, adipose tissue, or macrophages is absent or markedly decreased (＜10% of normal subjects)
C2) Plasma apoC-II is absent or markedly decreased (＜10% of normal subjects)
C3) Plasma apoA-V is absent or markedly decreased (＜10% of normal subjects)
C4) Autoantibodies against LPL, heparin, apoC-II, or GPIHBP1.
D. Genetic test
Identification of causative mutation(s) in *LPL*, *APOC2*, *GPIHBP1*, *LMF1*, or *APOA5*
E. Differential diagnosis
Type 3 hyperlipidemia, familial combined hyperlipidemia (FCHL), and secondary hyperlipidemia due to following: excess alcohol intake, nephrotic syndrome, anorexia nervosa, pregnancy, diabetes mellitus, lipodystrophies, Weber-Christian disease, hypothyroidism, acromegaly, Cushing's syndrome, Nelson's syndrome, multiple myeloma, systemic lupus erythematosis, malignant lymphoma, sarcoidosis, etc.; medications such as estrogens, steroids, diuretics, β-blockers, antipsychotics including selective serotonin reuptake inhibitors (SSRIs), retinoids such as isotretinoin, antiretroviral protease inhibitors, immunosuppressants, etc.
<Diagnosis>
Definite: Entry criterion (A) associated with at least one item from C or D
Probable: Entry criterion (A) associated with at least one item from B1-B4
Possible: Entry criterion (A) with or without item(s) from B5-B6

disappear over several weeks to a few months[2].

•**Lipemia retinalis**: Lipemia retinalis affects ~40% of the monogenic type[95, 96] and is characterized by retinal blood vessels with a milky appearance (a pale pink color) on fundoscopy (see references by Kumar J *et al.* and Yuan G *et al.* for photographs)[56, 102]. Vision is not impaired. It is usually visible when plasma TG levels increase to more than 4,000 mg/dL[2].

•**Hepatomegaly and splenomegaly**: Hepatomegaly and splenomegaly affect 10-50% of the monogenic type[95, 96] as a result of TG uptake by macrophages and other cell types in these tissues[1, 4]. Both conditions are reversible and rapidly improve within a week, along with reduction in plasma TG levels[2].

•**Other symptoms (fatigue, dyspnea, and neurological symptoms)**: Other clinical symptoms include fatigue, dyspnea, and neurological symptoms[1] such as memory impairment (transient memory loss), cognitive impairment, mild dementia, cloudy thought, brain fog, neurosis, irritability, anxiety, and depression[4, 95, 103-107]. Neurological symptoms affect ~8% of the monogenic type[95]. Although little is known about the underlying mechanisms of these symptoms, large surveillance studies among chylomicronemia patients have shown that they dominantly and adversely affect patients' quality of life and increase the burden of the disease[104-107].

11. Diagnosis of Chylomicronemia

Undertreatment and underdiagnosis of chylomicronemia are one of the major risks for acute pancreatitis[84, 87]. In order to achieve early diagnosis and treatment for chylomicronemia, simple diagnostic criteria that can be readily translated into general practice are required.

Based on TG levels that lead to suspicion of chylomicronemia (TG ＞1,000 mg/dL), clinical manifestations and the available data on diagnostic tests, here we propose diagnostic criteria for PCM

(Table 1).

It should be noted that PCM is genetically confirmed in less than 30-40% of patients suspected of monogenic chylomicronemia[19, 20]. Therefore, we have set three categories (definite, probable, and possible) so that PCM patients will not be missed even without a genetic diagnosis.

To achieve timely diagnosis and improve the diagnostic rate of PCM, screening of plasma TG levels in the following settings will be helpful. Clinicians across multiple disciplines, such as primary care physicians, gastroenterologists, gynecologists, and other doctors who have occasionally encountered severe HTG patients, should consult lipidologists concerning further diagnostic tests for chylomicronemia.

•**Health checkup or opportunistic blood test**: All patients who have TG levels of more than 1,000 mg/dL in universal lipid screening[108] or a routine clinic visit should be suspected of chylomicronemia[96, 109].

•**Acute abdomen (including pancreatitis)**: Those who have acute abdomen or are suspected of pancreatitis should have their plasma TG levels measured[96]. Plasma TG should be measured as early as possible after the onset of abdominal pain, as TG levels rapidly decrease within 24-48 hours of onset[110].

•**Pregnancy**: Many cases of monogenic chylomicronemia have been discovered in the third trimester of pregnancy[111-118]. HTG-induced acute pancreatitis in pregnancy can be lethal to both mother and fetus[119]. Gestational HTG may also increase the risk of hyperviscosity syndrome[120], pre-eclampsia[121], fetal macrosomia, and fetal pancreatitis-related complications (in-utero fetal death, preterm labor, and prematurity)[66]. Pregnant women who are suspected of pancreatitis should be tested for plasma TG. Pregnant women at high-risk for HTG-induced acute pancreatitis may benefit from plasma TG screening and monitoring on a weekly basis[122]. Such patients include: those with HTG or pancreatitis prior to or during pregnancy; high predisposition for HTG-induced acute pancreatitis due to diabetes mellitus, obesity, hypertension, hypothyroidism, renal disease, liver disease, family history of HTG, alcohol consumption, and medications that cause HTG; HTG with abdominal pain or other symptoms typical to chylomicronemia[84, 87, 122](See **sections 12 and 16(B)** for suggested risk factors of acute pancreatitis among HTG patients).

•**Family members of chylomicronemia patients**: Evaluation of plasma TG levels in family members is beneficial for early diagnosis and management of possible complications[96].

12. Features for Suspecting Monogenic Chylomicronemia

Clinical features that lead to suspicion of monogenic chylomicronemia have been suggested by previous studies and in expert opinions, but further validation in various cohorts is required[2-5, 15, 18, 53, 80, 96, 109, 123, 124]. These features may be useful not only for indicating the likelihood of monogenic chylomicronemia but also for predicting a higher risk of pancreatitis[53, 86, 94-96]:

- Intractable, severe HTG (TG >10 mmol/L or 1,000 mg/dL)
- Fasting severe HTG on multiple occasions
- Very severe HTG
- No history of normal to mild plasma TG levels (<200 mg/dL)
- Severe HTG with no secondary factors (except for pregnancy and oral estrogens)
- Severe HTG with pregnancy
- No response (TG decrease <20%) to hypolipidemic agents
- Severe HTG with type 1 rather than type 5 HLP
- History of recurrent abdominal pain or acute pancreatitis
- Younger age at onset
- Lower body mass index (BMI)
- Eruptive xanthomas
- Lipemia retinalis
- Hepatosplenomegaly
- Consanguinity

On the other hand, the polygenic type of chylomicronemia is more frequently associated with secondary/environmental factors, such as high-alcohol intake, diabetes mellitus, hypertension, and obesity[2, 18, 96].

13. Treatment of Chylomicronemia

The treatment goal of chylomicronemia is to lower plasma TG levels enough to reduce the risk of pancreatitis. Data from large healthcare databases suggest that sustained HTG (>500 mg/dL) increases the risk of pancreatitis (hazard ratio 1.79 [CI 95%: 1.10-1.28])[125] and lowering TG from >500 mg/dL to less than 200 mg/dL can reduce the incidence of acute pancreatitis from 1.1 to 0.4 per 100 person-year (adjusted OR 0.45 [CI 95%: 0.34-0.60])[126]. Due to the rareness of the disease, there have been no randomized control trials (RCTs) to determine treatment TG targets for prevention of pancreatitis. Mainly based on clinical experience, the opinion of

experts is to recommend maintaining plasma TG levels below 500-1,000 mg/dL to prevent pancreatitis[2, 4, 5, 12-14].

A) Control of Secondary Factors

Comorbid conditions that aggravate chylomicronemia should be thoroughly evaluated in order to rule them out. If any are present, they should be managed adequately. Bodyweight reduction, reduced calorie intake, and increased energy expenditure through regular physical exercise may help reduce plasma TG levels, particularly in overweight subjects. Regular physical exercise may also help in the non-obese[93, 127]. Bodyweight should be carefully controlled as rebound weight gain might elicit pancreatitis[13].

B) Dietary Therapy

Strict dietary control is currently the primary treatment modality for chylomicronemia, although it is often insufficient and difficult to maintain in the long term[128, 129]. Children and adolescents should be carefully monitored to ensure proper growth and development. Adjustment of social life might be a challenge throughout life[104-107].

•**Fat restriction**: The mainstay of dietary treatment is a low-fat diet. Restriction of total dietary fat to <15-20 g per day (<10-15 % of total energy intake) is usually required to reduce plasma CMs and prevent pancreatitis[128, 129]. Under fat restriction, adequate intake of essential fatty acids (EFA; 2-4% of daily calories) and fat-soluble vitamins (A, D, E, and K) should be ensured to avoid deficiency. Signs and symptoms typical of EFA deficiency include: inadequate growth in pediatric patients, dry or dull hair, dry or scaly skin, skin lesions, particularly raised bumps on the skin, soft and brittle nails, and impaired wound healing[129]. Food sources of EFAs include soybeans, tofu, flaxseeds, walnuts, and chia seeds for alpha-linolenic acid (ALA) and whole grains for linoleic acid (LA).

•**Medium-chain triglycerides (MCTs)**: In a very-low-fat diet, MCTs containing fatty acids of ≦ 10 carbon atoms in length may be used to provide sufficient calories in meals or infant formula[4, 36, 128, 129]. MCTs are absorbed directly into the circulation via the CM-independent pathway. MCTs may help reduce plasma TG levels[130]. In order to avoid possible adverse effects (diarrhea, abdominal pain, etc.), MCTs should be introduced slowly. The safety of long-term MCTs is not established and patients should be carefully monitored for possible complications such as hepatotoxicity. MCTs should not be confused with coconut oil, which contains lauric acid (C12) and other long-chain fatty acids[129].

•**Carbohydrate restriction**: Restriction of carbohydrates, particularly fructose and other simple and refined carbohydrates, is advisable for patients with increased VLDL levels such as those with diabetes mellitus, metabolic syndrome, and obesity. As both CMs and VLDLs are substrates for LPL, reduced production of VLDLs due to carbohydrate restriction enhances the catabolism of CMs by LPL[131]. In cases where carbohydrate intake needs to be adequate, such as in pregnancy-associated HTG, carbohydrate iv may be a better therapeutic choice, as oral carbohydrate intake may produce a greater rise in plasma TG than carbohydrate iv[122, 132].

•**Alcohol restriction**: Alcohol intake should be restricted[4, 128, 129].

C) Lipid-Lowering Medications

Current lipid-lowering medications (fibrates, n-3 polyunsaturated fatty acids (PUFAs), niacin, etc.) generally have little to no TG-lowering effects in patients with PCM, as they lower plasma TGs mainly by enhancing the LPL pathway and reducing VLDL levels. Treatment with n-3 PUFA or fish oil may be useful for lowering TG and preventing pancreatitis as suggested in patients with *APOA5* mutations[21]. However, the effect of n-3 PUFAs needs to be monitored carefully, as their effectiveness has only been suggested by small studies without controls[3, 5]. Fish oil supplements may increase the production of chylomicrons and are contraindicated according to an expert opinion[4]. In patients with autoantibodies against LPL pathway proteins (GPIHBP1, LPL, apoC-II), immune-suppressive agents may ameliorate HTG as well as the comorbid autoimmune diseases[7].

14. Treatment of HTG-Induced Acute Pancreatitis

The clinical course of HTG-induced acute pancreatitis may be more severe than acute pancreatitis due to other causes in terms of complications and mortality rates[12, 14, 133, 134], but more controlled studies are required to produce firm evidence. Meta analysis of acute pancreatitis is difficult due to the heterogeneity of scoring systems for its severity[86].

A) Standard Care for Acute Pancreatitis

Treatment of HTG-induced acute pancreatitis is based on standard care, including cessation of oral food intake, admission to hospital, intravenous hydration, hypocaloric parenteral nutrition avoiding excess calories and glucose infusions, pain management, prophylactic antibiotics, and protease inhibitors[12, 130, 135]. Any precipitating factors should be treated appropriately (e.g., insulin treatment for

diabetes). Patients should be carefully monitored for development of pancreatic complications (necrosis, abscesses, etc.).

B) Specific Therapy for HTG-Induced Acute Pancreatitis

When patients can tolerate, oral TG-lowering medications (fibrates, n-3 PUFAs, niacin, etc.) may be administered[12, 130, 135]. MCTs may help reduce plasma TG levels as well as the risk of pancreatitis[130]. With a few exceptions, current TG-lowering medications are not based on the etiology of chylomicronemia. In apoC-II deficiency, infusion of normal human plasma containing apoC-II can greatly reduce plasma TG levels, and plasmapheresis has been suggested as a treatment of choice for pancreatitis due to apoC-II deficiency[4, 58].

C) Management of Chronic Pancreatitis

As acute pancreatitis can lead to chronic complications, patients with a history of it are better monitored for complications such as chronic pancreatitis, pancreatic pseudocysts, pancreatic insufficiency, steatorrhea, and insulin-dependent diabetes mellitus[4, 86]. Although chronic complications are not invariably associated with HTG-induced acute pancreatitis[136], they are not uncommon despite modern medical care[95].

D) Other Therapeutic Options for HTG-Induced Acute Pancreatitis

•**Insulin (should be individualized)**: Insulin therapy is advised in patients with diabetes mellitus. Insulin stimulates LPL activity, thereby reducing plasma TG levels. Administration of insulin or insulin plus glucose may be considered in non-diabetic patients in the case of severe HTG-induced acute pancreatitis[14, 137-139]. Detailed protocols for insulin/glucose administration have been summarized elsewhere[137, 139].

•**Heparin (not usually recommended)**: Heparin infusion has been used as a therapeutic option but is not usually recommended as a monotherapy in treatment guides by experts[12, 14]. Heparin transiently increases plasma LPL levels by releasing LPL from the endothelial cell surface, which temporarily reduces plasma TG levels. However, heparin can also deplete LPL, causing a rebound increase in plasma TGs[140]. Heparin may increase the risk of pancreatic hemorrhage when pancreatic necrosis is present[66].

•**Heparin plus insulin (should be individualized)**: Combination of heparin and insulin may be a therapeutic option for severe HTG-induced acute pancreatitis[14]. Although heparin infusion alone is usually not advised, a recent study has suggested that combination of heparin and insulin may be effective[14]. Evaluation in RCTs is awaited.

•**Apheresis for HTG-induced acute pancreatitis (should be individualized)**: In the acute setting, apheresis (lipoprotein apheresis (LA), plasmapheresis, or plasma exchange (PEX), etc.)[141, 142] can rapidly reduce plasma TG levels (40-80%) by directly removing TGRLs, as reported in case reports, case series, and multi-center studies[12, 14, 36, 57]. However, it is not proven whether rapid TG reduction by apheresis leads to better clinical outcomes than other therapeutic modalities in terms of pancreatic complications and mortality[59]. Plasmapheresis is costly, has only a transient TG- lowering effect (usually for a day), and may have adverse reactions (e.g., allergic reactions, anaphylactic shock, infusion-related infections, thromboses, etc.)[14]. A recent systematic review and case-control studies indicated that while plasmapheresis decreased plasma TG, it did not conclusively affect the morbidity or mortality of acute pancreatitis[14, 86]. A recent RCT, the first one in HTG-induced acute pancreatitis, has demonstrated that although plasma apheresis lowers plasma TG more efficiently than insulin plus heparin, it is costly and does not lead to better clinical outcomes[143]. In the guideline of the American Society for Apheresis (ASFA), plasmapheresis is a category III indication with Grade 2C recommendation ("optimum role of apheresis therapy is not established. Decision making should be individualized"; "Weak recommendation, low-quality or very low-quality evidence due to observational studies or case series")[144], and generally not recommended by experts in treatment guides for chylomicronemia[4, 5]. Plasmapheresis may be a therapeutic option for: 1) severe HTG-induced acute pancreatitis with persistent TG elevation past the first 48-72h with no other therapeutic choice[57, 59, 86, 120]; 2) HTG-induced acute pancreatitis in pregnancy or postpartum with no other therapeutic choice[14, 36, 74, 120, 145-149]; or 3) severe HTG-induced acute pancreatitis with high levels of serum lipase, hypocalcemia, lactic acidosis, worsening inflammation or organ dysfunction[149, 150]. However, such advice is experience-based, not evidence-based.

•**Prophylactic apheresis to prevent HTG-induced acute pancreatitis (should be individualized)**: Prophylactic apheresis may be a therapeutic choice for preventing severe recurrent HTG-induced acute pancreatitis but evidence for it is limited to several case reports of HTG-induced acute pancreatitis[12, 14, 57, 151-154] and gestational HTG-induced acute pancreatitis[155, 156].

15. Treatment of HTG and HTG-induced Acute Pancreatitis in Pregnancy

There are currently no formal guidelines for gestational HTG and HTG-induced acute pancreatitis due to the rarity of these conditions and insufficient evidence. The treatment approach for gestational HTG and HTG-induced acute pancreatitis is well summarized by Wong *et al.* [66].

•**Dietary therapy (restriction of dietary fat, MCTs, n-3 PUFA)**: There have been reports of successful management of HTG and prevention of HTG-induced acute pancreatitis during pregnancy through early intervention with a low-fat or very-low fat diet, MCTs, and n-3 fatty acids[4, 66, 113, 122, 149, 157-162]. For pregnant women at high-risk of pregnancy-associated pancreatitis, extreme fat restriction to <2 g/day may be required during the 2nd and 3rd trimesters for successful delivery[1, 4, 122, 159]. Topical application of sunflower oil or corn oil in pregnancy with an extra-low-fat diet may help prevent EFA deficiency[122, 129, 159]. In pregnancy-induced HTG, carbohydrate may need to be restricted, but an adequate amount should be taken. Carbohydrate iv may be a better therapeutic choice during carbohydrate restriction, as carbohydrate per os may produce a greater rise in plasma TG than carbohydrate iv[122, 132]. The risk of MCTs to the fetus is thought to be low[66]. The safety of maternal n-3 fatty acid supplementation (DHA 2.2 g and EPA 1.1 g/day) for the mother and the fetus has been confirmed through a RCT[66].

•**TG-lowering medications (some are contraindicated in Japan)**: There have been several reports on the use of niacin, or fibrates (gemfibrozil and fenofibrate) for pregnancy-associated HTG [66,120,122,159,163-166]. However, the safety of niacin or fibrate use during pregnancy has not been established, and the use of fibrates during pregnancy is contraindicated in Japan.

•**Admission to hospital**: For gestational HTG, admission to hospital may be advised in the following cases: suspected pancreatitis, persistent abdominal pain, steep increase in plasma TG in the 3rd trimester, or TG >40 mmol/L (3540 mg/dL)[66, 122, 159]. Gestational acute pancreatitis is managed through standard care, which has been extensively reviewed by Papadakis EP *et al.*[73].

•**Other therapeutic options**: When uncontrollable, further management may include: insulin, insulin pus glucose, insulin plus heparin, or plasmapheresis[36, 66, 119, 120, 137-139, 149, 156, 161]. In a treatment guide for gestational HTG, the use of insulin is recommended only for hyperglycemic pregnant women, and the use of heparin is not recommended due to the paucity of clinical evidence [66].

16. Unanswered Questions

A) Molecular Basis and New Therapeutic Modalities

Unraveling the molecular basis of chylomicronemia may lead to the development of new therapeutic modalities[167].

Emerging therapeutic targets for chylomicronemia include: a microsomal triglyceride transfer protein (MTTP) inhibitor (lomitapide)[168-170]; an *APOB* antisense oligonucleotide (ASO) inhibitor (mipomersen)[171-173]; *APOC3* ASO inhibitors, e.g., volanesorsen[174], which has been approved by the EMA for genetically confirmed chylomicronemia at high-risk for pancreatitis[93]; diacylglycerol O-acyltransferase 1 (DGAT1) inhibitors (AZD7687, LCQ908 (Pradigastat))[175-177]; angiopoietin-like protein 3 (ANGPTL3) inhibitors, e.g., *ANGPTL3* ASOs (IONIS-ANGPTL3-LRx)[178] and ANGPTL3 antibody (evinacumab)[179-182].

For these new therapies, potential adverse effects need to be carefully evaluated, including fatty liver associated diseases for lomitapide and mipomersen[168-170, 172] as a consequence of their inhibition of VLDL secretion; thrombocytopenia for volanesorsen[174]; gastrointestinal adverse effects (diarrhea, nausea, etc.) for DGAT inhibitors[175-177], consistent with the fact that homozygous loss-of-function mutations of DGAT1 cause a congenital diarrheal disorder (OMIM: 615863)[183].

Other agents under development include CAT-2003, a niacin-eicosapentaenoic acid conjugate that blocks sterol regulatory element-binding protein (SREBP). Inhibition of SREBP-1c has ameliorated environment-induced severe HTG in mouse models of hyperlipidemia, including apoA-V deficient mice, by blocking secretion of large-sized VLDL particles[54, 55].

Orlistat, an inhibitor of intestinal lipase, may help reduce TG levels in PCM[21, 184, 185] but may have adverse effects such as oily stools and fat-soluble vitamin insufficiency[128].

Treatment that targets a specific genetic cause of PCM is not available. A gene therapy for LPL (alipogene tiparvovec) was approved by the EMA in 2012, but is costly and has been withdrawn from the market[94, 186].

B) Risk and Management of CM-Related Complications

Not all patients with severe HTG manifest pancreatitis. Suggested risk factors of acute pancreatitis among HTG patients include underlying genetic

etiology of monogenic type, underdiagnosis and undertreatment, younger age, higher baseline TG levels, prior history of acute pancreatitis, male, alcohol use, obesity, diabetes, hypertension, renal disease, liver disease, and hypothyroidism[84, 87, 94, 95]. Further elucidation and validation of the risk factors and genetic predisposition for HTG-induced acute pancreatitis is awaited[187-191]. Understanding the molecular basis of HTG-induced acute pancreatitis is necessary for developing diagnostic markers as well as effective therapeutic modalities.

There has been controversy as to the atherogenicity of HTG, including chylomicronemia[136, 192, 193]. Although it remains uncertain whether HTG is a causal factor or a mere marker of atherosclerosis[3, 91, 194-196], recent mendelian randomization studies have indicated an association between risk of cardiovascular diseases and variants in HTG-related genes, including causative genes of chylomicronemia (*APOA5*, *LPL*, etc.)[197-199]. Chylomicronemia, particularly when it is polygenic, may be associated with higher risk of cardiovascular diseases[53, 96, 200], which warrants further studies.

C) Genotype-Phenotype Relationship of PCM

The genetic etiology of chylomicronemia may influence the risk of complications such as pancreatitis and atherosclerotic diseases[86, 94-96]. The benefit, risk, and cost-effectiveness of genetic testing for chylomicronemia should be carefully evaluated[15, 109, 201-203]. Some expert reviews, which include the Consensus Panel report of the European Atherosclerosis Society, do not recommend routine genetic testing for severe HTG[3, 204].

D) Underdiagnosis and Undertreatment

Underdiagnosis of chylomicronemia is one of the major risks for pancreatitis[84, 87]. A web-based patient survey reported that patients with chylomicronemia typically visit 5 physicians (range, 1-30) on average before receiving a final diagnosis of chylomicronemia[106, 107]. Owing to the variety of symptoms and complications, patients with chylomicronemia may visit not only lipidologists and endocrinologists but also other diverse specialists, such as primary care physicians, pediatricians, obstetricians, emergency physicians, gastroenterologists, pancreatologists, and psychologists. Simple diagnostic criteria as well as cooperation among different medical specialists will be necessary to achieve timely diagnosis and treatment.

E) Unmet Needs and Burden of Disease

Due to the rarity of the disease, the clinical experience of each doctor is limited. Large registry studies[205, 206] as well as patient-oriented observational studies[104-107] from the patient's perspective are useful for understanding the unmet needs and burden of the disease from the physical, psychological, social, and financial viewpoints[104-107].

A recent web-based patient survey revealed physical, emotional, and cognitive symptoms that are relevant to patient's quality of life but have not been recognized by physicians[207, 208], including abdominal pain (41%), fatigue (23%), feeling sad/down/blue/depressed (18%), difficulty in concentrating (16%), impaired judgment (11%), brain fog (8%), forgetfulness (8%), and recent memory loss (5%)[106, 107]. This survey also revealed actual handicaps felt at school, in society, and work, and family-related issues[106, 107].

Self-monitoring of plasma TG may be an unmet need that could help patients with the long-term management of the disease. It may enable patients to individualize their low-fat diets, hopefully leading to fewer episodes of acute pancreatitis[209].

F) Support for Patients

The mainstay of the current treatment for chylomicronemia is dietary interventions. Supporting information and materials for patients on diets will help develop recipes and menu plans that would be more enjoyable and sustainable. Information and support for patients can be found at FCS Foundation (www.livingwithfcs.org; www.facebook.com/livingwithfcs), FCS Focus (fcsfocus.com), LPLD Alliance (UK) (www.lpldalliance.org), the National Organization for Rare Disorders (NORD) (https://rarediseases.org), and the Japan Intractable Diseases Information Center (https://www.nanbyou.or.jp/entry/4883). Supportive care from other healthcare professionals, such as medical social workers and mental health professionals, will be necessary to reduce the burden of the disease as well as to improve the quality of life of patients with chylomicronemia[105-107].

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