The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Review

J Atheroscler Thromb, 2021; 28: 791-801. http://doi.org/10.5551/jat.RV17052

Diagnosis and Management of Sitosterolemia 2021

Hayato Tada[1], Akihiro Nomura[1], Masatsune Ogura[2], Katsunori Ikewaki[3], Yasushi Ishigaki[4], Kyoko Inagaki[5], Kazuhisa Tsukamoto[6], Kazushige Dobashi[7], Kimitoshi Nakamura[8], Mika Hori[9], Kota Matsuki[10], Shizuya Yamashita[11], Shinji Yokoyama[12], Masa-aki Kawashiri[1] and Mariko Harada-Shiba[13] 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 Cardiovascular Medicine, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan
[2]Department of Molecular Innovation in Lipidology, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan
[3]Division of Neurology, Anti-Aging, and Vascular Medicine, Department of Internal Medicine, National Defense Medical College, Saitama, Japan
[4]Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Iwate Medical University, Iwate, Japan
[5]Division of Diabetes, Endocrinology, and Metabolism, Department of Medicine, Nippon Medical School, Tokyo, Japan
[6]Department of Internal Medicine, Teikyo University, Tokyo, Japan
[7]Department of Pediatrics, School of Medicine, University of Yamanashi, Yamanashi, Japan
[8]Department of Pediatrics, Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan
[9]Department of Endocrinology, Research Institute of Environmental Medicine, Nagoya University, Nagoya, Japan
[10]Department of Endocrinology and Metabolism, Hirosaki University Graduate School of Medicine, Hirosaki, Japan
[11]Rinku General Medical Center, Osaka, Japan
[12]Institute for Biological Functions, Chubu University, Aichi, Japan
[13]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).

Sitosterolemia is an inherited metabolic disorder characterized by increased levels of plant sterols, such as sitosterol. This disease is caused by loss-of-function genetic mutations in ATP-binding cassette (ABC) subfamily G member 5 or member 8 (*ABCG5* or *ABCG8*, respectively), both of which play important roles in selective excretion of plant sterols from the liver and intestine, leading to failure to prevent absorption of food plant sterols. This disorder has been considered to be extremely rare. However, accumulated clinical data as well as genetics suggest the possibility of a much higher prevalence. Its clinical manifestations resemble those observed in patients with familial hypercholesterolemia (FH), including tendon xanthomas, hyper LDL-cholesterolemia, and premature coronary atherosclerosis. We provide an overview of this recessive genetic disease, diagnostic as well as therapeutic tips, and the latest diagnostic criteria in Japan.

Key words: **Sitosterolemia, ABCG5, ABCG8, Familial hypercholesterolemia**

Introduction

Sitosterolemia (OMIM #210250, and #618666) is an autosomal recessive disorder of lipid metabolism characterized by increased absorption and decreased biliary excretion of plant sterols and cholesterol, resulting in prominently elevated serum concentrations of plant sterols, such as sitosterol, campesterol, and stigmasterol **(Fig. 1)**[1, 2]. This condition was first described by Bhattacharyya and Connor in 1974 [3]. Patients with sitosterolemia primarily exhibit tendinous and tuberous xanthomas and premature coronary atherosclerosis, resembling these characteristics in patients with familial hypercholesterolemia (FH)[4-9]. Severity of the phenotypes of sitosterolemia appears to be more variable than for FH possibly due to its greater dependency on dietary sterol intake[10, 11]. In addition, they have a wider variety, which includes hemolysis, splenomegaly, platelet abnormalities, and arthralgia/arthritis[12]. This disease is caused by biallelic (homozygous/compound heterozygous) loss-of-function (LOF) mutations in either ATP-binding cassette (ABC) subfamily G member 5 or member 8 (*ABCG5* and *ABCG8*, respectively) that play an important role in excreting sterols from the liver and intestine **(Fig. 1)**[13, 14]. Therefore, increased absorption of plant sterols from the intestine and their decreased secretion from the liver are the primary cause of sitosterolemia[15, 16]. Several (adaptive) secondary changes in lipid metabolism have been found to be associated with the accelerated sterol absorption; for

Address for correspondence: Masa-aki Kawashiri, Department of Cardiovascular Medicine, Kanazawa University Graduate School of Medical Sciences, 13-1 Takara-machi, Kanazawa, 920-8641, Japan E-mail: mk@med.kanazawa-u.ac.jp

Received: March 17, 2021 Accepted for publication: March 20, 2021

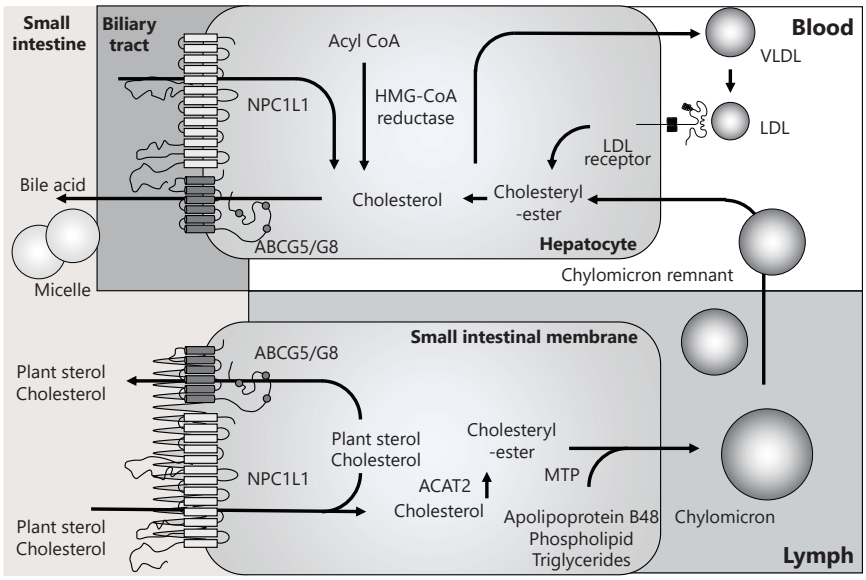

Fig. 1. Schema of sterol metabolism focusing on ABCG5/8 and NPC1L1

In the intestine, plant sterols and cholesterol are absorbed via NPC1L1, while they are excreted via ABCG5/8. The same pattern is observed in hepatocytes.

example, altered solubilization of sterols in intestinal micelles, increased activity of acyl CoA: cholesterol acyltransferase (ACAT), and changes in intracellular transport processes of sterols.

Sitosterolemia used to be considered an extremely rare disorder but recent studies indicate the possibility of a much higher prevalence in the general population[6-10].

Based on the pathophysiology of this disease, ezetimibe, an inhibitor of Niemann-Pick C1 Like 1 (NPC1L1) that mediates absorption of dietary cholesterol in the intestine[17], has been shown to be effective in reducing serum sitosterol as well as cholesterol in sitosterolemic patients, together with dietary management to restrict intake of these sterols[18, 19]. In this review article, we discuss the current understanding of sitosterolemia, its diagnostic criteria, and future perspectives.

Plant Sterols

Plant sterols (sitosterol, campesterol, and stigmasterol) are sterol molecules naturally contained at low levels in plant foods such as fruits, vegetables, nuts and cereals[20]. Sitosterol is usually the most abundant plant sterol in the diet[2] and the average Japanese diet and Western diets contain similar amounts of cholesterol and plant sterols. Although approximately 50% of dietary cholesterol is absorbed, less than 5% of plant sterols is absorbed in normal individuals[21-24], resulting in lower levels of plant sterols than cholesterol in the body. In a recent investigation of plasma concentrations of plant sterols in 667,718 subjects, they seemed to be dependent on age, gender, and apolipoprotein E genotype[25].

Accumulation of plant sterols in patients with sitosterolemia would contribute to atherogenesis. However, dietary intake of plant sterols is generally considered beneficial for normal individuals as they competitively inhibit cholesterol absorption, which is then selectively excreted resulting in lower cholesterol levels[26]. The European Atherosclerosis Society Consensus Panel currently recommends taking plant sterols for patients with a relatively high risk for cardiovascular disease and/or statin intolerance[20]. In addition, the proinflammatory properties of sitosterol appear to be much weaker than those of cholesterol[27].

Epidemiology

Sitosterolemia has long been considered an extremely rare disorder. Indeed, only 45 sitosterolemic subjects were reported in a review article published in 2003[28]. Its autosomal recessive inheritance may have caused us to think it is a rare disease. However, the Exome Aggregation Consortium (ExAC) Exome Browser, a public genetic database, has suggested that 1 in ~220 general individuals have LOF mutations in the *ABCG5* or *ABCG8* gene[29]. Therefore, a rough estimate of the number of homozygous/compound

heterozygous patients with sitosterolemia is 1 in ~200,000 general individuals. Moreover, a recent study has shown that a certain proportion of patients clinically diagnosed as FH could in fact have sitosterolemia[30]. Accordingly, this disorder appears to be much more prevalent than previously thought.

Genetic Backgrounds and Pathophysiology

In 2001, the cause of this disease was identified as double LOF mutations in the *ABCG5* or *ABCG8* gene[13, 14]. So far, most patients with recognized sitosterolemia have come from consanguineous marriages, which has lead to homozygous mutations in the *ABCG5* or *ABCG8* gene. However, recent advances in genetic analysis have revealed that there are also a number of cases with compound heterozygous mutations in the *ABCG5* and *ABCG8* genes. Relatively common pathogenic mutations are c.1166G>A/p.Arg389His, and c.1256G>A/p.Arg419His in *ABCG5* gene[31-33].

The ABCG5 and ABCG8 proteins form heterodimers and act as a complex, which functions as a transporter of sterols in the bile and intestine. Accordingly, patients with sitosterolemia exhibit either homozygous or compound heterozygous mutations in the *ABCG5* or *ABCG8* gene. Besides the above mutations, Tada *et al.* previously reported a unique case of sitosterolemia caused by double heterozygous mutations in the *ABCG5* and *ABCG8* genes, suggesting that specific combinations of mutations and/or quite deleterious heterozygous mutations may cause sitosterolemia[34].

Recent genome-wide association studies (GWAS) indicated that the *ABCG5* and *ABCG8* genes are significantly associated with LDL cholesterol levels and increased prevalence of coronary artery disease (CAD)[35, 36], suggesting that these genes contribute to high LDL cholesterol and high plant sterol levels in plasma and risk for CAD among the general population as well. In addition, Tada *et al.* have recently shown that deleterious mutations of the *ABCG5* or *ABCG8* gene contribute substantially to mimicking and exacerbation of the FH phenotype[30].

Clinical Manifestations

Individuals suffering from sitosterolemia primarily present with tendinous and tuberous xanthomas and premature coronary atherosclerosis, resembling those in FH. Therefore, a certain proportion of patients with sitosterolemia could be misdiagnosed as FH due to tendon xanthomas and elevated LDL cholesterol[30]. However, the severity of LDL cholesterol elevation and xanthomas appears to be more variable in sitosterolemia than in FH. In a case of myocardial infarction in a 25-year-old woman previously described by Kawamura *et al.*[9], Achilles tendon xanthomas, as well as significantly elevated LDL cholesterol levels and sitosterol levels were found, and she was initially misdiagnosed as FH. However, consideration of the recessive pattern of inheritance, great responsiveness to dietary counseling together with statin plus ezetimibe (LDL cholesterol was reduced from 220 mg/dl to 55 mg/dl) lead to the accurate diagnosis of sitosterolemia.

Typical cases in infancy have also been described. LDL cholesterol levels in FH tend to be constantly high, whereas those in sitosterolemia may vary with the latest dietary intake of sterols. The most extreme cases have been infants who are breastfeeding. They have been found to have cutaneous xanthomas associated with significant elevation in LDL cholesterol levels, resembling those in homozygous FH,[6, 37, 38]. It has been noted that weaning alone can reduce their LDL cholesterol levels, causing the cutaneous xanthomas to regress, despite sitosterol levels that remain significantly elevated. These observations suggest that they are quite vulnerable to a sterol-rich diet, and that dietary management is very important in infants with sitosterolemia. However, we have experienced several independent infantile cases of transient hypercholesterolemia associated with breastfeeding without any signs of cutaneous xanthomas, where the patients turned out to be carriers of heterozygous mutations of the *ABCG5* gene (data not shown). Thus, it appears that some infantile cases of "breastfed hypercholesterolemia" can be explained by heterozygous mutations of the *ABCG5* gene.

In addition, a variety of other phenotypes, such as hemolysis, splenomegaly, platelet abnormalities, arthralgia/arthritis have been documented among patients with sitosterolemia, and some of them have been shown to be associated with accumulation of sitosterol in an animal model[39]. The underlying mechanism responsible for the hematologic abnormalities observed in some patients with sitosterolemia appears to be accumulation of circulating sterols in blood cell membranes, leading to abnormal morphology and function[40]. Regarding arthralgia/arthritis, the case of a sitosterolemic patient who also had a history of recurrent arthritis has been described. Whole exome sequencing analysis revealed that this patient had another concomitant genetic disorder that had caused familial Mediterranean fever where arthritis is documented as one of the major manifestations[7].

Since sitosterolemia is a recessive disorder, in

many cases there is a consanguineous marriage in the background. This could lead to the coincidence of other recessive genetic disorders, although there is no clear evidence suggesting an association between their genotypes or inheritance patterns and the severity or variety of sitosterolemia phenotypes. Comprehensive genetic analyses in such patients could shed light on the causal (genetic) backgrounds of their phenotypes.

Sitosterol or Cholesterol?

Sitosterolemia was named for the significant elevation in serum sitosterol level in this disease. As sitosterol and other plant sterols have been shown to accumulate in atherosclerotic lesions of patients with sitosterolemia[4, 41], lowering serum sitosterol has long been considered to be a target for therapy. However, a causative relationship between marked elevation of sitosterol in serum and its tissue deposition and development of atherosclerotic cardiovascular diseases remains to be demonstrated. The results of studies regarding an association between serum sitosterol levels and atherosclerosis have been controversial[42-45].

Currently available data as well as the fact that sitosterolemic patients with premature atherosclerotic cardiovascular diseases tend to exhibit hyper-LDL cholesterolemia suggest that LDL cholesterol, rather than sitosterol is the main causal factor for atherogenicity. Therefore, further studies assessing the role of sitosterol in the development of atherosclerosis are needed

Diagnostic Criteria

Diagnostic criteria for sitosterolemia in Japan are described in **Table 1**. Serum sitosterol levels could be measured using high-sensitive gas chromatography. Their reference ranges in Japanese individuals have been determined as 0.99 - 3.88 μg/mL in males, and 1.03 - 4.45 μg/mL in females[46]. It is vitally important to perform differential diagnosis to distinguish it from FH **(Fig. 2A)**, autosomal recessive hypercholesterolemia (ARH) **(Fig. 2B, 2C)** and cerebrotendinous xanthomatosis (CTX) **(Fig. 2D, 2E)**. It is not easy to make a differential clinical diagnosis of sitosterolemia **(Fig. 2F, 2G)** just based on physical manifestations[47-50].

Diagnostic Tips for Sitosterolemia

As stated above, patients with sitosterolemia typically exhibit tendinous and tuberous xanthomas and premature coronary atherosclerosis, resembling the manifestations of FH. Therefore, patients with premature coronary atherosclerosis should be examined to see whether they have a special genetic background including that for sitosterolemia. Absence of a family history of hypercholesterolemia as well as premature CAD is likely to indicate sitosterolemia rather than FH. However, it is of note that some patients with sitosterolemia have a family history of hypercholesterolemia and tendon xanthomas despite its recessive pattern of inheritance. The tendon xanthomas of sitosterolemia tend to be more severe than those of heterozygous FH, despite lower levels of LDL cholesterol. Thus, sitosterolemia should be considered in differential diagnosis for heterozygous FH, which is now considered a relatively frequent genetic metabolic disease. In addition, LDL cholesterol levels of sitosterolemic patients tend to vary dramatically depending on their latest dietary intake of plant sterols, and this would be useful information in making a clinical diagnosis of this disease. ARH and CTX are extremely rare autosomal recessive diseases, and almost all patients with these diseases are from consanguineous marriages. It is sometimes quite difficult to differentiate sitosterolemia from ARH based on a single assessment; however, responsiveness to dietary counseling differs between sitosterolemia and ARH. On the other hand, patients with CTX can be differentiated from those with sitosterolemia based on several factors, such as absence of hypercholesterolemia, chronic diarrhea during childhood, juvenile cataracts, and neurological symptoms[49].

Table 1. Diagnostic criteria

A. Clinical manifestations
1. Cutaneous or tendon xanthomas
2. Premature coronary artery disease (male < 45 yr, female < 55 yr)
B. Laboratory testing
1. Serum sitosterol ≥ 1 mg/dL (10 μg/mL)
C. Differential diagnosis
Exclude familial hypercholesterolemia and cerebrotendinous xanthomatosis
D. Genetic analysis
Pathogenic mutations in ABCG5 or ABCG8 gene

Definite: fulfills A-1, B-1, C, and D
Probable: fulfills A-1, B-1, and C
Possible: fulfills A-1, A-2, and B-1

Management of Sitosterolemia

Restriction of plant sterols as well as cholesterol should be the first line strategy. Sitosterolemic patients should avoid plant sterol-rich foods, such as corn oil,

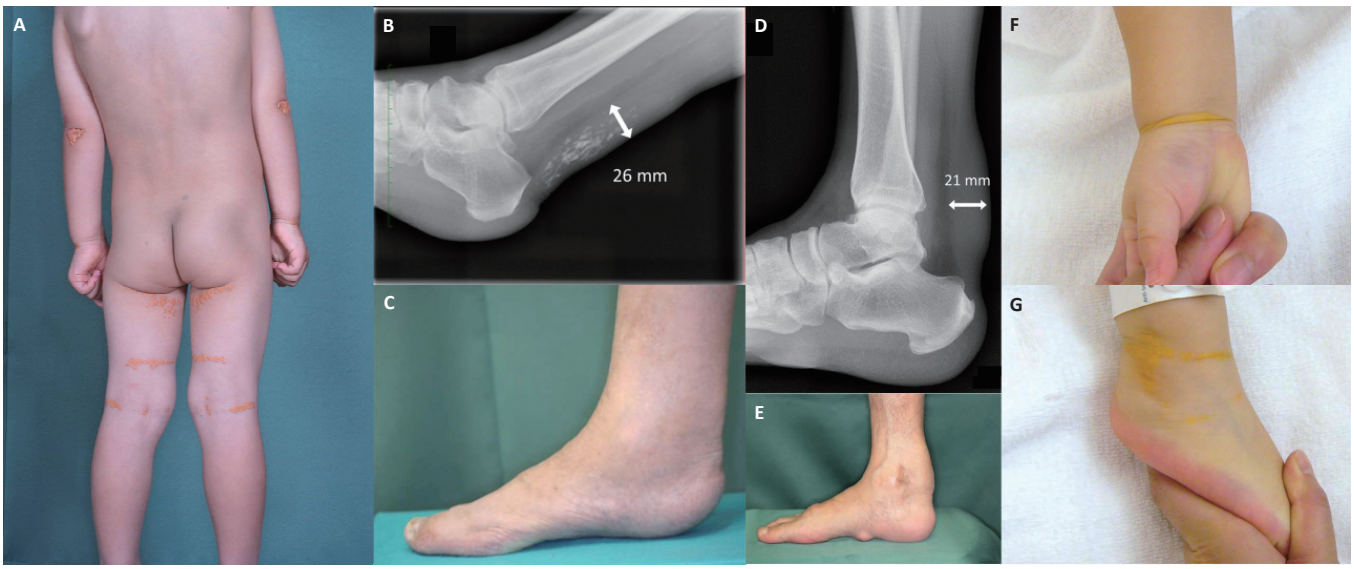

Fig. 2. Xanthomas in patients with dyslipidemias

(A) Systemic xanthomas in a patient with homozygous FH (3-year-old boy)
(B) X-ray of Achilles' tendon in a patient with ARH (67-year-male)
(C) Achilles' tendon xanthomas in a patient with ARH (67-year-male)
(D) X-ray of Achilles' tendon in a patient with CTX (63-year-male)
(E) Achilles' tendon xanthomas in a patient with CTX (63-year-male)
(F) Xanthomas at the ankle in a patient with sitosterolemia (1-year-old girl)
(G) Xanthomas at the wrist in a patient with sitosterolemia (1-year-old girl)

sesame seeds, peanuts, soybeans, rapeseed oil, sesame oil, rice oil, margarine, avocado, chocolate, and shellfish, whereas, other vegetables and fruits, such as potato, carrot, and apple contain less plant sterols[51]. In addition to plant sterols, they also need to avoid cholesterol-rich foods, including animal liver and eggs. Regarding medication, ezetimibe and bile-acid sequestrant resins have been established as standard therapies because the primary cause of this disease is increased absorption of plant sterols from the intestine and their decreased secretion from the liver[15]. Both could reduce sitosterol (~ 20% by ezetimibe, and ~ 30% by resins)[18, 52] and LDL cholesterol in sitosterolemia. Ezetimibe has also been shown to favorably increase platelet count[19].

Patients with sitosterolemia usually do not respond to statins because HMG-CoA reductase activity is already maximally inhibited[52]. However, statins are effective in reducing LDL cholesterol, at least in some sitosterolemic patients[9, 45], although they may increase sitosterol levels in others[53]. Considering the lack of a clear association between sitosterol levels and frequency of atherosclerotic cardiovascular disease[44], as well as the fact that some patients with sitosterolemia are treated with statins due to being misdiagnosed with FH[30], statins could at least be used for patients in a secondary prevention setting. For patients with advanced atherosclerotic lesions and resistance to the standard treatments mentioned above, LDL apheresis could be considered if applicable, although it is not officially covered by the Japanese national health insurance[8].

Liver transplantation was performed in a case of sitosterolemia with liver cirrhosis and reportedly resulted in a dramatic reduction in serum plant sterol levels[54]. Regarding target levels of LDL cholesterol, there is plenty of clinical evidence suggesting that lowering LDL cholesterol is associated with reduced risk for atherosclerotic cardiovascular diseases. In addition, sitosterolemia has been considered as a phenocopy of FH and therefore, the target LDL cholesterol level should be the same as that of FH. However, there has been no definite evidence for an association of sitosterol lowering and prevention of atherosclerotic cardiovascular diseases so far. Accordingly, LDL cholesterol, rather than sitosterol, should be the main biomarker when treating patients with sitosterolemia. Dietary restriction of plant sterols, ezetimibe, and bile-acid sequestrant resins have been shown to reduce both LDL cholesterol and sitosterol levels and thus these strategies should be considered as standard treatment for patients with sitosterolemia. The plant sterol content of foods and food ingredients varies widely from 7 mg/100 g in potatoes and

tomatoes to 686-952 mg/100 g in corn oil[55]. It is therefore rational to recommend patients with sitosterolemia and reduced function of ABCG5 or ABCG8 to avoid vegetables rich in plant sterols.

Conclusions and Perspectives

Sitosterolemia is a monogenic disorder that has been considered rather rare. However, its prevalence may currently be substantially underestimated[56], so we should be more careful to identify this disease among hypercholesterolemic patients with xanthomas. In particular, to raise awareness of sitosterolemia among pediatricians and dermatologists, education for them focusing on its typical manifestations is important. Measurement of serum sitosterol is not covered by Japanese national health insurance but we firmly believe that it is reasonable for it to be covered now that we have reference data for serum sitosterol levels among Japanese healthy individuals as well as patients with sitosterolemia. Ideally, prospective randomized controlled trials investigating if specific lowering of serum sitosterol leads to reduced risk for atherosclerotic cardiovascular diseases should be performed. More large-scale observational studies attempting to demonstrate an independent association between sitosterol levels and atherosclerotic cardiovascular diseases are also needed.

To establish the clinical importance of this disease for public health, more accurate prevalence and clinical manifestation data should be accumulated, supported by the health insurance system and comprehensive genetic analyses. Diagnostic criteria of sitosterolemia proposed by the Japanese Ministry of Health, Labor and Welfare scientific research team for hyperlipidemia would facilitate the accumulation of such data on this unique disorder.

Acknowledgments and Notice of Grant Support

This work has been supported by Health, Labour and Welfare Sciences Research Grant for Research on Rare and Intractable Diseases (H30-nanji-ippan-003).

Conflicts of Interest

Atsushi Nohara has nothing to disclose. Hayato Tada has nothing to disclose. Masatsune Ogura has received honoraria from Amgen Inc., Astellas Pharma Inc. Sachiko Okazaki has received scholarship grants from Minophagen Pharmaceutical Co., Ltd., Kowa Company, Ltd. Koh Ono has nothing to disclose. Hitoshi Shimano has nothing to disclose. Hiroyuki Daida has received honoraria from Amgen Inc., Daiichi-Sankyo Co., Ltd., Kowa Co., Ltd., and MSD K.K., Novartis Pharma K.K., Bayer Yakuhin, Ltd. and received clinical research funding from Canon Medical Systems Corporation, Philips Japan, Ltd., Toho Holdings Co., Ltd., Asahi Kasei Corporation, and Inter Reha Co., Ltd. HD has also received scholarship grants from Nippon Boehringer Ingelheim Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Sanofi K.K., MSD K.K., Daiichi-Sankyo Co., Ltd., Pfizer Co., Ltd., Mitsubishi Tanabe Pharma Corp., Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Teijin Pharma, Ltd., Shionogi & Co., Ltd., Actelion Pharmaceuticals, Ltd., Actelion Ltd., Kowa Co., Ltd., Bayer Yakuhin, Ltd. HD has also courses endowed by companies, including Philips Japan, Ltd., ResMed, Fukuda Denshi Co., Ltd., and Paramount Bed Co., Ltd. Kazushige Dobashi has nothing to disclose. Toshio Hayashi has nothing to disclose. Mika Hori has nothing to disclose. Kota Matsuki has nothing to disclose. Tetsuo Minamino has nothing to disclose. Shinji Yokoyama has nothing to disclose. Mariko Harada-Shiba has received stock holdings or options from Liid Pharma, honoraria from Amgen Inc., Astellas Pharma Inc., Sanofi, and scholarship grants from Aegerion Pharmaceuticals, Inc., Recordati Rare Diseases Japan, and Kaneka Corporation. Katsunori Ikewaki has nothing to disclose. Yasushi Ishigaki has nothing to disclose. Shun Ishibashi has received honoraria from Kowa Co., Ltd., and a scholarship grant from Ono Pharmaceutical Co., Ltd. Kyoko Inagaki has nothing to disclose. Hirotoshi Ohmura has nothing to disclose. Hiroaki Okazaki has received scholarship grants from Minophagen Pharmaceutical Co., Ltd., Kowa Company, Ltd. Masa-aki Kawashiri has nothing to disclose. Masayuki Kuroda has nothing to disclose. Masahiro Koseki has received clinical research funding from Kowa Company, Ltd., Rohto Pharmaceutical Co., Ltd. Takanari Gotoda has nothing to disclose. Shingo Koyama has nothing to disclose. Yoshiki Sekijima has nothing to disclose. Manabu Takahashi has nothing to disclose. Yasuo Takeuchi has nothing to disclose. Misa Takegami has nothing to disclose. Kazuhisa Tsukamoto has received honoraria from Bayer Yakuhin, Ltd., MSD Ltd., Takeda Pharmaceutical Company Ltd., and scholarship grants from Mitsubishi Tanabe Pharma Corporation., Bayer Yakuhin, Ltd., Sanofi K.K. Atsuko Nakatsuka has nothing to disclose. Kimitoshi Nakamura has nothing to disclose. Satoshi Hirayama has nothing to disclose. Hideaki Bujo has nothing to disclose. Daisaku Masuda has received clinical research funding from MSD K.K., Ono Pharmaceutical Co.,

Ltd., Takeda Pharmaceutical Co., Ltd., Kowa Co., Ltd. Takashi Miida has nothing to disclose. Yoshihiro Miyamoto has nothing to disclose. Takeyoshi Murano has nothing to disclose. Takashi Yamaguchi has nothing to disclose. Shizuya Yamashita has received honoraria from Kowa Company, Ltd., MSD K.K. Masashi Yamamoto has nothing to disclose. Koutaro Yokote has received honoraria from Kowa Company, Ltd., MSD K.K., Astellas Pharma Inc., Mitsubishi Tanabe Pharma Corp., Amgen K.K., Takeda Pharmaceutical Company Limited, Sanofi K.K., Ono Pharmaceutical Co., Ltd., AstraZeneca K.K., Daiichi-Sankyo Co., Ltd., Novartis Pharma K.K., Sumitomo Dainippon Pharma Co., Ltd., Kyowa Kirin Co., Ltd., Pfizer Japan Inc., Novo Nordisk Pharma Ltd., Nippon Boehringer Ingelheim Co., Ltd., Eli Lilly Japan K.K., Taisho Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K., and received clinical research funding from Taisho Pharmaceutical Co., Ltd. KY has also received scholarship grants from Mitsubishi Tanabe Pharma Corp., Takeda Pharmaceutical Co., Ltd., MSD K.K., Pfizer Japan Inc., Novo Nordisk Pharma Ltd., Taisho Pharmaceutical Co., Ltd., Kao Corporation, Ono Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Sumitomo Dainippon Pharma Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Daiichi-Sankyo Co., Ltd., Teijin Pharma, Ltd., Shionogi Co., Ltd., Bayer Yakuhin, Ltd. Jun Wada has nothing to disclose.

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