SITOSTEROLEMIA

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ABSTRACT

Sitosterolemia is a rare autosomal recessive disorder of non-cholesterol sterol metabolism, caused by mutations of the *ABCG5* or *ABCG8* transporter genes. This results in hyperabsorption and decreased biliary excretion of non-cholesterol sterol, especially sitosterol, from the gastrointestinal tract. Affected individuals have excessive accumulation of plant sterols and 5 alpha-saturated stanols in plasma and tissues, resulting in premature cardiovascular disease. The condition is often clinically confused with familial hypercholesterolemia. This article provided overview of this rare condition, including diagnostic evaluation and treatment.

BACKGROUND

Sterols are waxy insoluble substances and are synthesized from acetyl coenzyme A (CoA). Perhaps the most familiar example is cholesterol. In addition to cholesterol, over forty non-cholesterol sterols are also present in the human diet. Non-cholesterol sterols are contained in plants, fungi, and yeast. Instead of converting squalene to cholesterol, non-cholesterol sterols occur when squalene is converted to stigmasterol, sitosterol, campesterol, ergosterol, etc., while shellfish produce fucosterol.

In a typical Western diet, plant sterols, or phytosterols, are often consumed in nuts, seeds, legumes, and vegetable oils. They are present in amounts equal to cholesterol and processed by the intestine in a similar manner (Figure 1). While most individuals absorb, on average, 40-50% of dietary cholesterol, less than 5% of dietary plant sterols are absorbed (1-3).

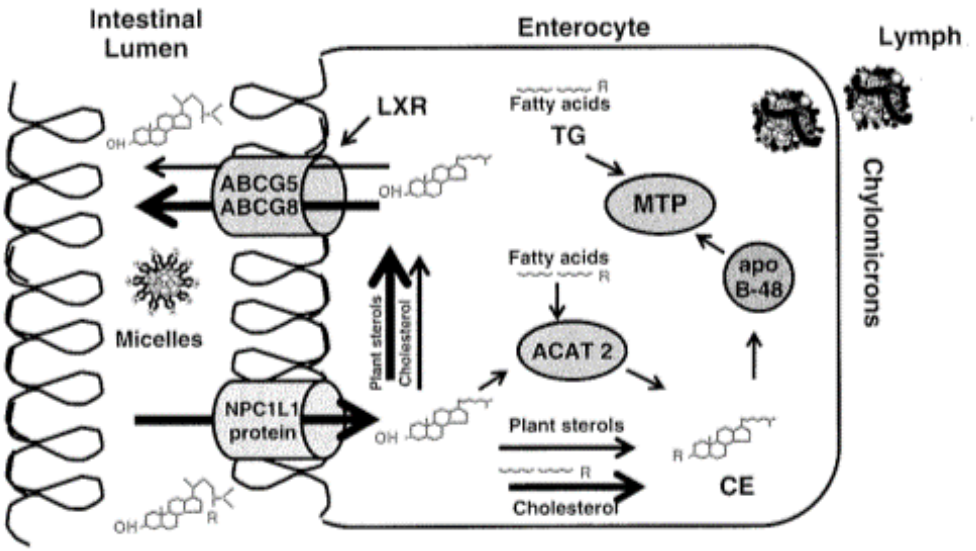

Figure 1. Enterocyte Trafficking of Cholesterol and Plant Sterols. From Phytoserolemia by Thomas Daysring, MD in Therapeutic Lipidology, Michael H Davis in, MD, Peter P Toth, MD and Kevin C Maki, PhD, Editors. 2007 Humana Press, Incorp. Totowa, New Jersey.

Phytosterols have no role in human metabolism. Therefore, except in inherited disorders of metabolism, there is limited systemic absorption of phytosterols, as their entry into the plasma is highly regulated by the intestine and liver. Concentrations of phystosterols in plasma are normally less than 0.5% that of cholesterol.

Stanols, i.e., saturated sterols, also exist in the diet, primarily from plant sources. Stanols are not normally absorbed from the GI tract. Both stanols and sterols interfere with the absorption of cholesterol. Therefore, both have been used as dietary supplements for over 5 decades to help reduce plasma cholesterol levels.

Phytosterols and free cholesterol are normally absorbed by the Niemann-Pick C1-Like 1 (NPC1L1) protein expressed on enterocytes (Figure 1) (4). Almost all of the absorbed plant phytosterols are excreted back into the intestinal lumen by the ABCG5 or ABCG8 transporters. The normal body is thus able to discriminate between cholesterol and non-cholesterol sterols (5). The function of *ABCG5* or *ABCG8* transporter genes, found at the STSL locus of human chromosome 2p21, is to limit intestinal absorption and promote biliary excretion (6, 7) (Figure 2).

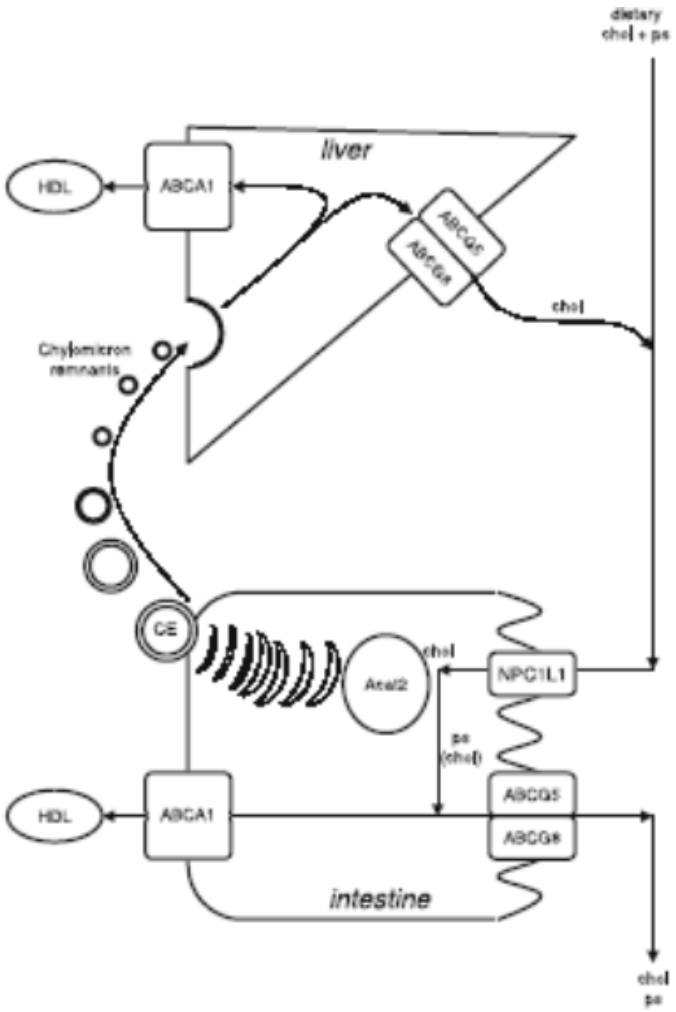

Figure 2. Normal Intestinal and Hepatic Transport of Cholesterol and Phytosterols. T. Plösch, A. Kosters, A.K. Groen, F. Kuipers. The ABC of Hepatic and Intestinal Cholesterol Transport. Chapter. Atherosclerosis: Diet and Drugs. Volume 170 of the series Handbook of Experimental Pharmacology pp 465-482.

SITOSTEROLEMIA

Sitosterolemia (also known as phytosterolemia) is a rare autosomal recessive disease of non-cholesterol sterol metabolism. It is characterized chemically by the accumulation of plant sterols and 5 alpha-saturated stanols in plasma and tissues. The condition occurs when either *ABCG5* or *ABCG8* are defective, leading to hyperabsorption of sitosterol from the gastrointestinal tract. The problem is compounded by decreased biliary excretion, resulting in accumulation of dietary phytosterols in different tissues (8, 9).

HISTORY AND ETHNICITY

Sitosterolemia was first reported in 1974 when two sisters with extensive tendon xanthomas were found to have normal plasma cholesterol levels and elevated levels of plant sterols (10). Several hundred cases

have since been reported but the condition is thought to be substantially underdiagnosed (11). The disorder has been found in a wide range of diverse populations, including the Old-Order Amish, Chinese, Finnish, Japanese, Norwegian, Indian and Caucasian South Africans, as well as others. The condition is transmitted as an autosomal recessive trait (12, 13)

CLINICAL FEATURES

Signs and Symptoms

Phenotypically, sitosterolemia is very heterogeneous in its presentation. The disorder is characterized by premature coronary artery disease (14-18) although the degree of atherosclerosis present varies significantly (19-24). Presenting signs and symptoms of sitosterolemia, such as lipid deposition in cutaneous and subcutaneous structures (xanthomas), can occur in the first decade of life, but sitosterolemia has been diagnosed in asymptomatic adults as well. Typical xanthomas occur most prominently in the extensor tendons of the hands and Achilles tendon, but can occur in the knees, elbows and buttocks. Xanthomas have been reported in children as young as one to two years of age (25-31). Spinal xanthomas, causing spinal cord compression, have also been reported (32)

The phenotype of sitosterolemia includes abnormal liver function tests, arthralgia, splenomegaly, and hematologic findings (hemolytic anemia, abnormally shaped erythrocytes and large platelets) (33-37). Occasionally, hematologic findings appear as isolated findings (11, 38-41), and there is a case report of an infant with cholestatic jaundice who was ultimately diagnosed with sitosterolemia (42). Aortic stenosis has also been reported (21, 43), as have arthralgias and arthritis (44, 45).

Occasionally, the diagnosis of sitosterolemia is made after an individual with total cholesterol and LDL-cholesterol in the range of familial hypercholesterolemia fails to achieve expected reductions with statin therapy (46). A recent study of 220 hypercholesterolemic children found that 6.4% had elevated and 1.4% had markedly elevated sitosterol levels, with 2 children ultimately diagnosed with genetically confirmed sitosterolemia (47). This has been demonstrated in other publications as well (48, 49). This reaffirms that sitosterolemia is likely underdiagnosed, and high clinical suspicion is warranted. This is particularly important as most genetic testing panels for familial hypercholesterolemia test for pathogenic variants in *LDLR*, *APOB*, *PCSK9*, and *LDLRAP1*; therefore, individuals with sitosterolemia will frequently have negative genetic testing results.

Although sitosterolemia is a recessive disorder, there is some data suggesting that heterozygous carriers of loss of function mutations can have higher sitosterol levels, higher LDL-cholesterol levels, and a 2-fold higher risk of ASCVD (50).

Differential Diagnosis

Besides sitosterolemia, other disorders that cause tendon xanthomas in children and adults include:

Heterozygous familial hypercholesterolemia (HeFH) - most commonly caused by a co-dominantly inherited disorder of the LDL-C receptor, presents with high total serum and LDL-cholesterol, normal plasma levels of plant sterols and at least one parent with hypercholesterolemia.

Homozygous familial hypercholesterolemia (HoFH) - in which hypercholesterolemia is present in both parents of an affected child. In addition, individuals

with HoFH have normal rather than enlarged platelets (macrothrombocytopenia).

Cerebrotendinous xanthomatosis (CTX) - can be distinguished by increased concentrations of plasma cholestanol, protracted diarrhea starting in childhood, and juvenile cataracts. Adults with CTX typically have neurologic involvement (cerebellar ataxia, cognitive decline, and dementia).

Alagille Syndrome, is accompanied by a characteristic syndromic facial appearance, high rates of congenital heart disease, and signs of liver cholestasis (51).

Sitosterolemia should be considered in a child or adult with tendon xanthomas and unexplained hemolysis and/or macrothrombocytopenia, as these hematologic abnormalities are not present in FH, CTX or Alagille syndrome.

Testing

Routine laboratory methods do not always distinguish plant sterols from cholesterol. Detection of plant sterol levels in blood requires gas-liquid chromatography (GLC), gas chromatography/mass spectrometry (GC/MS), or high-pressure liquid chromatography (HPLC).

Plant sterols, especially sitosterol, and the 5-alpha derivatives of plant sterols, are dramatically elevated in patients with sitosterolemia. Plasma concentrations of sitosterol above 1 mg/dL (10µg/mL) are considered to be diagnostic, although a recent study suggested a cutoff value of 15µg/mL had higher positive predictive value (52). Levels typically range from 8-60 mg/dL, 10-25 times higher than normal individuals. Age-dependent reference intervals for phytosterols have also been proposed (53). Molecular genetic testing of mutations in *ABCG5* and *ABCG8* can help confirm the diagnosis and direct clinical care (54).

In contrast to the very high levels of plant sterols in adults and adolescents with sitosterolemia, total cholesterol levels are sometimes normal or only moderately elevated (34). However, at least three cases of breastfed infants with sitosterolemia presenting with very elevated serum cholesterol levels have been reported. The mechanism of exceptionally high cholesterol levels in sitosterolemic children is unclear (25, 26, 55).

Increased plasma concentrations of plant sterols (especially sitosterol, campesterol, and stigmasterol) are only observed once foods with plant sterols are included in the diet and accumulate in the body. Care must be taken when evaluating infants, since commercial formula feedings with large amounts of vegetable oil may result in elevated sitosterol levels (56).

Children with parenteral nutrition associated cholestasis may have plasma concentrations of plant sterols as high as those seen in patients with hereditary sitosterolemia (i.e., total plant phytosterols of 1.3-1.8 mmol/L). Intralipid typically contains cholesterol, sitosterol, campesterol, and stigmasterol, the latter three of which are plant sterols. Adults receiving parenteral nutrition may also have elevated plasma plant sterol levels (57).

MANAGEMENT OF SITOSTEROLEMIA

Dietary Treatment

Treatment includes dietary restriction of non-cholesterol sterols, limiting intake of shellfish (clams, scallops, oysters), plant foods that contain high fats, such as olives, margarine, nuts, seeds, avocados, and

chocolate, and avoidance of vegetable fats and oils (10, 58-61). Fruits, vegetables and cereal products without germ may be used, however (62).

In homozygotes, plasma sterol levels may not improve significantly despite significant dietary sitosterol restriction (63, 64). Margarines and other products containing stanols (e.g., campestanol and sitostanol), which are recommended for use by individuals with hypercholesterolemia, are contraindicated in those with sitosterolemia as they can exacerbate plant stanol accumulation (65).

Medical Treatments

Ezetimibe (Zetia®), inhibits NPC1L1 and decreases the absorption of sterols. It is the first-line drug therapy, lowering plant sterols by 10 to 50% and may stabilize xanthomas (66-69). Hemolytic anemia and platelet abnormalities have been reported to improve as well (66).

Bile acid sequestrants, such as cholestyramine (8-15 g/d), may be considered in those with an incomplete response to ezetimibe(26) Regression of xanthomas has been reported in an 11-year-old after treatment with diet and cholestyramine (70). A 60-year-old man with compound heterozygous mutations in ABCG5 responded to a combination of ezetimibe and alirocumab (71).

Sitosterolemic patients do not have expected clinical responses to statins, which can help to distinguish these patients with elevated plasma sterols and xanthomas from those with familial hypercholesterolemia (64). As stated above, sitosterolemia should be suspected in individuals with hypercholesterolemia who fail to respond as expected to a statin treatment.

Surgical Treatments

Partial ileal bypass surgery (i.e., shortening of the ileum) has been used to increase intestinal bile acid loss. Partial or complete ileal bypass surgery in persons with sitosterolemia has resulted in at least 50% reduction of plasma and cellular sterol and stanol levels (72-74).

Surgical treatments for complications of sitosterolemia have been reported. Liver cirrhosis has been observed at least once in a patient with the *ABCG8* mutation. The patient underwent successful treatment by liver transplant, which led to a dramatic improvement in the sitosterolemia. It is possible that restoration of the *ABCG8* function in the liver alone may be sufficient to correct the biochemical abnormality (22).

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