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Plant sterols and stanols: Their role in health and disease

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Abstract. Mammalian physiological processes, and likely any organism with a biliary tree, can distinguish between dietary cholesterol and noncholesterols, retaining very little of the noncholesterol in their bodies. Historically, the distinction between plant sterols and cholesterol has been known about for more than a century. That plants sterols are not "absorbed" has been investigated for almost half a century. The ingestion of plant sterols in gram quantities has been shown to interfere with cholesterol absorption and is one of the oldest pharmacologic therapies for hypercholesterolemia. Although the basis for the latter has been shown to be caused by exclusion of cholesterol from intestinal micelles by plant sterols, it was identification of a rare genetic disease, sitosterolemia, first described in 1974, that led to the hypothesis that specific molecular mechanism(s) governed both the entry and excretion of sterols by the body. This work will cover the physiology of dietary sterol metabolism, genetics, and pathophysiology of sitosterolemia. Additionally, the role of plant sterols in normal and abnormal metabolism in humans as well as selected animal models will be discussed.

Dietary cholesterol absorption from the intestine is a critical component of cholesterol homeostasis. Under normal circumstances, the human diet contains approximately equal amounts of cholesterol and plant sterols. However, normal individuals retain, on average, approximately 50% of dietary cholesterol but <5% of dietary plant sterols.[1] The normal physiologic process for handling dietary sterols by the gastrointestinal tract involves processing 200 to 500 mg dietary cholesterol, but also 200 to 400 mg phytosterols, which are a component of plant sterols (Fig. 1). Almost all of the dietary phytosterols undergo fecal excretion, along with 800 to 1500 mg cholesterol plus its metabolic product, bile acids. The normal body is able to discriminate between cholesterol and noncholesterol sterols.[2] This suggests that a molecular mechanism exists in the body that specifically retains cholesterol over noncholesterol sterols.[3] The exact molecular mechanisms by which preferential cholesterol absorption occurs, whereas noncholesterol sterols are not absorbed has not been fully elucidated, but clues from a rare genetic disorder, as well as a novel drug, have led to a major insights.

The purpose of this review is to provide an overview of plant sterols and their role in health and disease. Included will be a discussion of the genetics of sitosterolemia, the role of plant sterols as markers for premature atherosclerosis, and potential treatment options for lowering plant sterol levels in the body.

Metabolism of cholesterol and plant sterols

The enterohepatic metabolism of cholesterol and plant sterols is complex (Fig. 2). The metabolic process occurs within the intestinal lumen, where dietary cholesterol (and plant sterols) is reduced to free sterols by esterases, and transferred into micelles (a mixture of bile salts, phospho-

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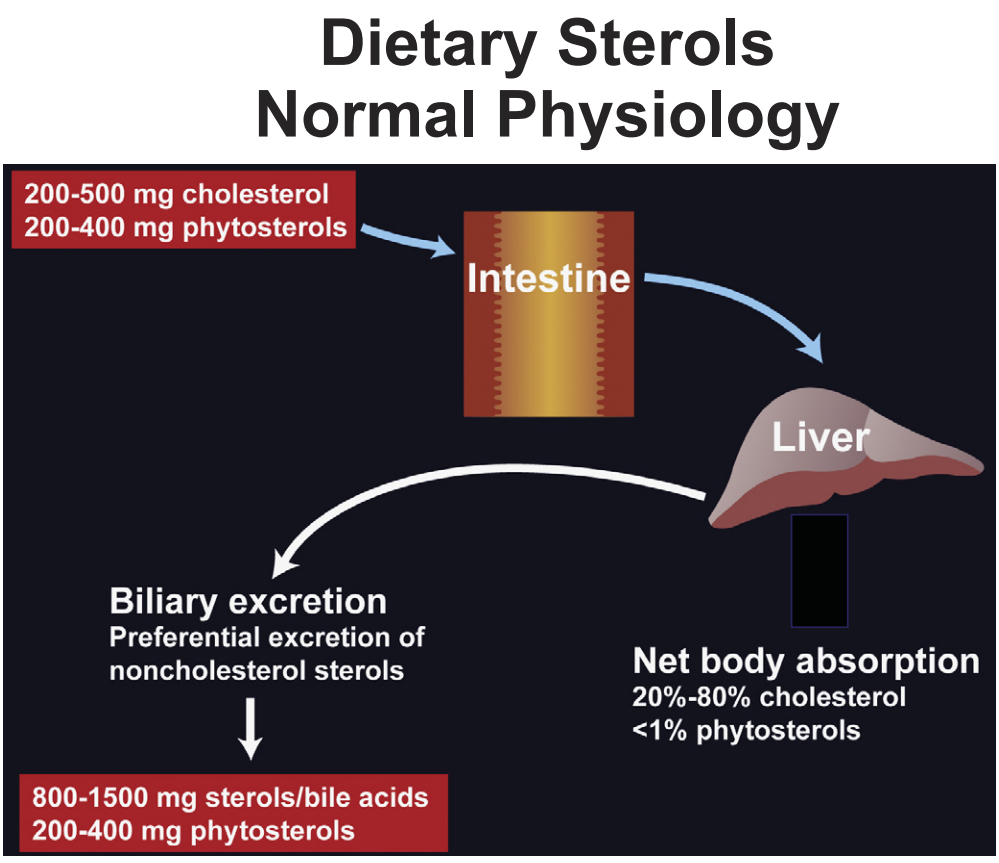

Figure 1 Normal physiology of dietary sterols. Although we ingest an equal amount of plant sterols and cholesterol, the net retention of the plant sterol is <5% on a daily basis, whereas an average of 55% of cholesterol may be absorbed. In addition, the liver excretes a significant amount of sterols, resulting in a net output of more than 1 g/day loss in the feces.

lipids, free sterols, and some fatty acids). These micelles interact with the enterocyte apical membrane (a process that has not been characterized at the molecular level) and allow entry of the sterols into the enterocyte. Cholesterol enters the metabolic pool, where it is esterified by Acyl coenzyme A: cholesterol acyltransferase-2,[4] and incorporated into chylomicrons that are secreted at the basolateral surface into the lacteals that eventually drain into the venous circulation. Chylomicrons are acted upon by lipoprotein lipase in the capillary beds of all the organs, which allows for dietary triglycerides as well as some fat-soluble vitamins to be delivered to these tissues. Sterols in these particles are not transferred out and remain as part of the remnant particles, which are now recognized by receptors on the liver and cleared. The bulk of the dietary sterols are then delivered to the liver. Cholesterol enters the metabolic pool and can be repackaged into very low–density lipoprotein and secreted back into the circulation, whereas noncholesterol sterols are excreted into the biliary tree and thus back into the lumen of the intestine.

How much dietary cholesterol do we absorb? The average person absorbs about 55% of normal dietary intake with a typical Gaussian distribution of rates; a small proportion of the population hyperabsorbs 90% of dietary cholesterol or underabsorbs <10%.[5] However, the dominant factor determining dietary cholesterol absorption for modern man is dietary intake rather than absorption efficiency. In contrast, intestinal absorption of plant sterols is believed to be negligible, although these different sterols are physically very similar (Fig. 3). The molecular mechanism underlying exclusion of noncholesterol sterols (xenosterols) was not considered until the discovery of a rare genetic disorder, sitosterolemia.

Sitosterolemia

A 22-year-old woman presented at the orthopedic clinic complaining of pain in both heels and knees. She had tendon xanthomas with a history of hand xanthomas beginning at age 8 years, which progressed to patellar, plantar, and Achilles tendon involvement. The patient has a sister with a similar phenotype. This combination of arthralgia and tendon xanthomas is associated with diagnosis of familial hypercholesterolemia. Familial hypercholesterolemia is characterized by hypercholesterolemia, tendon xanthoma, arthralgias, and a family history of premature heart disease. It is relatively common and occurs in 1 in 200 to 500 of the general population. Diagnosis is typically confirmed by a lipid panel, which reveals a low-density lipoprotein (LDL)-cholesterol level >200 mg/dL accompanied by a positive