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Editorial

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Noncholesterol Sterols and Sitosterolemia in Clinical Practice

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Since the pioneer study by Miettinen that measured serum or plasma noncholesterol sterols using gas-liquid chromatography in many clinical conditions[1, 2], it is well accepted that a concentration of the cholesterol precursor sterol lathosterol has been used as a surrogate marker of endogenous cholesterol synthesis; the plant sterols such as campesterol and sitosterol are used as markers of cholesterol absorption[3] (Fig. 1). HMG-CoA reductase inhibitors (statins) decrease lathosterol and increase campesterol and sitosterol; conversely, a cholesterol absorption inhibitor (ezetimibe) decreases campesterol and sitosterol and increases lathosterol[4]. Some large prospective trials and genome-wide association studies showed that high plasma levels of plant sterols are associated with increased risk of cardiovascular diseases, while others have reported no such association and even an inverse relationship[5]. A cross-sectional study of patients with coronary heart disease (CHD) showed that campes-

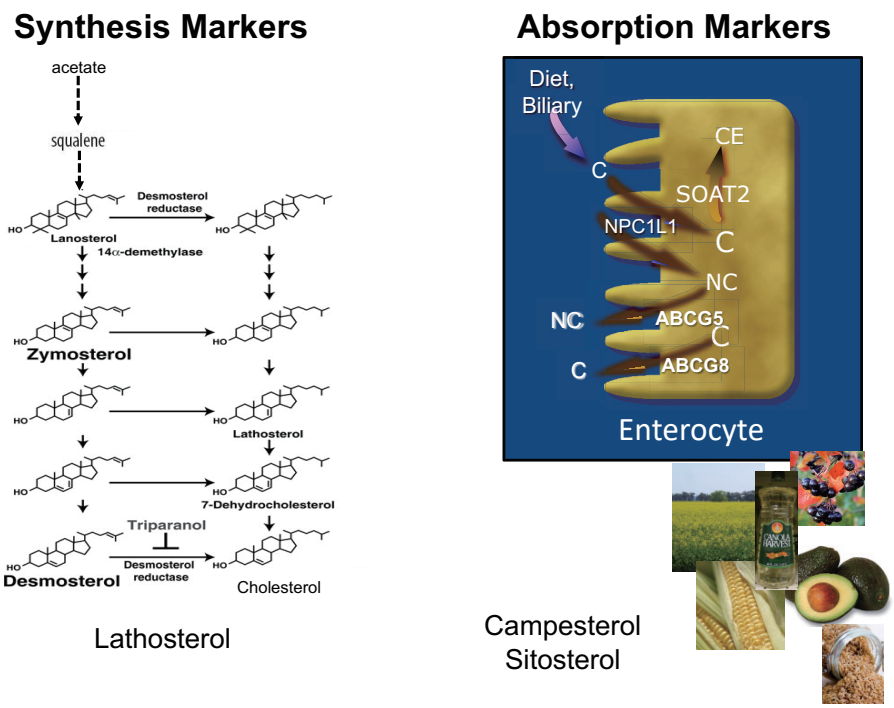

Fig. 1. Noncholesterol sterols

C = cholesterol; CE = cholesterol ester; SOAT-2 = sterol O-acyltransferases 2; NC = noncholeterol sterol; NPC1L1 = Niemann–Pick C1-like 1. This figure has been taken with permission from Dr. Ernst J. Schaefer.

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terol/total cholesterol ratios and campesterol/lathosterol ratios were significantly higher in patients with the progression of *de novo* coronary lesions after percutaneous coronary intervention under statin treatment compared with the others[6]. A subanalysis of the Heart Institute of Japan-Proper level of lipid lowering with pravastatin and ezetimibe in acute coronary syndrome (ACS) study showed that aggressive lipid-lowering treatment with combination of statin and ezetimibe on cardiovascular events were observed in only patients with ACS and high sitosterol[7].

Sitosterolemia is a rare, inherited, autosomal recessive disorder of lipid metabolism characterized by increased absorption and decreased biliary excretion of plant sterols and cholesterol, which is caused by mutations in either ATP-binding cassette subfamily G member 5 or member 8 (*ABCG5* and *ABCG8*, respectively)[8]. Subjects suffering from sitosterolemia have hyper low-density lipoprotein cholesterolemia, tendon xanthomas, and premature coronary atherosclerosis, which is known as "pseudo familial hypercholesterolemia," particularly in infant cases[8]. Accordingly, the measurement of serum sitosterol should be considered in patients with hypercholesterolemia, and it is helpful for the management of CHD.

Although many laboratories develop new methods for the determination of noncholesterol sterols using different chromatographic separation and mass spectrometric detection methods, unacceptably high interlaboratory variations for noncholesterol sterols have been reported[9]. A gas chromatography (GC) method is commonly used for clinical and research settings in Japan. Yoshida et al. first reported sex-segregated reference levels of sitosterol, campesterol, and lathosterol in healthy, heterozygous, and homozygous mutation of ABCG5/ABCG8 Japanese subjects using a practical and highly sensitive GC method to establish reference intervals of these sterols for clinical use[10]. The serum levels of sitosterol and campesterol were significantly higher in women than in men, whereas the serum levels of lathosterol were significantly higher in men than in women. Serum lathosterol levels were significantly lower in patients with sitosterolemia than in healthy subjects. The reference intervals of sitosterol, campesterol, and lathosterol were 0.99–3.88, 2.14–7.43, and 0.77–3.60 μg/mL in men and 1.03–4.45, 2.19–8.34, and 0.64–2.78 μg/mL in women, respectively. The present study included 10 heterozygous and four homozygous sitosterolemia cases. Further studies with higher number of patients with sitosterolemia are required to establish optimal cut-off level of serum sitosterol for the clinical diagnosis of sitosterolemia. Previous studies showed that levels of noncholesterol sterols were affected by both age and sex [3, 11]. Further studies are also needed to investigate the influence of age and apolipoprotein E genotype and differences between fasting and nonfasting samples or between serum and plasma samples. We anticipate that the measurements of noncholesterol sterols will be covered by the health insurance in the near future and such a situation will give us more chances to accurately diagnose sitosterolemia and cholesterol metabolism.

Conflicts of Interest

None.

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