Phytosterols may play role in atherosclerosis

Based on a presentation by Ira Tabas, MD, PhD

Ira Tabas, MD, PhD

NEW ORLEANS—Plant sterols (phytosterols) and stanols can reduce the absorption of cholesterol. They mimic and displace cholesterol in micellar particles. Although they may constitute 50% of the sterols consumed in the diet, the body very strictly limits their circulating amounts.

Ira Tabas, MD, PhD, professor of medicine, cell biology, and physiology at Columbia University College of Physicians and Surgeons in New York, said these compounds can be very detrimental if physiologic defects allow them to circulate.

He cited the rare example of patients with sitosterolemia, caused by mutations in ABCG5/G8, who have a markedly increased incidence of atherothrombotic events not easily explained by other risk factors. These patients also have tendon xanthomas associated with cholesterol-loaded macrophages, as also seen in familial hypercholesterolemia.

People in the upper quartile of sitosterol levels had a 1.8-fold increased risk of major coronary events compared with those in the lower 3 quartiles.

Dr Tabas said the rare condition of sitolsterolemia can inform us about disease processes in the general population. People absorb different amounts of plant sterols from the diet, and plasma levels vary between 1 and 25 micromolar (vs 250-1560 micromolar in beta-sitosterolemia).

The Prospective Cardiovascular Münster (PROCAM) study, a nested case-control study of about 20 000 men and women in Germany reported by Gerd Assmann at the 2003 Scientific Sessions of the American Heart Association (*Circulation*. 2003; 108:IV-730), found that people in the upper quartile of sitosterol levels had a 1.8-fold increased risk of major coronary events compared with those in the lower 3 quartiles (P = .014). In men with a 20% coronary event risk over 10 years, high sitosterol levels were associated with an additional 3-fold increase in risk (P = .032). "If verified by more studies, the variation in plant sterols in the general population may be important," Dr Tabas said.

A small study reported the year before (*Metabolism*. 2002;51:1519-1521) found that patients with a family history of coronary heart disease undergoing coronary artery bypass grafting had higher blood levels of the phytosterol campesterol compared with patients without such a family history (P = .004).

Plant sterols could therefore accelerate plaque formation and promote CAD.

While cholesterol may be bad for the heart, Dr Tabas said phytosterols may be even worse, and the body has developed an efficient mechanism to keep them out. Atherosclerotic plaques consist in part of dead macrophages. Early in lesion formation, macrophages esterify cholesterol through the action of acyl-coenzyme A: cholesterol acyltransferase (ACAT). But much later, ACAT fails, and they pick up free cholesterol, which is toxic to them. Cholesterol intercalates into the membrane of the endoplasmic reticulum, where it disrupts a calcium pump, the sarco-endoplasmic reticulum calcium ATPase.

The macrophages die, and they form the necrotic core of plaque—"a graveyard of dead macrophages," according to Dr Tabas. This core is rich in matrix proteases, inflammatory stimuli, and procoagulant factors that may facilitate plaque rupture and thrombus formation.

Plant sterols, molecules structurally similar to cholesterol but with a slight difference in their side chains, act in a similar manner. However, ACAT, the enzyme that esterifies cholesterol in macrophages early in plaque formation, does not recognize phytosterols, such as campesterol and beta-sitosterol. So the free forms of these molecules accumulate immediately, which may kill macrophages sooner rather than later. "When cholesterol gets into a macrophage, it is going to get esterified, which is a safety feature," Dr Tabas said. "The plant sterols can't do that" (Figure 1).

He hypothesized that plant sterols could therefore accelerate plaque formation and promote coronary artery disease (CAD), but the body has an efficient mechanism to eliminate them. Plant sterols and stanol esters are widely used as dietary supplements to inhibit cholesterol absorption. Low absorption does occur however, leading to low but finite increases in plasma levels. "As suggested by the PROCAM study, it raises, at least in my mind, potential questions," Dr Tabas said. He added that he raised the question on theoretical grounds and was not presenting evidence of known detrimental effects of these compounds.

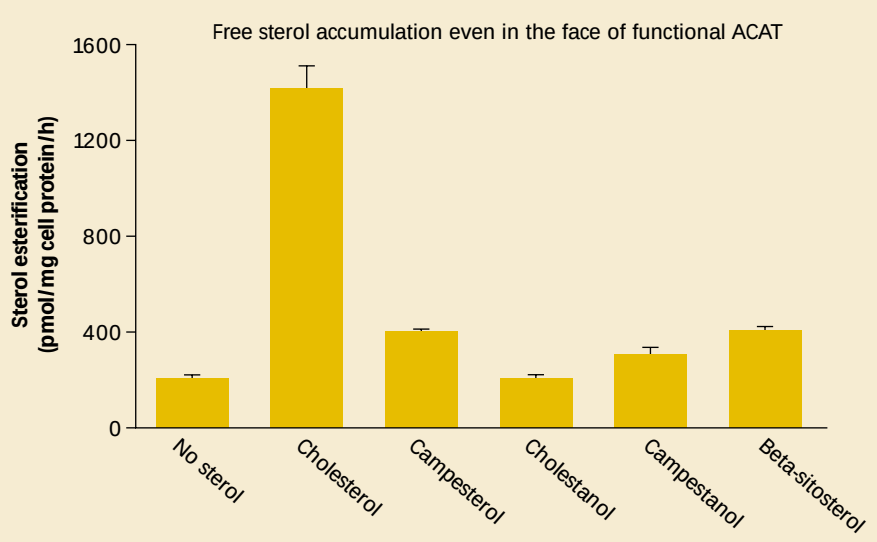
The same transport system in the intestinal wall that takes up cholesterol also takes up plant sterols, and ezetimibe blocks both. It is, in fact, a treatment for patients with sitosterolemia, a rare condition of hyperabsorption of phytosterols (Figure 2).

Dr Tabas concluded with these points:

- Very high levels of phytosterols (eg, in sitosterolemia) are associated with premature CAD.
- Moderately increased levels of phytosterols in the general population were associated with CAD in the PROCAM study.
- Atherogenicity of phytosterols may be related to their effects on macrophage ER membranes, killing the macrophages and leading to advanced atherosclerotic lesions.
- The question remains as to whether lowering serum levels of plant sterols with a drug such as ezetimibe will decrease the incidence of CAD in the general population (as well as in patients with sitosterolemia). ■

FIGURE 1

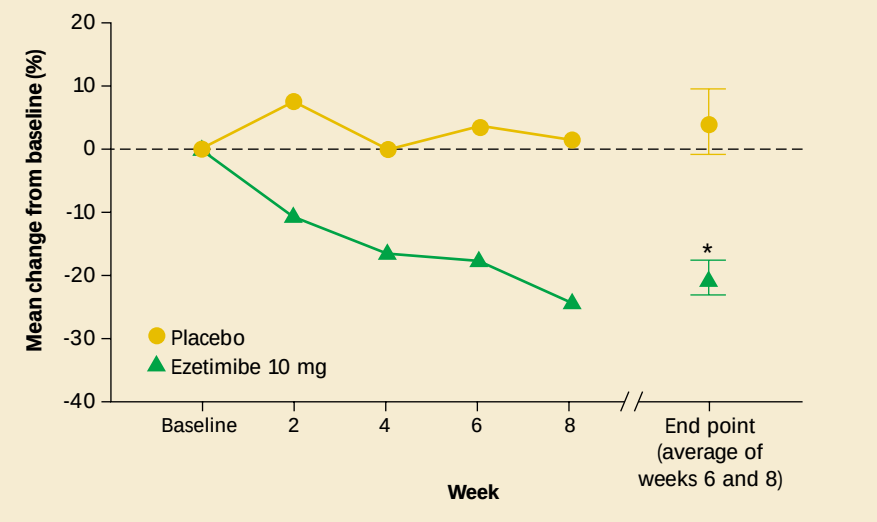
Phytosterols are poorly esterified in macrophages



ACAT = acyl-coenzyme A: cholesterol acyltransferase.

FIGURE 2

Ezetimibe inhibits phytosterol absorption in patients with sitosterolemia



*P < .001 compared with baseline and placebo.
Reprinted, with permission, from Salen G, et al. *Circulation*. 2004;109:966-971.