Plant Sterols and Tissue Cholesterol Levels

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AMONG the many dietary substances known to affect the level of cholesterol in blood and other tissues are the plant sterols.[1] Much of the data on this subject, which have been interpreted as being in conflict, have been obtained with considerable variation in experimental conditions. Soybean sterols or sitosterols fed to chickens in a cholesterol-enriched diet will prevent the usual elevation of plasma cholesterol which occurs on such a diet.[2–7] Liver deposition of cholesterol is also reduced and the occurrence of atheromatous plaques due to prolonged cholesterol feeding is significantly reduced.[3,4] Similar effects have been obtained with β-sitosterol, stigmasterol and ergosterol.[8,10] The effects of dihydrocholesterol, similar on short-term feeding,[9] are found to differ on prolonged administration.[48] Estrogen-induced hypercholesteremia in the chicken is not prevented by plant sterols.[5]

Prevention of hypercholesteremia[11,12] and of atherosclerosis[11] in cholesterol-fed rabbits has been obtained by feeding soy sterols, tall-oil sterols and β-sitosterol. Higher ratios of plant sterol to cholesterol (4:1–7:1) appear to be required in rabbits than in chickens since a 1:1 ratio was ineffective in rabbits.[13]

Swell *et al.*[14] found that feeding of soy sterols to rats, on a 2 per cent cholesterol diet, inhibited the increase in *whole blood* cholesterol. Rosenman and co-workers[15] and Alfin-Slater *et al.*[16] found no effect of dietary soy sterols on *plasma* cholesterol in the cholesterol-fed rat. No change occurred in total carcass cholesterol[16] but liver lipids and liver total cholesterol were much lower than in cholesterol-fed rats.[16,18,19] Deposition of fed cholesterol-C^{14} in rat livers was decreased by feeding soy sterols.[17] (It should be noted that the normal rat does not respond to cholesterol feeding with the enormous hypercholesteremia seen in the chicken and the rabbit.)

Human Studies: Reduction of blood cholesterol in man by feeding soy sterols was first reported by Pollak.[20] Many others have since reported reduction in serum cholesterol by feeding plant sterols. Data from five of these studies on 66 patients[21–25] indicate that about one-half showed reductions in serum cholesterol of less than 15 per cent and the other half greater than 15 per cent. In most cases a commercial suspension of sitosterols has been used, the composition of which other than sterols has not been stated. Some have used sitosterol in biscuit form.[26] Doses have varied widely from 9 to 25 g or greater, per day, consumed before meals. Serum cholesterol rose on cessation of sterol feeding but usually there has been no spontaneous rise during experimental periods even when continued as long as 18 months.[24]

Wilkinson and associates,[27] Friedman *et al.*[28] and Pomeranze and Chessin[22] have reported no effect of sitosterols on serum cholesterol, although the latter group have fed smaller amounts than others. In some hypercholesteremic individuals the fluctuations in serum cholesterol are greater than those obtained during periods of sitosterol therapy.[30] Similar observations have been made on monkeys.[31]

It is interesting that although most of the animal experimenters have mixed the plant sterols with dietary fat, this has been done in only a few cases in human studies. The effectiveness of plant sterols in reducing serum cholesterol appears to be greatly increased by incorporation into dietary fat. Peterson *et al.*[32] fed 5.7 g of soy sterols per day incorporated

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into butter consumed with meals and obtained reductions of up to 20 per cent in plasma cholesterol (mean 11 per cent), as great as most workers have obtained with three to four times this amount. Beveridge, Connell, and Mayer, using 7 g β-sitosterol per 950 calories in a homogeneous formula diet, obtained reductions of over 20 per cent in seven out of nine subjects.[33] Farquhar and Sokolow[35] obtained a 20 per cent reduction in β-lipoprotein cholesterol with either 81 g per day of safflower oil or 18 g of sitosterol. When both were fed, the fall was 32 per cent (mean of 15 patients). The effectiveness of plant sterols employed in this manner have led some[33] to suggest that sitosterol may be the cholesterol-depressing factor in corn oil. It would appear that the levels used were much higher than those present in corn oil, however, although these same workers have recently reported that much lower levels of sitosterol are also effective.[34]

ABSORPTION AND METABOLISM OF PLANT STEROLS

Using tritium-labeled β-sitosterol, Gould and associates[36] showed, in single dose feedings (10 mg), that it was absorbed by rats about one-fifth to one-tenth as completely as an equal dose of labeled cholesterol. The absorption rate on continuous feeding was about one-tenth that of cholesterol. β-sitosterol feeding did not depress cholesterol synthesis from acetate in rat liver or intestine.[37] Labeled β-sitosterol replaced about 7 per cent of the liver cholesterol in rats as compared with 49 per cent for labeled cholesterol and 3.5 per cent of carcass cholesterol compared with 26 per cent for cholesterol. In contrast to this the replacement of cholesterol by dihydrocholesterol was much greater.[36]

In five human subjects fed labeled β-sitosterol, the absorption rate, as judged by plasma sterol level, appeared to be about one-tenth that of labeled cholesterol. Gould suggests that the metabolism of β-sitosterol is different from that of cholesterol since the specific activity curves for red blood cell, plasma free, and plasma ester cholesterol did not approach equality as when labeled cholesterol is fed.[37] In one study on a terminal carcinoma patient 29 days after feeding, the highest sterol specific activity was found in the bile as compared with whole blood and liver. The lowest activity was found in a section of aorta containing plaques.[37]

Studies using the balance technic with rats showed that when soy sterols were fed from 16 to 26 per cent disappeared from the intestine, indicating absorption or destruction.[38,39] Soy sterols tended to increase the sterol content of the serum. When both cholesterol and soy sterols were fed, the sterol elimination was greater than the sum of the sterol elimination when either was fed alone.[39] More recently, using tritium-labeled β-sitosterol, Swell and associates[40] found that β-sitosterol increased the excretion of other sterols although more than half of the β-sitosterol itself disappeared from the intestinal tract. In spite of this, soy sterols tended to decrease the liver sterol content as compared with the same diet lacking soy sterols.[38] Swell and associates were unable to demonstrate the presence of soy sterols in either liver or plasma by chromatography, indicating that they represented less than 5 per cent of the total sterols.[38] Using an x-ray diffraction technic Shipley *et al.*[41] were unable to demonstrate β-sitosterol in livers of rabbits which had been fed β-sitosterol (4 g daily) for periods of over two years indicating that less than 2 per cent of the total sterols was β-sitosterol.

Some question may be raised as to whether or not balance studies on digitonin-precipitable sterols[38,39] are adequate to determine absorption since the possibility exists that conversion to non-β-sterol substances by intestinal bacteria may occur.[42,43]

One study on C^{14}-labeled ergosterol[44] showed that 2 to 5 per cent of 1–2 mg doses were absorbed by rats. Most of the radioactivity was excreted in the bile and the absorbed ergosterol was not converted to cholesterol.

It is apparent that little is known concerning the metabolism of plant sterols. Adequate analytical methods still remain to be developed for their detection and differentiation from other sterols.

Toxicity Studies

Because some misunderstandings have arisen it is desirable to point out that dihydrocholesterol does *not* occur among plant sterols and is a normal constituent of animal tissues. Although feeding of dihydrocholesterol in a cholesterol-enriched diet results in an inhibition of the increases in plasma cholesterol in chickens,[9,10] rabbits,[46] and rats,[47] it has been found that prolonged feeding (six months) of 2 per cent dihydrocholesterol to chickens produced severe arteriosclerosis and enlargement and lipid infiltration of the liver.[48] Rabbits fed 2 per cent dihydrocholesterol for seven months developed extensive plaque formation in the aorta and cirrhosis of the liver.[49] Increased β-sterols and cholesterol were found in livers and aortas.

On the other hand rabbits fed 2 per cent β-sitosterol for seven months developed no changes in liver or aorta or in total β-sterols of these tissues.[49] Feeding of both cholesterol and soy sterols to chickens for 28 weeks resulted in a degree of atherosclerosis that was no greater than that of control (non-sterol-fed) birds.[3]

The report of Curran and Costello[50] that the feeding of soy sterols to four rabbits for four weeks produced atherosclerosis and deposition of soy sterols in the aortas has not been confirmed by others[41,49] who have fed plant sterols for much longer periods. No description of the two control rabbits in Curran and Costello's experiment was given nor of the infrared technic used for determining the soy sterols. Shipley *et al.*[41] have fed very high levels of sitosterols to rabbits, rats, and dogs for periods up to two years without development of pathologic alterations of tissue or increase in sterol content.

Mechanism of the Effect of Plant Sterols

Soy sterols and β-sitosterol apparently do not effect decreased tissue levels of cholesterol by inhibiting its synthesis from acetate.[37,51] There is no effect on estrogen-induced lipemia in the chickens.[5] Nevertheless, plant sterols *have* been shown to decrease absorption of C^{14}-labeled cholesterol in rats[52,53] as measured by recovery of the labeled compound in thoracic duct lymph. Similar effects have been found with dihydrocholesterol and ergosterol.[54] Recovery of labeled cholesterol in livers of rats fed soy sterols was also decreased.[17] The hypocholesteremic effects produced in man may possibly be related to interference with reabsorption of cholesterol since dietary cholesterol appears to have little effect on blood cholesterol in man.[45]

Two mechanisms have been suggested for this effect: (1) that plant sterols form insoluble mixed crystals with cholesterol, decreasing its absorption;[11,55] (2) that the plant sterols compete with cholesterol for the absorption mechanism.[8,39,52,56] No evidence from animals has been presented for the first. The evidence for the second is indirect. The suggestion has been made that plant sterols may compete in a cholesterol esterification system involved in absorption[8,52,56] since cholesterol is esterified in the absorption process.[59,66] Soy sterols, ergosterol, and dihydrocholesterol fed as esters have diminished capacity to prevent increases in plasma and liver cholesterol in chickens.[8,10] Esterified β-sitosterol similarly has little effect on liver cholesterol in rats.[18,19]

Cholesterol, itself, fed as the ester, has diminished or lost completely the ability to increase plasma and liver cholesterol in the chicken[10] and in the rat.[57,58] The absorbability of the ester has been related to its rate of hydrolysis by pancreatic cholesterol esterase.[57] Evidently only *free* cholesterol is absorbed, and all ester cholesterol is *not* hydrolyzed in the intestinal tract. The esterification which occurs during absorption does not take place in the intestinal lumen, since the mucosa contains mostly free cholesterol[59] and cholesterol ester is less readily absorbed than free cholesterol. It has not been established that pancreatic cholesterol esterase is the esterifying enzyme involved in absorption, although it has been reported that exclusion of pancreatic juice decreases the content of esterifying enzyme in mucosa.[60] Although Hernandez *et al.* found that exclusion of pancreatic juice decreased cholesterol absorption in the rat[61] the results of Byers and Friedman[62] and Lin *et al.*[63] are in disagreement with this. Lin *et al.* suggest that the effect of pancreatic juice is to provide free fatty acid (needed for cholesterol absorption), a factor not provided for in Hernandez' experiments. Pancreatectomy does not reduce alimentary hypercholesteremia in the chicken.[64,65] Furthermore, absorbed cholesterol bears a constant ratio of ester to free cholesterol regardless of interference with absorption by other sterols,[54] suggesting that the plant sterol effect occurs at another level than that of the esterification occurring during absorption. Since it has been found by Swell *et al.*[14,56] that plant sterols are more slowly esterified by pancreatic cholesterol esterase than cholesterol itself, the possibility is suggested that the presence of plant sterols may in some manner favor the esterification of cholesterol in the intestinal tract, which as seen from the above discussion would tend to decrease cholesterol absorption.

Since it now appears that lowering of serum cholesterol may be accomplished by nutritional means it is probable that the use of plant sterols for this purpose may have but limited pharmacologic applications. However, further study of the mechanism of action of plant sterols and of their metabolism would appear to be valuable in elucidating the mechanisms involved in the absorption of cholesterol itself.

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