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The Link Between Soluble Fiber, Hypercholesterolemia and Atherosclerosis - Interest in the use of dietary fiber in the amelioration of such conditions as diabetes mellitus, coronary artery disease, and colon cancer has increased concomitant to the growing body of evidence depicting the advantages of both increased dietary intake and supplementary fiber ingestion within the context of the relatively fiber-deficient Western diet (Anderson and Gustafson, 1988). Dietary fiber, a collective term referring to a number of plant substances which resist human gastrointestinal digestion, may be classified on the basis of water solubility. Unlike insoluble fibers (e.g., cellulose, lignins, and some hemicelluloses) which decrease intestinal transit time, increase fecal bulk, and appear to delay hydrolysis of starch and absorption of glucose, soluble fibers (e.g., pectins, gums, mucilages, algal polysaccharides, and some hemicelluloses and storage polysaccharides) increase intestinal transit time while delaying gastric emptying (Glore et al., 1994). Note: Hypercholesterolemia as used in this paper is defined as total serum cholesterol greater than 200 mg/dL.

A review of recent literature reveals another, and perhaps the most significant, difference: of the two fiber types, elevations in only soluble fiber have been associated with a significant reduction in serum cholesterol, especially LDL. The clinical significance of this is based upon evidence suggesting a relationship between hypercholesterolemia and the development of coronary heart disease, which is, in turn, based upon the pathogenesis of atherosclerosis. It is known that in addition to the receptor-mediated pathways by which hepatic and other cells take up cholesterol, LDL is taken up by macrophages; the latter pathway is increasingly activated when plasma levels of LDL are elevated for a long period of time. It is also known that such macrophages adhere to the walls of arteries. In fact, the "response to injury" hypothesis (Ross and Glomset, 1976) suggests that the initiating factor for the adherence of these macrophages and the accumulation of other factors is endothelial injury. Interestingly, the involvement of cholesterol in endothelial injury is two-fold; it not only accumulates during the formation of the atheroma subsequent to the injury but it also may induce the initial injury. It has been shown in vitro that oxidized LDL can injure endothelial cells, promote the uptake of LDL into endothelial cells, and even inhibit the response of macrophages to chemotactic substances, thus reducing their mobility on the arterial wall (Malden et al., 1991). For these reasons, the clinical benefits of a rapid and significant decrease in serum cholesterol would be advantageous by potentially reducing an individual's risk for atherosclerosis.

Evidence For The Hypocholesteremic Effects of Soluble Fiber

To date, evidence for a soluble fiber-induced reduction in total cholesterol has been fairly substantial; a recent review points out that approximately eighty human trials have been performed since 1992 (Glore et al., 1994). Nevertheless determinations of the most beneficial sources of soluble fiber as well as the exact mechanism of hypolipidemic action have not been conclusively determined. As modulating soluble fiber intake may provide an alternative, or at least an adjunct, to drastic therapeutic interventions like cholesterol synthesis inhibitors (see below), an examination of the variety of soluble fiber sources and of the putative underlying mechanism of action may be helpful in a

clinician's attempts to address the concerns of a hypercholesteremic patient at a high risk for coronary heart disease.

It is known that even foods traditionally considered to be high in fiber content contain different amounts of both total dietary fiber and soluble fiber (e.g., per 100 g). Thus, the reduction in serum cholesterol associated with consumption of different high-fiber foods may vary. For example, Anderson and colleagues have, since the early 1980s, demonstrated that leguminous seeds, such as dried beans (pinto, white, kidney, etc.) and peas decrease total serum cholesterol significantly; consumption of navy and pinto beans (at 50 to 115 g/day) reduced serum cholesterol by 15% to 23% and LDL by 13% to 24% over a period of three weeks (Anderson et al., 1984). While the reduction in total cholesterol was similar to that of early studies, Anderson et al. in 1990 also demonstrated a 7% HDL reduction in a study of 24 hypercholesteremic men fed 120 to 162 g/day of canned, cooked beans. In light of the possible beneficial effects of HDL (Tribble and Krauss, 1993), this may be construed as a negative result. Nevertheless, an overall look at the cholesterol-reducing effects of beans and legumes shows that 10 out of 10 human trials since 1992 involved statistically significant serum cholesterol reductions in experimental subjects over controls (Glore et al., 1994).

While the leguminous seeds described above contain 7.8 g of soluble fiber per 100 g, rolled oats and oat bran, which also have been reported to have a hypocholesterolemic impact for many years, have only 5 g of soluble fiber per 100 g. Analysis of the effects of oats, which is complicated by the fact that oat bran can vary in its content of water-soluble fiber and beta-glucan (Topping et al., 1991), reveals a total cholesterol reduction somewhat more modest than that of beans. (It is somewhat difficult, however, to compare studies of different methodologies, durations, etc.) Nevertheless, Whyte et al. (1992) have shown that 123 g/day of oat bran reduced total cholesterol by 3% and LDL by 6%, and 19 of 23 recent human studies have shown significant reductions in total cholesterol (Glore et al., 1994). Similarly, pectins _ a subset of structural fibers located in fruits, especially apples _ have been shown to reduce cholesterol in a dose-dependent manner both in animal and human models. While early studies pointed to this effect, more recent research has questioned these results (Bell et al., 1990). Nevertheless, animal models (while attempting to demonstrate a mechanism of total cholesterol reduction) have shown drastic alterations in LDL with large doses of citrus pectin, even in the presence of high cholesterol diets (Fernandez et al., 1994).

In addition to the sources of soluble fiber described above, psyllium, which provides the basis of well-known bulk laxatives, has been explored as a potential cholesterol-lowering agent whose main advantage is ease of administration and relatively high fiber content per weight. In a recent study, hypercholesteremic men and women assigned to high- and low-fat diet groups showed small yet statistically significant decreases in total cholesterol and LDL. Total cholesterol and LDL levels decreased 5.8% and 7.2%, respectively, in psyllium recipients on high-fat diets and 4.2% and 6.4%, respectively, in subjects on low-fat diets over an eight-week trial period (with no statistically significant change in controls). Based on the National Cholesterol Education Program LDL cholesterol classification system, 39% of the psyllium recipients improved in terms of LDL

cholesterol levels (Sprecher et al., 1993). This study demonstrates that psyllium, like the other sources of soluble fiber discussed above, produces a modest improvement in total cholesterol and LDL in individuals on either low-fat or high-fat diets, but is not likely to entirely eliminate the need for medications in cases where a more drastic reduction in cholesterol is required.

Putative Mechanisms

As suggested above, human trials indicating potentially beneficial, cholesterol-reducing effects of soluble fibers from a wide variety of sources have been performed since the 1960s. While data from both animal and human models is abundant, elucidation of the mechanism of soluble fiber as a hypolipidemic agent is far from completion. Nevertheless, a number of probable mechanisms have been suggested and will be introduced since the most recent focus of research has been upon attempts to delineate the pathways involved. Primarily, fiber may act to reduce serum cholesterol simply by binding bile acids, which are therefore excreted rather than recycled to the blood; this reduces blood cholesterol which is taken up to reestablish an adequate supply of bile acids. This effect, in fact, has been directly demonstrated with a number of the sources discussed above, including psyllium (Stoy et al., 1992). In addition, soluble fiber may be fermented in the colon by bacteria, such that the short-chain fatty acids which are produced act to reduce cholesterol synthesis (Levrat et al., 1994). Furthermore, some animal studies aimed at determining whether the observed LDL reduction is a function of increased catabolism or decreased synthesis have suggested the latter mechanism; thus soluble fiber may act to directly regulate LDL metabolism (McCall et al., 1992). Finally, while some studies have suggested that soluble fiber may indirectly act to reduce serum cholesterol by replacing dietary cholesterol and saturated fat, the Sprecher et al. (1993) paper discussed above provides evidence that such reductions in total cholesterol and LDL may occur even with a high fat diet.

Concluding Remarks

Active research into familial hypercholesteremia has led to the development of several non-dietary treatments. Hypercholesteremic patients may be offered bile acid binding resins (e.g., cholestyramine) which indirectly reduces serum cholesterol levels by inducing a compensatory increase in cholesterol uptake from the blood for bile acid synthesis. In addition, the direct inhibition of de novo cholesterol production may be achieved through drugs like compactin and mevastatin, inhibitors of HMGCoA reductase, a crucial regulatory enzyme in the cholesterol synthesis pathway. What role will dietary options such as soluble fiber intake play in relation to such treatments? Specifically, can increased soluble fiber intake be the sole therapeutic choice for patients? Perhaps not, but it is important to remember that this answer may be dependent upon the exact mechanism of action; for example, if both soluble fiber and acid binding resins act by reducing the recycling of bile acids, then the magnitude of their additive effects may not be as large as desired.

Nevertheless, the sources of soluble fiber discussed above, when added to a prescribed low-fat diet, may indeed reduce the need for medications or may be an important adjunct to more drastic treatments of moderately high LDL levels. The availability of a wide variety of soluble fiber sources, the relative ease of intake of these natural foods or supplements, and their reported effectiveness _ a significant effect may be observed within three weeks of consuming as little as three tablespoons of psyllium per day _ are some of the factors which make soluble fiber an attractive cholesterol-reducing agent.

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