Effects of Dietary Fats on Plasma Cholesterol in Humans

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Introduction

Coronary heart diseases (CHD) is a multifactorial disease which is responsible for more than half a million deaths every year in the United States (Consensus Conference, 1985). Among the risk factors implicated in the genesis of CHD, hypercholesterolemia is a primary one. (Stamler et al., 1986). Epidemiological, clinical, and anatomo-pathological studies (Keys, 1970; Stamler et al., 1986; Solber et al., 1983) have demonstrated that the risk for CHD rapidly increases when the plasma concentration of cholesterol exceeds the value of 200 mg/dl. The Framingham study (Kannel et al., 1971) has provided the demonstration that the risk for CHD increases in measure of 2% for every 1% increase in plasma cholesterol. As further evidence, the Lipid Research Clinic trial (Lipid Research Clinic Program, 1971) has shown a 2% decrease in the CHD risk for every 1% decrease in plasma cholesterol levels. The tremendous consistency of this scientific data has led to the general conviction that lowering plasma cholesterol is one of the fundamental therapeutic interventions in order to decrease the incidence of CHD in the population.

Elevations in plasma cholesterol are caused by dietary and genetic factors (Brown et al., 1981). Although diet alone is responsible for the mild forms of hypercholesterolemia, with plasma cholesterol values generally ranging between 200 and 250 mg/dl, it must be pointed out that the normalization of these levels is extremely important for the prevention of CHD (Grundy, 1986). Furthermore, dietary treatment is also complementary for the therapy of moderate and severe hypercholesterolemias, in which the use of drugs is generally required.

Dietary cholesterol and fats are the agents through which the nutritional pattern affects the levels and the changes in plasma cholesterol. The real impact of dietary cholesterol on plasma cholesterol is still the object of controversy. Keys and co-workers (Keys et al., 1965) have asserted that the change in plasma cholesterol should be equal to the square root of the content in the diet. However, a certain degree of variability has been observed in the individual response to dietary cholesterol (Grundy, 1986). It seems conceivable that genetic traits are responsible for this different response to the diet. Nonetheless, the general attitude towards this problem is of prudently limiting the daily intake of cholesterol to a maximum of 300 mg (Grundy, 1986).

The role of dietary fats is certainly more prominent in relationship with the effects on cholesterol and lipoprotein levels. Different effects are, in fact, observed as a consequence not only of the amount but also of the type of fatty acids contained in the diet.

Saturated Fatty Acids

Saturated fatty acids are mainly found in animal products, with the exception of some vegetable fats such as coconut oil, palm oil and cocoa butter. Populations consuming high amounts of saturated fatty acids have been found to have higher cholesterol levels and higher prevalence of CHD (Keys, 1970).

The cholesterol-raising effect of dietary saturates has been quantitated by Keys and co-workers (Keys et al., 1965) who determined an increase in plasma cholesterol equal to 2.7 mg/dl for each 1% of the total calories supplied by saturated fat. The exact mechanism through which saturated fatty acids increase plasma cholesterol levels is not known. Spady et al. (Spady, 1985) suggested that these fats cause a reduction in the clearance of low density lipoproteins through a downregulation of the low-density lipoprotein (LDL) receptor system. According to these authors, this effect would be related to a decreased esterification rate of intracellular cholesterol, which would increase the content of free cholesterol. The increased amount of free cholesterol would be responsible for the lower synthesis of LDL receptors.

The raise in plasma cholesterol is not observed with all saturated fatty acids. Saturates with a chain length shorter than 12 carbon atoms have a different metabolism from longer chain ones. They are not absorbed through the intestinal lymphatics but enter the portal bloodstream directly via the intestinal capillaries (Keys et al., 1965). Once in the liver, they are rapidly oxidized (Bach et al., 1982), while only a small portion of them is being elongated. Due to these metabolic characteristics, these fatty acids do not increase plasma cholesterol (Grande, 1962).

Lauric (12:0), myristic (14:0), palmitic (16:0), and stearic (18:0) acids are the fatty acids responsible for the hypercholesterolemic effect. The efficacy of this effect is not identical for all of them but, rather, has been found to be higher for the first two of them and lower with the latter ones (Keys et al.,

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1965; Hegsted et al., 1965).

Further distinction is needed to discuss the action of stearic acid. This saturate is found in considerable amounts in meat fat, as well as cocoa butter. Even though, for practical purposes, this fatty acid is generally considered to have the same action of lauric, myristic and palmitic acids, there is evidence that, on the contrary, it might not raise plasma cholesterol. Ahrens and coworkers (Ahrens et al., 1957) showed that plasma cholesterol levels were lower on a cocoa butter-rich diet than on a butterfat-enriched diet. Cocoa butter has a high content in stearic acid and therefore these authors thought that this fatty acid might not be hypercholesterolemic. Recent data from our laboratory seem to confirm this finding (Bonanome et al., 1987). Also, this effect does not seem attributable to a malabsorption of this fatty acid.

Polyunsaturated Fatty Acids

Polyunsaturated fatty acids are classified into two groups, named omega 6 and omega 3, depending on the position of the first double bond from the methyl end of the molecule.

The most common sources of omega 6 fatty acids are vegetable oils, such as corn, safflower, soybean. Linoleic acid (18:2) is the most represented fatty acid in this group. This fatty acid is also defined as "essential," since it cannot be synthesized by the body. Moreover, linoleic acid plays an important functional role, serving as precursor of arachidonic acid (20:4), from which the series PGE1 and PGE2 of prostaglandins are derived.

Polyunsaturated fatty acids lower plasma cholesterol in measure of 1.3 mg/dl for every 1% of the calories that is supplied by these fats (Keys et al., 1965). Several mechanisms have been invoked to explain this hypocholesterolemic effect. While some investigators reported an increased excretion of biliary cholesterol when patients were fed diets high in polyunsaturates (Connor et al., 1969), others thought that lipoprotein particles containing considerable amounts of polyunsaturated fatty acids had a decreased capacity to transport cholesterol. According to this theory, this would be due to the larger space that polyunsaturated fatty acids would occupy within the particle itself (Spritz et al., 1969). However, the real mechanism underlying the effect of linoleic acid on plasma cholesterol levels seems to consist in an increased clearance of the LDL particles (Shepherd et al., 1980). A smaller number of these lipoproteins have been, in fact, observed in subjects consuming diets containing high amounts of this fatty acid (Vega et al., 1982). It remains to be established whether this is due to a higher production of LDL receptors or to a more efficient binding between the LDL particle and the receptor. Furthermore, the number of LDL particles might be reduced because of a lower production of their precursors, the very low density lipoproteins (Grundy, 1987).

The dietary substitution of saturated fatty acids with polyunsaturates has been widely encouraged because of the hypocholesterolemic effect described above. Nonetheless, it is now felt that high intakes in these fats might not be free from harmful side effects. First of all, a lowering of high density lipoproteins (HDL) levels has been observed after administering diets high in linoleic acid (Mattson et al., 1985). This lipoprotein fraction is known to be anti-atherogenic and a decrease in its levels might somehow mitigate the beneficial effects of the decrease in LDL levels. A higher risk for gallstone formation has also been reported in association with high polyunsaturated fat diets (Sturdevant et al., 1973). Finally, animal studies have suggested an increased susceptibility for chemical carcinogen induced tumors (Gamma et al., 1967). Along with these data, a certain degree of immunosuppression has been recently described in experimental animals fed with diets rich in linoleic acid. (Bennet et al., 1987).

Omega 3 fatty acids, more widely known as fish oils, have been recently brought to the attention of the general public because of their triglyceride-lowering properties (Phillipson et al., 1985). These fats are found in the meat of cold-water fish such as salmon, herring, mackerel, which feed themselves with plankton rich in eicosapentanoic (20:5) and docosahexanoic acids (22:6). The mechanism through which omega 3 fatty acids lower plasma VLDL levels is probably through a decrease in the production rate of these lipoproteins. A decrease in the plasma concentration of LDL levels has also been described as the consequence of the reduced number of VLDL (Illingworth et al., 1984).

Omega 3 fatty acids also modify the aggregative properties of platelets, decreasing their capacity to initiate the coagulative processes. In this sense, fish oils might have very beneficial effects in the prevention of arterial thrombosis, in patients affected by CHD. (Goodnight et al., 1982).

Many studies are currently being carried on regarding the effects of dietary supplementation with fish oils, since it is felt that further data is needed before a global judgement can be given on the action of these fats.

Monounsaturated Fatty Acids

Oleic acid (18:1) is the principal monounsaturated fatty acid. The main sources of this fatty acid are vegetable oils such as olive, high oleic safflower, rapeseed.

For quite a long time, the data regarding the metabolic effects of oleic acid has been controversial. On one side, it was thought that this fatty acid had no effect on plasma cholesterol (Keys et al., 1965; Hegsted et al., 1965), while on the other side there was epidemiological evidence of lower mean plasma cholesterol values and lower prevalence of CHD in populations consuming diets rich in oleic acid (Keys, 1970).

In the past few years, new data has been produced regarding the effects of oleic acid on plasma cholesterol and lipoprotein metabolism. A comparison between polyunsaturates and monounsaturates was performed by Mattson and Grundy (Mattson et al., 1985). These authors confronted the effects of these two diets with a third one high in saturated fat. Total and LDL cholesterol levels resulted equally low with both the unsaturated fat diets. Also, HDL cholesterol was significantly decreased by the high polyunsaturated fat diet, remaining practically unchanged with the high monounsaturated one. This study was subsequently followed by another one in which a diet high in oleic acid was this time challenged against a low-fat diet (Grundy, 1986). An equally effective hypocholesterolemic effect was observed with both diets. Interestingly, a significant increase in plasma triglycerides, as well as a significant lowering of HDL cholesterol levels, were

noted with the low-fat diet.

Recently, Mensink and Katan (Mensink et al., 1987) reported identical results while comparing diets having similar composition to those tested by Grundy. Finally, Garg et al. (1987) have published preliminary data relative to a clinical trial in which a diet high in oleic acid was compared with another one low in fat and rich in complex carbohydrates, in a group of patients affected by non-insulin-dependent diabetes mellitus (NIDDM). Again, while both diets lowered total and LDL cholesterol, a tendency to have higher plasma triglyceride and lower HDL levels was noted with the low-fat diet.

From the results of the trials mentioned above, it has become clear that diets rich in oleic acid have a hypocholesterolemic effect which is equivalent to that of other dietary regimens which were already known to lower plasma cholesterol. Furthermore, oleic acid seems to have the advantage of not lowering the HDL fraction and not raising plasma triglycerides. Also, monounsaturates seem to be free of side effects, as it can be assumed from the fact that, in populations consuming large amounts of olive oil, no correlation has been found between the use of this fat and any disease.

Conclusions

Several types of diet have been found to have beneficial effects in lowering plasma cholesterol and, consequently, decreasing the risk for CHD. The field of fatty acid metabolism and its relationship with atherosclerosis is continuously evolving, as more data are being gathered regarding the individual actions of these compounds. These studies have and will be able to provide a larger choice of "healthy" diets, the advantage of which will consist in a better compliance from the public and in the achievement of more widespread dietary intervention.

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Discussion

S. Smith: In your last data slide, and for the high stearic and high oleic acid diets, even though the diets are very low themselves in palmitic acid, the serum palmitic acid was rather high. It looked as though there may have been an even more rapid conversion of the 18-carbon fatty acids to palmitic acid than there was a conversion of stearic to oleic, especially since the high stearic diet was already about 40% oleate anyway. Could you comment on that?

A. Bonanome: It's true that it was pretty high; but I also must say that, normally, if you take a random assay of palmitic acid in plasma triglycerides, I believe it's right around 26%. That's the average range that we find normally in a population unless you put them on a very low-fat diet. It's also true that stearic acid can be shortened, but I would be inclined to assume that the effect we've seen produced the saturation, plus some animal studies. These studies were performed in 1965; Radio-labeled stearic acid was injected into rats and then the rats were sacrificed and where the labels had gone in the liver triglycerides was checked. Most of the label was recovered in oleic acid. So that's why we were inclined to think about this mechanism more than the other one.

M. Marchello: When you hydrogenated these fats to get saturated fatty acids, it's my understanding that usually we get trans-fatty acids instead of cis-fatty acids and there has been some evidence that trans-fatty acids could have a deleterious effect or act like saturated fatty acids. Do you have any information about this?

Bonanome: This observation was made by a company in Dallas, Anderson-Clayton, and from the data we had there were not many trans in that particular fat we obtained. It was mostly cis. But you are very right, trans-fatty acids are dangerous.