

Nutrition and blood lipids

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My subject is nutrition and blood lipids. That leaves out some interesting subjects such as the fish oil fatty acids, because they mainly act through other mechanisms, but there are plenty of interesting things left to discuss. Before that let me try to anchor the subject of blood lipids in the subject of this conference, which is longevity. Data from the Framingham study show the 30-year mortality rate as a function of initial serum cholesterol, and they show that those men with the highest cholesterol levels have the shortest life span and those with the lowest cholesterol levels live longest. This has been a controversial subject and only now that we get very long-term data is it becoming clear that indeed in healthy people without underlying diseases a high cholesterol level predicts a shorter life span.

So what determines cholesterol levels? Well, one thing we are sure of is that there are things which can profoundly change them; we see that from the international comparisons (Ancel Keys, 1970, the Seven Countries Study), men in Japan had a cholesterol of 170 mg/dL and in Eastern Finland, 270 mg/dL. We know from migration studies that much of these differences are environmental; there is some genetic effect, but most of it is environmental. At the time Ancel Keys felt that a major part was due to saturated fatty acids in the diet. I think this explanation has shifted slightly, not qualitatively but quantitatively. About half of the differences between men in the Seven Countries can be explained by saturated fatty acids. There are several other components of the diet that we now know to affect serum cholesterol, and most of them were already hinted at by Ancel Keys in his report.

Major dietary effects on cholesterol levels are due to (i) energy imbalance *ie* obesity, (ii) dietary fatty acids and (iii)

dietary cholesterol. Then there are a number of minor factors, such as soluble fiber and some other plant constituents, and miscellaneous factors.

I will start with one of the miscellaneous factors, namely the unique lipids from coffee, and then I will turn to the fatty acids; next I will discuss fats *vs* carbohydrate. I will end with another detour into the miscellaneous factors, namely plant sterols.

Coffee consumption in Europe varies greatly between countries: high intakes in Scandinavia, lower intakes in the Mediterranean countries, quite low in Greece. Coffee intake differs not only in the amount consumed, but also in the way people prepare it. The percolator is the way our parents or grandparents made coffee. The Napoletana, or moka machine is the way most Italians make coffee at home, and the French Press is a rather fashionable new construction with a piston, which is becoming popular in Northwestern Europe and the US. Strangely enough there is something in this French Press brew that potently raises cholesterol. In a trial that we did a few years ago, 22 subjects received French press coffee, and another 23 received a control coffee made with a paper filter. We saw a slow rise in cholesterol in the French press group that reached a plateau after about two months. The rise was about 0.5 mmol, almost 20 mg/dL, and we also saw a rapid rise in triglycerides which very slowly subsided over the following months. These effects are all due to a substance called cafestol, a diterpenoid lipid which is present in coffee beans and which potently raises cholesterol.

There are hundreds of different coffee machines and many types of beans: decaffeinated, mild, Robusta, Arabica, you name it. Since we have identified this substance, this cafestol, as the active cholesterol-raising principle from coffee beans we can now predict exactly for each type of coffee machine and type of beans what the effect of the brew will be on serum cholesterol. The filter coffee which many people drink has zero impact, so you can drink filter coffee as much as you like until your ears start ringing from the caffeine, but it is not going to affect your cholesterol. The moka or Napoletana has a slight effect, the

espresso has a slight effect, very variable between different machines and brands, but still you have to drink a lot of espresso to raise your cholesterol. The type of coffee that used to be popular in Scandinavia, including Finland, the Scandinavian boiled coffee has about the same effect as the French press coffee which I discussed above.

That brings me back to the Seven Countries study: if you calculate the amounts of coffee that people in Finland were drinking, which is 6 to 7 cups per day on average - large cups of strong coffee - then you can calculate that about 10 mg/dL of their high cholesterol levels at the time were due to the way they prepared their coffee. The Middle Eastern coffee which is used in various forms in Greece, Turkey and in Arabian countries and in a different form in Israel, markedly raises cholesterol, but still people in these countries do not have high serum cholesterol levels. This is due to the amount consumed. Although the Middle Eastern type of coffee raises cholesterol it does not play a role in mortality in Greece because the amounts consumed are small, just a few small cups per day. So it's not just what type of coffee you drink but also how much you drink of it; if you take 20 cups of espresso a day then, in addition to causing you sleepless nights, it's certainly going to raise your cholesterol.

This cafestol was one of the minor constituents that came into explaining the differences in cholesterol between the Seven Countries. Remember that the countries were selected for their large differences in cholesterol, they were not a random sample from the United Nations, so anything that raises cholesterol will be there in Finland, that's what they were selected for, including the genetic susceptibility, and anything that lowers cholesterol will be found in Japan, including for instance the phyto-estrogens and what have you. But the major player is still the dietary fats, the fatty acids.

Let me reiterate the ways in which fatty acids can differ. They can differ in length -- that's a subject I'm not going to discuss right now. They can also differ in the position which the fatty acids have on the triglyceride molecule -- some fatty acids can be in the middle, some on the outside -- but this has no effect on blood lipids as far as we know. Two major characteristics of dietary fatty acids important for blood lipids are the number of double bonds and the configuration of the double bond. A saturated fatty acid has no double bonds and an unsaturated fatty acid anything between one and six. As for the configuration of the double bond, the normal cis-unsaturated fatty acids are found in unhardened oils. Fatty acids with the trans - configuration are found in small amounts in dairy fats, butter and in the body fats of ruminants, and in much larger amounts in

hardened oils. Why do food manufacturers hydrogenate or harden oils? Well, the word 'hardened' already tells you why. It is because some foods are best made with hard fats, and hardening also removes the essential fatty acids which tend to oxidize and become rancid if the food is stored for a long time or if oils are heated many times.

Saturated and trans fats can be used more or less interchangeably in food preparation. What is the relative effect of saturates and trans, of these two different types of solid fats on blood lipids? Again we go back to Ancel Keys' work, like we always do in this field. In a paper from 1961, Francisco Grande and Ancel Keys compared cis-monounsaturated fatty acid with trans-fatty acids and with the saturates from butter. Serum cholesterol increased from cis to trans to saturated. There is also an increase in triglycerides on the trans; this observation lay dormant for about 25, maybe 30 years until we realized this was a real effect -- trans does raise triglyceride. But the effects on cholesterol at the time seemed less than threatening.

However, we have had a major change since the days of Ancel Keys, and that is that we no longer calculate risk purely in terms of total cholesterol. We now know we have to take into account the different lipoproteins. Low density lipoproteins or LDL deliver cholesterol to tissues and can cause cholesterol to accumulate in artery walls under certain conditions, leading to atherosclerosis. In contrast, high density lipoproteins probably carry cholesterol away from cells that have too much of it and bring it back into plasma. We still don't exactly understand why high density lipoproteins are associated with less risk, but it is very consistently seen in epidemiological studies, for instance the PROCAM Study. Even people with low total cholesterol have less risk if their HDL is high and more risk if their HDL is low. That holds even more for the high total cholesterol levels, where, of course, the absolute risks are much higher. This is seen very consistently in all epidemiological studies in the United States, in Western Europe, but also among Japanese within Japan: whenever people have a higher HDL their risk is lower. Therefore we have to differentiate the dietary effects by their effects on LDL and on HDL.

So what are the effects of fatty acids on these different lipoproteins? A meta-analysis which Ronald Mensink and I did a number of years ago showed the effect on LDL and HDL levels in blood when you replace saturated fatty acids by other fats or by carbohydrate. The saturates raise cholesterol, so anything else you put in lowers cholesterol, except for the trans fatty acids: these keep cholesterol at the same high level, at least the LDL cholesterol. The fall that was seen by Ancel Keys *et al* on trans relative to satu-

rates was not due to LDL, it was due to HDL, because there is a large fall in HDL when you put trans fatty acids in the diet at the expense of saturates. How can we combine the HDL and LDL data? Well one possibility is to take the total cholesterol-to-HDL ratio so you get a single number. There is a fall in this ratio, which is an improvement, when you replace saturates by monounsaturates such as oleic acid, or by polyunsaturates such as linoleic acid. There is no effect when you replace saturates by carbohydrate because carbohydrate lowers both LDL and HDL. Finally, there is a marked increase when you replace saturates by trans.

These types of data are very useful for insurance companies, because they can predict how many of their customers are going to die, and when and of what. However, they are not totally definitive as far as causality is concerned because we are not yet sure that the HDL part of this relationship is truly causal. As far as the total to HDL ratio is concerned, trans is worse than saturates, the unsaturated fatty acids are beneficial and carbohydrate don't do much. Whether trans also causes higher risk for coronary heart disease than saturated fat is not yet certain but the effect of trans on the total to HDL cholesterol ratio does make it plausible.

One other lipoprotein that could be relevant to atherosclerosis is lipoprotein(a); this is a LDL with an attached protein called apo(a), which has a homology with plasminogen, a pro-enzyme involved in dissolving clots. The serum concentration of lipoprotein(a) predicts coronary and other vascular diseases. This concentration is largely determined genetically; about the only food substance that has a clear effect on it is the trans-fatty acids. When trans-fatty acids replace saturated fatty acids, lipoprotein(a) goes up in just about every study.

What about mono- and the polyunsaturates? We need to face an inconvenient fact here: mono- and polyunsaturates also slightly raise lipoprotein(a) relatively to saturates. Thus saturates give you the lowest lipoprotein(a), there is a slight increase when you replace that by mono- or polyunsaturates, and there is a fairly clear-cut increase when you put in trans-fatty acids. Still, the effect of trans-fat is quite small compared with the genetic effects on lipoprotein(a). Also we are not sure that lipoprotein(a) is causally involved in atherosclerosis. Therefore the effects of trans-fat on lipoprotein(a) should not have too much weight in discussions on fatty acids. But it is something to keep in mind and it is also something that may have helped manufacturers of foods to change their minds about trans-fatty acids.

Indeed industry has taken the data on trans-fat to heart

and has changed some of its products. In 1980, Dutch vegetable full-fat margarines had 20%, or 20 g of saturated fat and another 20 g of trans-fat per 100 g of product, but over the years the trans content has gone down and it has now become very low in most margarines, almost 0; there has been a modest increase in the saturated content but nothing to compensate for the fall in trans: every 3 or 4 g of trans that has been replaced was replaced by 1 g of saturates plus 2 or 3 g of oleic or linoleic acid. A similar thing has happened to frying fats, or at least to the type of frying fats that housemen or housewives buy to fry French fries at home: again trans-fatty acids have gone down and they have mostly been replaced by cis-unsaturated fatty acids. Something similar is going on in most of Europe and elsewhere.

However, the wholesale fats sold by the food service industry, the type of fat that fast food outlets fry their French fries in is still very high in both saturated and trans-fatty acids -- about 35% saturates and another 35% trans. So by now in Western Europe French fries are a premier source of trans fatty acids and, of course, also of saturated fatty acids. Is not the mayonnaise that provides the wrong fats --mayonnaise is largely unhardened oil--, it's the fat used for deep fat frying. There could be a gain in health in people who eat fast food if these hydrogenated fats were replaced by unhydrogenated oils. People who eat a lot of fast food are sometimes already at increased heart disease risk because of other factors. They are often less educated, they tend to smoke more, and be more obese, so they are an important target for heart disease prevention. Therefore we should try to convince the fast food outlets to do something about the fat with which they fry.

The question then inevitably becomes: what should they use instead? Fast food producers will ask - if you don't like the trans can we use palm oil? Palm oil is high in saturates, not as high as butter, but it is still an important source of saturates. So the question we have to answer is: what are the effects of trans-fatty acids relative to saturated fatty acids on heart disease risk? Effects on LDL are unfavourable both for the trans and for the saturates, they both produce high LDL levels. Saturates produce high HDL levels, and trans produce low HDL levels, so the ratio of total to HDL cholesterol is worse on the trans than on the saturates. Lipoprotein(a) is also higher on the trans than on saturates, but the effect is fairly small and we do not know whether a nutritional change of our lipoprotein(a) will change risk. The epidemiologic observations of individuals within countries seems to confirm that trans intake is associated with coronary heart disease; the

evidence for that is really firming up. There is only a weak association between saturated fat intake and coronary heart disease within populations; there is a number of explanations for this, but certainly the effect of trans is more consistent. Between countries we have seen an association of both saturates and trans with coronary heart disease. So both saturates and trans are unfavourable, and replacing hydrogenated oils with tropical fats for deep fat frying does not really solve the problem; liquid unhydrogenated oils are to be preferred even though they are a bit more expensive.

There is of course one other way to get rid of both saturates and trans, and that is to go to low fat products. Should we switch to fat-free foods? Unfortunately the most popular fat-free food in affluent countries is not the low-fat food that was customary in the Mediterranean region, in China and in the rest of the Orient, but convenience food such as low-fat cookies and potato chips. The people who manufacture foods and the people who sell foods know one thing: people don't like to eat beans. Their customers do not want beans, they want cookies. So cookies is what they get and if scientists say that low-fat diets are good then people are going to get low-fat cookies. Unfortunately, this type of low-fat foods is chock full of carbohydrates, of sugar. Diets with this type of food -- low-fat, high-carbohydrate diets as are now being introduced in affluent countries -- lower HDL and raise plasma triglycerides, and therefore we cannot be confident that they lower heart disease risk. We also do not have the clinical trial data for low-fat diets which we have for unsaturated oils. We have well controlled randomized clinical trials suggesting that replacing fats from butter, meat and other hard or hardened fats by corn oil or soybean oil decreases coronary heart disease risk. In contrast, the trial evidence for low fat diets is very limited, and what there is doesn't show much of an effect.

Why do I stress effects on HDL? That is because I think that this issue has been neglected. There is a lot of evidence that HDL is causally involved in atherosclerosis. The epidemiological associations are strong and universal: just about anything that raises HDL lowers CHD risk. The exception is that if you give female sex hormones to men, their HDL goes up but they still get coronary heart disease. So not everything that raises HDL is good for you. But many conditions -- exercising, a moderate but regular alcohol intake, being lean, not smoking, being a woman -- anything associated with high HDL, decreases CHD risk.

There is also a number of genetic syndromes where HDL is low, and quite a number of these subjects have premature coronary heart disease. There is a number of interesting exceptions: for instance there is the Japanese mutation of the CETP, the cholesterol ester transfer protein, which produces high-HDL levels but still does not protect from CHD. But there are enough of these genetic syndromes where low-HDL is associated with high-CHD to suggest that a low-HDL can cause heart disease. If we look at the drug trials then we see that drugs which lower LDL, but which in addition raise HDL, produce an extra fall in CHD.

This brings me to the conclusion of this part about the fats, and my conclusion is that high-oil diets produce a more favorable lipoprotein profile and possibly a lower heart disease risk than diets high in sugar and starch. The major potential advantage of low-fat high-carbohydrate diets is weight loss, but this effect is still unproven.

Finally, what are the new developments?

An important development is foods enriched with plant sterols. The best known plant sterol is sitosterol. Sitosterol is found in vegetable oils, but also in wood, and if you eat a lot of sitosterol it blocks cholesterol absorption from the gut. If you add two hydrogen atoms to sitosterol you get sitostanol and that also blocks cholesterol absorption quite effectively. Tatu Miettinen and his group have developed this concept over the years in a series of experiments which has resulted in a new margarine with large amounts of sitostanol. This margarine has been a commercial success in Finland, and it will soon be on the US and European markets.

An important issue is whether this is food or a drug. A margarine enriched in sitosterol looks and tastes like food, and all its ingredients have previously been used in foods, but no normal food has previously contained such large amounts of plant sterols. Perhaps we should decide that it is halfway between food and a drug. That of course has consequences for the amount and type of research that is needed before we can consider such food safe. I think we are going to have a lot of foods like this, and that they will give rise to a lot of research of the type that was previously reserved for drugs.

Thus the field of diet and blood lipids is giving rise to new developments all the time, but the classical Mediterranean diet will probably remain an example of a diet that is not only favourable for blood lipids but also delicious to eat.