
Cholesterol lowering by diet: what can be achieved?

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The cholesterol concentration in the plasma is poorly regulated by the human organism and is therefore easily influenced by lifestyle. Indeed cholesterol levels differ between populations. An important question is how much diet can be held responsible for differences in cholesterol level between e.g. Finland and Japan at the beginning of the Seven Countries Study around 1960. This difference can partly be explained by a difference in saturated fat intake but there was probably an accumulation of both genetic cholesterol elevating factors present in the Finnish society and of cholesterol-lowering factors in the Japanese society. However, controlled trials do show a major effect of diet on cholesterol. With iso-caloric diets low in saturated fat and high in fibre a reduction in total cholesterol of 20-30% can be realized. The reduction can be larger if weight loss also occurs. Further reductions may occur when novel foods are introduced on the market e.g. margarines enriched with plant sterols that give an additional reduction in total cholesterol of about 10%. It can be concluded that diet can reduce total cholesterol levels substantially. The value of novel foods in this context has to be evaluated. (*Acta Cardiol* 1999; 54(3): 151-154)

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Introduction

It is a great initiative to commemorate Professor De Langen's work. The Dutch have a tendency to belittle themselves. When we say that something is typically Dutch, we never mean anything good by it. However, in this case, I think we have a countryman we can be proud of.

I studied molecular biology in Amsterdam. I became involved in nutrition research by chance because I participated in a study about vitamin A deficiency in Medan, on Sumatra in Indonesia. What I saw there fascinated me so much that I decided to leave DNA research and go into nutrition research. Many of the Dutch who are, or have been, involved with nutrition research seem to have had a similar start in the tropics, and particularly in Indonesia. De Langen was a pioneer as far as that is concerned as well.

It has become apparent from the Seven Countries Study that the distribution of serum cholesterol for men of middle age in east Finland and south Japan hardly overlaps. In the first place, I would like to point out that it is remarkable that the serum cholesterol content for ordinary, normal, adult men in south Japan differs so much from that of men in east Finland. Such differences do not exist for other clinical chemical variables. Plasma contains fixed quantities of potassium, creatinine, glucose and albumin, and the body maintains these quantities. An individual needs these levels in order to survive. The amount of cholesterol was apparently not so important in the course of evolution¹; the body allows it to fluctuate. It seems that, during the millions of years in which our genome was formed by mutation and selection, a high cholesterol level hardly ever led to death during the procreative years because primitive man was presumably thin, physically very active, and he did not smoke.

The body uses the plasma as a sort of sewer for cholesterol. All the cholesterol that is not wanted by the cells just floats around, and environmental factors determine how high the serum cholesterol level becomes. This is why cholesterol fascinates nutritionists; one can influence it. In this article, I want to review how much of that difference can be attributed to diet.

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Genetics as a determinant of cholesterol

It is clear that the difference in cholesterol distribution between Japan and Finland is not due to diet alone, for Ancel Keys did not select the two cohorts by throwing dice. They were very carefully chosen. Japan was chosen for a very low coronary heart disease mortality rate, and Finland because the rate was very high. This means that everything that increases the cholesterol concentration will be found in Finland. Every publication about cholesterol shows that things have gone wrong for the Finns as far as cholesterol and coronary heart disease is concerned. This is largely due to the environment, but a part of it is due to genetics. An investigation of the sensitivity of serum LDL cholesterol to saturated fats in healthy volunteers shows that the level of LDL cholesterol is dependent on their genetic constitution and specifically, the apolipoprotein E genotype². We find that this is also true for our students in Wageningen. Apolipoprotein E is an important protein involved in cholesterol metabolism, in which small variations can have great consequences. There are three commonly occurring genotypes, E-2, E-3 and E-4, and people with these genotypes react differently to saturated fats. The LDL cholesterol level of the E-3 group is about 0.4 mmol/l higher than that of the E-2 group; for the E-4 group, it is 0.55 mmol/l higher than that of the E-2 group. This is a summary from a large number of experiments. It is very difficult to get sufficient numbers. There is, therefore, a lot of noise that has a levelling effect. The real differences are probably somewhat greater. Research shows that genotype E-4 occurs more often in Finland and genotype E-2, in Japan. A difference in genetics thus explains a small part of the cholesterol difference between these countries.

Diet as a determinant of cholesterol

What effect on the serum cholesterol level can be achieved with diet? Professor Barry Lewis, with the help of the Wageningen group, did an experiment to find the answer³. The objective of the experiment was to identify diets that were more effective than the diets used in the 1980s for lowering the cholesterol level. This experiment was carried out in a cloister with 12 healthy monks aged 24 to 60 years. Why did it have to be monks? The participants in this experiment had to have every bite prescribed and prepared for four periods of 5 weeks, and blood samples had to be taken. The volunteers were fantastic. They were prepared to do a great deal if they thought it would be useful to their fellow men. They persevered for 6 months in an admirable way.

Three of the four diets are interesting in this context. Diet A was the reference diet; we refer to it as Western. Diet B was the classic cholesterol-lowering diet. This was a low-fat diet, high in polyunsaturated fatty acids, low in saturated fatty acids and low in fibre. Diet C was a step-two prudent diet. It was the same as diet B, except it had a lot of vegetable foods and was rich in vegetable protein and fibre. Forty percent of the energy value of the reference diet was derived from fat, as was 27% in each of the other two diets. About 20% of the energy came from saturated fat in the reference diet, as did about 8% in each of the other two diets. Diets B and C did not contain much cholesterol. The difference between diets B and C was especially in the quantity of fibre. Diet C contained a sizable quantity of foods rich in fibre, as well as many other so-called bioactive substances that are relevant to health. The reference diet was rich in cheese, butter, whole milk, egg yolk, a sauce made of much saturated fat and small amounts of vegetables and white bread. The most healthy diet, diet C, consisted of a little bit of low-fat cheese with some extra olive oil for the fatty acid composition, and sauce containing no saturated fat. In addition, it included a lot of salads, onions, beans, extra fruit and wholewheat bread.

This experiment showed that Diet B reduced the cholesterol level by almost 22%, and the LDL cholesterol by almost 30%. In comparison with the reference diet, it appeared that diet C lowered total cholesterol by 29% and LDL cholesterol by 34%. This is the maximum that can be achieved under these conditions. Of course we can obtain a further reduction with saturated fat. We could reach zero, but only with a diet that people could not maintain for 5 weeks in our living conditions.

Professor Lewis carried out a similar experiment with a number of patients⁴. He gave patients who came to the clinic a comparable diet. He gave this multifactorial diet to ordinarily lean, but hyperlipaemic patients in London. They started with a total cholesterol level of 7.8 mmol/l and went down to 6.1 mmol/l, a reduction of 22%. These patients were not admitted to hospital, but just came to the out-patients' clinic. There professor Lewis confronted them with the power of persuasion to convince them to use this healthy diet. This reduction of 22% is very impressive, but it is a far away from the difference in serum cholesterol level between the countryside of Japan and Finland.

Body fat as a determinant of cholesterol

What other dietary factors can play a role? To get some idea, we can look at what happens within populations. Professor Kesteloot has already pointed out

the increase of cholesterol with age. In the city of Shanghai, it seems that young Chinese have a cholesterol level of 3.4 mmol/l and that the cholesterol level rises with age, although not as much as in Europe⁵. Farmers in the country around Shanghai are noted for their traditional lifestyle. They showed no increase in cholesterol with age. This increase with age is much more evident in prosperous countries such as the Netherlands.

We tried to explain the increase in cholesterol level with age a number of years ago. This was done in research involving young men in the Dutch Army Drafted Study⁶. At that time, all young men were drafted into the armed services in the Netherlands at the age of 18 for a period of 1.5 years. Therefore, they were all examined medically. This provided a wealth of data about the health of men of that age. The data for almost 1,000 of these men, who were examined at the age of 18 to 19 years, were available to us. Their cholesterol levels were determined in Wageningen. We were able to get the data from the examiner. We contacted the men by letter 10 years later and asked whether they were willing to take part in a follow-up study. We asked those who agreed to step on the scales and tell us how much they weighed. We sorted the data we received. We examined the 25% of the men with the highest weight gain and the 25% with the lowest weight gain. We also took blood samples. Then we investigated the relationship between weight gain and serum cholesterol.

The results showed a change of about one unit in Quetelet index for the group with a low weight gain. This represents a gain in weight of about 3 kg. Members of the other group were 5 kg/m² heavier on average. This means that a person 1.80 m tall gained 16 kg in the period of 10 years. We saw an increase of 1.5 mmol/l cholesterol in the group that gained the most weight. Weight increase appeared to be the only variable that could explain the increase in cholesterol with age after extensive multivariate analysis. Besides the increase in total cholesterol, a reduction of HDL cholesterol was also observed. This shows that weight increase has an unfavourable effect on the various lipoprotein fractions. We concluded from this study that the increase in body fat between the ages of 18 and 28 years is an important predictor of the simultaneous occurrence of an increase in LDL cholesterol and a decrease of HDL cholesterol. It is not so easy to study this experimentally, but research by van der Kooy and Leenen⁷ in Wageningen, among others, produced similar results.

New developments

Can these results explain the difference in cholesterol content in Japan and Finland? I have never

looked into the method of determining weight in the Seven Countries Study, nor have I considered to what extent weight is a measure of body fat. Naturally, the distribution of fat also plays a role. I have the feeling that there must be more to the matter in Finland and Japan than differences in body weight and saturated fats. Enough factors remain to be measured. The great differences in coronary heart diseases worldwide also need an explanation. It is likely that there is more at the root of the cause than just saturated fat. I think that we have learned quite a bit since Mulder⁸ wrote his book in 1847 about diet and the spirit of the people.

An example of another factor to be considered is the risk of fatal myocardial infarction as a function of the consumption of alpha-linolenic acid. This is a so-called N-3 fatty acid or omega-3 fatty acid. It is the mother of the class of fatty acids to which the so-called fish fatty acids also belong. In 1985 Kromhout and colleagues⁹ first showed that fish (fatty acids) predict a lower risk of coronary heart disease. The consumption of alpha-linolenic acid also predicts a lower risk of coronary heart disease. The amount in question is about 1 g/day. Obviously this is a matter apart from cholesterol. Meanwhile, it has also been shown that vitamins have other effects in addition to the classical deficiency symptoms in cases of shortages. Folic acid, vitamin B12 and vitamin B6 influence the homocysteine level. Whether the relation between these vitamins and coronary heart disease involves homocysteine we do not know yet. However, diets that contain a large quantity of these vitamins do lower the risk of a large number of diseases, including cardiovascular diseases.

What can we expect in this area in the future? Plant sterols can lower the cholesterol content and can be added to margarines in the form of stanol esters. This type of margarine is a success in Finland, and I have heard from professor Kesteloot that it will soon be on the market in Belgium. These sterols, which are added to margarine in large quantities, can, in quantities of 20 to 30 g of margarine, lower the cholesterol content by 10%-15%^{10,11}. There is a great deal of interest in this trend, sometimes referred to as "nutraceuticals", a cross between "nutrition" and "pharmaceuticals". The fascinating question is whether we should take that direction. Where does healthful food end, and where do medicines dressed up as food begin? We are headed toward a very interesting discussion about this. How far should we go, what should be our attitude to this new type of foods? What are the advantages and disadvantages, and how can we use this development to promote public health? A very exciting, but also very difficult discussion. One in which Professor De Langen, if he

were living now, would have played a very active part. Unfortunately he is no longer with us, and we shall have to solve the problem ourselves, as I am sure we will do.

References

1. Katan MB. Effect of low-fat diets on plasma high-density lipoprotein concentrations. *Am J Clin Nutr* 1998; **67**: 573S-576S.
2. Lopez-Miranda J, Ordovas JM, Mata P, Liechtenstein AH, Clevidence B, Judd JT, Schaefer EJ. Effect of apolipoprotein E phenotype on diet induced plasma low density lipoprotein cholesterol lowering. *J Lipid Res* 1994; **35**: 1965-1975.
3. Lewis B, Hammet F, Katan MB, Kay RM, Merckx I, Nobels A, Miller NE, Swan AV. Towards an improved lipid-lowering diet: additive effects of changes in nutrient intake. *Lancet* 1981; **2**: 1310-1313.
4. Choudhury S, Jackson P, Katan MB, Marenah CB, Cortese CB, Miller Ne, Lewis B. A multifactorial diet in the management of hyperlipidaemia. *Atherosclerosis* 1984; **50**: 93-103.
5. Zhuang H-Z, Han Q-Q, Hao Z-C. Study of serum lipids and lipoproteins of healthy subjects in Shanghai. *Chin Med J* 1986; **99**: 657-659.
6. Berns MAM, Vries JHM de, Katan MB. Increase in body fat as a major determinant of changes in serum total and HDL cholesterol in young men over a 10-year period. *Am J Epidemiol* 1989; **130**: 1109-1122.
7. Lcenen R, Kooy K van der, Meyboom S, Seidell JC, Deurenberg P, Westrate JA. Relative effects of weight loss and dietary fat modification on serum lipid levels in the dietary treatment of obesity. *J Lipid Res* 1993; **34**: 2183-2191.
8. Mulder GJ. *Diet in relation to the public spirit* (in Dutch). Rotterdam, Kramers, 1847.
9. Kromhout D, Bosschieter EB, De Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N Engl J Med* 1985; **312**: 1205-1209.
10. Miettinen TA, Puska P, Gylling H, Vanhanen H, Vartiainen E. Reduction of serum cholesterol with sitostanol-ester margarine in a mildly hypercholesterolemic population. *N Engl J Med* 1985; **333**: 1308-1312.
11. Westrate JA, Meijer GW. Plant sterol-enriched margarines and reduction of plasma total and LDL cholesterol concentrations in normocholesterolaemic and mildly hypercholesterolaemic subjects. *Eur J Clin Nutr* 1998; **52**: 334-343.