



## Why do polyunsaturated fatty acids lower serum cholesterol?<sup>1,2</sup>

Anton C Beynen, PhD and Martijn B Katan,<sup>3</sup> PhD

**ABSTRACT** Replacement of saturated by polyunsaturated fatty acids in the diet may lower serum very low-density and low-density lipoprotein concentrations because the liver preferentially converts polyunsaturated fatty acids into ketone bodies instead of into very low-density lipoprotein triglycerides. Thus unlike saturated fatty acids, polyunsaturated fatty acids are transported to the tissues for oxidation without leaving a trail of lipoprotein remnants in the form of low-density lipoproteins. *Am J Clin Nutr* 1985;42:560-563.

**KEY WORDS** Diet, saturated fatty acids, polyunsaturated fatty acids, serum lipoproteins, ketone bodies

### Introduction

Replacement of dietary saturated by polyunsaturated fatty acids is a very effective way to lower serum cholesterol in man, but the mechanism of this effect is unclear. Several mechanisms of action have been proposed to explain the hypocholesterolemic effect of polyunsaturated fatty acids, but there is considerable controversy (1).

#### *LDL catabolism*

Some of the mechanisms proposed include the enhancement of the excretion of steroids, and increased lipoprotein catabolism through altered structure (1). The latter mechanism was recently substantiated by studies showing that low-density lipoprotein (LDL) from human donors on a diet rich in polyunsaturated fat is metabolized faster by fibroblast cultures than LDL isolated from subjects consuming a diet high in saturated fatty acids (2). The enhanced excretion of steroids with the feces in subjects consuming polyunsaturated fatty acids observed by some (3), but not by others (4), would simply be a secondary feature of the same mechanism, ie increased LDL catabolism. However, a recent review

of the literature (4) indicated that in several studies other factors in addition to dietary polyunsaturated fatty acids may have been responsible for the observed increase in fecal steroid excretion. A lack of effect of polyunsaturated fatty acids on steroid excretion would be in line with observations that these fatty acids did not affect cholesterol absorption in rats (1).

#### *VLDL production*

After a fat-containing meal, part of the dietary fatty acids is stored in adipose tissue, from which they are later mobilized as plasma free fatty acids. The liver uses such fatty acids for the production of triglycerides, which are then exported in very low-density lipo-

<sup>1</sup> From the Department of Laboratory Animal Science, State University, Utrecht and the Department of Human Nutrition, Agricultural University, Wageningen, The Netherlands.

<sup>2</sup> Address reprint requests to: Dr AC Beynen, Department of Laboratory Animal Science, State University, PO Box 80.166, 3508 TD Utrecht, The Netherlands.

<sup>3</sup> MBK is an established investigator of the Netherlands Heart Foundation.

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proteins (VLDL). In the plasma, VLDL rapidly loses its triglycerides and is converted into LDL, which is the main carrier of plasma cholesterol.

It has been proposed that polyunsaturated fatty acids cause a decreased production of lipoproteins. Lewis and coworkers (5, 6) have suggested that polyunsaturated fatty acids, as compared to saturated fatty acids, are less efficiently incorporated into triglycerides made by the liver for export in the form of VLDL. This would cause a drop in the concentration of VLDL and triglyceride in plasma. The drop in the concentration of VLDL would then be the cause of the drop in the concentration of LDL that is commonly observed after consumption of the polyunsaturated fatty acid linoleic acid (5-8). Depressed VLDL synthesis would also be responsible for the observed (6, 7, 9) reduction of the rate of LDL synthesis in subjects on diets rich in linoleic acid.

Dietary fish oils rich in omega-3 polyunsaturated fatty acids may lower fasting plasma concentrations of triglycerides and LDL cholesterol more effectively than equal amounts of vegetable oils rich in linoleic acid (10, 11). Illingworth et al (12) recently demonstrated that omega-3 fatty acids reduce LDL synthesis in healthy subjects. This effect may also be mediated by a decrease in VLDL synthesis. Nestel et al (11) showed that production of VLDL in humans was markedly lower after a diet rich in fish oil compared with safflower oil.

#### Ketone body synthesis

The hypothesis that polyunsaturated fatty acids induce a decrease in VLDL synthesis and, as a consequence, in LDL production, is attractive; but if part of dietary polyunsaturated fatty acids do not go into VLDL triglyceride formation, then where do they go? Accumulation in the body cannot be the explanation. Subjects eating about 41 g of linoleic acid/day for 5 yr accumulated an average 2 kg of linoleic acid, or 2.7% of the cumulative intake, into their body fat in the first 3 yr, adding little more after that (13).

Nestel et al (11) suggested that the decreased VLDL production induced by fish oil may partly reflect diversion of polyenoic fatty acids into pathways of oxidation and

ketogenesis. This may be extended in the proposal that polyunsaturated fatty acids (as compared to saturated fatty acids) are converted by the liver into ketone bodies rather than being incorporated into triglycerides and exported as VLDL, and then secreted into the bloodstream. Since cholesterol is required as a structural component of the VLDL surface, polyunsaturated fatty acids would also decrease VLDL cholesterol output by the liver. The cholesterol esters in the VLDL core are probably acquired from high-density lipoproteins in plasma, in exchange for VLDL triglycerides (14). A decrease in the flux of VLDL from the liver would also

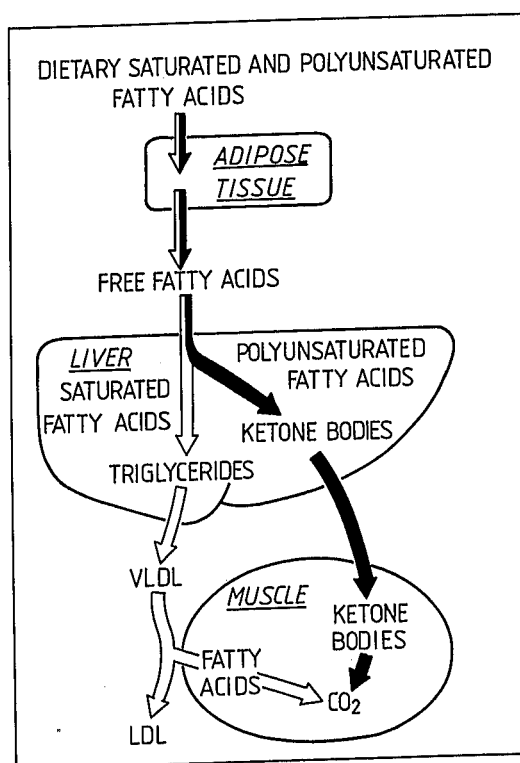


FIG 1. Relative rates of production of VLDL and ketone bodies from saturated and polyunsaturated fatty acids in the fasting state. In man, in the postabsorptive state the fatty acyl moiety of newly synthesized serum triglycerides is predominantly derived from serum fatty acids (15), which in turn originate from the adipose tissue. The fatty acid composition of the adipose tissue of humans reflects that of the diet (16). After a meal, dietary fatty acids are temporarily stored in a rapidly turning over-pool in the adipose tissue (17), and in the fasting state they enter the hepatic pathways of either triglyceride formation (esterification) or beta-oxidation followed by ketogenesis (18).

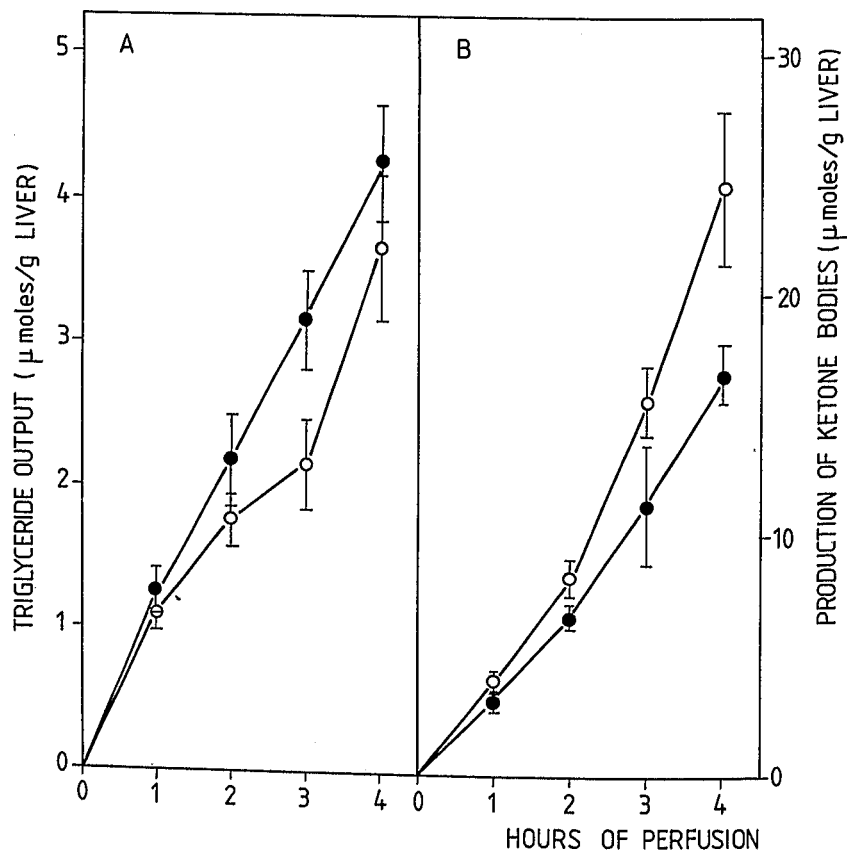
lower the amount of cholesterol esters acquired by VLDL, which in turn would lower the flux of cholesterol esters into the LDL pool. Thus, the carbons of polyunsaturated fatty acids are transported to muscle in the form of ketone bodies, unlike saturated fatty acids, which are transferred from the liver to the periphery as VLDL triglycerides, and in the process leave a trail of LDL. **Figure 1** depicts this concept.

There is some experimental evidence for this hypothesis. Kohout et al (19) showed that the output of triglycerides by the perfused rat liver is depressed if linoleic acid is the substrate compared to when the saturated fatty acid palmitic acid is the substrate (**Fig 2**). In addition, palmitic acid caused a two-fold higher accumulation of hepatic triglycerides than linoleic acid (19). At the same time, linoleic acid induced significantly higher rates of ketone body synthesis than palmitic

acid (**Fig 2**). Nestel and Steinberg (20) showed that rat liver slices incubated with equal concentrations of linoleic acid or palmitic acid preferentially channelled palmitic acid into the pathway of triglyceride synthesis, and linoleic acid into  $\beta$ -oxidation. The hypocholesterolemic and hypotriglyceridemic effect of fish oils may be explained by the same mechanism. The livers of rats fed fish oil have been shown to secrete significantly less VLDL and, in addition, secreted more ketone bodies than the liver from rats fed safflower oil (21).

### Conclusion

There are two competing theories to explain the lowering of plasma LDL cholesterol induced by feeding polyunsaturated fatty acids. One theory proposes increased LDL catabolism and the other decreased formation



**FIG 2.** Effect of palmitate (●) versus linoleate (○) on triglyceride (panel A) and ketone body output (panel B) by perfused rat liver. Data are given as means  $\pm$  SE (n = 8 or 9); Both fatty acids were added to the perfusion buffer at a concentration of 0.5 mM. Based on data from Kohout et al (19).

of LDL. We propose that if the second hypothesis is correct, fasting blood concentrations of ketone bodies should be higher on diets rich in polyunsaturated fatty acids than on high-saturated fat diets. This hypothesis is obviously based on a highly simplified view of intermediary metabolism, but it does explain how fuel needs by muscle tissues are fulfilled on different dietary fats, and it has the virtue of being easy to test.

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