

# DIET AND LIPOPROTEINS<sup>1</sup>

by

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## INTRODUCTION

The major transport systems in humans, blood and lymph, consist mainly of water, but must carry water-insoluble lipids of both dietary and endogenous origin. This is accomplished by combining the lipids with proteins into discrete particles called lipoproteins. The dietary lipids of primary concern to us are the triglycerides or fats-oils are liquid fats — cholesterol and the fatty acids associated with other lipids.

Lipoproteins, which occur in a wide range of sizes, are generally separated by two methods: (a) ultracentrifugal flotation in salt solutions of increasing density and (b) electrophoresis, both paper and gel. The composition and properties are presented in Table I. The information in Table I and in this section came from Reference 1 which is one of the newest and in my opinion, one of the best books on the subject.

Ultracentrifugation does not yield discrete classes of lipoproteins, as suggested in Table I and the groups separated by electrophoresis are not synonymous with the density classes, although the two are used interchangeably. Also, the quantities of lipoproteins are almost always determined indirectly by analysis of their cholesterol content. Direct determination can be done by analytical ultra-centrifugation, but the instrument is very expensive and, hence, not available to most laboratories.

The proteins or apoproteins associated with the lipoproteins are designated simply as A, B and C and have profound inhibitory and stimulatory affects on the metabolism of lipoproteins and the lipids therein. For example, Apo C-II is required for the activation of extrahepatic lipoprotein lipase. Note that as with many proteins, improved methods of separation and further study have revealed the heterogeneity of the apoproteins.

The chylomicrons whose fatty acids originate from dietary fats, are synthesized within the intestinal wall, are excreted into the lymphatic channels and then

transported to the blood. In a normal human, they are removed from the circulation in less than one hour, by the action of an extrahepatic lipoprotein lipase located in the capillary endothelium of both muscle and adipose tissue. If energy is needed, the fatty acids released by the lipoprotein lipase will be oxidized in muscle and other tissues. If not, then the excess fatty acids are transported to adipose tissue where they are incorporated into new triglycerides.

The sources of fasting plasma VLDL are the liver and the intestine. These lipoproteins are believed to be catabolized in much the same fashion as chylomicrons, producing however LDL. In the fasting state, the VLDL are the primary carriers of triglycerides in plasma and the amount increases enormously in certain types of hyperlipidemia.

In humans LDL makes up about 40-50% of the plasma lipoproteins; averaging in American males, about 400 mg/100 ml and in females, about 340 mg. Much of the plasma cholesterol is transported by LDL and it is usually this lipoprotein class in which the quantity rises in hypercholesteremia. Very little is known about the breakdown of LDL. The liver has been thought to be the site of catabolism, but recently Goldstein and Brown (2) have found significant degradation in cultured fibroblasts suggesting that peripheral tissues may be involved.

HDL is both produced and broken down in the liver. This lipoprotein has recently become the subject of intense research activity due to the rediscovery that high plasma levels of HDL are associated with low rates of coronary heart disease (3). Glueck et al. (4) found that the plasma LDL and HDL cholesterol levels in 124 free living subjects were; (mean  $\pm$  SE)  $121.8 \pm 4.1$  and  $53.4 \pm 1.1$  mg/100 ml respectively while the values in 14 persons with hyper-HDL and hypo-LDL were  $125.1 \pm 6.8$  and  $86.6 \pm 3.4$ . Life expectancy analysis of the groups revealed an average life expectancy of 82 years for males and 84 for women in the hyper-hypo group as compared to 71 and 75 years in the general population. The former group also had greatly reduced morbidity and mortality from myocardial infarction as compared to the normals. In some of the members of this group, the tendency for hyper-hypo was familial. All of the

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**TABLE 1**  
**COMPOSITION AND PROPERTIES OF HUMAN PLASMA LIPOPROTEINS<sup>a</sup>**

Properties	Chylomicrons	VLDL <sup>b</sup>	LDL <sup>b</sup>	HDL <sup>b</sup>
Density	0.95	0.95-1.006	1.006-1.063	1.063-1.210
Electrophoretic mobility	Origin	Prebeta	Beta	Alpha
Major apoproteins	Apo B Apo C-I Apo C-II Apo C-III	Apo B Apo C-I Apo C-II Apo C-III Arginine rich	Apo B	Apo A-I Apo A-II
Triglycerides <sup>c</sup>	90	60	10	5
Cholesterol <sup>c</sup>	3	10	60	20
Protein <sup>d</sup>	2	10	25	50

<sup>a</sup> Adapted from Ref. 1  
<sup>b</sup> VLDL-very low density lipoprotein; LDL-low density and HDL-high density.  
<sup>c</sup> mg/100 g lipid.  
<sup>d</sup> % of total.

group were age 80 or over and had either two siblings or a parent or a child living to age 80 or over. The complete data are in Table 2.

Miller and Miller (5) have hypothesized that a reduction in plasma HDL hastens the development of atherosclerosis and hence coronary artery disease by impairing the clearance of cholesterol from the arterial wall. To paraphrase, HDL apparently act as an "auger," removing excess cholesterol from the wall or perhaps preventing deposition of the sterol, which is then carried to the liver where degradation occurs.

In view of these persuasive findings, it would seem prudent to keep HDL levels high and means to do so are being investigated. Briefly however, high levels of plasma cholesterol or triglycerides, being a male, obesity, diabetes and a sedentary life style decrease HDL levels. It is also apparently important to select the right parents.

Any reasonable means to raise the levels of plasma HDL would seem to be indicated as a method to prevent or delay coronary heart disease, since atherosclerotic coronary heart disease and stroke are the major causes of mortality in the United States (6). A study conducted in Framingham, Massachusetts, identified three primary coronary risk factors: hyperlipidemia, hypertension and cigarette smoking. I will focus primarily on hyperlipidemia as related to diet.

*Hyperlipidemia*

Krehl (6) has listed four bodies of evidence that connect lipids, specifically cholesterol and saturated fats with the development of atherosclerosis. These are: (a) feeding diets containing cholesterol to a variety of animals produces atherosclerosis, and in man raises plasma cholesterol. (b) the atherosclerotic plaques or atheronmata contain lipids, primarily cholesterol, and these can be caused to regress. (c) the data from many epidemiological and clinical

**TABLE 2**  
**LONGEVITY ANALYSIS: EXPECTATION OF LIFE IN YEARS AT AGE 35 FOR OCTOGENARIAN KINDREDS WITH HYPERALPHA (HDL) AND HYPOBETA (LDL) LIPOPROTEINEMIA<sup>a</sup>**

Life tables for	Males 1969	Females 1969
U.S. White population	71.3	77.5
9 Kindreds with hyper-alpha-lipoproteinemia	81.3	86.7
5 Kindreds with hypo-beta-lipoproteinemia	77.6	85.3
14 Kindreds with hyper-alpha and Lypobetalipoproteinemia	82.0	86.3

<sup>a</sup> Adapted from Ref. 4.

studies provide a strong correlation between high plasma levels of cholesterol and coronary artery disease in humans and (d) there is, however, an uneven distribution of the disease among and in cultural groups, but, it is apparently more serious among the more affluent. Quite obviously, none of the lines of evidence either prove or disprove that heart attacks can be prevented by consumption of a particular diet. The concept is being fiercely debated and opinions at both ends of the spectrum can be found. (7,8).

Some comments on experimental methodology are necessary. In (a) above, some of the experimental animals are vegetarians, for example rabbits and the type of atherosclerosis produced may not be the same as that found in omnivores. Also Carroll (9) has recently proved that rabbits fed a cholesterol free, semi-purified diet containing casein became hypercholesterolemic and atherosclerotic. Both could be prevented by replacing casein with isolated soy protein. Quite obviously, many feeding trials will have to be repeated. To complicate the problem, many vegetable oils have been fed without first stripping the oil to remove phytosterols which block the intestinal absorption of cholesterol and if fiber is present, it may or may not bind cholesterol in the intestine, thus possibly preventing its absorption (10). Finally partially hydrogenated oils have been fed without any consideration of the loss of polyunsaturated acid function caused by both geometric (*cis* to *trans*) and positional (movement of the double bonds from their original position) isomerization. These changes are caused by the hydrogenation process.

More recently the problem of suitable animal models for the study of atherosclerosis has intensified since India has banned the export of Rhesus and other monkeys which were widely employed in feeding trials. Colonies of New World monkeys are being established, the pig has been used and the cat has been suggested as a possibility.

Further in (d), persons in the less affluent countries may not have the life expectancy to suffer from heart attacks because these generally occur at age 45 and older although atherosclerosis has been found almost universally in every population studies. Also, medical reporting as to cause of death may not be as efficient in these areas as in others. Finally, in comparisons of these groups, important environmental factors such as cigarette smoking and a sedentary life style have not always been considered.

Nevertheless, the lipid theory has many proponents. One of the primary questions remaining unanswered, is what are the events causing the initial lesion or yellow streak on which atheromata are be-

lieved to form? Ross and Glomset (11) have recently proposed a theory based on repeated or chronic injury to the arterial wall due to continuous hypercholesteremia. Compared to the cholesterol content of the entire body, about 140 g for a 70 kg man, the amount in the blood is 10.8 g (12). Since this is only about 8% of the total, it has been correctly stated that the amount in the blood is not indicative of the body burden, but it is not correct to say that the small quantity is incapable of causing chronic injury because the blood and its cholesterol are continuously circulated and a target site in an artery could be constantly irritated. The hypothesis of Ross and Glomset is outlined in Table 3.

The items causing the initial injury have not been identified, but it has been suggested that a mutagenic agent or a virus could be involved.

#### *Classification of the hyperlipoproteinemias*

Investigators at what was NHLI have classified these disorders into six types, but three are very uncommon and will not be discussed further. The types encountered most often along with abnormalities are listed in Table 4. The normal age adjusted values for plasma cholesterol, triglyceride and VLDL, LDL and HDL cholesterol are listed in (12). In general when we alter the plasma cholesterol content we are dealing with LDL and changes in triglycerides, are related to VLDL and I will discuss them accordingly.

#### *Diet and the Lipoproteins*

The dietary treatments to lower LDL involve decreases in dietary cholesterol and saturated fats and an increase in polyunsaturated fats. If elevated triglycerides are involved, the intake of alcohol and refined sugar must be cut. Plasma LDL can be reduced by about 15% in Type IIa and in some Type IV pa-

TABLE 3

#### THE PATHOGENESIS OF ATHEROSCLEROSIS<sup>a</sup>

1. Injury-mechanical, chemical, immunologic, etc.
2. Desquamation of arterial endothelium.
3. Platelet aggregation and adherence at site of desquamation to exposed subendothelial connective tissue. Platelet material enters arterial wall causing smooth muscle migration and multiplication, leaving slightly thickened intima.
4. In absence of chronic injury lesions may heal and regress.
5. If injury continues; hypercholesterolemia, the process will continue and spread, leading to thrombosis and infarction. Calcification and aneurysm may occur.

<sup>a</sup> Adapted from Ref. 11.

TABLE 4

CLASSIFICATION OF HYPERLIPOPROTEINEMIAS<sup>a</sup>

Type	Lipoprotein abnormality	Lipid abnormality
II-A	LDL ↑↑ <sup>b</sup>	C ↑↑ <sup>b</sup> , TG N <sup>b</sup>
II-B	LDL ↑↑ VLDL ↑ <sup>b</sup>	C ↑↑, TG ↑
IV	VLDL ↑↑	C N ↑, TG ↑↑

<sup>a</sup> Adapted from Ref. 1, P. 23.  
<sup>b</sup> ↑↑, marked elevated; ↑, moderately elevated; C, cholesterol; TG, triglyceride and N, normal.

tients the plasma triglycerides can be maintained at about 300 mg/100 ml plasma. Recalcitrant cases of all types may need additional treatment with drugs.

The results of several clinical dietary interventions have been reported with disappointing results, and some others are underway. Most of the experimental designs would not have pleased a biometrician; not double blind, failure to use persons at high risk, changing patient populations, etc. (13). Two current primary prevention studies, one sponsored by the World Health Organization and the other by the Lipid Research Clinics, are carefully designed but include drugs as part of the study. The MRFIT program includes three risk factors and while not long in existence seems promising in terms of cooperation from the community and medical professions (14).

A county, North Karelia in Finland, has probably the highest rate of coronary heart disease in the world (14). The Finnish government has mounted a massive program designed to reduce cardiovascular disease morbidity and mortality. The program focuses on cigarette smoking, serum cholesterol and hypertension. The program includes community education and in general a determined effort to reduce the risk factors. Cooperation after 4½ years is reported as being good and vividly demonstrates what a carefully organized, adequately supported and widely publicized community effort can accomplish.

*Research on HDL*

Although we have known for years that HDL cholesterol is inversely related to risk of coronary artery disease, it has only been recently that a drug and diet interventions designed to raise HDL are receiving attention. (3). Last year I ordered a MEDLARS computer search on HDL and out of almost 500 entries found only a few on diet and drug intervention. We have discussed the "at-risk"

potential of HDL and presented supporting data (Table 2). We will now consider further some of the factors influencing HDL levels. HDL were the subject of a recent symposium sponsored by the American Oil Chemist's Society and I have summarized some of the data presented at the meeting (15) which will eventually appear in a book and from other sources in Table 5.

Persons thought to be at high risk have less than 35 mg of HDL/100 ml, the average is 45-59 mg/100 ml while protection may be associated with levels of 75 mg or greater. At present, next to fortunate inheritance, vigorous exercise is almost the only intervention available to markedly increase HDL. So far data on the specifics of dietary intervention are sparse, but Bersot and Mahley (15) found that cholesterol feeding in man increases apoprotein E in HDL-I which is a major cholesterol carrying lipoprotein, but the cholesterol is apparently delivered to smooth muscle rather than the liver and this lipoprotein fraction may or may not be protective.

I have not seen this mentioned, but it might be possible to collect histocompatible HDL and use it therapeutically.

*General dietary changes*

I agree with Reiser (8) that we should determine the basic metabolic defects in the hyperlipoproteinemias as is being done with familial Type IIa, a lack of LDL receptors in cell membranes and design specific treatments. Prior to that only those persons at demonstrable risk should make drastic changes in their diets and then only with professional guidance most profitably from dietitians, nutritionists or prop-

TABLE 5

FACTORS AFFECTING HDL CONTENT IN PLASMA<sup>a</sup>

Decrease	Increase
Hypercholesterolemia	Hypertriglyceridemia
Hypertriglyceridemia	Female sex — prior to menopause
Male sex	Reduction in cigarette smoking
Obesity	Adherence to fat controlled diet
Diabetes	Moderate alcohol intake
Tangier disease	Reduction in LDL cholesterol
Genetic control	Loss in body weight
Sedentary life	Exposure to DDT
	Vigorous exercise
	Genetic control
	Estrogen — progestins

<sup>a</sup> See Refs. 3, 4, 5, 7, 15 and 16.

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erly trained physicians. On the other hand, I agree with Glueck and Connor (7) that our diet was not planned to be protective. Our food choices have been haphazard, based more on the foods we preferred as children and our income.

We need much more information on these subjects and the means to distribute it more effectively. We should seriously consider the Finnish effort and profit therefrom.

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