Serum Tocopherol, Cholesterol, and Triglyceride in Coronary Heart Disease

By Esko A. Nikkila, M.D., and Risto Pelkonen, M.D.

The vast number of studies made in recent years on serum lipids in patients with occlusive arterial disease has left no doubt of an association between a disordered lipid metabolism and this widespread disease. It is now well established that hyperlipidemia is not an absolutely necessary but a quantitatively very important factor in the development of human atherosclerosis and of ischemic tissue lesions. Extensive studies have also revealed that the incidence of hypercholesteremia in the apparently healthy population is fairly high in many countries.

The derangement of lipid metabolism underlying the hyperlipidemia may have its origin in dietary, genetic, or endocrine factors, general energy balance, age, or a combination of these. However, the closer nature of the basic biochemical error has not been identified. In addition, opinions differ on the relative importance of individual serum lipid and lipoprotein components for the genesis of atherosclerosis. Thus, from time to time each of the following factors has been listed as the most atherogenic serum compound: cholesterol, cholesterol/phospholipid ratio, total beta lipoprotein, Sf 3-12, Sf 12-20, and Sf 20-400 lipoproteins, the alpha/beta lipoprotein ratio, chylomicrons, and endogenous triglycerides. It is now evident that no single serum lipid abnormality will be found to explain all cases of atherosclerosis. Several lipid-containing particles can become incorporated into the arterial wall depending, among other things, on local conditions and biochemistry of intimal tissue.

In cases with clinically overt atherosclerosis the plasma lipid pattern may represent a pure hypercholesteremia or hypertriglyceridemia but often both are present simultaneously, suggesting the presence of a more general disturbance of lipoprotein metabolism.

The studies on plasma tocopherol and its turnover in patients with coronary heart disease, reported in this paper, were undertaken to learn the behavior of a purely exogenous lipid in this disease, and in this way possibly to get more insight into the pathology of lipoprotein kinetics. Tocopherol is transported in plasma bound to chylomicrons and all lipoprotein fractions, and a relationship between plasma cholesterol and tocopherol levels has been demonstrated in a number of pathologic states. Tocopherol is also found as a component of atheroma. This lipid thus seems appropriate for the study of lipoprotein metabolism, particularly since simple and accurate methods are available for its determination.

Preliminary results of this study have been reported.

Material and Methods

The subjects included in this study comprise 175 male survivors of myocardial infarction (coronary group), 214 blood donors, and 70 persons, who either were in full health or had been admitted to the hospital for examination of a possible congenital heart disease, and had no symptoms or signs or a family history of occlusive arterial disease. The blood donors were taken into the series as representatives of the general population without any health control (except what is routinely made in the transfusion service) or knowledge of the family history of arterial disease. The age of the subjects in the coronary group varied from 33 to 65 years, and in the whole control group from 19 to 65 years.

The group with clinically manifest coronary heart disease was derived from two sources. Some
subjects had had myocardial infarction 4 to 6 weeks before the study, and they were taken into the series during the last days of their hospital stay. At this time all were on anticoagulant treatment (phenylindandione), were allowed to move freely in the hospital, and received the usual hospital diet without any fat or other restrictions. None was treated with cholesterol-lowering drugs during the time of hospitalization. These patients, numbering 94, are called in the following as coronary group I. The second part was comprised of persons who had experienced a myocardial infarction 6 to 30 months before the study, and who were especially invited to the laboratory for this investigation. The majority of this population was not on anticoagulant treatment but had made some dietary arrangements, eating more or less regularly a diet low in saturated fat or restricted the use of all fats. Many were using corn oil supplements. These men are called the coronary group II. The results for these two groups are presented separately.

This division of the material was necessary because most survivors of myocardial infarction in the present days have radically changed their dietary habits from the preinfarction period, and may therefore present a serum lipid pattern, which in a sense is not their native one. This fallacy is not present in those patients who are studied soon after their coronary disease has become manifest. In these cases, on the other hand, it has been argued that the serum lipid pattern has been modified by the infarction itself.11, 12

All patients demonstrating signs of congestive heart failure were excluded from the study. Patients exceeding 65 years at the occurrence of their first myocardial infarction were not included. Otherwise no conscious selection of the cases was made. The material of myocardial infarction studied can therefore be regarded as a fairly representative sample of Finnish men who have a clinically overt coronary heart disease before the age of 65.

All subjects had fasted for 12 hours before the venous blood sample was drawn for analysis of lipids. Serum cholesterol was determined by the method of Pearson et al.,13 and triglyceride (total glycerides) according to a slightly modified procedure of Van Handel and Zilversmit.14 Tocopherol was measured after extraction and saponification by the ferric chloride-dipyrydyl color reaction.15 All determinations were made in duplicate and were repeated if the difference between the duplicates exceeded 10 per cent.

In comparison with the method of Abell et al.,16 the Pearson procedure has been found to give serum cholesterol values that are 8 to 12 per cent higher. The percentage difference seems, however, to be quite constant throughout the whole range of serum cholesterol levels. To be comparable with other materials, in which the Abell method has been applied, the cholesterol levels reported here should therefore be corrected by a factor of 0.9.

A tocopherol-loading test was performed in some of the subjects in the following way. The subjects were given orally 2 Gm. of α-tocopherol-acetate dissolved in 10 ml. of arachis oil and 100 ml. of 40 per cent cream. Plasma tocopherol and triglyceride were analyzed at different time intervals after the meal. In this report are contained only the plasma tocopherol values 24 hours after the tocopherol load (tocopherol-24), the detailed tocopherol and triglyceride response curves (including the data for different lipoproteins) being published separately.

Results

Plasma Tocopherol, Cholesterol, and Triglyceride Concentrations

The cumulative frequency distribution of the plasma levels of the three lipids in control and coronary populations (pooled groups I and II) is shown in figures 1, 2, and 3. The control series for cholesterol and tocopherol consists of 214 blood donors who were studied under nonfasting conditions. The triglycerides are fasting values in 41 subjects between 20 and 35 years of age. The sample characteristics are listed in table 1.

As is apparent from the distribution curves, plasma tocopherol follows an age trend similar to that of cholesterol. Otherwise the distribution of these two lipids is closely similar.
Cumulative frequency distribution of serum cholesterol level in 214 blood donors and in 175 men with myocardial infarction.

Cumulative frequency distribution of fasting serum triglyceride level in 41 control cases 20 to 35 years of age and in 175 men with myocardial infarction.

Table 1

<table>
<thead>
<tr>
<th>Age Below 35</th>
<th>Above 35</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>No.</td>
<td>No.</td>
</tr>
<tr>
<td>Age</td>
<td>Age</td>
<td>S.D.</td>
</tr>
<tr>
<td>Group</td>
<td>Group</td>
<td></td>
</tr>
<tr>
<td>(years)</td>
<td>(years)</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Cholesterol</td>
<td>15.0</td>
</tr>
<tr>
<td>(mg./100 ml.)</td>
<td>(mg./100 ml.)</td>
<td>mg./L.</td>
</tr>
<tr>
<td>70</td>
<td>231.0</td>
<td>47.1</td>
</tr>
<tr>
<td>41</td>
<td>87.2</td>
<td>101.1</td>
</tr>
<tr>
<td>69</td>
<td>11.1</td>
<td>142.0</td>
</tr>
<tr>
<td>34*</td>
<td>20.9</td>
<td>4.3</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>Triglyceride</td>
<td>140.0</td>
</tr>
<tr>
<td>(mg./100 ml.)</td>
<td>(mg./100 ml.)</td>
<td>mg./L.</td>
</tr>
<tr>
<td>70</td>
<td>231.0</td>
<td>47.1</td>
</tr>
<tr>
<td>41</td>
<td>87.2</td>
<td>101.1</td>
</tr>
<tr>
<td>69</td>
<td>11.1</td>
<td>142.0</td>
</tr>
<tr>
<td>34*</td>
<td>20.9</td>
<td>4.3</td>
</tr>
<tr>
<td>tocopherol 15</td>
<td>tocopherol 15</td>
<td>mg./L.</td>
</tr>
<tr>
<td>(mg. 15.0)</td>
<td>(mg. 15.0)</td>
<td>mg./L.</td>
</tr>
<tr>
<td>70</td>
<td>231.0</td>
<td>47.1</td>
</tr>
<tr>
<td>41</td>
<td>87.2</td>
<td>101.1</td>
</tr>
<tr>
<td>69</td>
<td>11.1</td>
<td>142.0</td>
</tr>
<tr>
<td>34*</td>
<td>20.9</td>
<td>4.3</td>
</tr>
</tbody>
</table>

All three lipids are significantly higher in the coronary group than in the whole control group. When the upper normal limit for each component is taken as the level, which is not exceeded by 90 per cent of the young control subjects (20 to 35 years of age), the following figures are obtained: tocopherol 15 mg./L., cholesterol 290 mg./100 ml., and triglyceride 140 mg./100 ml. In reference to these concentrations it is seen that 53 per cent of the coronary subjects are above the upper normal limit, whereas none of the cholesterol and tocopherol levels are raised above the upper normal limits, while only 9 per cent of the control subjects have triglyceride levels exceeding the upper normal limit.

*Circulation, Volume XXVII, May 1963*
whole coronary group had an elevated plasma tocopherol level, 62 per cent had an elevated serum cholesterol level, and 56 per cent showed hypertriglyceridemia.

**Plasma Tocopherol after Oral Tocopherol Administration**

After ingestion of 2 Gm. of tocopherol with a fatty meal the plasma tocopherol began to rise within 2 hours, attained a maximum level at about 10 hours, and slowly declined thereafter, but in all cases was considerably above the basal level at 24 hours. As stated under the methods, a number of patients with disordered lipid metabolism and of healthy subjects has been studied at different time intervals after the tocopherol load, but, for practical reasons, in the majority of subjects only a single tocopherol assay has been made 24 hours after the oral dose, and these results are included here. The 90-per cent tolerance limit for the 24-hour plasma tocopherol in normal subjects was 24 mg./L. This level was exceeded by 77 per cent of the subjects with coronary heart disease. The percentage of abnormal subjects is thus strikingly higher than in any of the lipid measurements under basal conditions. The mean and standard deviation in the different groups studied appear in table 1.

**Interrelationships of the Different Plasma Lipids in Coronary Patients**

The individual values of each of the plasma lipid measured and the mutual interrelations are depicted in the scattergrams in figures 5 to 10. The results of linear regression analysis applied to these relationships are listed in table 2.

None of the lipid measurements appeared to be fully independent variables. From figure 5 it is evident that in the majority of patients serum triglyceride and cholesterol were simultaneously either normal or high. An elevated triglyceride combined with normal cholesterol level was present in 12 per cent of the cases, and an increased cholesterol with normal triglyceride occurred in 19 per cent. However, in most of these cases the lipid abnormality was of only slight degree, and, thus, subjects with marked pure hypertriglyceridemia or hypercholesteremia seem to be relatively uncommon among patients with coronary heart disease.
Serum cholesterol and tocopherol were concordantly normal or high in 77 per cent of the cases. High tocopherol associated with normal cholesterol was present in only 6 per cent, while the reverse situation was found in 16 per cent. A highly significant regression was present for cholesterol versus tocopherol. On the other hand, the relationship between triglyceride and tocopherol was not so striking, although the regression was significant also here, except the group II. The triglyceride and tocopherol levels were discordant in 30 per cent of the cases (figs. 6 and 7).

Figures 8 to 10 plainly reveal that the plasma tocopherol level at 24 hours after an oral tocopherol load was abnormally high in almost all cases that exhibited signs of disturbed lipid metabolism in any of the fasting serum lipid levels. The regressions for 24-hour tocopherol on both cholesterol, triglyceride, and basal tocopherol were highly significant.

Relation of Serum Lipids to Age of the Patient at Occurrence of Myocardial Infarction

In table 1 the coronary patients have been divided into younger (below 50 years) and older (over 50 years) groups. It is seen that no significant difference exists between the groups in any of the serum lipid components. A slightly higher proportion of hypercholesteremic cases is found in the younger than in the older group, whereas the relative amount

of cases with hypertriglyceridemia was about equal in both age groups.

Comparison of Coronary Groups I and II

The mean lipid levels were all slightly higher in group I (recent cases) than in group II (old cases). The difference was significant, however, only for triglycerides. As is seen from table 2, most lipid intercorrelations, and particularly those involving triglyceride, were better in group I than in group II.

Table 2

Relationships of the Different Lipid Measurements in 175 Men with Myocardial Infarction. Regression Equations and Correlation Coefficients

<table>
<thead>
<tr>
<th>Group</th>
<th>Lipid 1</th>
<th>Lipid 2</th>
<th>Regression equation</th>
<th>P</th>
<th>Correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Cholesterol</td>
<td>Triglyceride</td>
<td>$X_0 = 265.8 + 0.319 X_1$</td>
<td>.001</td>
<td>.41</td>
</tr>
<tr>
<td></td>
<td>Cholesterol</td>
<td>Tocopherol-0</td>
<td>$X_0 = 128.4 + 12.42 X_1$</td>
<td>.001</td>
<td>.68</td>
</tr>
<tr>
<td></td>
<td>Cholesterol</td>
<td>Tocopherol-24</td>
<td>$X_0 = 180.3 + 5.25 X_1$</td>
<td>.001</td>
<td>.59</td>
</tr>
<tr>
<td></td>
<td>Triglyceride</td>
<td>Tocopherol-0</td>
<td>$X_0 = -96.5 + 17.88 X_1$</td>
<td>.001</td>
<td>.75</td>
</tr>
<tr>
<td></td>
<td>Triglyceride</td>
<td>Tocopherol-24</td>
<td>$X_0 = -101.3 + 9.89 X_1$</td>
<td>.001</td>
<td>.79</td>
</tr>
<tr>
<td></td>
<td>Tocopherol-0</td>
<td>Tocopherol-24</td>
<td>$X_0 = 4.05 + 0.411 X_1$</td>
<td>.001</td>
<td>.88</td>
</tr>
<tr>
<td>II</td>
<td>Cholesterol</td>
<td>Triglyceride</td>
<td>$X_0 = 293.4 + 0.202 X_1$</td>
<td>.05</td>
<td>.20</td>
</tr>
<tr>
<td></td>
<td>Cholesterol</td>
<td>Tocopherol-0</td>
<td>$X_0 = 160.2 + 10.07 X_1$</td>
<td>.001</td>
<td>.65</td>
</tr>
<tr>
<td></td>
<td>Cholesterol</td>
<td>Tocopherol-24</td>
<td>$X_0 = 141.0 + 5.81 X_1$</td>
<td>.001</td>
<td>.73</td>
</tr>
<tr>
<td></td>
<td>Triglyceride</td>
<td>Tocopherol-0</td>
<td>$X_0 = 109.2 + 2.44 X_1$</td>
<td>.</td>
<td>.16</td>
</tr>
<tr>
<td></td>
<td>Triglyceride</td>
<td>Tocopherol-24</td>
<td>$X_0 = 70.05 + 2.42 X_1$</td>
<td>.01</td>
<td>.33</td>
</tr>
<tr>
<td></td>
<td>Tocopherol-0</td>
<td>Tocopherol-24</td>
<td>$X_0 = 9.17 + 0.229 X_1$</td>
<td>.001</td>
<td>.49</td>
</tr>
</tbody>
</table>
Discussion

The data accumulated in the present study show that the most common abnormality of serum lipids in patients with occlusive coronary disease is a general hyperlipidemia, a simultaneous elevation of several lipid components. This pattern was present in 36 per cent of the patients investigated. Two of the three lipids measured were increased above normal in 20 per cent of the cases, and an elevation of only one lipid was present in 21 per cent. Most of the cases belonging to the latter group showed only slight or moderate increases, and, taking into account the fairly great intraindividual fluctuations, may on another occasion have been classified as normal. In 23 per cent of cases all three lipids were in normal range. It is thus quite apparent that a metabolic defect manifesting itself as an increased level of only one single lipid in the serum is of a fairly rare occurrence, at least among patients with coronary heart disease. This statement does not exclude, of course, the possibility that the primary error should often lie in the metabolism of a single lipid, and the other lipid changes be secondary, as is always the case in the disordered handling of tocopherol.

While the frequent occurrence of hypercholesteremia among patients with coronary artery disease has been long recognized, the triglyceride level of fasting serum has recently been implicated as another important pathogenetic factor of ischemic heart disease.17-23
Many authors consider the serum triglyceride level to be more closely associated with clinical coronary heart disease than is the serum cholesterol concentration. This view is not substantiated by the present material, although the relative mean increase of serum lipids in the coronary group above those of the control group was definitely greater in triglycerides (1.9-fold) than in cholesterol (1.4-fold) or tocopherol (1.4-fold). If the same criterion for the upper normal limit as in the present study is used, Albrink et al. found increased triglyceride levels in 90 per cent of their population with coronary heart disease. In the rather small coronary groups studied by Carlson and by Antonis and Bersohn hypertriglyceridemia was present in about 75 per cent. The deviation of these findings from the present ones in a Finnish material, where only 56 per cent of the male survivors of myocardial infarction showed this abnormality, is thus quite apparent. Several explanations may be offered for this divergence of results. It may be thought that racial differences exist in the incidence of various types of hyperlipidemia, all of which are more or less atherogenic, and that these are reflected in the serum lipid pattern of patients with occlusive arterial disease. On the other hand, it must be realized that a fairly large proportion (about 15 per cent in the present material) of the coronary population has serum triglyceride values in an upper normal range (120 to 140 mg./100 ml.), and these may be classified as pathologic, depending on the time of analysis and the level defined as normal maximum.

In an evaluation of the serum triglyceride levels it is also important to consider the caloric balance at, and a change of dietary habits before, the time of measurement. Gain of weight and carbohydrate-rich diet, both of which are known to increase fasting serum triglyceride concentration, are not infrequently encountered conditions in survivors of myocardial infarction, particularly in the period of convalescence.

The present study could not reveal any significant relation between the serum lipid pattern and the age of the coronary patients. This finding is, in a manner, in agreement with the experience derived from the materials of Albrink et al. and of Carlson, which were in this respect fully contradictory to each other. Thus, Albrink et al. found hypertriglyceridemia to occur most often in coronary patients past fifty, while Carlson observed elevated triglycerides particularly in young patients, and hypercholesteremia in older ones. It should be appreciated, however, that compared to their age-matched control subjects the younger patients of the present material had relatively higher lipid levels than the older ones. It is possible that in many of the men manifesting coronary artery disease in their later years the hyperlipidemia is of rather recent origin, and caused by the "physiologic" change of lipid metabolism with age. In the younger coronary subjects, on the other hand, the error of lipid metabolism may be more often inborn. Then, supposing that plasma cholesterol and triglycerides carry an equal risk of coronary disease, the serum lipid pattern in a population of young men manifesting this disorder is determined by the relative frequencies of gene abnormalities causing hypercholesteremia and hypertriglyceridemia.

Tocopherol, being a purely exogenous lipid,
seems to be an advantageous indicator of synthesis, disposal, and interconversions of plasma lipoproteins. However, although the path of endogenous synthesis is excluded, the kinetics of tocopherol in the body still remains too complex to allow an easy interpretation of observations. Recycling of the newly absorbed tocopherol occurs not only through the liver lipid pools and plasma lipoproteins but also through the biliary excretion and intestinal reabsorption. Any model of lipoprotein metabolism based on tocopherol studies is thus of necessity more or less speculative (fig. 11).

What can be inferred from the tocopherol data? It is known that newly absorbed tocopherol is incorporated into chylomicrons and all classes of lipoproteins more or less simultaneously. The incorporation rate is fairly rapid into all lipoprotein classes, and it cannot be inferred from the available data, including our own (unpublished), whether the Sf 3-12 and high-density lipoprotein particles obtain their new tocopherol by their synthesis in the liver or through the conversion of Sf 12-400 lipoproteins and chylomicrons at the periphery. The largest part of the absorbed tocopherol appears in the Sf 3-12 fraction and the slow plasma disappearance rate of tocopherol corresponds to the known long half-life of this particle. Considering the relatively rapid rate of tocopherol incorporation and its slow rate of disappearance, it seems that the maximum amount of tocopherol contained in Sf 3-12 and high-density lipoprotein particles after an oral loading dose gives a measure of the production rate of these lipoproteins. In cases of hypercholesterolemia the amount of tocopherol incorporated into Sf 3-12 lipoprotein is increased, whereas in subjects with predominant hypertriglyceridemia an increased incorporation occurs in the chylomicrons and Sf 20-400 lipoproteins and very little or nothing is found in the other lipoproteins.

It is noteworthy that many coronary patients with a normal basal tocopherol plasma level revealed to have a decreased plasma disappearance rate of tocopherol. Thus, a dynamic approach of lipid metabolism seems to uncover abnormal cases, which are not detected by determination of serum lipid level under basal conditions. This statement is supported by earlier studies of triglyceride metabolism that have shown that a high percentage of patients with ischemic heart disease have a delayed disappearance of radioactivity from blood lipids after oral administration of I131-triglyceride. This finding has been interpreted to show a defect in the clearing of chylomicon triglycerides from the blood. Actually, however, the data are more compatible with a defective clearance of the more long-lived Sf 20-400 lipoprotein triglyceride, which partly enters the blood from the thoracic duct, and partly is formed endogenously from the fed I131-labeled fatty acids that escape deiodination. This view could explain why the primary clearance rate of intravenously administered emulsified fat has been found to be normal in patients with ischemic heart disease.

The biochemical basis of the change of lipid metabolism that occurs with aging has never been adequately explained. A decreased release, possibly reflecting a decreased synthesis, of lipoprotein lipase has been demonstrated to be present in old age. As the incidence of a diabetic carbohydrate metabolism is also higher in the older age groups one comes to think of some interrelationship between the metabolism of tocopherol.
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two disorders. It is tempting to speculate that the pancreas should be involved in these alterations, since destruction of the alpha cells has been shown to be followed by hyperlipemia and the production of lipoprotein lipase is weak in pancreatic fibrosis.

Whether the high plasma tocopherol level has any metabolic significance, cannot be stated so far. It is probably more important that vitamin K, which is structurally closely related to tocopherol, is possibly handled in a similar manner. Thus, hypervitaminemia K should be expected to occur in hyperlipidemic states. This hypothesis, if verified, should explain the known resistance of hypercholesteremic patients to anticoagulant drugs, and possibly also bear a relationship to increased thrombogenesis.

Summary

The plasma tocopherol, cholesterol, and triglyceride were estimated in 175 male survivors of myocardial infarction and in control subjects. The control subjects comprised 214 blood donors (without healthy control) and 70 healthy persons. The coronary group derived from two sources: Group I had had myocardial infarction 4 to 6 weeks before the study; group II was composed of persons who had experienced a myocardial infarction 6 to 30 months before the study.

A tocopherol-loading test with 2 Gm. of tocopherol acetate was performed in 101 coronary subjects and in 34 control subjects. The 24-hour plasma tocopherol was estimated after the tocopherol load.

Ninety per cent of the young control subjects (20 to 35 years of age) had plasma tocopherol below 15 mg./L., cholesterol below 290 mg./per 100 ml., triglyceride below 140 mg./100 ml., and 24-hour tocopherol below 24 mg./L. In reference to these concentrations, 53 per cent of the whole coronary group had an elevated plasma tocopherol level, 62 per cent had an elevated serum cholesterol level, and 56 per cent showed hypertriglyceridemia. The 24-hour plasma tocopherol level in normal subjects was exceeded by 77 per cent of the subjects with coronary heart disease.

The mean lipid levels were all slightly higher in group I (recent cases) than in group II (old cases). The difference was significant, however, only for triglycerides.

The whole coronary group was divided according to age in two subgroups (age below and over 50). No significant difference existed in the two groups.

The regression analyses of the lipids showed that none of the lipid measurements appeared to be fully independent variables. A highly significant regression was present for cholesterol versus tocopherol. The relationship between triglyceride and tocopherol was not so striking, although the regression was significant also here except the coronary group II.

References


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Circulation. 1963;27:919-928
doi: 10.1161/01.CIR.27.5.919
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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