Serum Lipids and Lipoproteins in Men after Myocardial Infarction compared with Representative Population Sample

By Anders Gustafson, M.D., Dag Elmfeldt, M.D., Lars Wilhelmsen, M.D., and Gösta Tibblin, M.D.

SUMMARY
A nonselected series of 229 postmyocardial infarction (MI) patients was studied for up to 2 years following hospitalization. Their lipoprotein patterns, serum cholesterol, and triglyceride values were compared to those of a random population sample of men at comparable ages.

Hyperlipoproteinemia, cholesterol, and triglyceride elevations were more common in MI patients than in men in the random sample, occurring with greatest frequency in the younger patients. There was a trend toward higher mortality among patients with hyperlipoproteinemia. Types II A and B were very common in young patients.

Serum cholesterol values were significantly higher in the youngest patients and serum triglycerides higher than in the controls in age groups ≤ 40, 46–50, and 51–55 years.

Additional Indexing Words:
Hyperlipoproteinemia Cholesterol Triglycerides

Among several risk factors for coronary heart disease (CHD), serum lipids have long received a great deal of attention, and a relationship between elevated serum cholesterol and CHD has been found.1–3 Since 1960 there has been an increasing interest in the serum triglycerides in this respect.3–6

The water-insoluble serum lipid fractions are transported in the form of macromolecular compounds; i.e. lipoproteins and serum lipid changes are expressed as disturbances in the serum lipoprotein distribution. In 1964 Fredrickson et al.7 presented their serum lipoprotein typing system.

There are as yet no data published concerning the distribution of lipoprotein abnormalities in representative population samples, nor any prospective investigations concerning hyperlipoproteinemia either for the first myocardial infarction or for follow-up after MI. In this paper we present data from a cross-sectional population study and an unselected population of male patients surviving MI for at least 3 months.

Methods
In Göteborg, Sweden, total population 450,000, all diagnosed or suspected MI patients are sent to one hospital (Sahlgren's Hospital). Since January, 1968 all MI patients (both initial infarctions and reinfarctions) aged 55 or younger,
after leaving the hospital, were followed at a special post-MI clinic.

The present series consists of the 229 consecutive male cases 55 years of age or younger (mean age 49 years) at the post-MI clinic from January, 1968, through April, 1970 who had survived their infarct for 3 months. Lipid variables were studied serially 3 months, 1 year, and 2 years after MI. Since the patient series was set up by consecutively added patients the number of patients examined 3 months after the infarct is considerably larger than the number of patients studied after 1 year, which in turn is larger than those studied after 2 years.

General diet information was given to the patients during their hospital stay for MI. This information was aimed at normalizing a diet which, in Sweden, is often too rich in saturated fats and carbohydrates. When an actual lipoprotein disturbance was diagnosed at the examination 3 months after MI, a specific diet treatment was prescribed by a dietician for a trial period of 2–3 months. Subsequently chemotherapy was added if the disturbance persisted. As a rule clofibrate (Atromid-S) was given, both for dietary and hereditary lipoprotein abnormalities.

A control series was obtained in the following way. The sample consisted of all men born in 1913 on dates evenly divisible by 3 and living in Göteborg at the end of 1962 when the sampling took place. Thus, men born on dates 3, 6, 9, 12, etc. were included. The sample, thus obtained, consisted of 973 men, and 855 of these (88%) were examined in 1963. Characteristics of the nonparticipation group have been published elsewhere. In 1967, 803 men were reexamined. The nonrespondent group consisted of 52 men of whom 25 refused examination, 18 were deceased, and nine could not be traced.

From this sample (N = 803) a subsample was obtained which included all men born on the sixth of each month of the year. Of the 85 men belonging to this subsample, 76 (89%) took part in a reexamination in 1968. The reexamination consisted of blood samples being drawn at 8 AM after 1 hour's rest. The participants had been fasting since 8 PM the evening before.

Thus, all those men belonging to the control series were at least as old as the infarct patients. As the lipids are known to be stable or increase, within this age group, the differences obtained in this study can be considered negligible.

Blood samples were drawn in the morning after 12 hours of fasting. Serum was obtained after low-speed centrifugation. Serum lipids, as well as lipoprotein patterns, were obtained by the same technics, by the same technicians, and in the same laboratory for the patient and control groups. Serum cholesterol was determined (after lipid extraction) according to the Lieberman-Buchard reaction by the method of Cramér and Isaksson, and serum triglycerides determined according to Carlson and Wadström. Serum lipoprotein electrophoresis was performed on filter paper mainly according to the method described by Lees and Hatch, and on agarose gel principally according to the method described by Rapp and Kahlke. For the agarose gel electrophoresis, a plastic film (DuPont) was utilized as the supporting medium. A Spinco Durrum cell was utilized for the filter paper electrophoresis and for agarose gel electrophoresis the closed and water-chilled system described by Laurell was used. Lipoprotein bands on paper, as well as agarose gel, were developed by staining in a mixture of Oil Red O and Fett Rot 7B (Ciba). No attempts to quantify the lipoprotein bands were made.

The serum lipoprotein patterns were typed biochemically according to Fredrickson and Lees with the inclusion of subtypes II A and B, as now recommended in the most recent revision of this classification system. The patterns were judged biochemically after the visual evaluation of the lipoprotein electrophoresis in relation to the concomitantly obtained serum lipid analysis (cholesterol and triglycerides). In the absence of chylomicrons on the lipoprotein electrophoresis pattern, the serum triglyceride value was set in relation to the presence of a pre-beta-lipoprotein band. A pre-beta-lipoprotein elevation was considered when a distinct pre-beta-lipoprotein band was present simultaneously with serum triglycerides \( \geq 180 \text{ mg/100 ml} \). The presence of elevated beta-lipoproteins was judged from the lipoprotein electrophoresis where an elevated beta-lipoprotein band showed a slower migration rate as compared to the simultaneously run fresh, normal reference serum. The beta-lipoprotein cholesterol was estimated from the total serum cholesterol by subtracting the alpha-lipoprotein cholesterol and the pre-beta-lipoprotein cholesterol, the latter obtained from the serum triglyceride value multiplied by \( \% \) (Gustafson A, Abrahamsson H, Jäderberg K: Unpublished observations). In this equation alpha-lipoprotein cholesterol was estimated to 50 mg/100 ml, where the lipoprotein electrophoresis showed a fairly normal amount of lipid stain at the place for the alpha-lipoprotein. When lipoprotein electrophoresis revealed lower and higher alpha-lipoprotein content, respectively, values within the range of 35–65 mg/100 ml of alpha-lipoprotein cholesterol were arbitrarily chosen for the equation.

It has recently been shown that this method of evaluation is accurate enough in most cases except those with insulin-treated diabetes mellitus and in patients treated with lipid-lowering drugs (Gustafson A, Abrahamsson H, Jäderberg...
Table 1

<table>
<thead>
<tr>
<th>Sample</th>
<th>N</th>
<th>Age (yr)</th>
<th>Lipoprotein type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Range</td>
<td>Normal (%)</td>
</tr>
<tr>
<td>Random</td>
<td>76</td>
<td>55</td>
<td>77</td>
</tr>
<tr>
<td>Post-MI:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mo</td>
<td>229</td>
<td>27–55</td>
<td>53</td>
</tr>
<tr>
<td>1 yr</td>
<td>161</td>
<td>27–55</td>
<td>67</td>
</tr>
<tr>
<td>2 yr</td>
<td>84</td>
<td>27–55</td>
<td>69</td>
</tr>
</tbody>
</table>

K: Unpublished observations. A normal upper value of 200 mg/100 ml for beta-lipoprotein cholesterol was chosen for men in the actual age group. At different serum triglyceride and alpha-lipoprotein levels this beta-lipoprotein cholesterol value gives a total serum cholesterol value between 280 and 300 mg/100 ml. No attempt was made to define separately the rare type III pattern in these studies.

Statistical Methods

Conventional statistical methods were used for the calculation of means and standard deviations. The Student’s t test was used to study differences between the means of two groups. Analysis of variance followed by Scheffe’s method for constructing contrasts was used in the study of differences between means of several groups. Qualitative data were compared by means of chi-square analysis. Fischer’s exact probability test was used when necessary. A value of $P \leq 0.05$ was considered to be statistically significant.

Results

Serum Lipoproteins

Table 1 shows the distribution in percent of hyperlipoproteinemia in the control series and in the patient series. The two most frequently occurring lipoprotein types both in the control and MI patient groups were types II A and IV.

Three months after MI, 47% of the patients revealed abnormal lipoprotein patterns as opposed to 23% of the control subjects ($P < 0.001$). Type II B was 10 times more frequent in the patients than in the control subjects ($P < 0.025$), and type IV more than twice as frequent ($P < 0.05$). Type II A did not differ significantly between the two series, whereas type V, which occurred in 3% of the controls, was not found among the patients.

The numbers in table 1 suggest a decreasing percentage of hyperlipoproteinemia with longer follow-up. This must, however, be considered in relation to the different number of patients left for examination and the fate of those with normal lipoprotein pattern and hyperlipoproteinemia, respectively. When the 110 patients who had been examined on all three occasions (3 months, 1 year, and 2 years after MI) were studied, changes throughout the period became apparent (fig. 1). The proportion of patients with normal serum lipoproteins was fairly constant (about 55%) throughout the 2 years of follow-up. A reduction in the proportion of cases with hyperlipoproteinemia was observed, but this was at least partially compensated by a corresponding increase in number of patients lost, mainly because of death.

The mortality in the group of patients with initial hyperlipoproteinemia was significantly higher ($P < 0.01$) than in those patients with an initially normal lipoprotein pattern.

The reason for this could have been an...
overrepresentation of other features connected with a higher mortality in the group with hyperlipoproteinemia. This group was not, however, more afflicted than expected with SGOT elevation or heart enlargement, which are risk factors for death in this series.18

Patients with reinfarctions have a higher mortality than those with their first MI.18 In this study reinfarctions were more common among those who had hyperlipoproteinemia. The breakdown in these respects appears in figure 2. Among patients with reinfection, those with hyperlipoproteinemia had a higher mortality during the 2-year follow-up period (six of 11 patients died) than those without (one of nine died). The difference was, however, not significant (Fischer's test) due to the low numbers. Patients with their first MI and with hyperlipoproteinemia did not have a higher mortality (four of 39 died) than those without hyperlipoproteinemia (three of 51 died).

The fate of each patient following the first examination 3 months after the MI was analyzed according to lipoprotein type. In short, the results were that, of the 60 who initially had normal types, nine got type II A, and one type IV after 1 year. After 2 years, two more patients converted from a normal pattern to type II A. Some patients also moved from abnormal types to normal, which probably was due to treatment.

When the presence of hyperlipoproteinemia at 3 months after MI was related to age, a very high incidence of types II A and B was found in the age group 40 years or younger (fig. 3). In this age group no patient had lipoprotein type IV, but this type was seen in all other age groups. In all age groups the incidence of abnormal lipoprotein types was higher than in the control series (≤ 40 years: P < 0.001; 41–45 years: P < 0.05; 46–50 years: P < 0.001; and 50–55 years: P < 0.005).

Serum Cholesterol and Triglycerides

Mean serum cholesterol and triglyceride values for the whole group of patients (N = 229, mean age 49 years) were significantly higher than the corresponding values for the control series when the control subjects were 50 and 55 years old (table 2).

The mean values for serum cholesterol and triglycerides within the four age groups in the patient series and the control series are shown in table 3. The mean value for serum cholesterol was significantly higher for the younger patients (P < 0.05) than the control series, but for the other age groups of patients the differences were not significant. There were also significant differences (P < 0.05) when the mean cholesterol value of the youngest age group was compared with the values of the older age groups in the patient series. The mean values of serum triglycerides in three of

Figure 2

The 2-year follow-up of 110 patients with myocardial infarction including 20 cases with reinfection. The diagram gives the total numbers within different groups as well as number of deaths and mortality rate within parentheses.

Figure 3

Serum lipoprotein types in relation to age in a random sample of 55-year-old men and in men aged 27–55 years (mean 49) 3 months after MI.
the age groups in the patient series (40, 46–50, and 51–55 years) were significantly higher than in the control series.

To check the reading of the lipoprotein types in the patient and control series on different occasions during follow-up, cholesterol and triglycerides were given in relation to the different lipoprotein types throughout the follow-up period (figs. 4, 5). At 3 months and 2 years, but not after 1 year, after MI the serum triglyceride values in the patients with normal lipoproteins were significantly higher than those of the control series (P < 0.005 and P < 0.02, respectively). This was also true for serum triglycerides in patients with type II A 3 months after MI (P < 0.05).

The mean serum cholesterol value in patients with normal lipoproteins, with types II A and IV, agreed well with those values in the control series.

### Table 2

Comparison of Serum Cholesterol and Serum Triglycerides in Men after MI and in a Random Sample of Men

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>Serum cholesterol (mg/100 ml) x</th>
<th>s</th>
<th>Serum triglycerides (mg/100 ml) x</th>
<th>s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sample of men aged 50</td>
<td>855</td>
<td>248</td>
<td>40</td>
<td>108</td>
<td>65</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Men 3 months after MI*</td>
<td>229</td>
<td>276</td>
<td>51</td>
<td>158</td>
<td>79</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>&lt;0.005</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Random sample of men aged 55</td>
<td>74</td>
<td>257</td>
<td>41</td>
<td>110</td>
<td>50</td>
</tr>
</tbody>
</table>

Abbreviations: \( \bar{x} = \text{mean value; } s = \text{standard deviation.} \)

*Age = 27–55 years; mean age = 49 years.

### Discussion

Since there are great differences in the same lipids and serum lipoprotein distributions between different healthy populations, it is important to have access to data from the background population when data from patients are discussed. Prospective population studies are evidently most reliable in this respect, but lipoprotein typing is laborious in large samples, and has only been used in single collaborative studies. Interesting considerations will, however, emerge from comparisons of unselected populations and patient series. In addition, secondary risk factors can be studied in a series of patients.

Because comparability of methods for analysis is of great importance, all analyses were performed in the same way in this study. Also, it is important that all patients enter the study at the same time after MI as the serum lipids

### Table 3

Comparison of Serum Cholesterol and Serum Triglycerides in Men after MI and in a Random Sample of Men

<table>
<thead>
<tr>
<th>Population</th>
<th>Age (yr)</th>
<th>N</th>
<th>Serum cholesterol (mg/100 ml) x</th>
<th>s</th>
<th>Serum triglycerides (mg/100 ml) x</th>
<th>s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sample</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>74</td>
<td>257</td>
<td>41</td>
<td>110</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>≤ 40</td>
<td>9</td>
<td>333</td>
<td>61</td>
<td>203</td>
<td>121</td>
</tr>
<tr>
<td></td>
<td>41–45</td>
<td>37</td>
<td>273</td>
<td>48</td>
<td>155</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>46–50</td>
<td>75</td>
<td>278</td>
<td>51</td>
<td>147</td>
<td>75</td>
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<tr>
<td></td>
<td>51–55</td>
<td>108</td>
<td>270</td>
<td>50</td>
<td>162</td>
<td>79</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>229</td>
<td>276</td>
<td>51</td>
<td>158</td>
<td>79</td>
</tr>
</tbody>
</table>

Abbreviations: \( \bar{x} = \text{mean value; } s = \text{standard deviation.} \)
and the lipoproteins change with time in this disease.\textsuperscript{20,21} 

The good agreement in serum cholesterol values in various lipoprotein types in post-MI men and in the control group indicates that no “overtyping” occurred in the patients. Higher mean serum triglyceride values in corresponding lipoprotein types in patients as compared to control subjects also contradict overtyping.

According to our definition of hyperlipoproteinemia, 23\% of the control subjects from the general male population have hyperlipoproteinemia as opposed to 47\% among patients 3 months after MI. In other studies of selected MI patients, background populations have not been available for comparison. Similar frequencies of lipoprotein abnormalities have, however, been estimated.

In two other studies where selected male MI patients under the age of 50 years were studied, higher prevalence of hyperlipoproteinemia has been reported.\textsuperscript{28,29} These findings are comparable with the youngest group of the present study.

Heinle et al.\textsuperscript{30} reported 80\% abnormal lipoprotein types in patients under age 50 years with angiographically verified coronary heart disease. The distribution, however, was different from the distribution in the present study; in their series, types II A and IV were most frequent as opposed to types II A and B among the youngest patients in the present study.

No case with type V was found among the patients as opposed to an incidence of two of 76 among the control subjects. This finding supports the impression that type V is not closely related to CHD but is often secondary to other disturbances such as a high intake of alcohol.

The changing distribution of the lipoprotein types during the 2 years of follow-up are due to several causes. MI, as well as other acute diseases and injuries, causes a decrease in the cholesterol level, which is most obvious during the first 6–10 days. The initial level is often reached again during the first month, but frequently even later.\textsuperscript{20,31} Thus, a type II A might be hidden for some time after MI and may not be recognized even after 3 months.

Serum triglycerides and pre-beta-lipoprotein have been shown to increase above initial values for at least 2 months after MI.\textsuperscript{20,21,32} This might cause an overestimation of types II B and IV 3 months after MI. This was not an important cause of error in the present series since changes from type II B to II A and from type IV to a normal lipoprotein pattern were rare. Those patients who had elevated

\textbf{Figure 4}

Serum cholesterol (mean ± SEM) in different lipoprotein types in a random sample of 55-year-old men and in men aged 27–55 years (mean 49) 3 months, 1 year, and 2 years after MI.

\textbf{Figure 5}

Serum triglycerides (mean ± SEM) in different lipoprotein types in a random sample of 55-year-old men and in men aged 27–55 years (mean 49) 3 months, 1 year, and 2 years after MI.
SERUM LIPIDS AFTER MI


References


pre-beta-lipoproteins 3 months after MI preferentially alternated between types II B and IV during the 2 years of follow-up.

The loss, mainly due to the death of patients with hyperlipoproteinemia during the follow-up period, was another reason for changes in lipoprotein type distribution. Hitherto, the risk factors for death during the first years after MI have been related to extent of myocardial damage and certain arrhythmias.18, 33 The results of the present study indicate that hyperlipoproteinemia may turn out to be of predictive importance. The sparse reports in the literature are in disagreement as to the possible influence of serum lipids and lipoproteins on the prognosis in MI. The Berkeley group54 found a significantly lower level of pre-beta- and beta-lipoproteins (SF 0-400 lipoproteins) in those who survived MI beyond 5 years as compared to those who died in a reinfarction. Shanoff et al.,55 on the other hand, denied any such relation of lipoproteins on survival over a 10-year period from their data on 120 men who had survived for at least 3 months. Their patients, however, joined the study at very different points after MI.

At least 25% of the patients with MI died outside the hospital and an additional 12% died before their lipoprotein typing was performed.18 It is, therefore, impossible to evaluate any influence of lipoprotein type on the extension of MI and its immediate outcome. There are, as yet, no data available from prospective population studies concerning these questions.

At present, it is difficult to treat a large series of MI patients over several years without influencing dietary habits and physical activity. In some cases serum lipid-reducing drugs will also be considered necessary. For these reasons, changes in lipoprotein types during the follow-up period could be expected, but have hardly influenced the present results obtained at the time of the first examination at 3 months after MI.


32. **SMITH EB**: Lipoprotein patterns in myocardial infarction: Relationship between the components identified by paper electrophoresis and in the ultracentrifuge. Lancet 2: 910, 1957


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