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The prognostic value of hypocholesterolemia in hospitalized patients

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Abstract. Clinical observations show that severe illness often leads to hypocholesterolemia. To verify this finding and to define the relationship between serum cholesterol and a patient's prognosis, a study was conducted in two large hospital populations. Of 24,000 and 61,463 adult patients (populations I and II) an average of 3.8% and 3.6% died in hospital, respectively. The mean serum cholesterol levels of patients who died was significantly lower than that of those who survived (163.6 mg/dl versus 217.8 mg/dl; $P < 0.0001$). The average cholesterol of surviving patients was similar to that of 6,543 healthy controls. During hospitalization serum cholesterol levels of ≤ 100 mg/dl were encountered in 1.2% and 3.6% of patients of populations I and II, respectively. The mortality of these hypocholesterolemic patients was about tenfold higher than average and showed a strong, inverse, linear relationship with serum cholesterol concentrations. Patients whose serum cholesterol level dropped to less than 45 mg/dl did not survive. These data show that in severely ill patients serum cholesterol may decline to very low concentrations, and the prognosis is reflected by the degree of hypocholesterolemia, which thus may serve as a clinically useful prognostic parameter.

Key words: Hypocholesterolemia – Hospital mortality – Prognostic parameter

In contrast to hypercholesterolemia, very low serum cholesterol concentrations have been the subject of only a few studies. Epidemiological surveys report an increased mortality with elevated as well as low serum cholesterol concentrations [14, 18]. In healthy populations low cholesterol concentrations primarily result from either dietary habits with a very low fat content or genetic variants in lipoprotein metabolism – conditions uncommon in Western industrial countries [21]. Yet, severe hypocholesterolemia has often been reported in patients suffering from a variety of severe diseases, such as cancer, hematological disorders, hepatopathies and generalized illness [3, 6, 10, 15, 19, 22]. The possibility of a causal relationship between hypocholesterolemia and increased mortality has provoked discussions about the safety of cholesterol-lowering therapy in patients with cardiovascular disease [9, 14]. In hospitalized patients plasma cholesterol may drastically decline as a consequence of any major illness that affects cell function. This can either decrease lipoprotein synthesis in the liver or intestine or diminish plasma cholesterol levels as a result of higher uptake by peripheral tissues to compensate for decreased synthesis or for increased utilization of cholesterol as in rapidly growing tumor cells [6, 15, 19].

This investigation was designed to evaluate the incidence of hypocholesterolemia in hospitalized patients and its possible relationship to mortality. An analysis of two large hospital populations is reported that establishes the predictive power of low plasma cholesterol as a general parameter for the assessment of the prognosis of critically ill patients.

Materials and methods

Routine clinical chemical parameters (sodium, potassium, chloride, total protein, albumin, phosphate, total cholesterol, urea nitrogen, calcium, creatinine, bilirubin, uric acid) were measured by standard techniques used in clinical laboratories with established quality controls. Coefficient of variance was less than 3%. Throughout this study the methods of analyses remained unchanged. All patients were screened who were admitted to the university hospitals of Hamburg (population I) or Göttingen (population II) during 11 months or 4 years, respec-

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tively. Pregnant women and children were excluded from this study. The laboratory values obtained closest to discharge or death usually within the last day were evaluated. In a subset of patients laboratory values were compared with the first values obtained on admission to hospital. Those patients whose serum cholesterol concentrations were ≤ 100 mg/dl at least once at any time during their hospitalization were defined as hypocholesterolemic. A group of 6,543 healthy male workers aged between 40 and 60 years served as controls, and are described in detail elsewhere [17]. Diagnoses established or confirmed during hospitalization were obtained from hospital records. Multiple diagnoses, for most patients no more than 3, were recorded. Statistical analyses were performed according to standard procedures [4, 16]. Unless otherwise stated, values of groups are given as means ± 1 standard deviation.

Results

The total mortality in hospitalized patients in population I ($n = 24{,}000$ patients in Hamburg) and population II ($n = 61{,}463$ patients in Göttingen) was 3.8% and 3.6%, respectively. However, in patients with serum cholesterol levels ≤ 100 mg/dl at some stage of their illness mortality increased to 41.7% and 29,7% in population I and II, respectively.

Figure 1 shows that those patients of population II who were discharged from the hospital had a distribution of cholesterol values comparable to that of healthy 40- to 60-year-old industrial male workers. Thus, hospitalization per se did not lead to significant hypocholesterolemia. However, serum cholesterol values of patients who died during hospitalization were significantly lower before death than the values of patients who survived (mean 163.6 mg/dl vs 217.8 mg/dl) ($P < 0.0001$) (Fig. 1).

This observation was corroborated at low cholesterol concentrations using data of 178 hypocholesterolemic patients of population I, for whom routine laboratory values were available on admission and before discharge or death (Fig. 2). Even though serum cholesterol values on admission to hospital did not differ between patients who survived or died, significant differences were noted at the end of hospitalization (70.9 $\pm$ 22.2 mg/dl vs 85.9 $\pm$ 14.4 mg/dl; $P < 0.001$). Thus, mean cholesterol values decreased in hypocholesterolemic patients who died during hospitalization ($P < 0.001$), in contrast to serum cholesterol of those who survived.

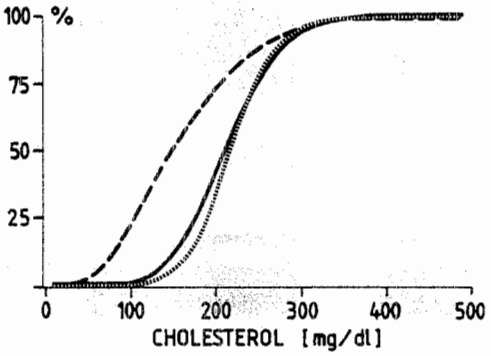

Fig. 1. Cumulative frequency distribution of total serum cholesterol in 6,543 healthy 40–60 male workers (·····), 59,204 patients that survived and were discharged from hospital (——), and 2,253 patients that died during hospitalization (– – –)

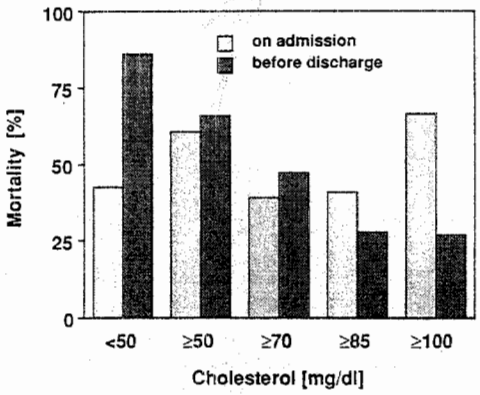

Fig. 2. Mortality of hypocholesterolemic patients during hospitalization according to serum total cholesterol concentrations on admission and before death or discharge. Hypocholesterolemic patients of population I ($n = 178$) were stratified according to cholesterol concentrations in groups for statistical analysis

There was no correlation between cholesterol values and mortality on admission, but between the last cholesterol values before discharge or death (Fig. 2). Low cholesterol values were associated with high mortality, and increasing concentrations of cholesterol correlated with better prognosis. In patients with serum cholesterol values of less than 50 mg/dl 86,7% died, in contrast to 27.6% of patients with cholesterol values between 85 and 99 mg/dl.

In order to assess other routine laboratory parameters that might discriminate between survivors and non-survivors, data were analyzed by a stepwise logistic regression. Routine laboratory parameters that were selected on the basis of univariate analyses to be clinically significant were used. Serum cholesterol, creatinine and bilirubin measured before death or discharge entered the

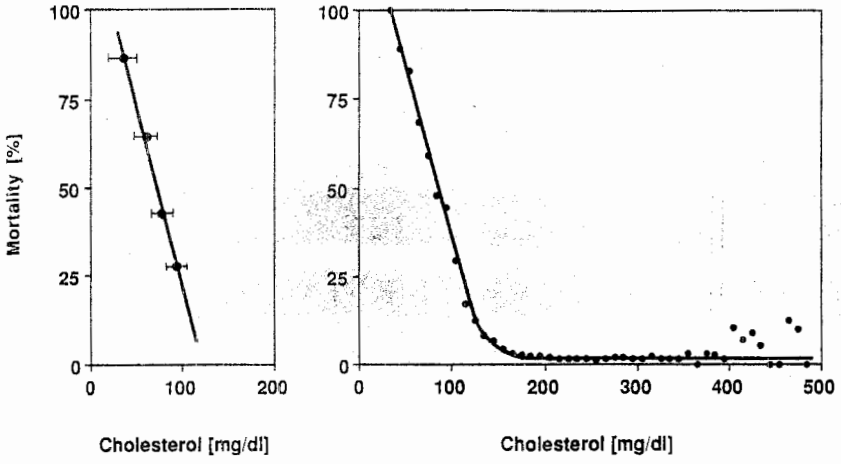

Fig. 3. Mortality of hospitalized patients in relation to serum total cholesterol concentrations. *Left panel*: 295 hypocholesterolemic patients of population I. Data represent means of cholesterol ranges indicated by *bars*. *Right panel*: 61,463 patients of population II. Data represent means of cholesterol ranges of 10 mg/dl

analysis at a level of significance of $P < 0.05$. Age did not reach statistical significance as a discriminating parameter, even though patients who died were slightly older than those who survived (58.5 ± 15.7 vs 50.3 ± 19.0 years; $P < 0.001$).

A plot of mortality versus the serum cholesterol values before death or discharge of all hypocholesterolemic patients of population I was linear (Fig. 3). A very similar relationship was obtained for the last cholesterol values of all patients of the large population II up to a cholesterol value of approximately 110 mg/dl (Fig. 3). Above 150 mg/dl mortality was low and constant up to very high cholesterol values where mortality tended to increase again. Extrapolation of the data on serum cholesterol against mortality yielded intercepts for a mortality of 100% at about 26 mg/dl or 40 mg/dl cholesterol in populations I and II, respectively (Fig. 3). No patient with a cholesterol of less than 45 mg/dl survived.

Discussion

The data from this investigation substantiate the clinical observation that severe illness is often accompanied by low cholesterol concentrations. Despite its wide acceptance, this phenomenon has not been investigated in detail [12, 20]. Lowered cholesterol values may be frequent, but in some patients concentrations decline to values below 100 mg/dl. Low serum cholesterol values in this range, which may be found in hypo- or abetalipoproteinemia, are rare and unlikely to influence the significance of hypocholesterolemia as a prognostic parameter in severe illness. In the control group of 6,543 healthy industrial workers there was only one subject with a cholesterol value below 100 mg/dl (95 mg/dl) (Fig. 1). These considerations stress the prognostic value of a severe decline in serum cholesterol during hospitalization.

Thus, the incidence of 1.1 to 3.6% of hypocholesterolemia in two populations deserves attention because of the exceedingly high mortality in this group. There may be two reasons for the apparent discrepancy in the incidence of hypocholesterolemia in populations I and II. One is selection bias, since population I consisted of patients mainly from an urban area, while population II included patients of a central hospital, to which more critically ill patients from rural areas are referred. Secondly, the search for low cholesterol values was fully computerized in population II, so that even single low cholesterol values were not missed, while in population I the screening was obtained from laboratory charts.

Our data show that the mortality was approximately tenfold higher in hypocholesterolemic patients as compared to the average of all hospitalized patients and in the same order of magnitude in both populations studied (41.7% in population I and 29.5% in population II compared to 3.8% and 3.6% total mortality). The somewhat lower mortality among hypocholesterolemic patients of population II may be due to better identification of low cholesterol values, so that cases with even slightly lowered values and only transient declines were included in the analysis.

Low cholesterol values show a linear relationship with mortality. This was not anticipated from the small increments of mortality reported in previous observational studies [9, 14]. Decrease in serum cholesterol levels below a threshold value of about 110 mg/dl indicated a progressively poor outcome. Extrapolation of the data indicated that below a cholesterol value of about 40 mg/dl a mortality of 100% can be expected. Indeed, no patient with a

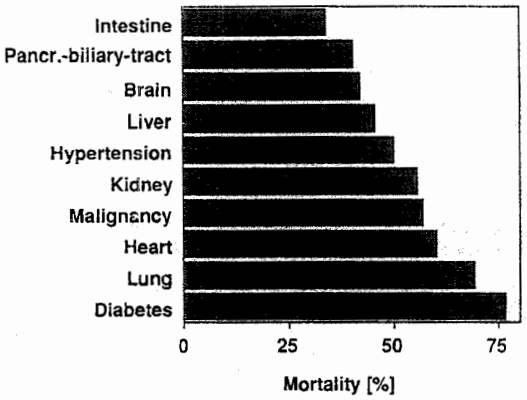

Fig. 4. Mortality of 178 hypocholesterolemic hospitalized patients according to clinical diagnosis or affected organ. Multiple diagnoses were assigned to each patient

serum cholesterol value below 45 mg/dl survived. This threshold cholesterol value below which death is imminent may be helpful in discerning the severity of illness.

Plasma cholesterol levels can decline due to enhanced utilization or diminished synthesis of lipoproteins by the liver and intestines. Various pathological conditions such as cancer may induce hypocholesterolemia either due to increased demand by malignant cells or overall enhanced utilization of cholesterol due to stimulatory effects of factors released by tumor cells [1, 8, 10, 15, 18, 22]. Most studies indicate that low cholesterol values develop in the course of the disease and may precede clinically overt cancer, yet are no cause for higher mortality, but rather a prognostic marker [1, 5, 7, 14, 18, 20]. Experimental data support the clinical observations. Low-density lipoprotein receptor activity has been found to correlate negatively with survival in patients with breast cancer or leukemia and has been suggested as a prognostic parameter [15, 23]. Drastic reduction of cholesterol synthesis by the liver and intestines may be responsible for hypocholesterolemia observed in patients with severe liver disease. Decline in serum cholesterol levels are common in patients immediately after myocardial infarction, but the reasons for this phenomena are still unknown.

Due to divergent mechanisms the severity of hypocholesterolemia and its correlation with mortality may differ in various pathological conditions. One prerequisite for the development of hypocholesterolemia is a sufficient duration and severity of a disease. Thus, only 34.2% of hypocholesterolemic patients with gastrointestinal disease in contrast to 76.9% of diabetics died during hospitalization (Fig. 4). Disorders of the liver and intestines that synthesize lipoproteins may lead to hypocholesterolemia at an earlier stage and lesser severity. Thus, in this group of patients hypocholesterolemia may be of less prognostic value. In contrast, in patients with organ disorders that are not actively involved in cholesterol synthesis like heart or lung hypocholesterolemia may indicate more severe, generalized illness with poorer prognosis. It would therefore be informative to correlate concentrations of serum cholesterol or lipoprotein fractions with the severity, prognosis and nature of diseases, as has been done in a few prospective studies [2, 6, 11, 15]. This study was not designed to provide such information, but rather to examine the relationship between reduction of cholesterol and mortality during hospitalization in a large population.

In this investigation measurement of total plasma cholesterol was preferred over determinations of the distribution of cholesterol in various lipoprotein subclasses. In our view the possible limitations of measuring only total cholesterol are outweighed by the reliability, simplicity and time factor of such measurements, enabling cholesterol determination in severely ill patients on a day-to-day basis. It would thus provide an additional parameter to predict progression or remission of a disease. No other laboratory parameter showed a better prognostic value than serum cholesterol. It must be pointed out, though, that population I was selected in terms of hypocholesterolemia, and population II did not allow such analysis due to technical limitations. Even though some laboratory values correlate well with the severity of certain diseases, such as creatinine kinase in myocardial infarction [13], the convenience of plasma cholesterol is its nonspecificity, which makes it suitable as a universal parameter for mortality in many critically ill patients. The determination of serum cholesterol has the advantage over other laboratory parameters that no therapeutic measures are directed towards its normalization and thus do not alter its levels.

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