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Hypocholesterolemia and risk of death in the critically ill surgical patient

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Abstract *Objective:* To evaluate the additional information provided by the determination of cholesterolemia to the Acute Physiology and Chronic Health Evaluation (APACHE) II score.
Design: Retrospective evaluation of patients admitted to the intensive care unit (ICU).
Setting: ICUs in a university hospital.
Patients: 638 consecutive critically ill surgical patients.
Interventions: Surgical and medical therapy according to clinical status.
Measurements and main results: Two indices were devised: DELCUPOS and DELCUNEG (cubed absolute value of the difference between measured cholesterol and the value of 190 mg/dl when cholesterolemia was, respectively, over and under 190 mg). The first estimation of cholesterolemia was taken upon admission to the ICU. The APACHE II score was computed from the worst values obtained during the first 24 h of the ICU stay, including the preoperative period for patients transferred from the operating theatre. Mortality (24.4%) over the whole time of hospitalization has been considered. A stepwise linear logistic regression on APACHE II, DELCUPOS, DELCUNEG, and on interactions among these three factors has been carried out. A U-shaped relationship between cholesterolemia and mortality was demonstrated. The significance of DELCUPOS ($p = 0.0021$) and DELCUNEG ($p = 0.0002$), considered together with the APACHE II score, has demonstrated an additive information content with respect to the APACHE score for the prediction of mortality.
Conclusion: Both hyper- and hypocholesterolemia have a highly significant relationship to mortality. Cholesterolemia improves the prognostic power of the APACHE II score. This result could be used to create a more powerful prognostic index.

Key words Hypocholesterolemia · Death rate · Cholesterol · Mortality · APACHE · Critical illness

Introduction

The relationship between hypercholesterolemia and cardiovascular risk in the surgical patient is largely accepted, but the risk related to hypocholesterolemia is not well known. Hypocholesterolemia is associated with many diseases [1–7]. A common pathophysiologic element of these chronic clinical situations could be the reduced availability, absolute or

relative, of nutritional factors related to energy metabolism.

Cholesterol is a basic element of cell membranes and is likely to be essential in large tissue repair processes, for instance in sepsis or after trauma. Therefore hypocholesterolemia may be an indicator of the metabolic response in stress.

We have studied the relationship between serum cholesterol levels and mortality in critically ill surgical patients. We have verified the hypothesis that cholesterolemia, particularly hypocholesterolemia, which has not been considered prognostically so far, could improve the predictive power of the prognostic index Acute Physiology and Chronic Health Evaluation (APACHE) II [8]. The hypothesis is plausible since cholesterolemia is related to metabolic functional status in a completely different way than the other APACHE II parameters.

Materials and methods

This investigation was carried out on 638 consecutive surgical patients admitted to the surgical intensive care unit (4 beds) and to the anesthesiological resuscitation unit (18 beds) of the Catholic University of the Sacred Heart, Rome. Patients were affected by diseases of general surgical interest, including both acute illness and complications of surgery. Most of these patients were septic (about 60%), with peritonitis, pancreatitis, complicated trauma, wound dehiscence, etc. (Table 1).

The analysis has been carried out considering the first estimation of cholesterolemia, which was taken on admission to the ICU. The APACHE II score has been computed from the worst values obtained during the first 24 h of ICU stay, including the preoperative period for patients transferred from the operating theatre.

Mortality over the whole time of hospitalization has been considered.

From the hypothesis that both high and low levels of cholesterol have a negative impact on prognosis, we have developed two indices: (a) DELCUPOS = cubed absolute value of the difference between measured cholesterol and the value of 190 mg/dl (the approximate mean over all patients considered) when cholesterolemia was more than 190 mg/dl; (b) DELCUNEG = cubed absolute value of the difference between measured cholesterol and 190 mg/dl, when cholesterolemia was less than 190 mg/dl.

DELCUPOS ranges from zero (cholesterol ≤ 190) to very high values when cholesterol rises above the normal range. This index, therefore, reflects the pathophysiologic impact of hypercholesterolemia, possibly related to cardiovascular risk. DELCUNEG ranges from zero (cholesterol ≥ 190) to very high values when cholesterol falls below normal levels. This index must be considered an expression of the pathophysiologic impact of hypocholesterolemia, possibly related to metabolic insufficiency.

The choice of a cubic function was made in order to have a steep slope in the outer arms of a U-shaped risk function, and it has proved itself to be sufficiently effective for the analysis at hand.

To verify whether cholesterol, in one or both of its two pathophysiologic meanings, is able to improve mortality prediction by APACHE II, a stepwise linear logistic regression on APACHE II, DELCUPOS, DELCUNEG, and on interactions among these three factors has been carried out.

Table 1 Major and associated diseases in the sample of patients ($n = 638$)

	%	No.
Mean age		
Males: 60 years	66	
Females: 59 years	34	
Major system affected		
Respiratory	10.2	65
Lung carcinoma		27
Thymoma		8
Trauma		22
Other		8
Cardiovascular	12.2	78
Leriche disease		30
Abdominal aortic aneurysm		20
Peripheral vascular disease		15
Other		13
Gastrointestinal	69	440
Secondary peritonitis		288
Postoperative peritonitis		29
Acute pancreatitis		26
Trauma		25
Gastrointestinal bleeding		57
Other		15
Neurologic	2.7	17
Metabolic	2.8	18
Renal	3.1	20
Associated chronic disease	53	
Hepatic	10.0	
Cardiovascular	24.5	
Pulmonary	12.2	
Renal	1.9	
Immune	4.4	
Significant categories		
Non-operative	11.3	
Emergency surgery	65.4	
Elective surgery	23.3	
Overall mortality	24.4	

Results

The overall observed mortality was 24.4%. Figure 1 shows the percentage mortality by the class of increasing cholesterolemia. The graph demonstrates the increased risk associated with both high and low serum cholesterol levels. No direct relationship was demonstrated between cholesterolemia and mortality: a Student's *t*-test between survivors and nonsurvivors for cholesterolemia was nonsignificant.

Table 2 shows the coefficients of the final linear logistic regression on APACHE II, DELCUPOS and DELCUNEG, together with their standard errors and their significance. No interaction factor was significant.

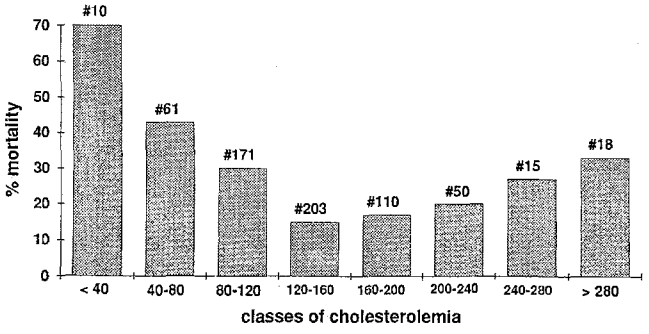

Fig. 1 Percentage mortality by the class of increasing admission cholesterolemia (mg/dl). # number of patients in class

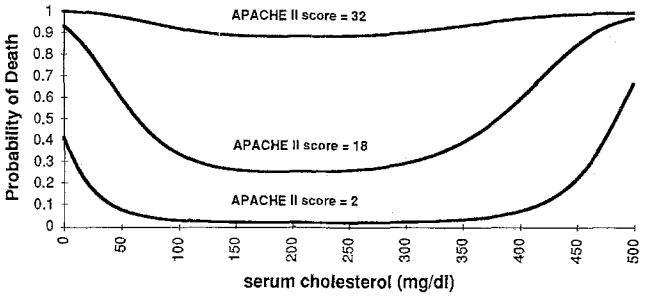

Fig 2 Model computed risk of death, as a function of cholesterolemia on admission for three sample constant levels (2, 18, 32) of admission APACHE II scores

Table 2 Coefficients *B* of the final linear logistic regression on APACHE II, DELCUPOS and DELCUNEG, together with their standard errors *SE*, degrees of freedom *df* and significance *Sig*

Variables in the equation				
Variable	B	SE	df	Sig
APACHE	0.1826	0.0172	1	$p < 0.0001$
DELCUPOS	1.58E − 07	5.137E − 08	1	$p < 0.0021$
DELCUNEG	5.31E − 07	1.403E − 07	1	$p < 0.0002$
Constant	− 4.3631	0.3272	1	$p < 0.0001$

The U-shaped relationship between cholesterolemia and mortality is demonstrated by significant coefficients for both DELCUPOS ($p = 0.0021$) and DELCUNEG ($p = 0.0002$).

The significance of DELCUPOS and DELCUNEG, when considered together with a highly significant APACHE II score, demonstrates the additional information that cholesterolemia provides to the APACHE score to predict mortality.

If

$$\lambda = \beta_0 + \beta_1 \text{ APACHE} + \beta_2 \text{ hyperchol} + \beta_3 \text{ hypochol}$$

and

$$P = e^{\lambda}/(\lambda + e^{\lambda})$$

are, respectively, the linearly determined exponent and the probability of death, it can be seen that the effect of hypercholesterolemia on λ is approximately half of that of hypocholesterolemia, their effects on P varying according to the actual level of the APACHE score and cholesterol in a nonlinear fashion. For very high values of APACHE II (very high risk of death) or for very low values of APACHE II (very low risk of death), the weight of cholesterolemia on prognosis is limited, while for intermediate values of APACHE II, where the departure of its component indices from their population mean is small, the additive effect of cholesterolemia on predictive power is greater (Fig. 2).

Discussion

In the critically ill surgical patients admitted to our ICUs, we observed a 38% frequency of cholesterolemia below 120 mg/dl. In a similar investigation carried out on all the patients admitted to the surgical wards of our hospital from 1969 to 1991 (7286 patients), a 17% prevalence of cholesterolemia < 130 mg/dl has been observed (unpublished data). These data underscore the fact that hypocholesterolemia is often observed in the whole population of surgical patients and occurs particularly frequently in critically ill patients.

Hypocholesterolemia has been observed in many chronic (neoplasia) and acute diseases (burns, trauma, infections, pancreatitis). Total serum hypocholesterolemia is associated with a lower than normal cholesterol content of the low density lipoprotein fraction of serum lipoproteins [9]. Caloric or protein deficiency could be one of the causes of hypocholesterolemia. Nevertheless, malnutrition is probably not the only cause. Experimental data have proved that endotoxins, cytokines, and mediators of inflammation are able to lower cholesterol levels through a different mechanism than malnutrition alone [10–12]. Furthermore, in some recent studies carried out on elderly subjects, gross malnutrition indices (weight, low lean body mass and low fat mass) did not correlate with hypocholesterolemia, even though it was present [13].

The absence of cholesterol in total parenteral nutrition solutions, which are often used in critically ill patients with acute abdominal illness, could be another cause of hypocholesterolemia, together with hypercatabolism and intestinal malabsorption.

It is reasonable to assume that all of these elements were present in the patients in our study. But a more exciting explanation of the reduced cholesterolemia in

critically ill patients and its association with mortality could be traced back to the role of cholesterol in cell membrane physiology. Even though cholesterol is synthesized in the endoplasmic reticulum, a rapidly developing cell needs six times as much as its maximal rate of biosynthesis is able to provide [14].

The importance of cholesterol content on cell membrane fluidity and microviscosity could explain the observed correlation between cholesterolemia and the alterations observed. Indeed, lipid microviscosity affects transmembrane transport phenomena, stimulus transmission, linkage with receptors, and enzymic activities. Cholesterol reduction would lower membrane lipid microviscosity, thus decreasing the exposure of membrane proteins and reducing membrane functions [15].

Hypocholesterolemia can be considered the result of a disequilibrium between cell requirements and cholesterol availability. Cellular growth, which accompanies tissue repair and activated immune defences, increases in conditions of stress, necessitating a greater amount of cholesterol to synthesize new membranes. Increased cholesterol uptake and decreased nutritional intake (malnutrition), together with the possible role of lowered hepatic synthesis, could explain why we observed low cholesterol levels.

Cholesterolemia could then be an overall indicator of insufficient metabolic adaptation to the rising needs [16]. We demonstrated a highly significant relationship between cholesterolemia and mortality in critically ill patients, with a likely pathophysiologic mechanism different from that of hypocholesterolemia. The mechanism could be the expression of the risk connected to the insufficient metabolic adjustment, while hypercholesterolemia could reflect the well known cardiovascular risk. In the study conducted on elderly subjects, the same U-shaped relationship between cholesterolemia and mortality was observed [13].

Even though APACHE II is a reliable prognostic score in critical situations, it does not include indices of metabolic compensation. Even pH, considered in the score, correlates more with contingent availability of oxygen to tissues than with overall metabolic compensation.

In their search for a more powerful prognostic index, the APACHE II authors propose to include albuminemia in the new APACHE III score [17], to benefit from the additional effects of a metabolic parameter which expresses protein synthesis [8]. Nevertheless, albuminemia is affected by many factors, depending on vascular permeability, tissue hydration, and therapeutic supplementation. Albuminemia often shows wide fluctuations from day to day, while cholesterol tends to be much steadier. In Fig. 3, the trends of serum albumin and cholesterol in one of our patients are shown.

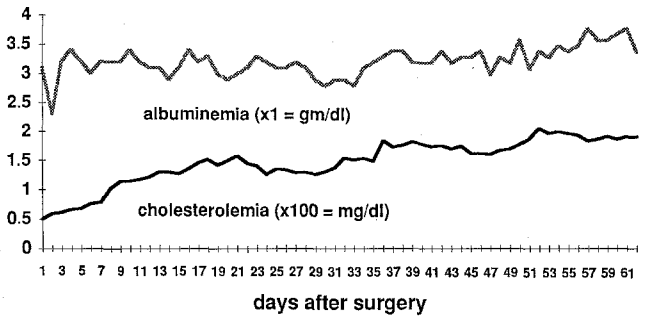

Fig. 3 Representative trends of serum cholesterol and serum albumin over time in one patient (62 days, patient 372, postoperative peritonitis after gangrene of the bowel)

The association between cholesterolemia and the APACHE II score, in its present formulation, improves the prognostic power of the latter: this is consistent with the hypothesis of the independent prognostic significance of cholesterolemia, which was not included in the original APACHE II parameters. The eventual incorporation of cholesterol in a revised score would depend upon the absence of colinearity between cholesterol and the other score components in the sample of patients considered. However, our result indicates the likelihood that cholesterol or other indices of metabolism would contribute additional independent information, as also suggested by physiologic considerations.

In analyzing APACHE in different risk classes, we have noticed that its predictive power is particularly good in extreme situations (very low or very high risk) and less accurate in the intermediate severity range. It is exactly in these situations that the additional effect of cholesterol is pronounced and useful for improving prediction of prognosis.

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