Editorial

Wien Klin Wochenschr (2003) 115/21–22: 740–742

wiener klinische wochenschrift
the middle european journal of medicine
Printed in Austria

Is cholesterol a conditionally essential nutrient in critically ill patients?

Cholesterol has such a low reputation in modern medicine that it is frequently overlooked what a broad spectrum of important physiologic functions it has to fulfil. Usually, cholesterol is mainly discussed in the context of hypercholesterolemia as a risk factor for vascular disease. In sharp contrast, hypocholesterolemia rarely is an issue and if so, mostly in association with psychiatric illness, depression, or suicidal and aggressive behavior as a side effect of cholesterol lowering therapy. However, because of the central role in metabolism and cell function cholesterol might even become a conditionally essential nutrient in disease states associated with a decrease in plasma cholesterol concentration.

Cholesterol and its many tasks

Cholesterol has a crucial role in membrane composition and function. Cholesterol and phospholipids are the principal constituents of biological membranes, the cholesterol/phospholipid molar ratio being the main factor that determines the microviscosity of lipid regions. This affects many membrane protein functions, including transport processes, signal transmission, receptor binding, enzymic activity, and protein phosphorylation.

Cholesterol has also an important function in VLDL formation and secretion (which is impaired in critical illness). As a constituent of bile cholesterol exerts a protective effect against the toxic action of bile salts on the mucosa (again important in intensive care patients).

In addition cholesterol has important functions in intracellular metabolism and acts as precursor of many hormones, such as steroid hormones and sex hormones and furthermore is involved in the metabolism of vitamin D.

Thus, it is not surprising that the body does not rely on exogenous cholesterol intake and the major fraction of cholesterol turnover is covered by endogenous production. Exogenous cholesterol however, presents a main regulator of endogenous cholesterol synthesis.

Hypocholesterolemia in the critically ill

It is an already old observation that plasma cholesterol decreases during acute illness. In recent years several reports have tried to further characterize this phenomenon [1–3]. The extent of the decrease of plasma cholesterol is related both to the duration and severity of disease. Furthermore, hypocholesterolemia has been observed during prolonged artificial (parenteral and enteral) nutrition (which is essentially cholesterol-free).

Other affected patient groups include the elderly, the malnourished patients, patients with hematological malignancies and with solid tumors [4, 5]. Since the liver is the main organ of cholesterol synthesis it is not surprising that patients with acute and/or (acute on) chronic liver failure have the lowest cholesterol concentrations.

In all these groups a tight association between the extent of hypocholesterolemia and prognosis has been demonstrated. Cholesterol in fact, has been proposed as a prognostic indicator in several patient groups [6–8].

Causes of hypocholesterolemia in critical illness

The potential mechanisms leading to hypocholesterolemia in the critically ill are poorly understood. The main cause certainly, is reduced endogenous cholesterol production. We must assume that this decrease in hepatic cholesterol production presents an element of the acute phase response, i.e. cholesterol presents a negative acute phase reactant [9, 10]. This is also underlined by the dependence of the extent of decrease of serum cholesterol on the severity of disease. An investigation of Bakalar B. and coworkers reported in this issue of *Wiener klinische Wochenschrift* demonstrates that in trauma patients the formation of precursors of cholesterol synthesis, such as lanosterol or lathosterol, is pronouncedly depressed [11].

In critical illness it must be assumed that cholesterol requirements for membrane formation are increased, that cholesterol catabolism is augmented, which could contribute to the fall in serum cholesterol.

One obvious cause of hypocholesterolemia is the low cholesterol intake with conventional artificial nutrition regimens. Currently, both enteral and parenteral nutrition regimes have a very low content of cholesterol and other steroids, mostly as plant sterols [12]. Available lipid emulsions have an average cholesterol content of less than 50 mg per liter.

Hypocholesterolemia in the critically ill: adaptive or maladaptive?

The central question is whether hypocholesterolemia should be accepted as a physiologic reaction of the body i.e. an adaptive response to critical illness or alternatively, whether the fall of plasma cholesterol can induce untoward side effects under certain conditions, such as during prolonged critical illness, and therefore cholesterol should be replaced. This discussion is paralleled by similar questions such as those relating to anemia, to hypoalbuminemia or to decreased selenium levels in the critically ill. It must be noted however, that evolution has taken place

without the availability of modern intensive care medicine. A "physiologically" reduced plasma concentration in critical illness does not necessarily imply that this decrease is beneficial, does not mean that it might not be advantageous to replace some of the negative phase reactants, as was shown for some nutrients (selenium).

Cholesterol as a component of artificial lipid emulsions

Because of these considerations we have sought a means of including cholesterol into a parenteral nutrition regimen. To achieve this goal we have designed the first cholesterol-containing lipid emulsion for intravenous nutrition therapy. Cholesterol was not mixed into an existing emulsion but was added *ex-ovo* during the production process of an otherwise identically composed conventional soybean oil – based lipid emulsion.

During the first investigations in healthy subjects we made an unexpected, surprising and unintended finding, a type of scientific discovery which often is termed as "serendipitous" and which is reported in this issue of *Wiener klinische Wochenschrift* [13]. Remarkably, the utilization (hydrolysis, lipid oxidation) of the artificial lipid emulsion was profoundly improved by the addition of cholesterol as compared to a conventional lipid emulsion.

During the last decades the development of lipid emulsions for parenteral nutrition has been focused mainly on the triglyceride moiety, the oil composing the lipid phase: soy bean oil, safflower oil, olive oil, coconut oil (as a source of middle chain triglycerides), fish oil (as source of ω-3 fatty acids) etc. (see also the editorial in this issue [14]). Cholesterol containing lipid particles have only been used as physiologic models to study lipoprotein metabolism and to mimic endogenous lipoprotein fractions [15–17]. These cholesterol containing emulsions have also been evaluated as drug carriers for drug targeting in neoplastic diseases [18]. For the use in parenteral nutrition, inclusion of cholesterol certainly would present the first fundamental change in the composition of lipid emulsions since their introduction in clinical medicine in the sixties.

Potential advantages of cholesterol supplemented lipid emulsions

Thus, the addition of cholesterol to a lipid emulsion presents a means not only to provide cholesterol in parenteral nutrition (the advantages of which have to be demonstrated in future studies) but also to improve the utilization of a lipid emulsion for parenteral nutrition. The addition of cholesterol reduced triglyceride levels, increased free fatty acid concentrations and exerted an insulin sparing effects compared to a conventional emulsion. There was also a higher formation of ketone with potential metabolic advantages such as the specific support of colonic mucosa and the prevention of intestinal translocation of bacteria.

There is a further interesting aspect. Various lipoproteins have the potential of binding endotoxin. During the last decade several artificial emulsions have been developed as an adjunct to sepsis therapy for removing endotoxin from the circulation. Cholesterol as a component of artificial lipid particles might have additional advantages in this context. Already more than 100 years ago the pharmaceutical company Bayer has issued a patent on an injectable cholesterol preparation for the treatment of infections ("Lipochol"). Certainly, it remains to be demonstrated whether cholesterol containing lipid emulsions have a higher ability to bind endotoxin than conventional preparations.

Outlook

The main question that remains unanswered, and cannot be answered at this time, is whether critically ill patients and especially those on prolonged artificial nutrition should receive cholesterol as a conditionally indispensable nutrient. This might be especially important in patients with acute or (acute on) chronic liver failure. There is increasing evidence that this might well be the case.

The second question is whether in the future lipid emulsions should contain cholesterol to reshape the artificial fat particles into a more chylomicron-resembling state with the aim to improve the utilization of intravenous lipids. Again, several lines of evidence would support such an approach. However, given the tremendous costs associated with the development of new therapies for intravenous use it remains questionable whether any pharmaceutical company will enter such a venture.

Wilfred Druml

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Key words: Cholesterol, intravenous therapy, essential nutrients, hypocholesterolemia, lipid emulsions, lipid utilization.

Correspondence: Prof. Dr. Wilfred Druml, Klinik für Innere Medizin III, Abteilung für Nephrologie, Währinger Gürtel 18–20, A-1090 Vienna, Austria,
E-mail: wilfred.druml@akh-wien.ac.at