Forget glucose: what about lipids in critical illness?

Although extensive research has focused on the role of lipids and lipoproteins in atherosclerosis and cardiovascular disease, less is known about their potential roles in critical illness. From the extensive cardiovascular literature, a high serum cholesterol concentration is a risk factor for cardiovascular disease and has commonly been linked with worse outcomes. It is now well recognised that, in many critically ill patients, the opposite is true, with hypcholesterolaemia being associated with poor outcomes.

For more than 80 years, authors have described alterations in serum lipid profiles associated with a variety of infections and inflammatory diseases. We have only a limited understanding of the extremely complex mechanisms that regulate the inflammatory response and the metabolic changes that accompany it. A decade ago, a review of the variables affecting outcomes from critical illness included a section on cholesterol concentrations, among other well-known factors such as age. It remains unclear whether these observed alterations in lipid profile are a consequence of the physiological disturbance and simply reflect the severity of illness or whether they have a more causative role, worsening organ dysfunction or predisposing to infection. We do not know if manipulations aimed at correcting these lipid changes in critically ill patients affect the pattern of disease, illness severity or patient outcomes.

**Basic lipid physiology**

Lipids are a vital component of almost all aspects of intermediate metabolism. They provide a source of energy, play a role in the structural integrity of cells, and are precursors for the synthesis of a variety of compounds required for vital cell functions throughout the body. Common compounds in the body classified as lipids include triglycerides, phospholipids and cholesterol. Triglycerides and phospholipids share a basic chemical structure, being composed of long chains of organic fatty acids. Although cholesterol does not contain fatty acids, it shares many of the physical and chemical properties of these other lipids because its sterol nucleus is synthesised from portions of fatty acid molecules. These fatty acids are categorised on the basis of chain length (short chain, \( <8 \) carbon atoms; medium chain, \( 8 \) to \( 14 \); and long chain, \( >14 \)) and also number of double bonds (fully saturated, when no double bonds exist between the carbon atoms; monounsaturated; and polyunsaturated). The polyunsaturated fatty acids (PUFAs) are further subdivided into \( n-3 \), \( n-6 \) and \( n-9 \) (also known as omega-3, omega-

**ABSTRACT**

A high serum cholesterol level is a risk factor for cardiovascular disease and has commonly been linked with worse outcomes. It is now well recognised that, in many critically ill patients, the opposite is true, with hypcholesterolaemia being associated with poor outcomes. In critical illness, particularly sepsis, total and high-density lipoprotein (HDL) cholesterol levels are commonly decreased, with varying changes in triglyceride levels. The magnitude of the changes seems to reflect the severity of inflammation.

Plausible biological explanations exist to explain these associations, including an interaction of lipoproteins with endotoxin and the regulation of cytokine production. It remains unclear whether these observed alterations in lipid profile are a consequence of the physiological disturbance or whether they have a more causative role, worsening organ dysfunction or predisposing to infection.

Lipid emulsions provide a vehicle for drug delivery, have become an important part of nutrition, and are emerging as a therapy for specific intoxications. The nature, dietary source and amount of lipid provided to critically ill patients may be enormously important and warrant more rigorous investigation. Further understanding of the alterations in lipid metabolism may have therapeutic implications in treatment of sepsis with specific compounds that manipulate lipid profiles, such as fibrates, statins, niacin and even reconstituted HDL.

6 and omega-9 fatty acids on the basis of the position of the final carbon–carbon double bond, as counted from the methyl end of the molecule. Humans are unable to synthesise some of these fatty acids (linoleic acid and \( \alpha \)-linolenic acid), which hence must be obtained from the diet and are termed essential. The chain length and number of double bonds have a major influence on the physical properties, including fluidity and membrane function, and potentially the nature of any acute phase response.

In an average Western diet, about 40% of calories are derived from fats (almost as many as are derived from carbohydrates); in addition, much of the carbohydrate absorbed is converted to triglycerides, which are stored as fat for later conversion to energy. The body can store only a small amount of glycogen (a few hundred grams) compared...
with kilograms of fat. Each gram of fat contains almost 2.5 times the energy of glycogen, and almost all cells except the brain and red blood cells can use fatty acids for energy. At least six hormones, including insulin, have a significant impact on fat utilisation, and many of these are altered in critical illness. Adrenaline and noradrenaline activate hormone-sensitive triglyceride lipase, dramatically increasing fat utilisation. Corticotropin, glucocorticoids and growth hormone also activate hormone sensitive lipases to a lesser extent. Thyroid hormone can increase fat utilisation, and the observation that cholesterol level is elevated in hypothyroidism and decreased in hyperthyroidism was used historically to guide thyroxine replacement therapy.4

The role of cholesterol
Although humans obtain some exogenous cholesterol from the diet, even more is synthesised in the body (endogenous cholesterol). Nearly all cells in the body can synthesise cholesterol. It is removed primarily by the liver, and large amounts are precipitated in the skin, where it is vital to the skin’s function as a barrier to both loss and absorption of water and water-soluble substances. The major non-membranous use of cholesterol is to form cholic acid in the liver, which is conjugated with other substances to form bile salts. A small quantity is used to form the adrenal hormones, oestrogen, progesterone and testosterone. Cholesterol and phospholipids are also structural components of membranes: the ratio of one to the other is vital in maintaining membrane fluidity. Phospholipids are also integral to compounds such as thromboplastin and sphingomyelin in the central nervous system and are donors of phosphate radicals for chemical reactions. They are an important constituent of lipoproteins and so have a central role in lipid transport.

Lipid transport: lipoproteins
In healthy, dietary fats are absorbed from the intestine into intestinal lymph. Digested monoglycerides and fatty acids are resynthesised into new triglyceride as they pass through intestinal epithelial cells. This enters the lymph as minute droplets (chylomicrons), which are transported to the venous circulation via the thoracic duct. For an hour or so after fat ingestion, the plasma may contain up to 1%–2% chylomicrons and appears yellow and turbid as a result. As circulating blood passes through adipose tissue and the liver, the chylomicrons are rapidly cleared by the enzyme lipoprotein lipase. This enzyme is particularly active in capillary endothelium, where it hydrolyses triglycerides and phospholipids of the chylomicrons to fatty acids, which rapidly cross the cell membranes. The activity of this enzyme may be altered in sepsis and several disease states, resulting in acute elevations in triglycerides, with potential clinical consequences, such as pancreatitis and pulmonary or hepatic dysfunction.5

At times other than after meals, most of the lipid in plasma is present as lipoproteins, which are much smaller particles than chylomicrons. There are four major types of lipoprotein (or six, if chylomicrons and chylomicron remnants are included). They have traditionally been classified by their densities on ultracentrifugation as:
- VLDL (very low-density lipoprotein), which contains triglyceride and moderate amounts of cholesterol and phospholipid;
- IDL (intermediate-density lipoprotein), which has some of the triglyceride removed;
- LDL (low-density lipoprotein), which has almost all triglyceride removed and so has a very high proportion of cholesterol and phospholipid; and
- HDL (high-density lipoprotein), which contains about 50% protein and much smaller concentrations of cholesterol and phospholipid.

Specific apoproteins are found on the surface of these lipoprotein molecules and determine their specific activities, often by interacting with particular enzymes or receptors. Improved understanding of the structure and function of lipoproteins has led to their being more appropriately classified on the basis of composition and role of the apoproteins. For example, HDL has several subclasses based on the type of apolipoprotein present — Apo A-I or Apo A-II. These apoproteins not only provide structural stability to the lipid complex but also are fundamental in mediating receptor uptake and enzyme interactions. It is possible that the apoproteins rather than the lipid moieties are responsible for many of the protective effects of lipoproteins, and more research is needed to better delineate these interactions.10

High-density lipoprotein
HDL is the major plasma lipoprotein in human plasma, accounting for 10- to 20-fold more particles than the total number of all other lipoprotein particles combined. It appears to have several unique structural and functional properties that are directly relevant in the critically ill, warranting special consideration. HDLs are the smallest, most tightly packed lipoproteins, and are better able to penetrate between endothelial cells, to be found in the highest concentrations in tissue fluid. HDL has been referred to as the “guardian” of the vascular system because one of its primary functions is reverse cholesterol transport, essentially mopping up cholesterol from the tissues and blood vessels and facilitating its carriage back to be degraded in the liver. The clinical importance of this role is highlighted by the inverse correlation between circulating HDL concentration and risk of atherosclerosis and cardiovascular events. It is now realised that HDL plays a more general endothelial protective role and may possess immunomodulatory and antioxidative properties.11
Lipoprotein alterations in critical illness

We know that an individual's lipid profile changes dramatically when they become ill, although the fundamental reasons are not well understood. These alterations have been described in patients with a wide range of disorders, including myocardial infarction, infection, burns and cancer, and postoperatively after major surgery. The type of critical illness appears to influence the alterations, and we now know that the magnitude and pattern of the changes appear to correlate with severity of illness and patient outcome.

Metabolic abnormalities in patients with severe infection are so important that sepsis has been defined as an acquired disease of intermediary metabolism. Early reports described a marked increase in triglyceride-rich lipoproteins. This cytokine-induced hyperlipoproteinaemia, clinically termed the “lipaemia of sepsis”, was originally thought to represent the mobilisation of lipid stores to fuel the host response to infection. The increased triglyceride was thought to be a consequence of enhanced hepatic VLDL production and inhibited clearance. Several subsequent studies noted a variable triglyceride response, with low levels that recover slowly over time. More consistent patterns have been observed for total and HDL cholesterol in sepsis, with a decrease in both. The magnitude of the change seems to reflect the severity of inflammation. Both the amount and composition of HDL change in sepsis, and this may have an effect on the inflammatory cascade and outcome. HDL has been postulated as a marker of illness severity, and so allows reverse cholesterol transport. Inhibition of this enzyme therefore decreases HDL formation. It appears most likely there is a multifactorial mechanism or several disease-specific processes.

What are the mechanisms for lipoprotein change?

At least four possible explanations exist for the observed changes in lipoprotein levels. Firstly, it has been postulated that the decrease in lipid levels is a result of its consumption through binding and neutralising of toxic bacterial substances. Many lipoproteins appear to bind and neutralise bacterial lipopolysaccharide. Of all the lipoproteins, HDL has the highest lipopolysaccharide-binding capacity, and this would be in keeping with the observation that its plasma levels decrease the most in sepsis. Lipoproteins may represent an important component of the innate, non-adaptive immune response to infection.

Secondly, perhaps high concentrations of cytokines suppress lipoprotein synthesis. Certainly, cytokine levels are elevated and correlate with reduced lipoprotein concentration. Cancer therapy trials have shown that infusion of tumour necrosis factor is associated with a significant, unexplained decrease in serum cholesterol.

A third explanation may be a dilutional effect, as reduced cholesterol levels correlate with haematocrit. Giovannini et al found that an association with prothrombin activity, haematocrit and alkaline phosphatase accounted for 65% of the variability of cholesterol levels, independently of the more commonly listed factors, such as basal cholesterol, nature, severity and stage of disease, and nutritional support regimen.

A fourth postulated explanation is that the decrease in HDL is mainly caused by decreased activity of the enzyme lecithin:cholesterol acyltransferase. This enzyme promotes maturation of HDL by accumulation of cholesterol esters and so allows reverse cholesterol transport. Inhibition of this enzyme therefore decreases HDL formation. It appears most likely there is a multifactorial mechanism or several disease-specific processes.

The place of lipid therapies in the ICU

Future therapeutic options in the treatment of sepsis may include specific compounds to manipulate lipid profiles, such as fibrates, statins, niacin, and even reconstituted HDL. Transgenic mice with elevated HDL or LDL are all resistant to endotoxin. In small studies in human volunteers, the effect of endotoxin has been blocked by HDL infusions. While some authors believe more refined lipid products hold promise, others express concern that the basic biology has not yet been fully understood, and perhaps the apoproteins, rather than the lipid moiety, are central to the process.

In general, statin therapy increases HDL levels in addition to its LDL-lowering effects. The effect of statin therapy on the lipid profile in sepsis remains poorly understood and is
currently under investigation.\textsuperscript{37,38} Although alterations in the lipoprotein balance may have effects on inflammation, these agents also possess several other properties that could prove beneficial for patients with sepsis.\textsuperscript{39}

It is also possible that recovery of cholesterol level is a common pathway for several therapies, such as early nutrition, improved glycemic control and steroid supplementation.\textsuperscript{12} Data from a subset of patients in a large trial of intensive insulin therapy found a strong and persistent correlation between correction in lipid levels, intensive insulin therapy and outcome.\textsuperscript{40} This may explain, in part, some of the benefits of targeting blood glucose control. Cholesterol, particularly HDL cholesterol, is a vital precursor for cholesterol synthesis. It has been postulated that, at times of stress and increased demand, a lack of cholesterol may influence cortisol synthesis.\textsuperscript{12,41,42}

**You are what you eat!**

Lipid-based nutrition provides essential fatty acids and has a high specific energy content, which can reduce use of carbohydrates and allay concerns about CO\textsubscript{2} production and hepatic side effects.\textsuperscript{43,44} The fat content and fatty acid composition of foodstuffs vary widely, with different food sources containing fatty acids with different chain lengths and saturation patterns. Of particular relevance may be the balance of the n-6 PUFA, arachidonic acid, which is the precursor of inflammatory prostaglandins and leukotrienes, and the n-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Fish oil is rich in n-3 PUFA\textsuperscript{45}, with the resultant widespread suggestions that it reduces inflammation by increasing EPA and DHA. The Western diet is now dominated by the potentially proinflammatory n-6 PUFA\textsuperscript{46}, which may adversely affect many diseases. Although a detailed assessment of dietary n-3 fatty acids is beyond the scope of this review, it is now well established that diets rich in n-3 PUFA\textsuperscript{47} can lower hypertriglyceridaemia and are beneficial for patients with heart disease.\textsuperscript{45} It is less clear, but possible, that they have a role for patients with mental illness (including delirium) or metabolic syndrome.\textsuperscript{3}

Of more relevance to intensive care is the possibility that n-3 PUFA\textsuperscript{48} offer therapeutic advantages in a range of conditions, including acute respiratory distress syndrome (ARDS), sepsis, atrial fibrillation, and perhaps even after major surgery or trauma.\textsuperscript{46,47} Leading nutrition guidelines now recommend a diet of anti-inflammatory lipids, such as n-3 PUFA\textsuperscript{3} (omega-3), for patients with ARDS.\textsuperscript{48}

Lipid emulsions have become an important part of total parenteral nutrition and provide a vehicle for drug delivery, most notably of the sedative agent propofol. They are also emerging as a therapy for specific intoxications. Recent reports suggest a role for intravenous lipid infusions as rescue therapy for patients with cardiovascular collapse after local anaesthesia and some other drug toxicities.\textsuperscript{49,50}

Several of these emulsions available worldwide contain varying mixtures of phospholipids and triglycerides designed to mimic chylomicrons. They have a triglyceride core coated with stabilising phospholipid and are generally handled by the body in a similar way to chylomicrons.\textsuperscript{5} It has been suggested that, if intravenous lipid emulsions contain excess phospholipid, this may alter the metabolism of both the administered solution and endogenous lipoproteins.\textsuperscript{51} It is clear that the nature, dietary source and amount of lipid provided as nutrition to critically ill patients may be of enormous importance and warrant more rigorous investigation, as current data remain inconclusive.\textsuperscript{52,53}

**Conclusion**

Alterations in plasma lipids may be profound in critical illness, particularly in patients with infection. Administration of lipid, as either nutrition or targeted therapy, may have a significant impact on metabolism and inflammation. However, much of the basic scientific research in this field has been conducted in animal models, particularly rats, which have LDL as the predominant lipoprotein rather than HDL as seen in humans.\textsuperscript{54} This fundamental difference casts doubt on the generalisability of animal data. Future research with therapies that target the altered lipid profile seen in critical illness may help clarify causal relationships, provide insights into basic biology and possibly improve patient outcomes.

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