Nutritional Support in Intensive Care Unit (ICU) Patients

Topic 18

Module 18.3

Lipids and Carbohydrates: How to Prescribe

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Learning Objectives

- Obtain knowledge of different lipids used in medical nutrition: specific metabolic and immune effects of fatty acids;
- The role of carbohydrates;
- Fat as substrates and fatty acid classification and main functions;
- Potential indications and controversies around omega-3 PUFA and the various IV fat emulsions;
- To be able to incorporate lipids and carbohydrates in a nutritional prescription.

Contents

Key Messages

- Fatty acids are essential to the critically ill patient;
- Intravenous lipids are an integral component of parenteral nutrition (PN); a balanced combination of fatty acids is required;

- Fatty acids have different profiles regarding immune and metabolic status;
- Carbohydrates are essential as energy source, within min. and max. values.

1. Lipids and Specific Fatty Acids

1.1 What Is a Lipid?

Lipids play an important role as source of energy in the human body (1).They provide structural and metabolically functional components of biological membranes (1). In parenteral nutrition, the lipids used contain fatty acids in the form of triglycerides (2). A triglyceride consists of 3 fatty acid molecules bonded to a glycerol molecule (1). A fatty acid is composed of hydrocarbon chains with a methyl group at one end of the chain and a reactive carboxyl group at the other end (2).

1.2 Fatty Acid Classification

Among lipids fatty acids are classified according to structural characteristics including chain length, the presence of double bonds in the chain, the position of double bonds, and their configuration (i.e. cis vs. trans) (2). They may be classified as saturated (no double bonds in the chain) or unsaturated (one or more double bonds in the chain), with the latter sub-classified as monounsaturated (one double bond in the chain: MUFA) or polyunsaturated (two or more double bonds in the chain: PUFA). According the chain length, fatty acids are termed short chain (< 8 carbons), medium chain (8 to 14 carbons: MCT) or long chain (16 or more carbons: LCT); fatty acids with chains of 20 or more carbons are sometimes referred to as very long chain. With regard to the position of the double bond within the fatty acid chain, three families are typically distinguished: omega-9, omega-6 and omega-3 (also referred to as n-9, n-6 and n-3). This terminology describes the position of the double bond closest to the methyl end of the chain.

1.3 Importance of Lipids

Fatty acids serve many functions including acting as energy sources, contributing towards the structure and physical properties of cell membranes, acting as precursors of bioactive lipid metabolites such as prostaglandins, and regulating cell responses including gene expression (1).
In clinical practice, they facilitate the process to provide enough calories within limited fluid volume (3).
Many fatty acids can be synthesized within the human body but two fatty acids (linoleic acid, an 18-carbon n-6 fatty acid, and alpha-linolenic acid, an 18-carbon n-3 fatty acid) cannot. These fatty acids must be supplied to humans and are referred to as essential fatty acids. The ICU patient requires 9 to 12 g/day of linoleic acid and 1 to 3 g of alpha-linolenic acid. The essential fatty acids are synthesized in plants and are found in high amounts in plant oils (e.g. corn, sunflower, soybean). They can be further metabolized to longer chain, more unsaturated fatty acids including arachidonic acid (n-6), and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (both n-3). Fish oil contains EPA and DHA. Olive oil contains the n-9 monounsaturated fatty acid oleic acid.
The two 18-carbon polyunsaturated fatty acids (PUFAs), linoleic (n-6) and alpha-linolenic (n-3) acid, are therefore essential dietary constituents. These two PUFAs as well as a rarer dietary n-6 fatty acid, gamma-linolenic acid (GLA) undergo elongation and desaturation in

the formation of the 20-carbon PUFAs: eicosapentaenoic acid (EPA; C20:5 n-3), arachidonic acid (AA; C20:4 n-6) and dihomo-gamma-linolenic acid (DGLA; C20:3 n−6). 20-Carbon fatty acids are incorporated into membrane phospholipids such as phosphatidyl-choline at the n-2 position and serve as precursors of the ubiquitous eicosanoids, oxygenated lipid mediators that modulate tissue function, vascular tone and inflammation. Docosahexaenoic acid (DHA, C22:6 n-3) can be formed from EPA and is a precursor for the 22-carbon docosanoids (4).

1.4 Metabolic and Immune Effects

n-3 and n-9 fatty acids differ in interactions and have different biological pathways. The link with inflammatory status is thereby made (5). Omega-9 fatty acids (e.g. olive oil) do not produce eicosanoids (5). The actions of olive oil based emulsions are correlated with reduced lipid peroxidation, reduced impairment of immune function and a neutral effect on inflammation (6-9).
Actions of n-3 poly unsaturated fatty acids could be correlated with different effects on immune cell functions and gene expression (10).
The various fatty acids may be used via enteral and parenteral routes, the latter being confronted with difficult stability issues, which explains the slow evolution towards emulsions with balanced fatty acid composition (11). Whatever the route, the proportion of the different fatty acids in the feeds will be the determinant of the body's membrane composition after their integration.
Oxidative stress is an imbalance between reactive oxygen species production and antioxidant systems (12). Free radicals are responsible for disruption of cellular processes. Oxidative degradation leads to cell damage. Increased numbers of double bonds (as in PUFAs) may increase the risk of lipid peroxidation. Although some suggestions are made, most studies reveal no difference in oxidative stress markers between olive oil-based and soybean oil-based, MCT/LCT or fish-oil based Intravenous Lipid Emulsions (ILEs)(13).

1.4.1 Metabolic Side Effects

Intestinal failure associated liver disease (IFALD) was often previously attributed exclusively to PN, hence the outdated term parenteral nutrition associated liver disease (PNALD). IFALD is a hepatobiliary disorder, ranging from simple steatosis (most common in adults) to cholestasis (most frequent in neonates + infants), cholelithiasis, and hepatic fibrosis which may progress to end-stage liver disease. It occurs in up to 15% of adult patients on long-term PN, and is even more frequent in children. The aetiology is multifactorial but includes macronutrient excess, specifically of lipids (LCTs are associated with lipid peroxidation in the liver), or general overfeeding. Ensuring that the patient is not overfed and stopping lipids will be the first options in such cases, but the introduction of n-3 PUFAs at low dose offers a therapeutic alternative. In adults and children, n-3 PUFAs have shown beneficial effects on liver function. In adults, differences are already significant after 5 days of PN, with much smaller increases of the liver enzymes (14). In children with intestinal failure and elevated bilirubin and other liver tests, the introduction of n-3 PUFA containing emulsions reduces these alterations in a few days (15).

In the majority of studies hepatobiliary marker levels are within normal ranges or within 1.5 times the upper limit of normal; in a review of 24 studies and 3 meta-analyses no clear pattern became obvious (16, 17).

The monitoring of the use of parenteral nutrition includes measuring plasma levels of triglycerides. Hypertriglyceridaemia in ICU is associated with sepsis, propofol use, lipid emulsions and overfeeding. Concentrations of triglycerides exceeding 500 mg/l (5.6 mmol/L), levels that are considered very high in non-critically ill subjects, should trigger prompt investigation. The regular determination of blood cholesterol (total or HDL) has however never been shown to be of relevance during critical illness (18).

1.5 Outcome

Currently there is limited evidence that one intravenous lipid emulsion offers any significant benefit over other ILEs on mortality. In subgroups of patients certain specific fatty acids might have potential benefits with clinical relevance.

1.6 Specific Intravenous Lipid Emulsions

1.6.1 LCT

Soybean oil-based lipid emulsions are historically the first safe lipid emulsions and have been used widely all over the world for more than 40 years (6). They are recognized as the reference lipid emulsion and have been studied in most of the conditions of critical illness. They are composed of LCTs containing mainly n-6 fatty acids, and their infusion is associated with high blood levels of the n-6 fatty acid linoleic acid and its metabolite arachidonic acid. This may produce pro-inflammatory eicosanoids that can upregulate inflammatory mediators like TNF-alpha (7).

1.6.2 LCT/MCT Mixtures

Most of the MCT studies were done in the 1990s, when they were introduced to the market. When LCT and MCT/LCT administration were compared, TNF-alpha production was lower with the latter (19). MCT/LCT mixtures have been associated with higher plasma prealbumin and insulin concentrations (20) and better nitrogen balances (21). It was shown that infusion of MCT resulted in significant ketogenesis (22), a reason for their mixing with LCT. LCT/MCT emulsions demonstrated a lower immunosuppressive effect in laboratory studies (23) and yielded fewer clinical infections. In a group of patients after orthotopic liver transplantation, the reticulo-endothelial function recovery was significantly better in the LCT/MCT group. These beneficial effects were observed while maintaining essential fatty acid status (24).

1.6.3 Olive Oil

Olive oil has built a reputation of safety and neutrality on immune response (25). A small randomized trial in burn patients investigated the metabolic effects of PN containing LCT/MCT compared to an olive oil-based emulsion (26). No difference was found in the levels of acute-phase proteins but a reduction in the inflammatory cytokine TNF-alpha was observed. Another retrospective study (27) found no differences in infection rate, acute-phase proteins, or major health outcomes in critically ill patients. The peak leukocyte count

and the fibrinogen level at the end of the study were higher in the olive oil group. Compared to LCT these emulsions cause fewer liver alterations (14). A review of the available literature confirmed their safety across a wide range of diagnostic categories (25).

1.6.4 N-3 Fatty Acids

N-3 fatty acids decrease the production of inflammatory cytokines and eicosanoids. They act both directly (by replacing arachidonic acid (AA) as an eicosanoid substrate and by inhibiting AA metabolism) and indirectly (by altering the expression of inflammatory genes through effects on transcription factor activation). Thus, long-chain n-3 fatty acids may benefit patients at risk of hyperinflammation and sepsis (28).
Intravenous fish oil, providing EPA and DHA, perfused to septic shock patients modifies the plasma free fatty acid composition to predominance of the n-3 acids EPA and DHA over AA (29). Mechanisms of action have been summarized elsewhere (30).

1.6.5 Mixtures of Fatty Acids

Technical developments have enabled the development of mixtures of lipids composed of LCTs, MCTs, fish oil and olive oil, which have been shown to provide better antioxidant status in stressed patients in the ICU. The latest randomised trials and meta-analysis show that these emulsions are safe, and cause less liver alteration than pure soya oil LCT emulsions (31-33). A meta-analysis of randomised controlled trials shows that these 4-oil emulsions are safe, and generally associated with less liver dysfunction and with attenuation of the inflammatory response (33).

1.6.6 Enteral Feeding Studies with Fatty Acid Modulation

Two prospective, controlled studies published in 2006 (33, 34) comparing two high fat enteral formulas previously used in Gadek's ARDS study (35) on critically ill patients showed promising results in conditions such as ARDS and severe sepsis. In Pontes-Arruda et al's randomized trial (33), including 165 patients with severe sepsis or septic shock and a PaO_2/FiO_2 ratio of < 200 mm Hg, n-3 enriched feeds improved clinical outcome and mortality rate, which was 32.7% versus 52.1% in the control group. New organ dysfunction was also reduced in the intervention group. Improvement in oxygenation and independence from mechanical ventilation were more readily achieved in patients receiving n-3 containing feeds. Singer et al's trial included 100 critically ill patients with ARDS or ALI (34), ventilated with a lung protective strategy. Compared to their baseline PaO_2/FiO_2, the n-3 group demonstrated significantly better increases in oxygenation on days 4 (48%) and 7 (25%) as well as faster recovery of lung compliance. Length (duration) of ventilation (LOV) was also shorter in the treatment group, but there were no significant differences in length of ICU/ hospital stay and mortality between the two groups. The problem with the studies was the high proportion of fat (52% of total energy in both groups) delivered to the patients which was not "standard", and probably explains why later randomised studies using lower amounts of fat did not show similar benefits (36, 37).
One of these trials which delivered n-3 twice-daily enteral supplementation was stopped for futility reasons (38). The interpretation of this later study was complicated by the fact that the intervention group received 5 times less protein, both groups being underfed.

In a study published in 2019 the effect of enteral fish oil on mortality was investigated in patients with acute respiratory distress syndrome (39). Seven studies were included in the meta-analysis and a favourable effect of the experimental approach was proven.

1.6.7 Parenteral Lipid Studies

The historical development and the time of the appearance of the fatty acid emulsions on the market explains the sequence of the published studies (11).
Intravenous lipid emulsions are first an energy source that provides 9 to 10 kcal/g of lipid. Further, they provide essential fatty acids (linoleic acid and alpha-linolenic acid). They can be administered safely at the rate of 0.7 to 1.5 g/kg/day (40), if triglyceride levels are monitored. They are found in esterified form in the bloodstream linked to glycerol (21).
Lipid formulations used in PN are composed of triglycerides with phospholipids as emulsifiers. There are a number of different formulations (40):

- Soybean oil-based; often referred to as long chain triglycerides (LCT) (although of course olive oil and the fish oils are also composed of LCTs);
- Mixtures (usually 50:50) of "LCT" and medium chain triglycerides (MCT);
- Mixtures (20:80) of "LCT" and olive oil;
- Structured lipids (these are triglyceride mixtures with predetermined-structured chain length formed by enzymatic manipulation of LCT and MCT) – structured lipids will soon disappear from the market as they are very expensive to produce;
- N-3 lipids from fish oil for use as a supplement to be combined with other oils;
- Mixtures of lipids including fish oil in variable amounts (e.g. 30:30:25:15 mixture of "LCT", MCT, olive oil and fish oil ; 40:50:10 mixture of "LCT", MCT and fish oil).

1.6.8 Clinical Studies

Use of IV fat emulsions containing olive and fish oil, is associated with improved clinical outcomes (41). A large unblinded, multicentre study including 661 critically ill patients (SAPS II score 32) showed that the impact of the n-3 emulsions on infection rate, antibiotic requirements, length of stay and on survival was dose-related, with an optimal impact with doses between 0.1 and 0.2 g/kg/day (42). The strongest effects were observed in patients with abdominal sepsis. Most studies have used n-3 PUFA in smaller doses and in surgical patients. Randomized trials consistently show a benefit on length of stay, with no impact on survival (43). This was confirmed by a meta-analysis including 23 studies and 1502 patients; the inclusion of n-3 in the lipid delivered with PN resulted in lower infection rates and shorter lengths of stay, yielding potentially important economic savings (44). An analysis including 451 adult patients on mechanical ventilation within 48 hours of ICU admission, receiving exclusive PN for $\geq$ 5 days, and on the same parenteral fat emulsion type during the data collection period seems to confirm the safety of n-9 and n-6 PUFA emulsions, and a survival advantage (45).
Meta-analysis from 2015 reinforced the conclusion of no difference in mortality from the use of intravenous fish oil (FO) lipid emulsions. A trend towards significance was found in the enteral feeding regimens. FO-containing lipid emulsions did reduce infections significantly. A reduction in hospital stay was significant in high quality trials (46). The most recent systematic review with meta-analysis comparing n-3 fatty-acid enriched parenteral nutrition to standard parenteral nutrition in adult patients evaluated 49 trials.

At an adequate amount of calories provided, the risk of infection and sepsis was reduced, and a non-significant reduction in mortality was observed (47).

1.7 Recommendations

'Lipids in the ICU' Expert group from ESPEN declared that fish oil enriched enteral and parenteral nutrition has additional benefits in surgical patients. They support the use of olive oil and fish oil in nutrition support (48).
The most recent 2018 ESPEN Guidelines state that a blend of fatty acids should be considered, including medium chain triglycerides, n-9 monounsaturated fatty acids and n-3 polyunsaturated fatty acids. There is no evidence for recommendation for fish oil enriched emulsions in non-surgical ICU patients as a standalone measure (49).

2. Carbohydrates

Carbohydrates comprise a combination of carbon, hydrogen and oxygen atoms. The formula of glucose is $C_6H_{12}O_6$. Different classes of carbohydrates are defined by their constituent monomers (eg glucose, fructose) and by different degree of polymerization (50).
Carbohydrates are the preferred substrate for the production of energy. In critical illness insulin resistance and hyperglycaemia are often present. Certain body cells such as brain cells but also red blood cells and cells from the immune system prefer glucose. An internal source of carbohydrates is the production by for example the liver: endogenous energy production. This activity is increased in critical illness and is not reduced when nutrients and insulin are administered. This in contrast with healthy volunteers, where suppression is possible (51).
Excessive glucose administration to patients can be associated with hyperglycaemia, enhanced CO_2 production, enhanced lipogenesis and increased insulin requirement.
This is why the amount of glucose (the only carbohydrate used in parenteral nutrition, although hypothetical alternatives are possible) or carbohydrates (enteral nutrition) administered to ICU patients should not exceed 5mg/kg/min (49).

3. Glucose Control

Hyperglycaemia is associated with adverse outcomes but ideal blood glucose target remains unclear. When a strict protocol is used tight glucose control can be effective in patients receiving parenteral nutrition (51).
Clinical guidance suggests checking plasma glycaemia every 4h on day 1 in ICU, but even more frequently in unstable patients. In stable patients it can be less frequent. The selected target could be 6-8 mmol/L (110-145 mg/dL) but discussion remains on this topic (18).

4. Clinical Guidance

Lipids and carbohydrates are started when nutrition therapy is indicated, as part of optimal nutrition. The upper limits are respected and different nutrients are balanced. This way the global benefits of nutritional therapy can be present including the effects of specific fatty acids (49).

The 2019 ESPEN Guidelines state: glucose max. 5 mg/kg/min, lipids max. 1.5 g/kg/day and that intravenous lipid emulsions should be a part of PN.

5. Summary

Fatty acids are special substrates for artificial nutrition. The addition of n-3 PUFA in enteral feeding, is scientifically sound and has been associated with clinical improvement in patients suffering from acute respiratory distress syndrome, acute lung injury and severe sepsis. Their administration is recommended in these conditions. When IV lipid emulsions are used, we may choose between various formulas. They may include soy-derived LCT and MCT, but also n-3 or n-9 fatty acid-enriched emulsions, as well as a mixture of all of the above. Clear clinical advantages of these newer emulsions have not yet been shown.
Different lipids and thereby fatty acids have different characteristics and lipids are a fundamental part of optimal nutrition. Carbohydrates need monitoring and anticipation of their effects on plasma glucose levels. Recommendations on the use of different intravenous lipid emulsions and dosing are available.

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