Diabetes and dyslipidemia

Module 22.2

Nutritional support in dyslipidaemia

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Learning Objectives

· To understand the influence of nutritional support on circulating lipids;
· To assess the risk of hypertriglyceridaemia in patients on parenteral nutrition;
· To know which conditions are associated with poor tolerance to lipid emulsions;
· To be aware of complications of increased plasma lipid level;
· To know how to feed patients with pre-existing hypertriglyceridaemia.

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Key Messages

· Dyslipidaemia is not a contraindication for nutrition support;
· Metabolism of lipid emulsions is similar to the metabolism of natural chylomicrons;
· Hypertriglyceridaemia is the main problem in clinical practice, mainly in parenteral nutrition;
· Dyslipidaemia during parenteral nutrition can be caused by many factors;
· Nutrition goals must be fulfilled in patients with dyslipidaemia who require nutritional support;
· Minimal amounts of lipid should be given to prevent essential fatty acid deficiency during artificial nutrition even in patients with dyslipidaemia;
· MCT and fish-oil containing lipid emulsions are promising in patients with dyslipidaemia.
1. Introduction

Lipid metabolism is dependent on genetic factors, disease processes, drug treatment and nutritional status. High concentrations of plasma lipids and lipoproteins are associated with chronic diseases, which are discussed in module 21.3. However, during acute illness an increase in plasma lipid level may negate any beneficial effects of nutritional support. An acute increase in plasma lipids, particularly triglycerides (TG), during artificial nutrition is usually the consequence of disturbed lipid metabolism combined with artificial, mainly parenteral, nutrition (PN).

The potential consequences of increased plasma lipid levels are:
- Phagocytosis of lipoproteins by macrophages with consequent activation of inflammation and depression of immune reaction;
- Rise of plasma phospholipid rich particles with subsequent cholestatic liver damage;
- Alteration of pulmonary haemodynamics;
- Impaired microcirculation;
- Acute pancreatitis.

Because an underlying abnormality of lipid metabolism is an important prerequisite for excessive elevation of plasma lipids during artificial nutrition, the aim of this module is to inform the reader about parenteral and enteral nutrition support in subjects with dyslipidaemia.

2. Lipid metabolism and nutrition

It is known that lipid metabolism and plasma lipid levels are very tightly influenced by food intake. An oral intake of fat, usually TG, leads to an increase in circulating chylomicron concentration and lipid levels, particularly TG. Milky plasma often follows a fatty meal, because chylomicrons produced by intestinal cells bypass the liver and, via the lymphatic system are transported directly into the systemic circulation (Fig 1). On the other hand medium chain fatty acids (MCT) are not re-esterified in enterocytes and are directly absorbed into the portal circulation. They are then oxidized in the liver or elongated and secreted into the systemic circulation as lipoproteins (VLDL and LDL). In the circulation, chylomicron particles exchange with HDL and LDL, a process mediated by CETP (cholesteryl ester transfer protein). The first gain cholesteryl esters and apoproteins while the latter gain TG and vitamin E. A large portion of TG present in chylomicrons is hydrolysed by the lipoprotein lipase present in the endothelium of various peripheral tissues (skeletal muscle and adipose tissue), leading to the formation of chylomicron remnants which are then taken up by the liver. The fatty acids released during this process are either oxidized by muscle or stored in adipose tissue.

In contrast to the chylomicrons, which are produced by the intestine, VLDLs are produced by the liver and transport triglycerides to peripheral tissues. After their secretion into the circulation, which takes place during the interprandial periods, VLDL undergoes an intravascular metabolism fairly similar to that of chylomicrons, leading to the formation of IDL particles. While a proportion of IDL is taken up by the liver, the remainder is converted to LDL.

Chylomicrons and VLDLs carry most of the circulating TG, the former during the postprandial period and the latter during the interprandial periods.
The final plasma lipid (or lipoprotein) level is the net result of a number of processes which raise or lower lipid levels:

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<th>Factors which increase plasma lipids</th>
<th>Factors which decrease plasma lipids</th>
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<td>- The rate of fat absorption and intestinal production of chylomicrons</td>
<td>- The rate of lipoproteins (VLDL, LDL, chylomicrons) clearance in peripheral tissues</td>
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<td>- The rate of lipoprotein VLDL production in the liver</td>
<td>- The rate of lipoproteins clearance in the liver (IDL, remnants)</td>
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Lipid emulsions administered during parenteral nutrition are composed of lipid particles similar to lipoproteins. These emulsions are oil-in-water mixtures made from a wide variety of lipids: n-6 polyunsaturated fatty acids from soybean oil, n-9 monounsaturated fatty acids from olive oil, n-3 polyunsaturated fatty acids from fish oil and MCT. The emulsions are available in final lipid concentrations of 10% or 20%. The egg yolk phospholipid, used as an emulsifier, is held constant, irrespective of the final lipid concentration. These particles are fairly similar to endogenous chylomicrons regarding their size (0.3µm diameter) and their lipid composition (a hydrophobic nucleus rich in TG with a surface rich in phospholipids). However, they do not contain any apoproteins, have a tiny amount of cholesterol with a relatively large abundance of phospholipids, but more importantly, a very different fatty acid profile.

The intravascular metabolism of lipid emulsions is comparable to some extent with that of chylomicrons. Upon their infusion into the circulation, these artificial particles rapidly acquire different apoproteins by transfer from HDL. Apo C-II, in particular, is critical for the recognition and binding to endothelial lipoprotein lipase which hydrolyses exogenous TG. In parallel, these particles transfer TG to endogenous LDL and HDL in exchange for cholesteryl esters, a process mediated by CETP and leading to the formation of remnants. The emulsion remnants are then taken up by the liver and other tissues for intracellular hydrolysis. In patients on continuous PN with fat emulsions, circulating TG is carried mostly by VLDL and emulsion particles, and in some conditions by chylomicrons (Fig. 2).
3. Influence of nutrition support on circulating lipids

Because TG is by far the most abundant fat used in artificial nutrition, as in oral nutrition, the main problem with nutritional support is hypertriglyceridaemia.

3.1 Enteral nutrition

A major increase in plasma lipid concentration is unusual during enteral nutrition because of the presence of several steps (digestion, absorption, reesterification), which prevent a critical rise of plasma lipids. Acute and critical increases in plasma lipids during enteral nutrition occur only in patients with genetic dyslipidaemia (especially type IV and rarely type I, II and V).

Enteral formulae contain mainly a selection of different vegetable fatty acids, and contain saturated, mono-unsaturated and poly-unsaturated fatty acids. Some formulae are enriched with medium chain triglycerides (MCT) to improve lipid hydrolysis and absorption. These are transported via the portal vein to be metabolized by the liver and therefore do not increase plasma lipid levels. MCT formulae are also used for enteral nutrition in subjects suffering from impairment of lymphatic circulation (chylothorax and chyloous ascite).

3.2 Parenteral nutrition

Negative effects of lipid emulsions were described thirty years ago when cotton oil and soy phospholipids were used for parenteral nutrition. These were not only due to the type and quality of lipid but also to the manufacturing process. Contamination of lipid emulsions played a role in causing serious side effects such as fever, thrombocytopenia, and bone marrow failure (S. Dudrick – personal communication). The safer lipid emulsion (Intralipid) that was developed by A. Wretlind was free of these side effects. However, the high phospholipid to triglyceride ratio present in Intralipid 10%, used in the early years of parenteral nutrition (4) probably contributed to an increase in lipoprotein X with hypertriglyceridaemia and to the development of hyperbilirubinaemia and cholestasis. The 20% lipid emulsions with a lower proportion of phospholipids are much better tolerated and are standard for nutrition support.

In one prospective study, hypertriglyceridaemia during PN in acute patients was observed in 26% of patients (3).

Several factors have been shown to predict hypertriglyceridaemia during PN:
- obesity (in particular abdominal);
• diabetes mellitus;
• renal failure (6) (in particular during dialysis);
• AIDS (in particular treated with HAART);
• chronic use of alcohol;
• critical illness (7) (burns, sepsis, acute pancreatitis);
• glucocorticoids (8);
• immunosuppressive drugs (cyclosporine, sirolimus);
• antipsychotic drugs (atypical or 3rd generation antipsychotics);
• propofol - is dissolved in lipid emulsion and can cause hyperlipidaemia.

Several features of the parenteral nutrition itself may also affect the risk of hypertriglyceridaemia: the total daily dose of fat emulsion, the rate of infusion of fat, the phospholipid-to-TG ratio (as discussed), the presence of MCT and fish oil (9), the nature of the container and the amount of glucose infused.

It was found that, not only the type of lipid emulsion but also the lipid container material is important for the tolerance of lipid emulsion. Administration of the same lipid emulsion in plastic bags compared with glass containers is associated with higher rates of hypertriglyceridaemia in critically ill neonates (10). The authors suggest that this is due to a higher proportion of large-diameter fat globules in plastic bags compared with those in glass container (11). Moreover, lipid emulsion particles seem to be less stable in plastic than in glass containers(12).

Total parenteral nutrition may alter plasma lipids and it is therefore important to monitor plasma lipids, particularly in those patients who have a pre-existing lipid abnormality.

4. Nutritional support in patients with dyslipidaemia

4.1 Enteral nutrition
In patients who need enteral nutrition support and who suffer from dislipidaemia, enteral nutrition is usually quite well tolerated. This is mainly due to the fact, that fat digestion, fatty acid absorption and production of chylomicrons delay plasma lipid appearance.

However, the type of dislipidaemia can influence effect of enteral nutrition support on plasma lipid levels. An increase in plasma lipid levels due to decreased clearance of chylomicrons or remnants (type I and III) can be prevented by reduction of lipid intake. MCT can be also useful, because medium chain fatty acids do not increase intestinal chylomicrons synthesis.

When the hyperlipidaemia is associated with glucose intolerance and diabetes (often in type IV), a decrease in carbohydrate intake may be more useful than a change in fat composition. It should be stressed that, during nutrition support for longer than 7 days, the total energy intake should be sufficient to prevent worsening of nutritional status. The only exception is the obese patient who needs simultaneous nutritional support and body weight reduction (see Module 21.2). Full nutritional support should be started after normalization of the plasma lipid level.

4.2 Parenteral nutrition

4.2.1 General rules
To prevent hypertriglyceridaemia, the amount of fat infused should be limited to a maximum of 1g·kg⁻¹·day⁻¹ using a slow rate of infusion (0.12 g·kg⁻¹·hour⁻¹). Continuous lipid infusion over 24 hours facilitates lipid oxidation and improves plasma fatty acid profiles in comparison with cyclic lipid infusion. The lipid infusion rate can be maintained at around 0.12 g·kg⁻¹·hour⁻¹, but lower rates may be necessary in critically ill patients or patients with impaired lipid clearance (see paragraph 3.2).

When propofol is prescribed, the PN lipid dosage should be adjusted to avoid hypertriglyceridaemia. Therefore, the amount of lipid provided by the propofol (0.1g·ml⁻¹) dose should be subtracted from the intended lipid dose in the PN formulation.
The use of 20% rather than 10% fat emulsion should be encouraged in order to decrease the phospholipid-to-triglyceride ratio and the level of lipoprotein-X that exacerbates the risk of hypertriglyceridaemia.

4.2.2 Pre-existing dyslipidaemia
Patients receiving PN must be monitored by measuring baseline serum TG concentrations before PN initiation and again once the lipid goal is reached (13). Other determinations such as serum phospholipids, fatty acids, cholesterol, and lipoprotein X levels are not performed routinely. Daily lipid infusion should be withheld when the serum is lipaemic or when serum TG concentrations exceed 3 mmol·l\(^{-1}\). In cases of pre-existing type IV lipid abnormality it is also necessary to limit glucose infusion to 4 mg·kg\(^{-1}\)·min\(^{-1}\) to avoid stimulating the production of VLDL rich in TG by the liver (14, 15). Some studies suggest that fat emulsions containing fish oil or structured lipids containing MCT are associated with a faster TG clearance (8).

To prevent essential fatty acid (EFAs) deficiency during low-fat or fat-free PN, 2–4% of total caloric intake should be provided as linoleic acid and 0.25-0.5 % as linolenic acid. Providing 250 ml of the 20% lipid emulsion twice weekly is sufficient to prevent essential fatty acid deficiency in adult patients. Hypocaloric or cyclic fat-free PN may extend the period of time before essential fatty acid deficiency occurs. In this case, it is thought that EFAs are mobilized from adipose tissue as the result of increased lipolysis due to a low insulin concentration during the periods without nutrition. Hypocaloric feeding can also improve liver dysfunction that may occur if the caloric deficit caused by the removal of fat emulsions is corrected by increasing the glucose calories to reach the energy goal. Lipid utilization can be improved by addition of cholesterol to lipid emulsions (16). This effect may be due to the reshaping of artificial lipid particles by cholesterol to a more chylomicron-resembling composition.

4.2.3 Pancreatic complications
One particular case of interest is the use of intravenous fat in acute pancreatitis (17). Hypertriglyceridaemia itself can provoke acute severe pancreatitis, especially when triglyceride levels exceed 10-12 mmol·l\(^{-1}\). Initially fluid resuscitation and parenteral nutrition must not contain lipid emulsion. When plasma lipid level normalizes, a low lipid intake (20 g·day\(^{-1}\)) to prevent EFAs deficiency is recommended (18). After normalization of plasma triglyceride concentration, a step by step increase to reach max. 3 mmol·l\(^{-1}\). This approach was not associated with adverse events, such as fatty acid deficiency or worsening of hypertriglyceridaemia (19).

However, enteral nutrition is undoubtedly the first choice for nutrition support in acute pancreatitis. Parenteral nutrition is reserved for those patients intolerant of enteral feeding.

5. Summary
Lipid metabolism is dependent on genetic factors, disease processes, drug treatment and nutritional status. Because of lifestyle the proportion of patient with dislipidaemia is rising and also therefore the proportion of patients with dyslipidaemia requiring nutrition support. Decreased tolerance to lipid emulsions is caused by endogenous factors (genetics or disease) but also by drug treatment.

Dyslipidaemia is not a contraindication for either enteral or parenteral nutritional support. Nutrition goals must be fulfilled to prevent catabolism and substrate deficiencies. Enteral nutrition is the preferred method of nutrition support in dyslipidaemic patients because it prevents sharp increase of plasma lipid level. When parenteral nutrition is necessary plasma lipid levels should be closely monitored. Although low fat parenteral nutrition is indicated in some cases, lipid intake must still guarantee the indispensable intake of essential fatty acids. In type IV hyperlipidaemia, the intake of carbohydrate must also be controlled. New lipid emulsions based on MCT and fish oil could be of some interest in these patients.

References
2. Carpentier Y. Lipids In L. Sobotka (editor), Basics in Clinical Nutrition, Galen 2004:72-78


