LLL Session - Nutrition support in diabetes and dyslipidemia

Prescription of artificial nutrition in patients with dyslipidemia

M.D. Ballesteros-Pomar (ES)
Nutrition support in diabetes and dyslipidemia

Prescription of artificial nutrition in patients with dyslipidemia

Dr. María D. Ballesteros-Pomar
Department of Endocrinology and Nutrition
León, Spain
Dyslipidemia

- Clinical consequences of high blood lipids
- Pathways of lipid transport

Dyslipidemia and LLDs in critically ill patients

- Lipoprotein alterations in the critically patient
- The place of lipid therapies in the ICU
- Statin withdrawal

Dyslipidemia in the patient on nutritional support

- Lipid metabolism of enteral nutrition and IVFEs
- Nutritional support induced hypertriglyceridemia
- Pre-existing dyslipidemia and nutrition support
Potential consequences of increased plasma lipid level

- Atherosclerosis
- 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.
Pathways of Lipid Transport

Dietary fat → Chylomicrons

FHTG (IV, VLDL)
LPL/apo CII deficiency (I, Chm)

FCHL (IIb, VLDL&LDL)

RRD (DysβL) (III, IDL)

FH (IIa, LDL)

Peripheral tissues

LDL-R cholesterol

HDL

CETP

FH (IIa, LDL)

LRP

Cholesterol

Bile acids cholesterol

Hepatic lipase

HipoαL

Adapted from Knopp. NEJM 1999

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Lipoprotein alterations in critical illness

• In critical illness, particularly sepsis, severe metabolic alterations have been described
  – insulin resistance
  – increased levels of triglycerides
  – total and HDL cholesterol levels decreased.

• HDL and LDL are regulators of the host immune response during endotoxemia
  – neutralize LPS
  – direct anti-inflammatory actions.
Lipoprotein alterations in critical illness II

The magnitude and pattern of the changes appear to correlate with severity of illness and patient outcome.

Higher mortality and infectious complications

- Hypocholesterolemia may be part of the negative acute phase response to acute illness
  - **Consequence** of the physiological disturbance and simply reflect the severity of inflammation
  - More **causative role**, modifying the host response to inflammation and worsening organ dysfunction or predisposing to infection.
# Changes in lipoprotein composition during infection and inflammation

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Effects</th>
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<tbody>
<tr>
<td><strong>TG, VLDL</strong></td>
<td>Cytokines (TNF-α, IL-1, IL-6) LPL activity ↓, TG hydrolysis ↓, Fat oxidation ↓</td>
</tr>
<tr>
<td><strong>Free FA</strong></td>
<td>TG synthesis ↑</td>
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<td><strong>HDL, LDL</strong></td>
<td>LPS, Cytokines</td>
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Changes in lipoprotein composition during infection and inflammation: TG

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<td><strong>TG, VLDL</strong></td>
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<td>Cytokines (TNF-α, IL-1, IL-6)</td>
<td>VLDL secretion ↑</td>
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<tr>
<td>LPL activity ↓</td>
<td>De novo fatty acid and hepatic TG synthesis ↑, fatty liver ↑</td>
</tr>
<tr>
<td>TG hydrolysis ↓</td>
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</tr>
<tr>
<td>Fat oxidation ↓</td>
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- Marked increase in triglyceride-rich lipoproteins (VLDL):
  - clinically termed the “lipemia of sepsis”

Changes in lipoprotein composition during infection and inflammation: IR

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<tr>
<td>Free FA</td>
<td>Free FA $\uparrow$ $\rightarrow$ diacylglycerol $\uparrow$ $\rightarrow$ PKC $\uparrow$</td>
</tr>
<tr>
<td></td>
<td>PKC $\uparrow$ $\rightarrow$ GLUT-4 translocation to cell surface $\downarrow$</td>
</tr>
<tr>
<td></td>
<td>PKC $\uparrow$ $\rightarrow$ IκB-α $\downarrow$ $\rightarrow$ NF-κB $\uparrow$</td>
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<tr>
<td></td>
<td>$\rightarrow$ $\downarrow$ cellular insulin-mediated glucose uptake</td>
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- $\uparrow$ plasma TG levels are critical determinants of inflammation-induced insulin resistance and are capable of amplifying the proinflammatory response.

Changes in lipoprotein composition during infection and inflammation: HDL, LDL

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<tr>
<td>HDL, LDL, Cytokines</td>
<td>Cholesterol synthesis ↓, LPL activity ↓, apoA-I ↓, apoA-II ↓, LCAT ↓, CETP ↓, PLTPmass ↓, PLTP activity ↑ → plasma HDL and LDL ↓ → conversion of HDL to pre-β-HDL (low in esterified cholesterol) → reverse cholesterol transport ↓ → HDL carrier function for antioxidative proteins ↓</td>
</tr>
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</table>

- These changes occur early during the course of systemic inflammation with cholesterol content in LDL and HDL decreasing within hours and are attributed to the effects of LPS and cytokines.
Lipoprotein alterations in critical illness: HDL

- Both amount and composition of HDL change: effect on the inflammatory cascade and outcome.

- Acute-phase HDL is smaller in size
- Contains less esterified cholesterol
- ApoA-I is replaced by serum amyloid A.
- SAA also displaces paraoxonase decreasing the antioxidative capacity of HDL

Crit Care Resusc 2009; 11: 305–309
Changes in LDL and adrenal failure

- Although decreased total and HDLc may reflect disease severity and be a manifestation of the negative acute phase response, the low cholesterol levels may predispose critically ill pts to endotoxemia, sepsis and MODS.

Cholesterol, particularly HDL cholesterol, is a vital precursor for cortisol synthesis.

It has been postulated that, at times of stress and increased demand, a lack of cholesterol may influence cortisol synthesis.

Low HDL levels may play an important role in reversible adrenal failure in critically ill patients.

It is also possible that recovery of cholesterol level is a common pathway for several therapies, such as early nutrition, improved glycaemic control and steroid supplementati on.
The place of lipid therapies in the ICU

Statins:
Beneficial effects independently of their lipid-lowering effects, including anti-inflammatory and immunomodulatory roles

• The effect of statin therapy in sepsis has not been proven
  – No beneficial role of continuing preexisting statin therapy on sepsis and inflammatory parameters
    

  – Continuing statin therapy in ICU septic patients was not associated with reduction in the severity of organ failure
    
Statin withdrawal: should statins be discontinued in patients with nutritional support?

**Acute vascular stress**

- Available clinical data suggest that interrupting statin therapy even for 1 day is associated with worse hospital outcomes. “STATIN WITHDRAWAL SYNDROME,”

- All measures that assure statins are continued, including administration via nasogastric tube, must be established.

**Chronic stable vascular atherosclerotic disease,**

- Statin discontinuation was not found to be associated with a greater incidence of adverse cardiovascular events. (TNT trial)

A background of an acute vascular injury is needed for discontinuation of statins to negatively impact patient outcomes.

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Enteral nutrition

- Lipid metabolism follows the same route
  - LCT packaged into chylomicrons and released into the lymph.
  - MCT transported by the portal blood directly to the liver

- Major increase in plasma lipid unusual because of the presence of several steps (digestion, absorption, reesterification),

- Only in patients with primary dyslipidaemia (especially type IV and rarely type I, II and V).
Intravenous fat emulsions (IVFEs)

IVFEs are designed to be similar to endogenous chylomicrons.

They are cleared by the enzyme LPL, which hydrolyzes Tg, releasing FFA, glycerin, and PLs.

TG remnants resulting from the peripheral hydrolysis of the emulsion droplets are further hydrolyzed by the liver at endothelial sites or within hepatocytes by the enzyme HL.

They can also inhibit the endocytic uptake of TG remnants by the liver, again increasing TG concentrations.

TG released during peripheral hydrolysis acquire Apo to form lipoproteins.

PL-Apo E complexes can decrease the enzymatic activity of LPL, potentially diminishing peripheral hydrolysis and thereby increasing TG concentrations.

LDL particles may be taken up by hepatocytes or macrophages.

**IVFEs and dyslipemia**

- Reported AEs associated with the use of IVFEs include hypertriglyceridemia, acute pancreatitis, cholestasis, and increased risk of infection.

- Three factors affect the plasma clearance of IVFEs:

  | Phospholipid content (10% vs 20%) | The PL content of the 10% and 20% formulations is the same; Proportionally more free PL available in the 10% formulation. Free PLs interfere with LPL activity ↓ IVFE clearance and ↑ AEs. |
  | Particle size | Clearance of 20% IVFE is faster than that of 10% IVFE • relatively lower concentration of free phospholipids • larger particle size. |
  | Infusion rate | Administration of an IVFE to adults at a rate >2.5 g lipid/kg/day may result in an excessive lipid load. |

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*Ann Pharmacother 2010;44:688-700*
Fat-overload syndrome

- Excessive lipid dose
- Rapid administration rates

- Hyperlipidemia
- Pyrexia
- Gastrointestinal disorder
- Anemia
- A bleeding tendency
- Thrombocytopenia
- Hepatosplenomegaly
- Possible pulmonary problems, including hypoxia
Nutritional support induced hypertriglyceridemia

• Metabolic complication associated with PN, from 6% to 38%.

• Often coincides with hepatic steatosis.

• Severe hypertriglyceridemia (>1000 mg/dL = 11.4 mmol/L)
  – can induce acute pancreatitis,
  – also can affect micro circulation.
  – not known whether long-term hypertriglyceridemia in PN patients is associated with increased cardiovascular risk.

• Plasma triglyceride concentrations should be kept below 400 mg/dL (4.6 mmol/L) during PN infusion.
Nutritional support induced hypertriglyceridemia

- HTG may occur as a result of IVFE administration
  - if the rate of infusion exceeds the capacity of lipoprotein lipase to clear triglycerides
  - or if the patient has risk factors for the development of hypertriglyceridemia.

- Prospective, observational study of adult patients receiving PN, HTG (serum triglyceride >265 mg/dL)
  - 24.9% patients who received <1.5 g/kg/day of lipids
  - 54.5% of those who received >1.5 g/kg/day.

Nutritional support induced hypertriglyceridemia

- HTG occur as a result of IVFE administration
  - if the rate of infusion exceeds the capacity of lipoprotein lipase to clear triglycerides
  - or if the patient has risk factors for the development of hypertriglyceridemia.

- The risk was significantly increased by the presence of
  - Renal failure (OR 10.56; 95% CI 3.35 to 33.28),
  - Glucose >180 mg/dL (OR 2.63; 95% CI 1.19 to 5.81),
  - Prednisone >0.5 mg/kg/day (OR 7.98; 95% CI 3.13 to 20.29),
  - Pancreatitis (OR 4.38; 95% CI 1.66 to 11.53),
  - Sepsis (OR 4.48; 95% CI 2.04 to 9.83).

- 28.8% patients with one or more risk factors, but in only 13.3% patients without risk factors
Other factors for HTG

Infectious diseases and inflammatory activity have also been related to the development of HTG

- Therefore, in addition to withdrawing lipids from the PN, possible infectious foci should be identified and treated.

LCFAs cause oxidative stress as a result of peroxidation, are responsible for disturbances in lipid metabolism, and may cause immunological dysfunction

- Reducing the concentration of LCFAs in the lipid emulsion and replacing it with medium-chain triglycerides, fish oil rich in ω-3 fatty acids, and olive oil.
Pre-existing dyslipidemia and nutrition support: enteral nutrition

• Major increase in plasma lipid unusual: only in patients with primary dyslipidaemia (especially type IV and rarely type I, II and V).

<table>
<thead>
<tr>
<th>Dyslipidemia type I and III</th>
<th>Dyslipidemia type IV</th>
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<tr>
<td>Decreased clearance of chylomicrons or remnants</td>
<td>associated with glucose intolerance and diabetes</td>
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<tr>
<td>Reduction of lipid intake. MCT can be also useful</td>
<td>Decrease in carbohydrate more useful than a change in fat composition</td>
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Pre-existing HTG: parenteral nutrition:

- Severe hyperlypemia is one of the few contraindications of lipid emulsions.
- Plasma triglyceride concentrations should be kept below 400 mg/dL (4.6 mmol/L) during PN infusion.
- Appropriate infusion rates for fat emulsions (from 0.8 to 1.5 g/kg per day) and temporarily discontinue infusion if persistent (>72 h)
- Slow rate of infusion (0.12g/kg/hour). (Lower rates in critically ill patients or impaired lipid clearance)
- Continuous lipid infusion over 24 hours facilitates lipid oxidation and improves plasma FA profiles
- Propofol (lipid 0.1g/ml) --PN lipid dosage should be adjusted
- If the serum TG level cannot be maintained below 12 mmol/L (1000 mg/dL), drug therapy is indicated to decrease VLDL production and prevent more severe HTG.
Type IV familial hypertriglycerideridemia
(↑ VLDL production and ↓ elimination)

- IVFEs should be avoided when possible and carbohydrate should be used in the smallest possible amounts (<4 mg/kg/min).
- Fat emulsions containing fish oil or structured lipids containing MCT associated with a faster TG clearance?

- 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.
- Hypocaloric or cyclic fat-free PN may extend the period of time before essential fatty acid deficiency occurs.

Pre-existing HTG: parenteral nutrition 3:
Pre-existing hypercholesterolemia

Familial hypercholesterolemia

• Clinical studies performed in the times of hyperalimentation

• PN performed at a well-adjusted caloric intake (<40 kcal/kg) provided an adequate control of the serum cholesterol level.
Nutrition support and dyslipidemia

- Critically ill patients show different lipid alterations which may be associated to a worse outcome.
- Nutritional support is sometimes related to hypertriglyceridemia, which could coincide with hepatic steatosis.
- Following “safety rules” most patients with hypertriglyceridemia may receive IVFE in a safe manner.