

## Lipid emulsions in parenteral nutrition: does one size fits all?

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### Abstract

Dietary lipids significantly contribute to preserve the efficiency of human metabolism and restore it during disease. Therefore, in the absence of absolute contraindications, it would not appear reasonable to exclude lipid emulsions when prescribing parenteral nutrition (PN). The metabolic role of lipids has been elucidated, and is far more complex than a mere energy-dense source. Indeed, it is now clear that fatty acids impact differently on the inflammatory and immune responses, either promoting or blunting them. Omega-6 fatty acids are the substrate for the production of potent mediators of inflammation, whereas omega-3 fatty acids promote the synthesis of less active factors. Omega-9 fatty acids exert a more neutral impact on immune and inflammatory responses. These specific metabolic activities should therefore be considered when prescribing lipid emulsions in PN. Ideally, the metabolic profile of patients should guide the prescription of lipid emulsions in order to promote the inflammatory response or blunt it according to the clinical needs. This new approach would wholly exploit the metabolic activities of lipid emulsions by providing patients not only with an energy-dense source, but also by priming and/or modulating the immune and inflammatory responses in order to favour healing.

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Lipids are essential components of a healthy diet. This is not simply because some fatty acids cannot be synthesised by human cells and need to be supplied by the diet to prevent clinically relevant deficiencies.<sup>1</sup> Lipids also represent an energy-dense source, and their hydrophobic properties are also critical for the metabolic efficiency of body composition. In the latter regard, cell membranes are largely made by lipids, which are important in maintaining compartmentalisation and cellular integrity. Lipids are also metabolically active, since they serve as the skeleton upon which many hormones are synthesised and influence human metabolism per se. Finally, lipids are thought to have also contributed to the evolution of the human race by serving as a metabolic signal during periods of food availability, thereby triggering the onset of a metabolic milieu favouring energy intake and storage of excess energy as fat depots.<sup>2</sup> Therefore, it should not be surprising that the inclusion of lipid emulsions is recommended when providing PN to patients unable to meet their protein and energy needs via the oral and enteral route.<sup>3</sup> Indeed, if we consider artificial nutrition as a tool to replace oral diet when the latter is not feasible, it seems unreasonable to exclude lipids and the question arises as to whether we adopt that approach when advising a patient who could eat. Nevertheless, lipid emulsions are frequently not considered when prescribing PN and the practice may be related to concerns regarding their potential toxicity, although it is now clear that their use according to the existing guidelines provides more benefits than harm.

### Metabolic effects of lipid emulsions

One gram of lipids provides approximately 9 Kcal. In this regard, lipid emulsions represent an efficient energy source, and contribute to reduce the potential toxicity associated with glucose-based PN and hyperglycaemia.<sup>1,4,5</sup> Lipids are also known to directly influence the inflammatory and immune responses. This effect is mostly related to the specific biochemical structure of fatty acids, and therefore it may vary according to the different composition of lipid emulsions used in PN. It is important to note that commercially available lipid emulsions differ in their fatty acid compositions, and may exert different modulations of inflammatory and immune responses. Therefore, they should be prescribed according to the metabolic profile of the patient, in order to accelerate healing and recovery.

Fatty acids are classified according different classes. The omega nomenclature classifies unsaturated fatty acids according to the distance, in carbon atoms, of the first double bond from the omega end of the carbon chain. The first double bond in position 3 characterises omega-3 fatty acids (i.e.  $\alpha$ -linolenic acid). Omega-6 fatty acids (i.e. linoleic acid) have the first double bond 6 carbons from the omega end. Omega-9 fatty acids (i.e. oleic acid) are characterised by the first double bond being in position 9. Although apparently minimally relevant, the position of the double bond significantly influences the metabolic effects of lipids.

The most relevant omega-3 fatty acids in clinical nutrition are polyunsaturated fatty acids found in plants (i.e.  $\alpha$ -linolenic acid)

and fish oil [i.e. eicosapentaenoic acid (EPA), docosahexanoic acid (DHA)]. Omega-6 fatty acids are the characterising polyunsaturated fatty acids found in soybean oil (i.e. linoleic acid) and in fats of animal origin. Oleic acid is a monounsaturated fatty acid, which is the primary omega-9 fatty acid found in olive oil.

### Oxidative stress

The possibility to fully oxidise glucose via aerobic glycolysis represents one of the major steps contributing to the evolution of species from primordial cells into multicellular organisms. On the other hand, respiration, primarily within mitochondria, is a major source of reactive oxygen species (ROS). ROS are highly active molecules, which act as pro-oxidant.<sup>6</sup> By damaging DNA and proteins, they contribute to killing invading microbes and inducing inflammation, but when produced in excess and not counterbalanced, they induce cell damage and apoptosis. Therefore, pro-oxidant effects of ROS must be counterbalanced by a series of natural antioxidants, including vitamins C and E, glutathione and other such nutrients.<sup>6</sup> Imbalance in the equilibrium between ROS production and antioxidant systems leads to oxidative stress.<sup>6</sup> Oxidative stress may result either because of an overproduction of ROS or because of the insufficiency/depletion of antioxidant systems. The development of oxidative stress is clinically relevant since it is thought to contribute to organ failure.<sup>7</sup> Indeed, oxidative stress is associated with injury to major organs and systems, since it exerts adverse cardiac,<sup>8</sup> neurologic,<sup>9</sup> renal,<sup>10</sup> pulmonary<sup>11</sup> and haematologic<sup>12</sup> effects.

Lipid peroxidation is a determinant of oxidative stress.<sup>13</sup> Omega-6 and omega-3 fatty acids are preferential targets for free radical attack and lipid peroxidation because of their multiple double bonds,<sup>14</sup> and the hydroperoxide formed may oxidise proteins and DNA. On the other hand, the single double bond characterising omega-9 fatty acids makes them less prone to lipid peroxidation. In-vitro studies have shown that the production of ROS, a marker of oxidative stress, is influenced by the type of fatty acids, being higher when polyunsaturated fatty acids are used as substrate when compared with monounsaturated fatty acids.<sup>15,16</sup> The clinical relevance of this differential influence on oxidative stress still needs to be completely elucidated. However, Goulet et al. showed that VLDL and LDL peroxidation in paediatric patients receiving long-term PN was reduced when lipid emulsions rich in omega-9 fatty acids vs omega-6 fatty acids were used.<sup>17</sup>

### Inflammatory and immune response

Fatty acids influence the inflammatory and immune response by their incorporation into cell membranes, and thus modulating gene expression, membrane fluidity and exposure of receptors on the cell surface.<sup>1</sup> Omega-3 and omega-6 fatty acids may compete for the same enzymes for metabolism in a state of enzyme saturation.<sup>1</sup> The products formed from omega-3 fatty acids (i.e. the odd-series eicosanoids) are typically less potent mediators of inflammation than those formed from omega-6 fatty acids (i.e. the even-series eicosanoids), whereas the metabolism of omega-9 fatty acids does not produce eicosanoids.<sup>1</sup> The inflammatory response is generally an

adaptive, beneficial response to trauma or illness and interference with the normal host inflammatory response may prove detrimental in some patients.<sup>18</sup> However, it may be beneficial to modulate an exaggerated inflammatory response (i.e. as seen with sepsis). Likewise, a chronic pro-inflammatory state (i.e. in patients receiving long-term PN) may have adverse effects.

Omega-6 fatty acids have dose-dependent immunosuppressive effects. In vitro and in vivo evidence indicates that omega-6 fatty acids lead to impairment of neutrophil chemotaxis and phagocytosis<sup>19</sup> lymphocyte proliferation and reactivity,<sup>20</sup> natural killer (NK) and lymphokine-activated killer cell activities<sup>21</sup> as well as monocyte chemotaxis and proliferation.<sup>22</sup> Furthermore, administration of omega-6 polyunsaturated fatty acids has been associated with prolonged graft survival in animal transplant models<sup>23</sup> When given in excess, omega-3 fatty acids may have an immunosuppressive effect,<sup>24</sup> but perhaps the ratio of omega-6 to omega-3 may be important in determining the extent of immunosuppression.<sup>25</sup> Omega-3 polyunsaturated fatty acids are also generally regarded as anti-inflammatory. In addition to shifting eicosanoid production toward those that are less pro-inflammatory, omega-3 polyunsaturated fatty acids may suppress inflammation through production of resolvins and protectins (which facilitate resolution of inflammation) and through regulation of gene expression (i.e. cytokine expression).<sup>1</sup> Clinical studies have demonstrated favorable changes in the fatty acid and eicosanoid profiles of surgical patients receiving fish oil-containing versus soybean oil-based lipid emulsions.<sup>26</sup> Similar benefits have been observed in septic patients in a study which used fish oil alone at a dose that was more than 3 times greater than the recommended maximum dose.<sup>27</sup> In contrast, omega-9 monounsaturated fatty acids have shown limited to no impact on lymphocyte proliferation or NK cell activity in vitro or ex vivo.<sup>28,29</sup>

### Lipid emulsions in clinical practice

For many years, PN has been considered as a life saving and effective tool to feed patients who cannot eat. In this light, lipids were regarded as a mere energy-dense source. It is now clear that many nutrients, and specifically amino acids (i.e. glutamine, leucine, arginine,) and lipids, do exert metabolic effects. It is therefore reasonable to propose that such essential nutrients as lipids should be prescribed to patients in order to nutritionally support them and influence their metabolism, in order to facilitate healing and recovery. Actually, many examples can be taken from animal biology, supporting the efficacy of changes of dietary habits in priming specific metabolic pathways to better prepare animals to significant challenges. In this respect, the dietary behaviour of the semipalmated sandpiper (*Calidris pusilla*) before autumn migration is extraordinary. In preparation for the long flight from Canada to South America, this shorebird is able to enhance the energy efficiency of its wing muscles by acutely changing its diet and thus eating almost exclusively omega-3 rich mud shrimps.<sup>30</sup> During the last centuries, human beings have lost their ability of selecting specific foods to better fight disease, but it is now possible to start considering the metabolic profile of the patients as a criterion according to which specific lipid emulsions should be

prescribed. Trauma is associated with an inflammatory response which is necessary to trigger the immune response. An exaggerated inflammatory response may increase the risk for complications, delayed recovery and even increased mortality. However, excessive inhibition of the inflammatory response via pharmacological or nutritional means may be equally detrimental. Indeed, Namas et al have recently demonstrated in trauma/haemorrhage patients that an adequately robust early inflammatory response is a hallmark of survival.<sup>18</sup>

It is therefore advisable that in clinical practice, lipid emulsions should not be considered as interchangeable and their metabolic effects should be taken into consideration. In patients in whom a robust inflammatory response is desirable, omega-6 fatty acids may be preferred. In clinical conditions where attenuation of inflammatory response is clinically meaningful, then omega-3 fatty acids should be considered. When perturbation of the physiologic inflammatory and immune response and/or exacerbation of oxidative stress could be associated with increased risk of complications, then omega-9 fatty acids may be preferred.

Based on our better knowledge on the metabolic effects of lipid emulsions, it is now tempting to speculate their use as “drugs” could provide an adequate amount of immuno-modulating fatty acids on top of the calculated energy needs. In this context, omega-9 fatty acids could be provided as the energy source because of their “immuno-neutrality”, while omega-3 and omega-6 fatty acids could be provided as metabolic modulators. It is acknowledged that the available literature cannot yet support this approach, but it can also not be denied that such an approach would favourably exploit the potential clinical benefit of lipid emulsions. While waiting for clinical trials addressing the feasibility and relevance of this approach, it is important to be reminded that in matters concerning lipid emulsions “one size may not fit all (patients)”.

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