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## Digestive Disorders Federation Conference BAPEN and Nutrition Society Symposium: Immuno nutrition & novel substrates

### Novel nutritional substrates in surgery

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Pharmaco-nutrients have beneficial effects on protective and immunological mechanisms in patients undergoing surgery, which are important for recovery after injury and in combating infectious agents. The aim of this review article was to outline the potential of the administration of nutritional substrates to surgical patients and the underlying mechanisms that make them particularly important in peri-operative care. Surgery causes a stress response, which has catabolic effects on the body's substrate stores. The amino acid glutamine is a stimulating agent for immune cells. It activates protective mechanisms through its role as a precursor for antioxidants and it improves the barrier function of the gut. Arginine also enhances the function of the immune system, since it is the substrate for T-lymphocytes. Furthermore, *n*-3 PUFA stabilise surgery-induced hyper-inflammation. Taurine is another substrate that may counteract the negative effects of surgical injury on acid–base balance and osmotic balance. These pharmaco-nutrients rapidly become deficient under the influence of surgical stress. Supplementation of these nutrients in surgical patients may restore their protective and immune-enhancing actions and improve clinical outcome. Moreover, pre-operative fasting is still common practice in the Western world, although fasting has a negative effect on the patient's condition and the recovery after surgery. This may be counteracted by a simple intervention such as administering a carbohydrate-rich supplement just before surgery. In conclusion, there are various nutritional substrates that may be of great value in improving the condition of the surgical patient, which may be beneficial for post-operative recovery.

#### Glutamine: Arginine: *n*-3 PUFA: Taurine: Carbohydrates: Surgery

In the last few decades, adequate peri-operative care has shown to be of great value in improving clinical outcome in surgical patients. Although the importance of nutritional support is increasingly acknowledged, it is still not incorporated in common peri-operative practice. Also, the potential positive effects of specific pharmaco-nutrients for surgical patients have not yet been optimally exploited. A stress response after surgery and the concomitant impaired

immune function are important factors that negatively influence clinical outcome. The administration of specific nutritional substrates, such as glutamine, arginine, *n*-3 PUFA and taurine, to surgical patients may balance this surgical stress response and the associated inflammatory reaction, support the cell-mediated immune function and may consequently improve outcome. Despite large amounts of research data on these substrates, the

**Abbreviations:** CHO, carbohydrate; iNOS, inducible nitric oxide synthase; LOS, length of hospital stay; MDSC, myeloid derived suppressor cells; Th, T-helper.

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implementation in current clinical practice is disappointing. Also, fasting before surgery is still common practice in pre-operative care in many Western countries, even though international guidelines of various professional nutrition societies state that pre-operative fasting is unwanted. A simple intervention such as the supplementation of carbohydrates (CHO) just 2 h before surgery may improve the metabolic condition of the patient and thereby clinical outcome. The purpose of this article is to review the underlying mechanisms explaining the pharmacological actions of several novel substrates and their potential role in nutritional care in surgical patients.

### Glutamine

The immune system is of fundamental importance for the recovery from surgery. It is not only essential in preventing or limiting infections, but also in the overall process of repair and recovery from injury. Glutamine is a conditionally essential amino acid during metabolic stress, induced by major surgery. Glutamine is an important amino acid for the immune system, for the glutathione system and also for gut mucosa integrity.

#### Background

**Immune system.** In immune cells glutamine regulates the inflammatory response and is important for cell proliferation and differentiation<sup>(1)</sup>. Glutamine functions as the primary fuel for these cells, because it is the substrate for glutamate synthase (NADPH), which is essential for intracellular energy supply. T- and B-lymphocytes are the major components of the adaptive immune system, which prevents and eliminates pathogenic invasion. Extracellular glutamine regulates the proliferation of T-lymphocytes and antigen presentation. B-lymphocyte differentiation is also glutamine dependent and their proliferation rate significantly increases when glutamine levels are increased. Macrophages are immune cells that destroy cellular debris and pathogens; accordingly to do so, macrophages need glutamine as their energy substrate<sup>(2)</sup>. Furthermore, glutamine depletion limits the activation of lymphokine-activated killer cells, which have a very broad target cell spectrum, to kill target cells<sup>(3)</sup>.

**Protective capacity.** Glutamine is important for cell protection against oxidative stress. Firstly, glutamine has a protective capacity due to its role as a substrate for the synthesis of glutathione, the major intracellular antioxidant<sup>(4)</sup>. Glutathione has the ability to counteract oxidative injury caused by oxygen-derived free radicals and peroxides, as seen in surgery. When muscle glutamine concentrations decrease during stress, glutathione depletion may occur<sup>(4)</sup>. However, supplementation of glutamine during surgical stress can sustain adequate glutathione levels<sup>(5)</sup>.

Another mechanism of glutamine against the damaging effects of oxidative stress is its stimulating role in the expression of the tissue heat shock protein 70<sup>(6,7)</sup>. Heat shock protein 70 is essential for cellular recovery after injury and is protective against tissue damage. Absence of heat shock protein 70 may lead to increased cellular apoptosis.

The gut has an important barrier function with concomitant protection mechanisms, since it is intensively exposed to exogenous pathogens. Following physical stress associated with surgery, the barrier function of the gastrointestinal tract may be impaired. This loss of barrier function may play a role in the translocation of bacteria and endotoxins across the gut wall, subsequently resulting in a prolonged systemic inflammatory response and sepsis. Glutamine is an important regulator of the intestinal integrity, because it alters the expression of tight junction proteins and improves the epithelial barrier function<sup>(8)</sup>. Glutamine is also utilised as a major fuel and nucleotide substrate by intestinal mucosal cells and the gut-associated lymphoid tissue system<sup>(2)</sup>.

**Precursor for other pathways.** Part of the benefits of glutamine supplementation is a consequence of its role as a precursor for endogenous synthesis of arginine through an intestinal–renal pathway involving interorgan transport of citrulline<sup>(9,10)</sup>. It contributes to a greater intestinal release of citrulline when given enterally and higher plasma levels of citrulline<sup>(11)</sup>. Also glutamine can serve as a precursor for the production of taurine<sup>(12)</sup>. Arginine and taurine and their role in nutritional care in surgery will be discussed later.

#### Glutamine supplementation in surgical patients

It is proposed that supplementation of glutamine in surgical patients is important, because it may protect cells against injury and patients against complications associated with the key roles described earlier. Thus, glutamine should be administered to build up sufficient levels in order to sustain an appropriate response to stress or injury and protect the patient against a poor clinical outcome.

Glutamine can be given via either the enteral or parenteral route. In both ways it is given as a dipeptide; because glutamine itself has limited stability in aqueous solutions, adding alanine or glycine to form a dipeptide makes it easily hydrolysed and stable.

Delivery of parenteral glutamine raises systemic levels of glutamine more than a similar dose of glutamine given by the enteral route. Although glutamine can maintain gut integrity even when delivered from the vascular side of the intestinal epithelial cell, enteral supplementation is more beneficial in preserving the gut barrier function<sup>(13)</sup>. Furthermore enteral glutamine supplementation is suggested to contribute more to the *de novo* synthesis of arginine than does parenterally administered glutamine<sup>(14)</sup>.

**Parenteral route: pre-operative supplementation.** Few studies are available on the effect of glutamine supplementation before surgery. In one study, where glutamine was given 5 d before surgery and was stopped on the day before surgery, no beneficial effects were seen. Despite the fact that the potential effects of glutamine were not sustained after surgery, the pre-operative immune indices (leucocytes, granulocytes and lymphocytes) were increased by glutamine supplementation<sup>(15)</sup>.

**Parenteral route: peri-operative supplementation.** Peri-operative glutamine administration is associated with reduced immune suppression, an improved capacity to inactivate endotoxins and a significant increase in CD4+ count (marker of immune cells) after surgery<sup>(16,17)</sup>.

In colorectal surgery, peri-operative supplementation of glutamine showed a decrease in complications and length of hospital stay (LOS) after surgery<sup>(18)</sup>. In another study, no effect was seen after abdominal surgery for cancer; however, this may be caused by an underdosing treatment (0.2 g/kg per d)<sup>(19)</sup>. In patients with a risk of malnutrition before gastrointestinal surgery, supplementation of glutamine may shorten intensive care unit stay and improve insulin levels<sup>(20)</sup>. In cardiac surgery, a peri-operative high-dose glutamine administration (0.5 g/kg per d) did increase the glutathione concentration, and these increased glutathione levels remained after surgery<sup>(21)</sup>. Glutathione is known to be protective against myocardial ischaemia/reperfusion injury, which is associated with increased morbidity and mortality<sup>(22)</sup>. Glutamine supplementation has a preserving effect on contractile function of cardiomyocytes after open heart surgery<sup>(23,24)</sup>. In patients undergoing gastrointestinal surgery, peri-operative supplementation may be beneficial in ameliorating immune depression and shortening hospitalisation<sup>(17,25)</sup>.

*Parenteral route: post-operative supplementation.* Characteristic features after surgical stress are hyperglycaemia and cumulative nitrogen losses, which may increase the risk of infection, delay wound healing and diminish muscle strength after surgery, resulting in a prolonged hospital stay<sup>(26)</sup>. This response can also be counteracted with post-operative parenteral glutamine supplementation. Glycaemic control is associated with decreased total post-operative infections<sup>(27)</sup>. Intravenous post-operative glutamine supplementation in surgical patients reduces infectious complication rates, shortens LOS and decreases hospital costs<sup>(28–31)</sup>. The greatest benefit of intravenous supplementation was observed in patients receiving high-dose glutamine. Thus, a high degree of benefits is found in studies that used high doses of glutamine<sup>(30,31)</sup>. The most optimal dose is probably 0.5 g/kg per d<sup>(32)</sup>.

In critically ill patients, low levels of glutamine also have been associated with immune dysfunction and higher mortality<sup>(33)</sup>. Also glutathione becomes depleted during critical illness and this is associated with a poor clinical outcome<sup>(34)</sup>. In critically ill patients, intravenous administration of glutamine increased glutathione levels<sup>(35)</sup>. Supplementation of parenteral glutamine in critically ill patients was associated with a reduction of urinary tract infections and nosocomial pneumonia<sup>(36)</sup>.

*Enteral route.* Enteral supplementation has an advantage over parenteral supplementation. An early initiation of post-operative enteral nutrition shortens LOS, shows fewer complications and reduces infectious complications in patients undergoing major abdominal surgery compared with delayed enteral nutrition<sup>(37)</sup>.

In trauma patients, supplementation of enteral glutamine lowered the incidence of pneumonia<sup>(38)</sup>. In critically ill patients the addition of glutamine to enteral nutrition reduced LOS by more than 4 d<sup>(39)</sup>. In trauma patients undergoing shock resuscitation, enteral glutamine administration was safe and enhances gastrointestinal tolerance<sup>(40)</sup>. Post-operative ileus is a common complication after gastrointestinal surgery; however, glutamine acts as a motility-recovery agent<sup>(41)</sup>. Not only is enteral glutamine protective via the enteral route for myocardial injury and clinical

complications in patients undergoing cardiac surgery<sup>(42)</sup>, it also has a protective effect on the epithelial barrier function. Enteral glutamine supplementation increases intestinal fractional extraction of glutamine. This higher intestinal fractional extraction is probably important to sustain physiological levels of glutathione and preserve heat shock protein 70 and it serves as a substrate to the gut-associated lymphoid tissue system.

Guidelines of professional nutrition societies currently recommend intravenous supplementation of glutamine in critically ill patients, as recent data support the use of glutamine in order to reduce mortality in these patients<sup>(43)</sup>. Parenteral glutamine administration may also be beneficial in patients undergoing major surgery. The European Society for Parenteral and Enteral Nutrition guidelines state that 'some evidence exists' that intravenous glutamine administration to these patients can improve LOS and infection risk<sup>(44)</sup>. These guidelines recommend the enteral route to deliver immune nutrients, but so far sufficient data are not available to support enteral glutamine supplementation in surgical patients in general<sup>(45)</sup>. In a recent American Society for Parenteral and Enteral Nutrition position paper on the use of parenteral glutamine supplementation, it is stated that it may be beneficial for certain adult surgical patients, for example, patients undergoing major abdominal surgery. However, the heterogeneity of the investigated patient populations makes this statement controversial. A growing body of data shows that glutamine supplementation with an optimal dose of 0.5 g/kg per d may be beneficial for the recovery after surgery. The best results may be achieved by administering glutamine by both enteral and parenteral routes as soon as possible after surgery<sup>(46)</sup>. However, caution is advised in patients with renal failure and severe hepatic dysfunction, since studies suggest that glutamine may be harmful and more evidence for this patient population is needed<sup>(47,48)</sup>. Further high-quality research is necessary to confirm the aforementioned perspectives. The results of the REDOX trial will be available soon, which may give more insight into the role of glutamine in clinical care<sup>(49)</sup>.

## Arginine

### Background

Arginine is a conditionally essential amino acid with several pharmacological properties, which becomes depleted during stress associated with surgery and trauma. Arginine is an immune enhancing nutrient, because it is essential for an adequate immune response, since it is the substrate for normal T-lymphocyte development<sup>(50)</sup>. T-lymphocytes depend on adequate arginine levels for proliferation, the expression of the T-lymphocyte receptor complex and the  $\zeta$ -chain peptide, and the development of immunological memory<sup>(51)</sup>. Furthermore, arginine is the sole precursor for NO. This versatile substance has cytotoxic properties to kill parasites, bacteria and viruses. It has an important signalling role for immune cells by regulating cytokine activation and receptor presentation, and it is the regulator of organ perfusion. In addition, arginine improves the process of wound healing<sup>(52)</sup>. Because of

all these properties, arginine is often called an immune nutrient.

Patients undergoing surgical injury develop an arginine deficiency and consequently an impaired immune function<sup>(53)</sup>. Since arginine levels drop  $\geq 50\%$  within a few hours after surgery, it is suggested that arginine deficiency is caused not by decreased intake, but rather through a disturbance in arginine metabolism<sup>(53)</sup>. Arginine is mainly catabolised by two competing enzymes: inducible nitric oxide synthase (iNOS) and arginase. NOS metabolises arginine into NO. Arginine availability is the regulating factor of NO production. Arginase, which converts arginine into urea and ornithine, is the only enzyme that is really capable of decreasing arginine levels and thus NO production.

After traumatic injury, for example, surgery, immature cells of myeloid origin are found in the circulation, lymph nodes, liver and spleen. These so-called myeloid derived suppressor cells (MDSC) express the enzymes iNOS and arginase<sup>(54)</sup>. The expression of both enzymes is regulated by cytokines of T-helper (Th) cells. Th1 cytokines are pro-inflammatory and promote iNOS expression; Th2 cytokines are anti-inflammatory and induce arginase expression<sup>(55)</sup>. In physiological conditions this regulation is in balance; however, in patients with injury the balance is disturbed. Surgical stress causes a predominant production of Th2 cytokines and this promotes the MDSC to express arginase<sup>(56,57)</sup>. Thus, after surgery, arginase-producing MDSC appear and cause an arginine deficiency. Consequently, NO metabolites are decreased in patients with physical injury because of a perturbation in NO production<sup>(58)</sup>. This results in the suppression of the T-lymphocyte dependent immune function and NO activity and this is a plausible explanation for the impaired immune function after surgery.

The described mechanism suggests that physical injury caused by surgery induces an arginine deficiency, which can be restored with arginine supplementation. Experimental studies have shown that arginine administration improves wound healing, restores macrophage and T-lymphocyte function and augments resistance to infectious pathogens<sup>(50,52)</sup>. Furthermore, arginine supplementation increases NO and improves microcirculation after injury<sup>(59)</sup>. Other studies have shown that pre-operative arginine-enriched nutrition improves immune function and decreased the production of Th2 cytokines<sup>(60,61)</sup>. Several clinical studies have shown that a correction of the arginine deficiency by arginine-enriched nutrition restores T-lymphocyte count and function in surgical patients<sup>(50,62)</sup>.

Other promising ingredients in immune nutrition are *n*-3 PUFA, which are often administered in combination with arginine. *n*-3 PUFA also interfere with arginine metabolism by decreasing Th2 cytokines and thereby maintaining the Th1/Th2 balance. This results in a decrease in arginase activity and inhibits arginine breakdown<sup>(63)</sup>. The role of *n*-3 PUFA in surgery will be outlined in more detail.

#### *Arginine supplementation in surgical patients*

Adequate clinical data on the effects of parenteral arginine supplementation in surgical patients are lacking.

Nevertheless, in the past 20 years many randomised clinical trials have been performed to examine the effects of arginine-enriched enteral nutrition in various settings and nutrition compositions. Six major meta-analyses reviewing these trials in surgical and trauma patients have been published<sup>(64–69)</sup>. The two most recent studies by Marik *et al.* and Drover *et al.* describe both substantial reduction in post-operative complications and a shorter LOS with the use of arginine administration. They found no overall effect on mortality compared with standard peri-operative nutritional care. Pre-, peri- and post-operative administration of arginine-enriched nutrition is associated with a reduction of post-operative complications, and both peri-operative and post-operative use of arginine supplementation were associated with a reduction in LOS. A greater effect of arginine is assumed when it is administered in both the pre- and post-operative phases. However, there exists considerable heterogeneity in the different trials examining the effects of arginine-enriched diets, likely due to differences in patients, local practice protocols, health care systems, study designs, diet compositions and other methodologies. Furthermore, there are only a few studies using arginine as a sole pharmaco-nutrient in the intervention group. In most studies the immune-enhancing diet consisted of arginine in combination with glutamine, *n*-3 PUFA and antioxidants, which makes it hard to ascribe the effects to a sole nutritional substrate. The variety in study methodology may also be ascribed to the wide time span in which the trials are performed, because the results of later studies might be influenced by new treatment opportunities.

The use of arginine-enriched nutrition in oncology deserves special attention. Almost all clinical trials mentioned earlier included patients who underwent curative oncological surgery. A malignant tumour also disturbs the arginine metabolism of the host<sup>(70)</sup>. The initial concept is quite similar to the alterations seen after surgery. Cancer by itself recruits MDSC from the moment of carcinogenic initiation<sup>(71)</sup>. During the first phases of carcinogenesis the tumour derived MDSC seem to produce arginase to prevent the immune system from fighting the malignant cells. However, during outgrowth of the malignant tumour, the Th1/Th2 balance switches to an increased Th1 cytokine production in the tumour environment, which promotes the MDSC to activate high amounts of iNOS<sup>(72)</sup>. In this stage, arginine is converted into NO by iNOS. This results in pathologically high NO levels, promoting angiogenesis and microcirculation in the tumour environment. Furthermore, in the presence of increased iNOS activity and low arginine levels, radical N species will be formed, which damage the surrounding cells even more. This might explain the controversial outcomes of studies in patients with inoperable advanced metastatic cancer. Arginine supplementation in this advanced metastatic phase may even worsen clinical outcome. This is supported by studies on the effects of supplemental arginine in critically ill patients with sepsis. In sepsis, the Th1/Th2 balance is also shifted to the Th1 side and extra exogenous arginine in septic patients causes no benefit, and perhaps even harm<sup>(73)</sup>. However, it is hypothesised that the pronounced positive effects of peri-operative arginine



supplementation<sup>(74,75)</sup> may be explained by the return of the Th1/Th2 balance (and therefore the iNOS/arginase balance) to the Th2 side after surgery.

The guidelines from leading nutrition societies in the world recommend the use of immune enhancing arginine-enriched nutrition in peri-operative care of patients undergoing major abdominal surgery, head and neck surgery and after severe trauma, with caution in patients with severe sepsis<sup>(76,77)</sup>. Peri-operative arginine supplementation in patients with a malignancy of the digestive tract may be beneficial<sup>(78)</sup>; however, arginine administration to patients with progressive non-curable cancer has to be avoided. Bozzetti has stated that immune-enhancing diets containing arginine are preferable to the standard enteral formulae in the pre-operative setting<sup>(79)</sup>. It can be concluded that arginine-supplemented enteral diets should be prescribed to all patients undergoing elective surgery.

### *n-3 PUFA*

Inflammation is a common sequel to surgery. The regulation of inflammation depends on a balance between pro- and anti-inflammatory mediators. When regulated adequately, inflammation is essential for recovery after surgical injury. However, when the balance is disturbed, this intentional protection mechanism becomes damaging for the host<sup>(80)</sup>. Pathological inflammation is a result of this disturbance and may evolve into severe complications, for example, sepsis, multi-organ failure or acute respiratory distress syndrome<sup>(81)</sup>. The pharmaco-nutrients *n-3* PUFA have anti-inflammatory properties and may overcome this post-operative morbidity by restoring the balance between pro- and anti-inflammatory mediators.

### *Background*

*n-3* PUFA from fish oil may impair inflammatory responses<sup>(82)</sup>. Eicosanoids and leukotriene mediators are signalling molecules with an important regulatory function in the inflammatory response. These signalling mediators are the products of either *n-3* PUFA or *n-6* PUFA. In general, the *n-6* PUFA are the precursors for pro-inflammatory mediators and the *n-3* PUFA are metabolised into less inflammatory mediators<sup>(83)</sup>. The *n-3:n-6* PUFA balance in the membranes of inflammatory cells, for example, neutrophils and macrophages, regulates the inflammatory response. In this way, *n-3* PUFA have anti-inflammatory actions, as substitutes for *n-6* PUFA in the cell membranes of inflammatory cells and thereby diminish pro-inflammatory mediator production. Furthermore, *n-3* PUFA block the production of *n-6* PUFA derived mediators by competing for the metabolic enzymes necessary for the conversion into the pro-inflammatory mediators<sup>(84)</sup>. In addition, another anti-inflammatory effect of *n-3* PUFA is caused by their role as precursors for resolvins and protectins. These resolvins and protectins have multiple anti-inflammatory properties, for example, inhibition of accumulation of dendritic cells and neutrophils, stimulation of macrophages and decreasing the production of pro-inflammatory cytokines<sup>(85)</sup>. The inflammatory condition or even the systemic inflammatory

response syndrome seen after surgery may be a result of a misbalance between *n-3* PUFA and *n-6* PUFA. As a result of the high intake of *n-6* PUFA and the low intake of *n-3* PUFA, cell membranes of Western populations are dominated by *n-6* PUFA. Adequate supplementation of *n-3* PUFA may restore the membrane composition and thereby resolve the regulation of the inflammation response and promote recovery after surgery<sup>(86)</sup>.

### *n-3 PUFA supplementation in surgical patients*

Supplementation of *n-3* PUFA is expected to have beneficial effects in inflammatory circumstances, such as surgery and systemic inflammatory response syndrome. Three recent systematic reviews outlined the effects of the supplementation of *n-3* PUFA and two of them focused on parenteral supplementation<sup>(87–89)</sup>.

*Parenteral route.* Based on a meta-analysis, it may be presumed that parenteral supplementation of *n-3* PUFA in patients undergoing major surgery is not only safe, but may also decrease the risk of post-operative infections and reduce LOS<sup>(87,89)</sup>. Van der Meij *et al.* evaluated the effects of *n-3* PUFA in both general surgery and oncological surgery separately. This qualitative review did not find any effects of peri-operative *n-3* PUFA supplementation on infection rate and mortality in surgical patients. In patients undergoing surgery for a malignancy receiving parenteral *n-3* PUFA, LOS was shorter. In patients without cancer, the effects of parenteral *n-3* PUFA supplementation on LOS were inconsistent. Although the studies did not report a significant improvement in mortality rate in patients receiving parenteral *n-3* PUFA, a trend towards a decrease in hospital costs was observed compared with control groups<sup>(90)</sup>. A recently published study on the effect of post-operative parenteral *n-3* PUFA supplementation in surgical critically ill patients showed a significant decrease in the hyper-inflammatory response after major surgery, a reduction in the production of pro-inflammatory cytokines and a tendency for less post-operative infections in the intervention group<sup>(86)</sup>. In most studies, the parenteral solution with *n-3* PUFA was administered in the post-operative period. Only a few studies combined post-operative and pre-operative administration of *n-3* PUFA<sup>(91,92)</sup>, and meaningful conclusions on the ideal administration period of *n-3* PUFA cannot be drawn from these studies. However, parenteral administration of *n-3* PUFA down-regulated the *n-6:n-3* ratio in plasma and cell membrane in a relatively short time span (1–3 d)<sup>(88)</sup>. This suggests that the highest treatment effect can be reached by starting the administration of parenteral *n-3* PUFA a few days before surgery.

*Enteral route.* The systematic review of van der Meij *et al.* found only three randomised controlled trials of acceptable quality looking into the effects of enteral nutrition enriched with *n-3* PUFA in surgical oncology<sup>(88)</sup>. No studies investigated the effects of these nutrients on general non-cancer surgery. Overall, these studies did not provide evidence for clinical benefits of post-operative enteral supplementation of *n-3* PUFA. However, a tendency for fewer infectious complications in surgical patients who received an enteral formula with *n-3* PUFA

for 7 d post-operatively was reported<sup>(93,94)</sup>. In a recently published study of high quality in patients undergoing oesophageal cancer surgery, peri-operative *n*-3 PUFA supplementation did not affect the immune function and clinical outcome<sup>(95)</sup>. However, one study showed preservation of the body weight and lean body mass, whereas both decreased in the control group<sup>(96)</sup>. Basal research in healthy volunteers shows that the incorporation of *n*-3 PUFA after enteral supplementation occurred after approximately 4–7 d and reaches a new steady state composition within approximately 4 weeks in a dose–response fashion<sup>(97)</sup>.

Clinical studies examining the effects of enteral nutrition containing high amounts of *n*-3 PUFA as well as  $\gamma$ -linolenic acid and antioxidants, consistently showed significant clinical benefits in patients with other inflammatory diseases, for example, acute respiratory distress syndrome or sepsis<sup>(81,98,99)</sup>.

The supplementation of *n*-3 PUFA is widely investigated in studies using commercially available enteral immune enhancing formulae, containing *n*-3 PUFA in combination with arginine, antioxidants and other immune modulating nutrients. Although these studies report many beneficial clinical effects of these immune enhancing formulae and international guidelines recommend the administration of this nutrition in patients undergoing major surgery, interpretation of the data in this area is difficult due to various amounts of *n*-3 PUFA present in the different enteral formulations and the inclusion of other immune modulating nutrients in the formulae<sup>(65,83)</sup>.

From the available clinical data it can be concluded that there is insufficient evidence to recommend the oral or enteral supplementation of *n*-3 PUFA in oncological or general patients undergoing surgery. However, *n*-3 PUFA might improve inflammatory response after surgery relying on its potential anti-inflammatory properties. In patients with acute respiratory distress syndrome and sepsis, the administration of enteral nutrition containing *n*-3 PUFA is recommended. Parenteral supplementation of *n*-3 PUFA-enriched formulae might be considered in the peri-operative period (e.g. during post-operative recovery or complications such as acute respiratory distress syndrome or sepsis).

### Taurine

Taurine is a nutrient with regulating properties in both the immune system and energy supply. Clinical data on the effect of taurine supplementation in surgical patients are lacking, but the potential of this pharmaco-nutrient in peri-operative care will be outlined.

Taurine is a semi-essential aminosulfonic acid and its sulfonate group makes taurine highly acidic, which makes it a zwitterion. As a zwitterion, taurine is able to function as a buffer when pH is low and function as a H ion donor when pH is high. Thus, taurine is very important in maintaining the acid–base homeostasis in the body. A disturbance in this homeostasis may be induced by surgery and associated factors, for example, mechanical ventilation, medication, the stress response and alterations in the fluid compartments of the body during surgery.

Taurine is an osmolyte that controls fluid movement and ion fluxes across cell membranes<sup>(100)</sup>. Surgery causes oxidative stress in several organs, for example, through ischaemia/reperfusion injury, which exerts an osmotic imbalance. This may be reflected as post-operative oedema: an excessive shift from body fluids to the intracellular space. However, when taurine is released from the swollen cells, ions and water will move from the intracellular space to the extracellular space, suggesting that oedema occurs when taurine is conditionally essential. In this way, taurine might be a potential protector against surgery-induced oxidative damage.

Furthermore, other experimental data show that taurine plays a role in the inflammation response and immune system. Taurine has been shown to down-regulate pro-inflammatory cytokines and function as an antioxidant at the site of inflammation<sup>(101,102)</sup>. Moreover, taurine uptake by T-cells is crucial for the survival and the immune reactions of these cells and a decrease in taurine uptake results in a reduction of T-cell responses<sup>(103)</sup>.

In response to surgical injury, plasma taurine levels decrease, which suggests an increased metabolic requirement<sup>(104)</sup>. Substantial evidence for the effects of taurine supplementation in surgical patients is absent and further studies are needed. However, with no known harmful effects and with much evidence suggesting a potential role for taurine in the recovery from surgical injury and inflammation, taurine supplementation may have positive effects.

### Carbohydrates

For some years, guidelines have stated that pre-operative fasting is an unwanted phenomenon<sup>(105)</sup>. However, fasting before surgery is still common practice in pre-operative care in many Western countries<sup>(106)</sup>.

#### Background

Fasting for 8 h before surgery results in depletion of glycogen stores in the liver. Subsequently, glucose has to be released in alternative ways, mainly by the mobilisation of glycogen from the muscle by eliciting a stress response. This response has consequences for the physical condition of the patient, because levels of cortisol, adrenaline and other signalling mediators are elevated. This interplay may result in insulin resistance at the level of the liver and muscle. Moreover, energy stores are depleted in the gastrointestinal tract, liver, kidneys, heart and lungs. Insulin resistance is not a favourable state of the body, because it may lead to increased infectious complications and prolonged hospital stay.

#### Pre-operative carbohydrate loading

To avoid this unwanted stress response, patients can be given a sufficient amount of CHO, via the intravenous route or via the enteral route shortly (2–3 h) before surgery. CHO loading preserves the energy status of the liver and most importantly reduces insulin resistance<sup>(107)</sup>. Also, it improves intestinal integrity and reduces bacterial translocation<sup>(108)</sup>.

**Table 1.** Summary of recommendations on substrates in surgery

Substrate	Patients	Application
Glutamine	Surgical ICU patients Burn and trauma patients	Preferable in EN, glutamine dipeptide <ul style="list-style-type: none"> <li>– Start EN in the ICU setting</li> <li>– When PN is indicated, add glutamine dipeptide</li> <li>– 0.3–0.5 g/kg per d glutamine dipeptide</li> </ul>
Arginine	Major abdominal surgery Head and neck surgery Severe trauma	Preferable in immune enhancing EN <ul style="list-style-type: none"> <li>– Start 7–5 d before surgery</li> <li>– Until 10 d after surgery</li> </ul>
<i>n</i> -3 PUFA	Major abdominal surgery Head and neck surgery Severe trauma	Preferable in immune enhancing EN <ul style="list-style-type: none"> <li>– Start 7–5 d before surgery</li> <li>– Until 10 d after surgery</li> </ul>
Taurine	– (Limiting data)	– (Limiting data)
CHO loading	All elective surgery	CHO-rich drink before surgery <ul style="list-style-type: none"> <li>– 400 ml containing 50 g CHO</li> <li>– 2 h preoperatively</li> </ul>

ICU, intensive care unit; EN, enteral nutrition; PN, parenteral nutrition; CHO, carbohydrate.

**Parenteral route.** Clinical studies in patients showed that intravenous CHO supplementation in sufficient amounts reduces the post-operative infection rate and improves wound healing<sup>(109,110)</sup>. In patients undergoing cardiac surgery, intravenous CHO loading is effective in overcoming the fasted state and this results in less myocardial damage<sup>(111)</sup>. Although intravenous CHO loading has proved to be successful in overcoming a fasted state and in exhibiting beneficial effects, this way of administration has certain disadvantages. For instance, high dosages (5 mg/kg per min or more) are needed to counteract the insulin resistance<sup>(112)</sup>. Also, intravenous administration of glucose requires concomitant insulin infusion, which needs frequent monitoring of blood glucose levels and the risk of fluid overload.

**Enteral or oral route.** An easier way to reach an optimal metabolic effect is by giving an oral CHO drink<sup>(106)</sup>. To attain beneficial effects in a clinical setting, the drink must contain at least 48 g CHO; which is the amount needed to overcome the fasted state and change it to a fed state. Up to 2 h before surgery an iso-osmolar CHO drink has proven to be safe in patients. After ingestion, the stomach empties the CHO drink within 90 min, thereby not increasing the risk of gastric aspiration during anaesthesia<sup>(113)</sup>. Pre-operative supplementation of CHO in amounts of 800 ml during the evening before the operation and 400 ml 2–3 h before the operation was investigated extensively. Regarding clinical parameters, a reduction in pre-operative discomfort (e.g. feeling of thirst and hunger), post-operative nausea and vomiting, and a shorter LOS were demonstrated in prospective, randomised trials<sup>(114–118)</sup>. Also, the unwanted insulin resistance after surgery was shown to be reduced<sup>(118,119)</sup>. Other studies demonstrated an earlier return of gastrointestinal function and a preserved muscle mass and strength<sup>(117,120)</sup>. Recently, a study demonstrated that pre-operative CHO loading causes less immune suppression in terms of the human leucocyte antigen HLA-DR expression in monocytes<sup>(116)</sup>.

Pre-operative CHO loading has many positive clinical effects and no disadvantages have been reported. However, outcome measures such as morbidity and mortality have

not yet been explored. Also, the effects of CHO loading in populations with a proposed altered CHO metabolism, such as obese or overweight patients, have not been investigated. It may be concluded that a simple intervention with a pre-operative CHO supplementation may contribute to the well-being of the patient and that in this perspective, pre-operative fasting is outdated.

### Summary

In summary, surgical injury causes various changes in the immune function and the body's homeostasis. This review outlines the potential role of several pharmac-nutrients in peri-operative care, to improve recovery (Table 1). The combination of both parenteral and enteral glutamine supplementation might improve post-operative outcome; however, the results of large randomised trials of high quality are awaited. Supplementation of immune enhancing formulae with arginine and *n*-3 PUFA in the peri-operative setting has been shown to be beneficial, with special attention to surgical oncology. Although data are limited, taurine has the potential to improve the physical condition of the surgical patient. Besides the specialised nutrients, adequate CHO intake 2 h before surgery should now be common practice.

It is important to realise that a relatively simple intervention with these pharmac-nutrients may improve the post-operative recovery of surgical patients. Nutritional interventions should gain more ground in peri-operative care.

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