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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[1]. 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[2]. Furthermore, glutamine depletion limits the activation of lymphokine-activated killer cells, which have a very broad target cell spectrum, to kill target cells[3].

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[4]. 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[4]. However, supplementation of glutamine during surgical stress can sustain adequate glutathione levels[5].

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[6,7]. 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[8]. Glutamine is also utilised as a major fuel and nucleotide substrate by intestinal mucosal cells and the gut-associated lymphoid tissue system[2].

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[9,10]. It contributes to a greater intestinal release of citrulline when given enterally and higher plasma levels of citrulline[11]. Also glutamine can serve as a precursor for the production of taurine[12]. 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[13]. Furthermore enteral glutamine supplementation is suggested to contribute more to the *de novo* synthesis of arginine than does parenterally administered glutamine[14].

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[15].

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[16,17].

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In colorectal surgery, peri-operative supplementation of glutamine showed a decrease in complications and length of hospital stay (LOS) after surgery[18]. 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)[19]. In patients with a risk of malnutrition before gastrointestinal surgery, supplementation of glutamine may shorten intensive care unit stay and improve insulin levels[20]. 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[21]. Glutathione is known to be protective against myocardial ischaemia/reperfusioninjury, which is associated with increased morbidity and mortality[22]. Glutamine supplementation has a preserving effect on contractile function of cardiomyocytes after open heart surgery[23,24]. In patients undergoing gastrointestinal surgery, peri-operative supplementation may be beneficial in ameliorating immune depression and shortening hospitalisation[17,25].

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[26]. This response can also be counteracted with post-operative parenteral glutamine supplementation. Glycaemic control is associated with decreased total post-operative infections[27]. Intravenous post-operative glutamine supplementation in surgical patients reduces infectious complication rates, shortens LOS and decreases hospital costs[28–31]. 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[30,31]. The most optimal dose is probably 0·5 g/kg per d[32].

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

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[37].

In trauma patients, supplementation of enteral glutamine lowered the incidence of pneumonia[38]. In critically ill patients the addition of glutamine to enteral nutrition reduced LOS by more than 4 d[39]. In trauma patients undergoing shock resuscitation, enteral glutamine administration was safe and enhances gastrointestinal tolerance[40]. Post-operative ileus is a common complication after gastrointestinal surgery; however, glutamine acts as a motility-recovery agent[41]. Not only is enteral glutamine protective via the enteral route for myocardial injury and clinical complications in patients undergoing cardiac surgery[42], 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[43]. 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[44]. 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[45]. 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[46]. 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[47,48]. Further high-quality research is necessary to confirm the aforementioned perspectives. The results of the REDOXS trial will be available soon, which may give more insight into the role of glutamine in clinical care[49].

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[50]. T-lymphocytes depend on adequate arginine levels for proliferation, the expression of the T-lymphocyte receptor complex and the ζ-chain peptide, and the development of immunological memory[51]. 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[52]. Because of

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

Patients undergoing surgical injury develop an arginine deficiency and consequently an impaired immune function[53]. Since arginine levels drop ≥ 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[53]. 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[54]. 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[55]. 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[56,57]. 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[58]. 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[50,52]. Furthermore, arginine supplementation increases NO and improves microcirculation after injury[59]. Other studies have shown that pre-operative arginine-enriched nutrition improves immune function and decreased the production of Th2 cytokines[60,61]. 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[50,62].

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[63]. 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[64–69]. 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[70]. The initial concept is quite similar to the alterations seen after surgery. Cancer by itself recruits MDSC from the moment of carcinogenic initiation[71]. 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 outgrow 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[72]. 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[73]. However, it is hypothesised that the pronounced positive effects of peri-operative arginine

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supplementation[74,75] 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[76,77]. Peri-operative arginine supplementation in patients with a malignancy of the digestive tract may be beneficial[78]; 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[79]. 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[80]. 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 [81]. 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[82]. 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[83]. 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[84]. 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[85]. 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[86].

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[87–89].

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[87,89]. 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[90]. 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[86]. 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[91,92], 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)[88]. 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[88]. 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

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for 7 d post-operatively was reported[93,94]. In a recently published study of high quality in patients undergoing oesophagastric cancer surgery, peri-operative *n*-3 PUFA supplementation did not affect the immune function and clinical outcome[95]. However, one study showed preservation of the body weight and lean body mass, whereas both decreased in the control group[96]. 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[97].

Clinical studies examining the effects of enteral nutrition containing high amounts of *n*-3 PUFA as well as γ-linolenic acid and antioxidants, consistently showed significant clinical benefits in patients with other inflammatory diseases, for example, acute respiratory distress syndrome or sepsis[81,98,99].

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[65,83].

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 homoeostasis in the body. A disturbance in this homoeostasis 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[100]. 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[101,102]. 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[103].

In response to surgical injury, plasma taurine levels decrease, which suggests an increased metabolic requirement[104]. 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[105]. However, fasting before surgery is still common practice in pre-operative care in many Western countries[106].

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[107]. Also, it improves intestinal integrity and reduces bacterial translocation[108].

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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 – Start EN in the ICU setting – When PN is indicated, add glutamine dipeptide – 0.3–0.5 g/kg per d glutamine dipeptide
Arginine	Major abdominal surgery Head and neck surgery Severe trauma	Preferable in immune enhancing EN – Start 7–5 d before surgery – Until 10 d after surgery
n-3 PUFA	Major abdominal surgery Head and neck surgery Severe trauma	Preferable in immune enhancing EN – Start 7–5 d before surgery – Until 10 d after surgery
Taurine	– (Limiting data)	– (Limiting data)
CHO loading	All elective surgery	CHO-rich drink before surger – 400 ml containing 50 g CHO – 2 h preoperatively

ICU, intensive care unit; EN, enternal nutrition; PN, parenternal 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[109,110]. In patients undergoing cardiac surgery, intravenous CHO loading is effective in overcoming the fasted state and this results in less myocardial damage[111]. 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[112]. 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[106]. 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[113]. 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[114–118]. Also, the unwanted insulin resistance after surgery was shown to be reduced[118,119]. Other studies demonstrated an earlier return of gastrointestinal function and a preserved muscle mass and strength[117,120]. 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[116].

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 pharmaco-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 pharmaco-nutrients may improve the post-operative recovery of surgical patients. Nutritional interventions should gain more ground in peri-operative care.

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References

1. Coeffier M, Marion R, Ducrotte P *et al.* (2003) Modulating effect of glutamine on IL-1beta-induced cytokine production by human gut. *Clin Nutr* **22**, 407–413.
2. Melis GC (2004) Glutamine: recent developments in research on the clinical significance of glutamine. *Curr Opin Clin Nutr Metab Care* **7**, 59–70.
3. Juretic A, Spagnoli GC, Horig H *et al.* (1994) Glutamine requirements in the generation of lymphokine-activated killer cells. *Clin Nutr* **13**, 42–49.
4. Vermeulen MA (2007) Specific amino acids in the critically ill patient–exogenous glutamine/arginine: a common denominator? *Crit Care Med* **35**, S568–S576.
5. Flaring UB, Rooyackers OE, Wernerman J *et al.* (2003) Glutamine attenuates post-traumatic glutathione depletion in human muscle. *Clin Sci (Lond)* **104**, 275–282.
6. Singleton KD, Serkova N, Beckey VE *et al.* (2005) Glutamine attenuates lung injury and improves survival after sepsis: role of enhanced heat shock protein expression. *Crit Care Med* **33**, 1206–1213.
7. Ziegler TR, Ogden LG, Singleton KD *et al.* (2005) Parenteral glutamine increases serum heat shock protein 70 in critically ill patients. *Intensive Care Med* **31**, 1079–1086.
8. Li N (2009) Glutamine deprivation alters intestinal tight junctions via a PI3-K/Akt mediated pathway in Caco-2 cells. *J Nutr* **139**, 170–714.
9. van de Poll MC, Ligthart-Melis GC, Boelens PG *et al.* (2007) Intestinal and hepatic metabolism of glutamine and citrulline in humans. *J Physiol* **581**, 819–827.
10. van de Poll MC, Siroen MP, van Leeuwen PA *et al.* (2007) Interorgan amino acid exchange in humans: consequences for arginine and citrulline metabolism. *Am J Clin Nutr* **85**, 167–172.
11. Melis GC, Boelens PG, van der Sijp JR *et al.* (2005) The feeding route (enteral or parenteral) affects the plasma response of the dipetide Ala-Gln and the amino acids glutamine, citrulline and arginine, with the administration of Ala-Gln in preoperative patients. *Br J Nutr* **94**, 19–26.
12. Boelens PG (2003) Plasma taurine concentrations increase after enteral glutamine supplementation in trauma patients and stressed rats. *J Nutr* **131**, 2569S–2577S.
13. Nose K (2010) Glutamine prevents total parenteral nutrition-associated changes to intraepithelial lymphocyte phenotype and function: a potential mechanism for the preservation of epithelial barrier function. *J Interferon Cytokine Res* **30**, 678–680.
14. Ligthart-Melis GC, van de Poll MC, Dejong CH *et al.* (2007) The route of administration (enteral or parenteral) affects the conversion of isotopically labeled L-[2–15N]glutamine into citrulline and arginine in humans. *JPEN J Parenter Enteral Nutr* **31**, 343–348.
15. Asprer JM, Llido LO, Sinamban R *et al.* (2009) Effect on immune indices of preoperative intravenous glutamine dipeptide supplementation in malnourished abdominal surgery patients in the preoperative and postoperative periods. *Nutrition* **25**, 920–925.
16. Exner R, Tamandl D, Goetzinger P *et al.* (2003) Perioperative GLY-GLN infusion diminishes the surgery-induced period of immunosuppression: accelerated restoration of the lipopolysaccharide-stimulated tumor necrosis factor-alpha response. *Ann Surg* **237**, 110–115.
17. Yao GX, Xue XB, Jiang ZM *et al.* (2005) Effects of perioperative parenteral glutamine-dipeptide supplementation on plasma endotoxin level, plasma endotoxin inactivation capacity and clinical outcome. *Clin Nutr* **24**, 510–515.
18. Oguz M, Kerem M, Bedirli A *et al.* (2007) L-alanine–L-glutamine supplementation improves the outcome after colorectal surgery for cancer. *Colorectal Dis* **9**, 515–520.
19. Jo S (2006) Missing effect of glutamine supplementation on the surgical outcome after pancreaticoduodenectomy for periampullary tumors: a prospective, randomized, double-blind, controlled clinical trial. *World J Surg* **30**, 1974–1982.
20. Mercadal OG & Llop Talaveron JM (2011) Effectiveness of perioperative glutamine in parenteral nutrition in patients at risk of moderate to severe malnutrition. *Nutr Hosp* **26**, 1305–1312.
21. Engel JM, Muhling J, Kwapisz M *et al.* (2009) Glutamine administration in patients undergoing cardiac surgery and the influence on blood glutathione levels. *Acta Anaesthesiol Scand* **53**, 1317–1323.
22. Domanski MJ, Mahaffey K, Hasselblad V *et al.* (2011) Association of myocardial enzyme elevation and survival following coronary artery bypass graft surgery. *JAMA* **305**, 585–591.
23. Lomivorotov VV, Efremov SM, Shmirev VA *et al.* (2011) Glutamine is cardioprotective in patients with ischemic heart disease following cardiopulmonary bypass. *Heart Surg Forum* **14**, E384–E388.
24. Wischmeyer PE, Vanden Hoek TL, Li C *et al.* (2003) Glutamine preserves cardiomyocyte viability and enhances recovery of contractile function after ischemia-reperfusion injury. *JPEN J Parenter Enteral Nutr* **27**, 116–122.
25. Yeh CN, Lee HL, Liu YY *et al.* (2008) The role of parenteral glutamine supplement for surgical patient perioperatively: result of a single center, prospective and controlled study. *Langenbecks Arch Surg* **393**, 849–855.
26. Schricker T & Lattermann R (2007) Strategies to attenuate the catabolic response to surgery and improve perioperative outcomes. *Can J Anaesth* **54**, 414–419.
27. Fukushima R, Inaba T, Iinuma H *et al.* (2004) [Perioperative nosocomial infection preventive measures]. *Nihon Geka Gakkai Zasshi* **105**, 696–701.
28. Avenell A (2006) Glutamine in critical care: current evidence from systematic reviews. *Proc Nutr Soc* **65**, 236–241.
29. Estivariz CF, Griffith DP, Luo M *et al.* (2008) Efficacy of parenteral nutrition supplemented with glutamine dipeptide to decrease hospital infections in critically ill surgical patients. *JPEN J Parenter Enteral Nutr* **32**, 389–402.
30. Novak F, Heyland DK, Avenell A *et al.* (2002) Glutamine supplementation in serious illness: a systematic review of the evidence. *Crit Care Med* **30**, 2022–2029.
31. Wang Y, Jiang ZM, Nolan MT *et al.* (2010) The impact of glutamine dipeptide-supplemented parenteral nutrition on outcomes of surgical patients: a meta-analysis of randomized clinical trials. *JPEN J Parenter Enteral Nutr* **34**, 521–529.
32. Wischmeyer P (2011) Nutritional pharmacology in surgery and critical care: 'you must unlearn what you have learned'. *Curr Opin Anaesthesiol* **24**, 381–388.
33. Oudemans-van Straaten HM, Bosman RJ, Treskes M *et al.* (2001) Plasma glutamine depletion and patient outcome in acute ICU admissions. *Intensive Care Med* **27**, 84–90.
34. Flaring UB (2005) Temporal changes in whole-blood and plasma glutathione in ICU patients with multiple organ failure. *Intensive Care Med* **31**, 1072–1078.
35. Eroglu A (2009) The effect of intravenous alanyl-glutamine supplementation on plasma glutathione levels in intensive care unit trauma patients receiving enteral nutrition: the results of a randomized controlled trial. *Anesth Analg* **109**, 502–505.
36. Grau T, Bonet A, Minambres E *et al.* (2011) The effect of L-alanyl–L-glutamine dipeptide supplemented total

https://doi.org/10.1017/S0029665112003047 Published online by Cambridge University Press

parenteral nutrition on infectious morbidity and insulin sensitivity in critically ill patients. *Crit Care Med* **39**, 1263–1268.
37. Marik PE & Zaloga GP (2001) Early enteral nutrition in acutely ill patients: a systematic review. *Crit Care Med* **29**, 2264–2270.
38. Houdijk AP, Rijnsburger ER, Jansen J *et al.* (1998) Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. *Lancet* **352**, 772–776.
39. McClave SA & Heyland DK (2009) The physiologic response and associated clinical benefits from provision of early enteral nutrition. *Nutr Clin Pract* **24**, 305–315.
40. McQuiggan M, Kozar R, Sailors RM *et al.* (2008) Enteral glutamine during active shock resuscitation is safe and enhances tolerance of enteral feeding. *JPEN J Parenter Enteral Nutr* **32**, 28–35.
41. Mochiki E, Ohno T, Yanai M *et al.* (2011) Effects of glutamine on gastrointestinal motor activity in patients following gastric surgery. *World J Surg* **35**, 805–810.
42. Sufit A, Weitzel LB, Hamiel C *et al.* (2012) Pharmacologically dosed oral glutamine reduces myocardial injury in patients undergoing cardiac surgery: a randomized pilot feasibility trial. *JPEN J Parenter Enteral Nutr* **36**, 556–561.
43. Heyland DK (2009) Clinical Practice Guidelines. http://www.criticalcarenutrition.com
44. Braga M, Ljungqvist O, Soeters P *et al.* (2009) ESPEN guidelines on parenteral nutrition: surgery. *Clin Nutr* **28**, 378–386.
45. Schulman AS, Willcutts KF, Claridge JA *et al.* (2005) Does the addition of glutamine to enteral feeds affect patient mortality? *Crit Care Med* **33**, 2501–2506.
46. Kim M (2013) Glutamine. *World Rev Nutr Diet* **105**, 90–96.
47. Hubl W (1994) Importance of liver and kidney for the utilization of glutamine-containing dipeptides in man. *Metabolism* **43**, 1104–1107.
48. Rama Rao KV (2012) Glutamine in the pathogenesis of acute hepatic encephalopathy. *Neurochem Int* **61**, 575–580.
49. Heyland DK, Dhaliwalm R, Day A *et al.* (2007) Optimizing the dose of glutamine dipeptides and antioxidants in critically ill patients: a phase I dose-finding study. *JPEN J Parenter Enteral Nutr* **31**, 109–118.
50. Popovic PJ (2007) Arginine and immunity. *J Nutr* **137**, 1681S–1686S.
51. Ochoa JB, Strange J, Kearney P *et al.* (2001) Effects of L-arginine on the proliferation of T lymphocyte subpopulations. *JPEN J Parenter Enteral Nutr* **25**, 23–29.
52. Witte MB & Barbul A (2003) Arginine physiology and its implication for wound healing. *Wound Repair Regen* **11**, 419–423.
53. Zhu X, Herrera G & Ochoa JB (2010) Immunosupression and infection after major surgery: a nutritional deficiency. *Crit Care Clin* **26**, 491–500, ix.
54. Makarenkova VP, Bansal V, Matta BM *et al.* (2006) CD11b+/Gr-1+ myeloid suppressor cells cause T cell dysfunction after traumatic stress. *J Immunol* **176**, 2085–2094.
55. Holan V, Pindjakova J, Krulova M *et al.* (2006) Production of nitric oxide during graft rejection is regulated by the Th1/Th2 balance, the arginase activity, and L-arginine metabolism. *Transplantation* **81**, 1708–1715.
56. Chiarla C, Giovannini I & Siegel JH (2006) Plasma arginine correlations in trauma and sepsis. *Amino Acids* **30**, 81–86.
57. Bansal V & Ochoa JB (2003) Arginine availability, arginase, and the immune response. *Curr Opin Clin Nutr Metab Care* **6**, 223–228.
58. Jacob TD, Ochoa JB, Udekwu AO *et al.* (1993) Nitric oxide production is inhibited in trauma patients. *J Trauma* **35**, 590–596.
59. Krauss H, Jablecka A, Sosnowski P *et al.* (2009) Influence of L-arginine on the nitric oxide concentration and level of oxidative stress during ischemia-reperfusion injury in a rat model. *Int J Clin Pharmacol Ther* **47**, 533–538.
60. Matsuda A, Furukawa K, Takasaki H *et al.* (2006) Preoperative oral immune-enhancing nutritional supplementation corrects TH1/TH2 imbalance in patients undergoing elective surgery for colorectal cancer. *Dis Colon Rectum* **49**, 507–516.
61. Tepaske R, Velthuis H, Oudemans-van Straaten HM *et al.* (2001) Effect of preoperative oral immune-enhancing nutritional supplement on patients at high risk of infection after cardiac surgery: a randomised placebo-controlled trial. *Lancet* **358**, 696–701.
62. Braga M, Gianotti L, Vignali A *et al.* (2002) Preoperative oral arginine and *n*-3 fatty acid supplementation improves the immunometabolic host response and outcome after colorectal resection for cancer. *Surgery* **132**, 805–814.
63. Marik PE & Flemmer M (2012) Immunonutrition in the surgical patient. *Minerva Anestesiol* **78**, 336–342.
64. Drover JW, Dhaliwal R, Weitzel L *et al.* (2011) Perioperative use of arginine-supplemented diets: a systematic review of the evidence. *J Am Coll Surg* **212**, 385–399.
65. Marik PE & Zaloga GP (2010) Immunonutrition in high-risk surgical patients: a systematic review and analysis of the literature. *JPEN J Parenter Enteral Nutr* **34**, 378–386.
66. Montejo JC, Zarazaga A, Lopez-Martinez J *et al.* (2003) Immunonutrition in the intensive care unit. A systematic review and consensus statement. *Clin Nutr* **22**, 221–233.
67. Heyland DK, Novak F, Drover JW *et al.* (2001) Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. *JAMA* **286**, 944–953.
68. Beale RJ, Bryg DJ & Bihari DJ (1999) Immunonutrition in the critically ill: a systematic review of clinical outcome. *Crit Care Med* **27**, 2799–2805.
69. Heys SD, Walker LG, Smith I *et al.* (1999) Enteral nutritional supplementation with key nutrients in patients with critical illness and cancer: a meta-analysis of randomized controlled clinical trials. *Ann Surg* **229**, 467–477.
70. Vissers YL (2005) Plasma arginine concentrations are reduced in cancer patients: evidence for arginine deficiency? *Am J Clin Nutr* **81**, 1142–1146.
71. Rodriguez PC (2008) Arginine regulation by myeloid derived suppressor cells and tolerance in cancer: mechanisms and therapeutic perspectives. *Immunol Rev* **222**, 180–191.
72. Redente EF (2007) Tumor signaling to the bone marrow changes the phenotype of monocytes and pulmonary macrophages during urethane-induced primary lung tumorigenesis in A/J mice. *Am J Pathol* **170**, 693–708.
73. Heyland DK & Samis A (2003) Does immunonutrition in patients with sepsis do more harm than good? *Intensive Care Med* **29**, 669–671.
74. Braga M, Gianotti L, Radaelli G *et al.* (1999) Perioperative immunonutrition in patients undergoing cancer surgery: results of a randomized double-blind phase 3 trial. *Arch Surg* **134**, 428–433.
75. Buijs N, van Bokhorst-de van der Schueren MA, Langius JA *et al.* (2010) Perioperative arginine-supplemented nutrition in malnourished patients with head and neck cancer improves long-term survival. *Am J Clin Nutr* **92**, 1151–1156.
76. McClave SA (2009) Guidelines for the provision and assessment of nutrition support therapy in the adult

critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr* **33**, 277–316.
77. Weimann A (2006) ESPEN guidelines on enteral nutrition: surgery including organ transplantation. *Clin Nutr* **25**, 224–244.
78. Paccagnella A (2011) Nutritional intervention for improving treatment tolerance in cancer patients. *Curr Opin Oncol* **23**, 322–330.
79. Bozzetti F (2011) Peri-operative nutritional management. *Proc Nutr Soc* **70**, 305–310.
80. Calder PC (2010) Omega-3 fatty acids and inflammatory processes. *Nutrients* **2**, 355–374.
81. Wischmeyer P (2011) Nutritional pharmacology in surgery and critical care: 'you must unlearn what you have learned'. *Curr Opin Anaesthesiol* **24**, 381–388.
82. Santora R & Kozar RA (2010) Molecular mechanisms of pharmaconutrients. *J Surg Res* **161**, 288–294.
83. Stapleton RD, Martin JM & Mayer K (2010) Fish oil in critical illness: mechanisms and clinical applications. *Crit Care Clin* **26**, 501–14, ix.
84. Cahill NE, Dhaliwal R, Day AG *et al.* (2010) Nutrition therapy in the critical care setting: what is 'best achievable' practice? An international multicenter observational study. *Crit Care Med* **38**, 395–401.
85. Stables MJ & Gilroy DW (2011) Old and new generation lipid mediators in acute inflammation and resolution. *Prog Lipid Res* **50**, 35–51.
86. Han YY, Lai SL, Ko WJ *et al.* (2012) Effects of fish oil on inflammatory modulation in surgical intensive care unit patients. *Nutr Clin Pract* **27**, 91–98.
87. Chen B, Zhou Y, Yang P *et al.* (2010) Safety and efficacy of fish oil-enriched parenteral nutrition regimen on post-operative patients undergoing major abdominal surgery: a meta-analysis of randomized controlled trials. *JPEN J Parenter Enteral Nutr* **34**, 387–394.
88. van der Meij BS, van Bokhorst-de van der Schueren MA, Langius JA *et al.* (2011) *n*-3 PUFAs in cancer, surgery, and critical care: a systematic review on clinical effects, incorporation, and washout of oral or enteral compared with parenteral supplementation. *Am J Clin Nutr* **94**, 1248–1265.
89. Wei C, Hua J, Bin C *et al.* (2010) Impact of lipid emulsion containing fish oil on outcomes of surgical patients: systematic review of randomized controlled trials from Europe and Asia. *Nutrition* **26**, 474–481.
90. Gao J, Ji CY & Wu GH (2012) Use of fish oil lipid emulsion in patients undergoing major surgery and those with systemic inflammatory response syndrome: a cost-effectiveness analysis. *Zhonghua Wei Chang Wai Ke Za Zhi* **15**, 452–456.
91. Heidt MC, Vician M, Stracke SK *et al.* (2009) Beneficial effects of intravenously administered $N-3$ fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a prospective randomized study. *Thorac Cardiovasc Surg* **57**, 276–280.
92. Weiss G, Meyer F, Matthies B *et al.* (2002) Immunomodulation by perioperative administration of *n*-3 fatty acids. *Br J Nutr* **87** Suppl. 1, S89–S94.
93. Kenler AS, Swails WS, Driscoll DF *et al.* (1996) Early enteral feeding in postsurgical cancer patients. Fish oil structured lipid-based polymeric formula versus a standard polymeric formula. *Ann Surg* **223**, 316–333.
94. Swails WS, Kenler AS, Driscoll DF *et al.* (1997) Effect of a fish oil structured lipid-based diet on prostaglandin release from mononuclear cells in cancer patients after surgery. *JPEN J Parenter Enteral Nutr* **21**, 266–274.
95. Sultan J, Griffin SM, Di FF *et al.* (2012) Randomized clinical trial of omega-3 fatty acid-supplemented enteral nutrition versus standard enteral nutrition in patients undergoing oesophagogastric cancer surgery. *Br J Surg* **99**, 346–355.
96. Ryan AM, Reynolds JV, Healy L *et al.* (2009) Enteral nutrition enriched with eicosapentaenoic acid (EPA) preserves lean body mass following esophageal cancer surgery: results of a double-blinded randomized controlled trial. *Ann Surg* **249**, 355–363.
97. Rees D, Miles EA, Banerjee T *et al.* (2006) Dose-related effects of eicosapentaenoic acid on innate immune function in healthy humans: a comparison of young and older men. *Am J Clin Nutr* **83**, 331–342.
98. Pontes-Arruda A, Aragao AM & Albuquerque JD (2006) Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock. *Crit Care Med* **34**, 2325–2333.
99. Singer P, Theilla M, Fisher H *et al.* (2006) Benefit of an enteral diet enriched with eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury. *Crit Care Med* **34**, 1033–1038.
100. Schaffer S, Takahashi K & Azuma J (2000) Role of osmoregulation in the actions of taurine. *Amino Acids* **19**, 527–546.
101. Bhavsar TM, Patel SN & Lau-Cam CA (2010) Protective action of taurine, given as a pretreatment or as a posttreatment, against endotoxin-induced acute lung inflammation in hamsters. *J Biomed Sci* **17**, Suppl. 1, S19.
102. Nakajima Y, Osuka K, Seki Y *et al.* (2010) Taurine reduces inflammatory responses after spinal cord injury. *J Neurotrauma* **27**, 403–410.
103. Kaesler S, Sobiesiak M, Kneilling M *et al.* (2012) Effective T-cell recall responses require the taurine transporter Taut. *Eur J Immunol* **42**, 831–841.
104. Paauw JD & Davis AT (1990) Taurine concentrations in serum of critically injured patients and age- and sex-matched healthy control subjects. *Am J Clin Nutr* **52**, 657–660.
105. American Society of Anesthesiologists Committee (2011) Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. *Anesthesiology* **114**, 495–511.
106. Crenshaw JT (2011) Preoperative fasting: will the evidence ever be put into practice? *Am J Nurs* **111**, 38–43.
107. van Hoorn DE, Boelens PG, van Middelaar-Voskuilen MC *et al.* (2005) Preoperative feeding preserves heart function and decreases oxidative injury in rats. *Nutrition* **21**, 859–866.
108. Bouritius H, van Hoorn DC, Oosting A *et al.* (2008) Carbohydrate supplementation before operation retains intestinal barrier function and lowers bacterial translocation in a rat model of major abdominal surgery. *JPEN J Parenter Enteral Nutr* **32**, 247–253.
109. Furnary AP, Zerr KJ, Grunkemeier GL *et al.* (1999) Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. *Ann Thorac Surg* **67**, 352–360.
110. Rassias AJ, Marrin CA, Arruda J *et al.* (1999) Insulin infusion improves neutrophil function in diabetic cardiac surgery patients. *Anesth Analg* **88**, 1011–1016.

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111. Berggren H, Ekroth R, Hjalmarson A *et al.* (1985) Enhanced myocardial protection from preoperative carbohydrate infusion in addition to maintained beta-blockade. *J Cardiovasc Surg (Torino)* **26**, 454–456.
112. Ljungqvist O & Soreide E (2003) Preoperative fasting. *Br J Surg* **90**, 400–406.
113. Nygren J, Thorell A, Jacobsson H *et al.* (1995) Preoperative gastric emptying. Effects of anxiety and oral carbohydrate administration. *Ann Surg* **222**, 728–734.
114. Hausel J, Nygren J, Lagerkranser M *et al.* (2001) A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. *Anesth Analg* **93**, 1344–1350.
115. Hausel J, Nygren J, Thorell A *et al.* (2005) Randomized clinical trial of the effects of oral preoperative carbohydrates on postoperative nausea and vomiting after laparoscopic cholecystectomy. *Br J Surg* **92**, 415–421.
116. Melis GC, van Leeuwen PA, von Blomberg-van der Flier BM *et al.* (2006) A carbohydrate-rich beverage prior to surgery prevents surgery-induced immunodepression: a randomized, controlled, clinical trial. *JPEN J Parenter Enteral Nutr* **30**, 21–26.
117. Noblett SE, Watson DS, Huong H *et al.* (2006) Pre-operative oral carbohydrate loading in colorectal surgery: a randomized controlled trial. *Colorectal Dis* **8**, 563–569.
118. Wang ZG, Wang Q, Wang WJ *et al.* (2010) Randomized clinical trial to compare the effects of preoperative oral carbohydrate versus placebo on insulin resistance after colorectal surgery. *Br J Surg* **97**, 317–327.
119. Svanfeldt M, Thorell A, Hausel J *et al.* (2007) Randomized clinical trial of the effect of preoperative oral carbohydrate treatment on postoperative whole-body protein and glucose kinetics. *Br J Surg* **94**, 1342–1350.
120. Yuill KA, Richardson RA, Davidson HI *et al.* (2005) The administration of an oral carbohydrate-containing fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively – a randomised clinical trial. *Clin Nutr* **24**, 32–37.

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