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(54) Title: FOOD COMPOSITION FOR INTRA-OPERATIVE TUBE FEEDING

(57) Abstract: The present invention pertains to a liquid nutritional composition comprising fat and proteinaceous matter, wherein said fat contributes for at least 41 En% and said proteinaceous matter contributes for at least 23 En% to the total energy content of said composition, for mitigating, attenuating or preventing an acute inflammatory response during or after surgery of a patient undergoing said surgery, wherein said composition is to be administered to said patient by intra-operative tube feeding, as well as to specific liquid nutritional compositions, suitable for use as a tube feed, and especially for mitigating, attenuating or preventing an acute inflammatory response during or after surgery of a patient.



FOOD COMPOSITION FOR INTRA-OPERATIVE TUBE FEEDING

FIELD OF THE INVENTION

The invention pertains to liquid nutritional compositions and to the use thereof for mitigating, attenuating or preventing an acute inflammatory response during or after surgery by intra-operative administration by tube feeding of a lipid-rich and protein-rich liquid nutritional composition.

BACKGROUND

The body of mammals may respond to stressors with an inflammatory reaction. Stressors can be of infectious or non-infectious origin. Examples of stressors are microorganisms (viral, bacterial, fungal, or parasitical) or non-endogenous proteins or peptide-related materials which have invaded a tissue locally, physical traumas including surgery, severe blood loss, extra-corporal circulation or extensive soft tissue damage and multiple fractures, ischemia/reperfusion events, or damage to cells or tissue due to burns, chemotherapy, radiation or intoxication. During the inflammatory reaction, many factors play a role. Inflammatory mediators, including acute-phase proteins, interleukins, prostaglandins, cytokines and leukotrienes, contribute to a concerted number of responses within the body in order to obtain an appropriate metabolism and host defence reaction (i.e. blood flow to the affected tissue, repair processes and combat against undesired exogenous components and apoptosis of endogenous cells) in order to obtain an appropriate host defence-reaction, in particular to rapidly and effectively neutralise stressors, obtain rapid wound healing, prevent tissue damage as caused by ischemia/- reperfusion processes or chemo- or radiotherapy and achieve a fast repair of tissue function.

Despite diagnostic and therapeutic advances in medical care, a dysregulated systemic inflammatory response remains a major complication in surgical, trauma and critically ill patients, which is associated with increased morbidity and mortality. Modulation of the early excessive inflammatory response represents a potential therapeutic option to improve outcome. Although experimental studies demonstrated promising results of interventions aimed at inhibition of single pro-inflammatory mediators, clinical implementation has failed to be successful.

Enhanced insight in disease pathology and development of novel treatment modalities which broadly affect the inflammatory response are warranted to reduce morbidity and mortality.

Patients that are subjected to surgery are mostly fasted prior to surgery in order to prevent potential vomiting and aspiration of stomach contents. In addition, patients often experience serious problems in feeding themselves properly in the period directly after surgery. Statistics demonstrate that many hospitalised patients suffer from complications. Such complications vary from delayed wound healing, swelling and pain, bad recovery of function of the stressed tissue, local infections, and may in some instances even result in systemic complications like sepsis and multiple organ dysfunction, which are aggravated by decreased nutritional intake.

Recently, early enteral administration before or after surgery of nutrients was shown to improve immune competence and clinical outcome in surgical and critically ill patients (ref. 8-10).

Enteral feeding of patients during surgery is known for patients suffering from severe burn injuries (ref. 48-49). However, the feeding is not performed to mitigate, attenuate or prevent an acute inflammatory response during or after surgery but to meet their significant nutritional demands, reduce caloric deficit and because such patients cannot be fed otherwise. Furthermore, surgery is limited to skin surgery, i.e. non-invasive surgery.

Hence, until now, it has not been proposed to routinely feed patients during surgery, i.e. intra-operatively, in order to mitigate, attenuate or prevent an acute inflammatory response during or after surgery and which nutritional composition would be best suited for such purpose.

SUMMARY OF THE INVENTION

It is a purpose of the invention to provide a liquid nutritional composition for mitigating, attenuating or preventing an acute inflammatory response during or after surgery, preferably invasive surgery, of patients who are at risk for or are already experiencing complications as a result of these stressors, by intra-operative enteral administration of a lipid- and protein-rich liquid nutritional composition, more in particular by intra-operative tube feeding, in particular by continuous intra-operative tube feeding. It is also an object to provide a method for mitigating, attenuating or preventing an acute inflammatory response during or after surgery, preferably invasive surgery, of patients who are at risk for or are already experiencing complications as a result of these stressors, by intra-operative enteral administration of a lipid- and protein-rich liquid nu-

tritional composition, more in particular by intra-operative tube feeding, in particular by continuous intra-operative tube feeding. The administration of said enteral nutrition is practical to apply by the use of known enteral feeding devices, in particular tubes, and prevents in particular the development of a (too) strong or dysregulated inflammatory response during and following the presence of the stressor and the subsequent healing process by a rapid mode of action. When the inflammatory reaction has already started, it prevents a further increase of the inflammatory reaction, a so-called hyperinflammation. A reduction of the hyperinflammatory response has been associated with an enhanced recovery after surgery.

Hence, the problem to be solved by the invention is to provide a liquid nutritional composition capable of rapidly averting short-time inflammatory effects, in particular with a surgical medical intervention, preferably an invasive surgical medical intervention. An invasive surgical medical intervention is one which penetrates or breaks the skin or enters a body cavity. Examples of invasive procedures include those that involve perforation, an incision, a catheterization, or other entry into the body. An specific invasive surgical medical intervention is an open surgery cutting skin and tissues so the surgeon has a direct access to the structures or organs involved. The structures and tissues involved can be seen and touched, and they are directly exposed to the air of the operating room. Examples of open surgery include the removal of organs, such as the gallbladder or kidney, and most types of cardiac surgery and neurosurgery. Open surgery involves large incisions, in which the tissues are exposed to the air. The problem was solved by the provision of a liquid nutritional composition having a high amount of fat and a high amount of protein. Without being bound by theory, the lipid-rich nutrition is beneficial for attenuating or preventing an acute inflammatory response and organ damage via a cholecystokinin (CCK)-mediated vagovagal reflex. It is also believed that protein is beneficial for attenuating or preventing an acute inflammatory response and organ damage via a cholecystokinin (CCK)-mediated vagovagal reflex. The fat provides a fast and high CCK response whereas the protein delivers a lower but more sustainable CCK release. Surprisingly, both responses together deliver the optimal mediation of the cholecystokinin-mediated vagovagal reflex. In addition, the high amount of protein provides the necessary amino acids (in particular glutamine) for the recovery of patients, in particular by (i) minimizing catabolic protein response, (ii) maintaining gut function and gut immunity, and (iii) supporting the acute phase protein synthesis.

Within the context of this application, it is understood that intra-operative feeding is the main application area of the invention. In the relevant prior art, the wording "peri-operative" and/or "peroperative" feeding is often found to denote a feeding protocol which includes pre-operative (i.e. before surgery) and/or post-operative (i.e. after surgery) feeding, but excludes intra-operative feeding. Within the context of this application, it is understood that the term "intra-operative feeding" refers to a feeding regime during operation and does not refer to pre- or post-operative feeding. However, the liquid nutritional composition of the invention can also be suitably used for pre- and post-operative feeding. In fact, the enteral feeding can be started before the surgical procedure, i.e. in the pre-operative phase, and can be continued after the surgical procedure, i.e. in the post-operative phase. Hence, the invention also relates to the liquid nutritional composition of the invention for peri-operative use.

Within the context of this invention, a percentage of the total energy of the composition is abbreviated as En% and is used to denote the energetic value of a digestible compound (fat, protein, carbohydrates, fibres) (in particular in a human or other mammal). In particular, the energetic value is based on the contribution of proteinaceous matter (including proteins, peptides and amino acids), lipids or fat and digestible carbohydrates, using the following calculation factors (Atwater factors): 4 kcal/g for digestible carbohydrates and proteinaceous matter, 9 kcal/g for lipids and 2 kcal/g for digestible fibres.

BACKGROUND PRIOR ART

The beneficial effect of a high fat enteral composition for the treatment and/or prevention of sepsis or for combating inflammatory conditions is known from the prior art. However, the beneficial effect of a high protein content in combination of a high fat content is not disclosed, nor is such a composition according to the invention.

EP 1 411 951 B1 (NV Nutricia) discloses the use of a composition containing a fat fraction comprising phospholipids, triglycerides and cholesterol in a weight ratio of 3-90 : 3-80 : 1, a protein fraction and a digestible carbohydrate fraction for the treatment and/or prevention of sepsis, endotoxemia and/or bacteraemia, which may be associated with major surgery, critical illness, inflammatory bowel disease etc., caused by bacteria.

EP 1 589 834 B1 (NV Nutricia) similarly discloses the use of a composition containing a fat fraction comprising phospholipids and triglycerides in a weight ratio of greater than 1, with

less than 0.5 weight% of cholesterol, a protein fraction and a digestible carbohydrate fraction, for the treatment of sepsis and associated conditions. The beneficial role of a high protein content is not disclosed, nor is a composition according to the invention.

US 5,968,896 (Beth Israel Deaconess Medical Center) discloses a solid or semi-solid nutritional supplement for pre-operative feeding comprising 26 - 46 En% of fat, 20 - 40 En% of proteins and 25 - 45 En% of digestible carbohydrates for individuals preparing for an imminent major surgical procedure, preferably a non-baked extruded nutritional bar of approximately 200 kcal (one serving).

EP 1 041 896 B1 (NV Nutricia) discloses compositions containing a fat blend comprising [gamma]-linolenic acid, stearidonic acid and eicosapentaenoic acid (2 : 1 : 2) and phospholipids as an enteral food for the treatment of chronic inflammatory diseases, lipid metabolism disorders and weakened immune functions.

EP 1 090 636 (INRA) discloses a composition for use in the treatment of sepsis or inflammatory shock, which comprises more than 35 En% of lipids. The lipid fraction comprises 25-70 weight% MCT oil. Less than 15 weight% saturated fatty acids excluding MCT and the n-6/n-3 ratio is about 2-7 : 1.

EP 0 265 772 (Abbott) claims a nutritional formula comprising 45 - 60 En% of fat, 20 - 37 En% of digestible carbohydrates and 8 - 25 En% of proteins for humans suffering from glucose intolerance. The disclosed examples are limited to high fat compositions comprising at most 20 En% of proteins.

EP 0 691 079 (Clintec) claims a nutritional formula comprising 30 - 45 En% of fat, at most 50 En% of digestible carbohydrates and 8 - 25 En% of proteins for use with diabetic patients. The disclosed example is limited to a composition comprising at 18 En% of proteins.

EP 0 189 160 (Abbott) claims a high fat, low carbohydrate enteral nutritional composition comprising 45 - 60 En% of fat, at most 30 En% of digestible carbohydrates and 8 - 25 En% of proteins for treating patients with respiratory insufficiency. The example discloses a composition comprising 55 En% of fat, 19 En% of protein and 26 En% of carbohydrates.

EP 0 611 568 (Fresenius) claims a nutritional composition for cancer patients suitable to be used as a tube feed, comprising 40 to 65 En% of fat, 20 to 45 En% of digestible carbohydrates and 12 to 25 En% of proteins. All examples disclose compositions with at most 20 En% of proteins.

US 7,691,906 (Nestec S.A.) discloses an enteral composition for the treatment or prevention of sepsis or inflammatory shock, optionally administered by tube feeding, comprising at least 35 En% of fat which comprises at least 40 to 70 weight% of an MCT, 10 to 25 En% of proteins and 12 to 55 En% of carbohydrates.

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DESCRIPTION OF THE INVENTION

The invention pertains to liquid nutritional compositions comprising a high amount of fat and a high amount of proteinaceous matter and to the use thereof for mitigating, attenuating or preventing an acute inflammatory response during or after surgery of a patient undergoing said surgery, wherein said composition is to be administered to said patient by intra-operative tube feeding. This setting requires an immediate effect of the feeding, wherein the effect of the feeding consists in attenuation of the inflammatory response. The immediate response means that the attenuation starts within 30 minutes, preferably within 15 minutes, and lasts for several hours, in particular for 1 to 3 hours after the intervention has stopped.

According to one embodiment, the invention relates to a liquid nutritional composition comprising fat and proteinaceous matter, wherein said fat contributes for at least 41 En% and said proteinaceous matter contributes for at least 23 En% to the total energy content of said composition or mitigating, attenuating or preventing an acute inflammatory response during or after surgery of a patient undergoing said surgery, wherein said composition is to be administered to said patient by intra-operative tube feeding.

According to another embodiment, the invention relates to a liquid nutritional composition comprising fat, proteinaceous matter and digestible carbohydrates, wherein said fat contributes for at least 41 En%, said proteinaceous matter contributes for at least 23 En%, and said digestible carbohydrates contribute for at most 36 En% to the total energy content of said composition, optionally further comprising at least 1.5 gram, more preferably, at least 1.7 gram of L-glutamine (bound and/or free) per 100 ml of said composition, as well as to its use as a tube feed, in particular for mitigating, attenuating or preventing an acute inflammatory response during or after surgery of a patient.

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Proteinaceous matter

The liquid nutritional composition according to the invention comprises at least a source of proteinaceous matter.

5 The liquid nutritional composition according to the invention comprises at least 23 En% of proteinaceous matter, preferably between 23 En% and 59 En%, more preferable between 23 En% and 45 %, most preferably between 23 En% and 40 En% of proteinaceous matter relative to the total energy content of said composition.

As used herein, proteinaceous matter is defined as protein, peptides and amino acids. Hence, proteinaceous matter of the liquid nutritional composition according to the invention is the sum of all proteins, peptides and amino acids, free or in any bound form, present in the liquid
10 nutritional composition according to the invention.

According to one embodiment, the proteinaceous matter comprises a source of vegetable proteinaceous matter and a source of dairy proteinaceous matter. Preferably, the proteinaceous matter comprises 20 to 80 weight% of vegetal proteinaceous matter and 20 to 80 weight% of
15 dairy proteinaceous matter.

In the context of this application, the wording "vegetable" relates to proteinaceous matter from plant origin, such as, for instance originating from vegetables such as carrot, pea, chickpea, green pea, kidney bean, lupine, rice, soy, canola, hemp, zein, maize, corn, barley, flax, linseed, and wheat. Equivalent wording may be used, such as "vegetal", "leguminous" or "plant-derived".
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In the context of this application, the wording "dairy" proteinaceous matter relates to milk-derived proteinaceous matter, i.e. to proteinaceous matter from animal milk, such as derived from species such as camel, cow, goat, horse, human, reindeer, sheep, water buffalo and yak.

According to another embodiment, the proteinaceous matter comprises a hydrolysed protein, for example an hydrolysate of soy, casein, whey or wheat proteins. Preferably, in this embodiment, the proteinaceous matter substantially consists of hydrolysed protein, preferably at
25 least 90 weight%, more preferably at least 95 weight%. In one embodiment, the hydrolysed proteins are obtained by the enzymatic hydrolysis of proteins, for example whey proteins. An example of suitable proteins can be found in Peptamen® (Nestlé), a 100% whey peptide based enteral tube nutrition, ensuring optimal absorption and better protein utilization.

Preferably, the proteinaceous matter comprises any one or more of casein, whey, soy, pea and wheat protein. According to one embodiment, the liquid nutritional composition according to the invention preferably comprises one or more of said casein, whey, soy and wheat protein each individually in an amount between 0.1 and 10 gram of proteins per 100 ml of said liquid nutritional composition, more preferably between 1 and 10 gram per 100 ml of said liquid nutritional composition, more preferably 2, 3, 4, 5, 6, 7, 8 or 9 gram of proteinaceous matter per 100 ml of said liquid nutritional composition, or any integer and non-integer fraction in between.

According to a preferred embodiment, the liquid nutritional composition according to the invention comprises casein and wheat protein, each individually in an amount between 0.1 and 10 gram of proteins per 100 ml of said liquid nutritional composition, more preferably between 1 and 10 gram per 100 ml of said liquid nutritional composition, more preferably 2, 3, 4, 5, 6, 7, 8 or 9 gram of proteinaceous matter per 100 ml of said liquid nutritional composition, or any integer and non-integer fraction in between.

According to a preferred embodiment, the liquid nutritional composition according to the invention comprises 30 to 50 weight% of casein and 30 to 50 weight% of wheat protein relative to the total weight of the proteinaceous matter. More preferably, the casein:wheat protein weight ratio is about 1.

According to a preferred embodiment, the liquid nutritional composition according to the invention comprises 2 to 4 gram of casein and 2 to 4 gram of wheat protein per 100 ml of said liquid nutritional composition.

According to one embodiment, the proteinaceous matter comprises an amount of L-glutamine (bound and/or free) which exceeds the amount naturally present in intact vegetal or dairy proteins. Preferably, such amount of L-glutamine is at least 20 gram, more preferably at least 25 gram per 100 gram of total proteinaceous matter. L-Glutamine (abbreviated as Gln or Q) is one of the 20 amino acids encoded by the standard genetic code. It is not recognized as an essential amino acid but may become conditionally essential in certain situations, including intensive athletic training or certain gastrointestinal disorders. Its side-chain is an amide formed by replacing the side-chain hydroxyl of L-glutamic acid with an amine functional group. Therefore, it can be considered the amide of L-glutamic acid. The term "glutamine" or "L-glutamine" also comprises a glutamine equivalent, which is a compound that can be converted to L-glutamine in the body, such as an L-glutamine dipeptide or a 2-acylaminoglutaric acid monoamide.

It is specifically stated here that (L-) glutamic acid is excluded from the definition of glutamine.

Preferably, the liquid nutritional composition according to the invention comprises at least 1.5 gram, more preferably, at least 1.7 gram of L-glutamine (bound and/or free) per 100 ml of total liquid nutritional composition. Preferably, the liquid nutritional composition according to the invention comprises between 1.5 gram and 5 gram, more preferably between 1.7 gram and 4 gram, most preferably between 1.9 and 3 gram of L-glutamine (bound and/or free) per 100 ml of total liquid nutritional composition.

The amount of L-glutamine required according to the invention cannot be provided by intact vegetal or dairy proteins alone and an L-glutamine-enriched source should be present. Preferably, the source of L-glutamine is selected from the group of wheat protein, which is rich in L-glutamine, the free amino acid L-glutamine, and an L-glutamine-containing dipeptide, such as L-alanyl-L-glutamine. Preferably, said L-alanyl-L-glutamine dipeptide is synthetically produced. Preferably, the dipeptide is used, since the free amino acid is not stable during sterilization.

15 **Fat**

The liquid nutritional composition according to the invention comprises at least a source of fat. The total amount of energy supplied by the fat should be at least about 41 En%, at least about 42 En%, at least about 43 En% or at least about 44 En% per 100 ml of said liquid nutritional composition.

According to another embodiment, the total amount of energy supplied by the fat should be preferably between 41 En% and 77 En%, more preferably between 41 En% and 70 En%, most preferably between 41 En% and 65 En%, relative to the total energy content of said composition.

With regard to the type of fat, a wide choice is possible, as long as the fat is of food quality.

The fat may be an animal fat or a vegetable fat or both. Although animal fats such as lard or butter have essentially equal caloric and nutritional values and can be used interchangeably, vegetable oils are highly preferred in the practice of the present invention due to their readily availability, ease of formulation, absence of cholesterol and lower concentration of saturated fatty acids. In one embodiment, the present composition comprises rapeseed oil, corn oil and/or sunflower oil.

The fat may include a source of medium chain fatty acids, such as medium chain triglycerides (MCT, defined as 8 to 10 carbon atoms long), a source of long chain fatty acids, such as long chain triglycerides (LCT) and phospholipid-bound fatty acids such as phospholipid-bound EPA or DHA, or any combination of the two types of sources.

5 According to one embodiment, the liquid nutritional composition according to the invention comprises medium-chain fatty acids (MCTs), having a chain length of 8, 10 or 12 carbon atoms, preferably in an amount of 0 to 25 weight%, more preferably 0 to 20 weight%, and especially less than 3 weight%, and myristic acid (C 14:0). MCTs are beneficial because they are easily absorbed and metabolized in a metabolically-stressed patient. Moreover, the use of MCTs
10 will reduce the risk of nutrient malabsorption. LCT sources, such as canola oil, rapeseed oil, sunflower oil, soybean oil, olive oil, coconut oil, palm oil, linseed oil, marine oil or corn oil are beneficial because it is known that LCTs may modulate the immune response in the human body.

According to one embodiment, the fat in the liquid nutritional composition according to the invention comprises at most 25 weight% of medium chain triglycerides (MCTs), relative to
15 the total weight of said fat.

According to one embodiment, the fat comprises a glyceride fraction. This may contain mono-, di- and tri-glycerides. Preferably, in order to facilitate rapid digestion, part of the glyceride fraction consists of mono and/or diglycerides of fatty acids. The mono- and diglycerides were also found to assist in administering relatively large amounts of lipids, without excessively
20 raising the caloric content of the composition.

According to one embodiment, the lipid comprises at least 5 weight%, at least 6 weight%, or at least 7 weight% of polyunsaturated fatty acids (PUFA's), calculated relative to the total amount of fatty acids, preferably eicosapentaenoic acid (EPA) and docosapentaenoic acid (DHA). The latter PUFA's are known to exhibit an anti-inflammatory action and may prevent hyperin-
25 flammation.

According to one embodiment, the lipid comprises at least 400 mg of PUFA's, preferably eicosapentaenoic acid (EPA) and docosapentaenoic acid (DHA) per 100 ml of liquid nutritional composition according to the invention, more preferably between 400 and 1000 mg, more preferably between 450 to 750 mg per 100 ml of said liquid nutritional composition.

According to one embodiment, the fat in the liquid nutritional composition according to the invention may contain phospholipids or cholesterol. According to one embodiment, the fat in the liquid nutritional composition according to the invention comprises less than 10 weight% of phospholipids, relative to the total weight of said fat, or the fat comprises less than 0.5 weight% of cholesterol, relative to the total weight of said fat.

Digestible carbohydrates

Optionally, the liquid nutritional composition according to the invention comprises a digestible carbohydrate.

With regard to the type of digestible carbohydrates, a wide choice is possible, as long as the digestible carbohydrates are of food quality. The digestible carbohydrates positively influence the energy level of a subject, and add to the advantageous effect of the nutritional composition according to the invention. The digestible carbohydrate may comprise simple and/or complex digestible carbohydrates, or any mixture thereof. Suitable for use in the present invention are glucose, fructose, sucrose, lactose, trehalose, palatinose, corn syrup, malt, maltose, isomaltose, partially hydrolysed corn starch, maltodextrins, glucose oligo- and polysaccharides.

According to one embodiment, the digestible carbohydrate contributes for at most 36 En% to the total energy content of the liquid nutritional composition. Preferably, the digestible carbohydrate contributes for at most 35 %, 34 % , 33 En%, 32 En%, 31 En% or 30 En% to the total energy content of the liquid nutritional composition.

A low digestible carbohydrate amount lowers the stress-induces hyperglycaemia, insulin resistance, and therefore the infection rate.

Further components

The composition of the invention may further contain other nutritional components, such as trace elements, vitamins, minerals, dietary fibres, e.a. in an amount which is adapted to suit the needs of the patient.

Specific compositions

The liquid nutritional composition according to the invention may be characterized by one or more of the following features:

- 5 (i) comprising at least 41 En% of fat, at least 23 En% of proteinaceous matter and at most 36 En% of digestible carbohydrates ;
- (ii) comprising less than 250 kcal, preferably less than 200 kcal, more preferably less than 160 kcal, most preferably about 125 kcal per 100 ml of said composition ;
- (iii) comprising 5 to 10 gram of proteins, 4 to 10 gram of fat, and 4 to 14 gram of digestible carbohydrates per 100 ml of said composition ; and
- 10 (iv) comprising at least 1.5 gram, more preferably, at least 1.7 gram of L-glutamine (bound and/or free) per 100 ml of said composition.

In one particular embodiment, the liquid composition according to the invention comprises fat, proteinaceous matter and digestible carbohydrates, wherein said fat contributes for at least 41 En%, said proteinaceous matter contributes for at least 23 En%, and said digestible carbohydrates
15 contribute for at most 36 En% to the total energy content of said composition, further comprising at least 1.5 gram, more preferably, at least 1.7 gram of L-glutamine (bound and/or free) per 100 ml of said composition.

In one particular embodiment, the liquid composition according to the invention comprises about 45 En% of fat, about 23 En% of proteinaceous matter , about 29 En% of digestible carbo-
20 hydrates, and about 2 gram of L-glutamine per 100 ml of said composition.

Viscosity

The composition is a liquid composition, wherein liquid is defined as a substance being suitable for enteral administration by tube at room temperature, using for example a feeding
25 pump, gravity, syringe administration and the like.

Said composition has a certain viscosity, which is adapted to said enteral administration.

In one embodiment of the present invention, the viscosity of the liquid enteral nutritional composition is lower than 500 mPa.s, measured at 20 °C (i.e. room temperature) at a shear rate of 100 s⁻¹, preferably between 10 and 200 mPa.s, more preferably between 10 and 100 mPa.s, most
30 preferably below 50 mPa.s. The viscosity may suitably be determined using a rotational viscosity meter using a cone/plate geometry. This viscosity is ideal for orally administering the liquid en-

teral nutritional composition according to the invention because a person may easily consume a serving having a low viscosity such as that displayed by the present invention. This viscosity is also ideal for unit dosages that are tube fed.

In one embodiment of the present invention, the density of the composition ranges between
5 1.00 g/ml and 1.20 g/ml, especially between 1.05 g/ml and 1.15 g/ml.

Dosage unit

The liquid enteral nutritional composition according to the invention may have the form of a complete food, i.e. it can meet all nutritional needs of the user. As such, the liquid enteral nutritional composition according to the invention preferably contains 1000 to 2500 kcal per daily
10 dosage. Depending on the condition of the patient, a daily dose is about 25 to 35 kcal/kg body-weight/day. Therefore, a typical daily dose for a 70 kg person contains about 2000 kcal. The complete food can be in the form of multiple dosage units, e.g. from 8 (250 ml/unit) to 2 units (1 l/unit) per day for an energy supply of 2000 kcal/day using a liquid enteral nutritional composition according to the invention of 1.0 kcal/ml. Preferably, the nutritional composition is adapted
15 for tube feeding, i.e. in the form of a tube feed.

The liquid enteral nutritional composition can also be a food supplement, especially for use as a tube feed to be administered to a patient undergoing surgery by intra-operative tube feeding. Preferably, as an enteral supplement, the liquid enteral nutritional composition contains per daily
20 dosage less than 1500 kcal, in particular as a supplement, the liquid enteral nutritional composition contains 500 to 1000 kcal per daily dose. The food supplement can be in the form of multiple dosage units, e.g. from 2 (250 ml/unit) to 10 units (50 ml/unit) per day for an energy supply of 500 kcal/day using the liquid enteral nutritional composition according to the invention. Depending on the surgical procedure, the dosage unit may be adapted in size and composition.

Preferably, the nutritional composition is packaged, stored and provided in a container such as plastic bag or a pouch or the like. A variety of such containers is known, for example 500 ml, 1000 ml, and 1500 ml containers are known in the art. It should be noted that any suitable container can be used to package, store and provide the nutritional composition according to the invention.
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In one embodiment of the present invention, the liquid enteral nutritional composition is provided in a ready to use liquid form and does not require reconstitution or mixing prior to use.
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The liquid enteral nutritional composition according to the invention can be tube fed or administered orally. For example, the composition according to the invention can be provided in a can, on spike, and hang bag. However, a composition may be provided to a person in need thereof, in powder form, suitable for reconstitution using an aqueous solution or water such that the enteral
5 nutritional composition according to the invention is produced. Thus, in one embodiment of the present invention, the present composition is in the form of a powder, accompanied with instructions to dissolve or reconstitute in an aqueous composition or water to arrive at the liquid nutritional enteral composition according to the present invention. In one embodiment of the present invention, the present liquid nutritional enteral composition may thus be obtained by dissolving
10 or reconstituting a powder, preferably in an aqueous composition, in particular water. A suitable packaging mode is a powder in a container, e.g. a sachet, preferably with instructions to dissolve or reconstitute in an aqueous composition or water.

Preparation

15 The liquid nutritional composition according to the invention may be prepared using standard preparation methods known to the skilled person and they will not be further described.

Due to a prerequisite of at least six months of shelf life in general, preferably at least 12 months, the liquid nutritional composition according to the invention need to undergo some sort of sterilization treatment in order to reduce the number of or remove possible pathogens, for instance spores, bacteria and other microorganisms, which cause spoilage of the protein composition, preferably by using heat (sterilization, pasteurization), radiation (UV-treatment), or filtration
20 methods (ultrafiltration, diafiltration, nanofiltration). Preferred sterilization treatments include heat treatments at high temperatures for a short period, such as using a UHT (Ultra High Temperature) treatment.

25 Preferably, the liquid nutritional composition according to the invention is in a sterilized or pasteurized form.

USE OF THE COMPOSITION

According to one embodiment, the liquid nutritional composition of the invention may
30 be used as a tube feed, i.e. for tube feeding a patient. Said tube feeding may be provided continuously, or intermittently.

According to another embodiment, the liquid nutritional composition of the invention may be used for tube feeding of a patient undergoing surgery, in particular non-invasive surgery such as skin-surgery, invasive surgery such as organ surgery, cardiac surgery and neurosurgery, by intra-operative tube feeding.

5 The liquid nutritional composition of the invention is also advantageously used for mitigating, attenuating or preventing an acute inflammatory response during or after surgery of a patient.

According to one embodiment, the patient is a patient that is undergoing surgery, that has undergone surgery or that is a critically-ill patient.

10 The invention will now be described by way of examples ; these are not meant to be limiting.

List of Figures

Figure 1. Experimental design. Subjects are admitted to the intensive care unit (ICU) after an overnight fast. One hour prior to LPS administration, subjects are prehydrated and the continuous administration of enteral nutrition started in the nutritional intervention groups, lasting until six hours after LPS administration. Blood is withdrawn at indicated time points during the experiment. Subjects leave the hospital 12 hours after intravenous administration of LPS and return the day after for final blood sampling.

20 **Figure 2.** Enriched nutrition modulates the inflammatory response during endotoxemia. Mean plasma concentrations of TNF- α (A), IL-6 (B), IL-1RA (C) and IL-10 (D) following intravenous LPS administration. Enriched nutrition attenuates TNF- α , IL-6 and IL-1RA levels compared with control nutrition ($p < .05$) and fasting ($p < .0001$). Administration of the control product displays a trend towards lower TNF- α levels ($p = .06$). The enriched nutrition enhances IL-10 release ($p < .0001$ vs fasted), while a trend is observed with control nutrition ($p = .07$ vs fasted).

25 **Figure 3.** Administration of LPS results in sub-clinical intestinal damage. Intravenous administration of LPS results in a gradual increase of plasma i-FABP levels in all groups (A). Subjects fed enriched nutrition display a smaller increase in circulating i-FABP levels (A-B), although this does not reach statistical significance.

30 **Figure 4.** Postpyloric administration of control or enriched nutrition increases plasma levels of CCK. Continuous enteral administration of both the control and enriched nutrition results in an

increase in CCK plasma levels compared with fasted subjects. Both nutritional interventions demonstrate a slight decrease in CCK plasma levels at 4 hours following LPS administration. After cessation of nutrient infusion, plasma CCK levels fall below detection level (A). There is no significant difference in total CCK release between control and enriched nutrition (B). ND, not detectable.

EXAMPLES

Example 1 : Tube-feed according to the invention (all values per 100 ml of total liquid composition)

Energy	kcal	128
Protein	g	7.5
	En%	23
Carbohydrate	g	9.4
	En%	29
Fat	g	6.4
	En%	45
Protein composition		
- casein	g	2.9
- soy protein	g	0.1
- wheat	g	2.9
- L-alanyl-L-glutamine dipeptide	g	1.5
of which :		
- total L-glutamine	g	2.0
- total (glutamine+glutamic acid)	g	2.9
Fat composition		
- saturated	g	2.0
- of which MCT	g	1.3
mono-unsaturated	g	2.5
poly-unsaturated	g	1.9
Total glutamine	mg	2000

Example 2 : Investigation of the immunomodulatory potential of enteral lipid- and protein-enriched nutrition during experimental human endotoxemia.

5 Materials and Methods

Subjects

This study was registered at ClinicalTrail.gov as NCT01100996. After approval of the local ethics committee of the Radboud University Nijmegen Medical Centre, 12 healthy male subjects gave written informed consent to participate in the experiments in accordance with the Declaration of Helsinki. Samples of fasted subjects ($n = 6$) were obtained from the placebo-group that participated in another double-blind LPS study (NCT00513110). There were no differences in subject characteristics (Table 1). All subjects tested negative for HIV and hepatitis B and did not have any febrile illness in the two weeks preceding the study. The subjects did not use any prescription drugs, aspirin or nonsteroid anti-inflammatory drugs.

Table 1. Subject characteristics

	Fasted	Enriched	Control	<i>P</i> value between groups
Age (y)	24 ± 1	23 ± 1	25 ± 2	.30
BMI (kg/cm²)	22.0 ± 0.7	23.0 ± 0.6	23.1 ± 0.9	.60
TER (kcal)	2822 ± 44	2845 ± 79	3020 ± 137	.22
Rate of infusion (kcal/min)	NA	2.0 ± 0.1	2.1 ± 0.1	.31

Data are represented as mean $\pm$ SEM; BMI, body mass index; TER, total energy requirement; NA, not applicable.

Experimental Human Endotoxemia

Subjects were prehydrated with 1.5 L glucose 2.5%/NaCl 0.45% after which they received an intravenous bolus of 2 ng/kg body weight U.S. reference *E. coli* endotoxin (*Escherichia coli* O:113, Clinical Center Reference Endotoxin, National Institute of Health, Bethesda, MD) administered in one minute [22]. LPS-induced symptoms were rated using grades ranging from 0 (no symptoms) to 5 (most severe ever experienced), resulting in a cumulative sickness score. Blood was drawn before the start of postpyloric feeding and serially thereafter up to 24 hours after LPS administration (Figure 1). Routine hematology parameters were determined using flow cytometry (Sysmex XE-2100; Goffin Meyvis, Etten-Leur, the Netherlands).

Postpyloric Feeding

On the experimental day, two groups received a nutritional intervention in a double-blind randomized fashion, while one group was fasted during the entire experiment (all groups: n = 6). The nutritional intervention groups received continuous postpyloric infusion of a liquid, enriched or an isocaloric control enteral nutrition for 7 hours via a self-advancing nasal-jejunal feeding tube (Tiger 2, Cook Medical, Bloomington, IN, Figure 1), which was placed on the evening before the experiment. The rate of feeding for each subject was based on their individual total energy requirement (TER). The TER was calculated by multiplying the basal metabolic rate of each subject with their activity level (1.55 times for all subjects) using the Harris-Benedict equation (Table 1).

Feeding Composition and CCK Measurement

The enriched nutrition contained 44 En% fat, 25 En% protein and 31 En% carbohydrates. The protein consisted of intact casein, whey protein and soy protein hydrolysate. The control nutrition contained 20 En% fat, 16 En% protein and 64 En% carbohydrates. Both the enriched and control nutrition provided 1 kcal/ml. Systemic CCK levels were determined in plasma using a CCK-radioimmunoassay (Eurodiagnostica, Malmö, Sweden).

Determination of Plasma Cytokines and Sub-Clinical Intestinal Damage

TNF- α , IL-6, IL-10, and IL-1 receptor antagonists (IL-1RA) were measured batchwise using a multiplex Luminex Assay according to the manufacturer's instructions (Millipore, Billerica,

MA). Intestinal-fatty acid binding protein (i-FABP) was determined in plasma using an in-house developed ELISA.

Statistical Analysis

5 All values are depicted as mean $\pm$ SEM. Two-way analysis of variance was used to detect differences between groups for serial data. Differences in serial data within groups were analyzed by one-way ANOVA with Bonferroni's post-hoc test. Data were excluded from the analysis after being identified as significant outlier using the Grubb's test (extreme studentized deviate method). Prism 5.02 for Windows (GraphPad Software Inc., San Diego, CA) was used for com-
10 putations. A p-value less than 0.05 was considered statistically significant.

Results

Hematologic and Clinical Response

As summarized in Table 2 administration of endotoxin resulted in changes in hematologic and
15 clinical parameters in the fasted and nutritional intervention groups.

In all groups, mean arterial blood pressure decreased from 90 minutes after LPS administration onwards ($p < 0.001$), while a compensatory rise in heart rate was observed ($p < 0.001$). Also, endotoxemia resulted in a rise in core body temperature ($p < 0.001$) and white blood cell count ($p < 0.001$) in both the fasted and nutritional intervention groups. The LPS-induced changes in hemo-
20 dynamic parameters, body temperature and white blood cell count were not affected by enteral nutrition.

Administration of endotoxin resulted in flu-like symptoms such as headache, nausea, vomiting, shivering and myalgia, which were expressed as sickness score. The sickness score of all subjects peaked at 90 minutes following LPS administration. Administration of enriched or control nutri-
25 tion did not affect the sickness score compared with fasted subjects ($p = 0.43$ and $p = 0.28$, *respectively*).

Table 2. Hemodynamic parameters, blood leukocyte count and sickness score during human endotoxemia

		T = 0	T = 1	T = 2	T = 3	T = 4	T = 8	T = 24	p value between groups
MAP, mm Hg	Fasted	96 ± 3	94 ± 5	85 ± 5	81 ± 4	81 ± 3	88 ± 3	ND	.66
	Enriched	104 ± 5	95 ± 4	91 ± 5	89 ± 3	83 ± 2	85 ± 1	ND	
	Control	100 ± 2	98 ± 3	94 ± 5	89 ± 3	82 ± 3	87 ± 2	ND	
HR, beats/min	Fasted	68 ± 2	77 ± 4	78 ± 4	87 ± 3	85 ± 4	79 ± 2	ND	.08
	Enriched	63 ± 3	66 ± 3	75 ± 3	91 ± 2	82 ± 3	77 ± 4	ND	
	Control	68 ± 6	81 ± 5	84 ± 6	90 ± 5	90 ± 6	79 ± 5	ND	
Temperature, °C	Fasted	36.7 ± 0.2	37.0 ± 0.2	38.0 ± 0.3	38.5 ± 0.4	38.3 ± 0.3	37.5 ± 0.1	ND	.72
	Enriched	36.7 ± 0.2	37.1 ± 0.2	37.7 ± 0.2	38.3 ± 0.3	38.1 ± 0.2	37.5 ± 0.1	ND	
	Control	36.7 ± 0.1	37.0 ± 0.1	38.0 ± 0.3	38.3 ± 0.2	38.3 ± 0.2	37.4 ± 0.2	ND	
Leukocytes, x10 ⁹ /L	Fasted	5.7 ± 1.2	3.1 ± 0.9	5.2 ± 0.7	ND	8.7 ± 0.2	11.7 ± 0.7	7.5 ± 0.9	.81
	Enriched	5.9 ± 0.6	2.7 ± 0.7	5.2 ± 0.4	ND	9.7 ± 0.8	12.2 ± 0.9	7.1 ± 0.5	
	Control	5.2 ± 0.4	3.1 ± 0.6	5.6 ± 0.6	ND	9.7 ± 0.9	13.2 ± 1.3	7.9 ± 0.6	
Sickness score	Fasted	0.3 ± 0.3	1.3 ± 0.8	2.3 ± 0.6	1.8 ± 0.6	0.5 ± 0.3	0.5 ± 0.3	ND	.12
	Enriched	0 ± 0	1.7 ± 1.3	4.0 ± 1.4	3.2 ± 1.4	1.3 ± 0.6	0.7 ± 0.5	ND	
	Control	0.3 ± 0.3	3.5 ± 0.9	1.7 ± 0.3	1.7 ± 0.4	0.8 ± 0.6	0.3 ± 0.2	ND	

T, time expressed in hours after lipopolysaccharide administration; MAP, mean arterial pressure; HR, heart rate; ND, not determined.

Data expressed as mean ± SEM. *p* values are comparisons between groups over time and were determined by two-way repeated measures-

5 analyses of variance.

Enteral Feeding with Enriched Nutrition Modulates the Cytokine Profile During Experimental Human Endotoxemia

Intravenous administration of LPS resulted in a marked pro-inflammatory response. The TNF- α values of one subject in the enriched nutrition group were removed from the analysis after being identified as significant outlier. Treatment with enriched nutrition significantly attenuated TNF- α levels compared with fasted ($p < 0.0001$) and control nutrition ($p < 0.05$; Figure 2A). Enriched nutrition lowered peak TNF- α levels with $40 \pm 8\%$ compared with fasted subjects and $29 \pm 10\%$ compared to control nutrition. The control nutrition demonstrated a trend towards lower TNF- α plasma levels compared with fasted subjects ($p = 0.06$).

Enriched nutrition significantly reduced IL-6 plasma concentrations during the endotoxemia protocol compared with control nutrition ($p < 0.001$) and fasting ($p < 0.05$; Figure 2B), while the control nutrition did not affect IL-6 compared with fasted subjects ($p = 0.63$). Administration of enriched nutrition attenuated peak levels of IL-6 with $41 \pm 9\%$ compared to fasted subjects and $54 \pm 7\%$ compared to control nutrition.

Intravenous injection of LPS is known to trigger a complex compensatory anti-inflammatory response. The specific IL-1 receptor antagonist, IL-1RA is released during inflammation and is thought to control the immune-modulatory effects of IL-1. Enriched nutrition decreased circulating IL-1RA during the experiment compared with control nutrition ($p < 0.0001$) and fasted ($p < 0.0001$; Figure 2C). Peak levels of IL-1RA were $37 \pm 8\%$ lower in the enriched nutrition group compared with fasted subjects and $25 \pm 6\%$ compared with control nutrition. The control nutrition did not affect IL-1 RA levels compared with fasted.

Continuous postpyloric infusion of enriched nutrition resulted in elevated plasma concentrations of IL-10 over time compared with fasted ($p < 0.0001$), while the control nutrition demonstrated a trend towards higher IL-10 levels ($p = 0.07$; Figure 2D). Enriched nutrition enhanced peak levels of IL-10 with $231 \pm 19\%$ compared with fasted subjects and $130 \pm 12\%$ with control nutrition.

Enterocyte damage remains unaffected by enteral nutrition

In all subjects, administration of LPS resulted in a gradual increase in i-FABP plasma levels until 4 hours post-LPS, representing the occurrence of enterocyte damage (Figure 3A). From 4 hours post-LPS to 8 hours, levels of i-FABP in all groups returned to baseline. Fasted subjects and subjects receiving control nutrition displayed a more prominent increase in i-FABP levels during the experiment compared with subjects fed with enriched nutrition. Total i-FABP release tended to be lower for the enriched nutrition group compared with control nutrition and fasted subject, although this did not reach statistical significance (Figure 3B).

Increased plasma CCK levels during administration of enteral nutrition

In order to assess the effect of continuous duodenal infusion on CCK release, plasma CCK levels were assessed on indicated time points (Figure 1). CCK levels increased from non-detectable values (< 0.3 pmol/l) before administration of enteral nutrition ($t = -1$ hrs) to 2.3 ± 0.5 pmol/l at 1 hour after onset of continuous administration of enriched and control nutrition ($t = 0$; Figure 4A). Four hours after intravenous LPS injection CCK plasma levels in the control group dropped (0.7 ± 0.2 pmol/l; $p < 0.05$) compared with the levels at 1 hour. The drop in CCK levels tended to be smaller in the enriched group. There were no significant differences in total plasma CCK release between enriched or control nutrition (Figure 4B). CCK levels dropped to none detectable levels at 8 hours after cessation of the nutrient infusion. In fasted subjects, plasma CCK levels were below detection level throughout the protocol.

Discussion

The present study is the first to investigate the immediate immunomodulatory effect of continuous enteral administration of nutrition enriched with lipids and protein in human. Our data reveal that enriched nutrition modulates the innate immune response during human endotoxemia, resulting in attenuated plasma levels of TNF- α , IL-6, IL-1RA and elevated circulating IL-10, indicating a reduced pro-inflammatory response and an augmented anti-inflammatory response.

During the last decades, the catabolic state of surgical and critically ill patients increasingly gained interest [23, 24].

The observed negative correlation between catabolism and clinical outcome resulted in more liberal nutritional regimes, such as reduced pre-operative fasting and early administration of enteral nutrition [24]. Implementation of these renewed nutritional support regimes reduced morbidity and length of hospital stay [9, 10]. Although the exact mechanisms behind these beneficial effects are not well known, it is assumed that adequate nutritional support prevents immunodeficiency induced by caloric deficits [25]. In addition to caloric support, prolonged ingestion of nutrition enriched with intrinsic anti-inflammatory compounds, such as long-chain n-3 polyunsaturated fatty acids and glutamine results in immune-modulating effects and improves outcome by influencing specific metabolic processes, including eicosanoid production, glutathione synthesis and generation of heat shock proteins [26, 27]. In a previous study, enteral lipid-enriched nutrition was shown to limit inflammation and reduce organ damage via a CCK-mediated activation of the cholinergic anti-inflammatory pathway in several rodent models [16-19, 28].

Virtually every surgical, trauma and ICU patient suffers from systemic inflammation. The complex interplay between pro- and anti-inflammatory mechanisms during such a systemic inflammatory response is still incompletely understood [29]. The human endotoxemia model does not replicate these clinical conditions, but has been extensively employed to study the acute systemic inflammatory response *in vivo* [21]. Administration of endotoxin affects various systemic physiologic and metabolic processes in a manner similar to the early phase of injury and infection, making it a suitable human model for proof-of-principle studies [21].

Excess release of TNF- $\bullet$ is known to contribute to the development of systemic inflammatory response syndrome, organ damage and mortality in sepsis [30]. Furthermore, circulating levels of TNF- $\bullet$ and IL-6 are correlated with the severity of sepsis in patients [31]. In line with our animal data [16, 17], the current study demonstrates that enriched nutrition limits inflammation during human experimental endotoxemia by attenuating circulating levels of TNF- $\bullet$ and IL-6. Moreover, the intervention with enriched nutrition resulted in decreased IL-1RA plasma levels. These data are conform previous reports, demonstrating that TNF- $\bullet$ and IL-6 enhance IL-1RA release during endotoxemia, while inhibition of these cytokines lowers circulating IL-1RA [32, 33]. In accordance, attenuation of the inflammatory response using epinephrine or glucocorticoids downregulates IL-1RA and IL-1 plasma levels [34, 35]. In parallel with these reports, our findings that enriched nutrition not only decreases plasma levels of TNF- $\bullet$ and IL-6 but also of IL-1RA, reflect

an overall reduced pro-inflammatory state. Interestingly, postpyloric administration of enriched nutrition amplified the anti-inflammatory response to endotoxin as evidenced by a pronounced increase in circulating IL-10 compared with fasted subjects. IL-10 is considered to be part of the host-protective mechanism that counterbalances the pro-inflammatory response during acute infection and inflammation [34]. Furthermore, administration of IL-10 has been shown to reduce endotoxin-induced lethality in mice [36]. The beneficial effect of enriched nutrition on the immune response during human endotoxemia is in line with previous studies using well-known pharmacological agents, including epinephrine and glucocorticoids which inhibit plasma levels of pro-inflammatory cytokines and augment circulating IL-10 [34, 37]. Together, these data indicate that enriched enteral nutrition is a promising and physiological intervention to control acute inflammation.

Intestinal epithelial cell damage often accompanies sepsis, trauma and major surgery and is related to the degree of gastrointestinal hypoperfusion [38-40]. Additionally, intestinal compromise has been implicated in the development of inflammatory complications following injury [41]. Here, we show that intravenous administration of LPS resulted in increased i-FABP levels. The rise in plasma i-FABP levels tended to be smaller in subjects treated with enriched nutrition compared with control nutrition or fasted subjects, although this did not reach statistical significance. These data are supported by rodents studies demonstrating that lipid-enriched nutrition preserves intestinal integrity [17, 19]. The small increase in i-FABP plasma levels is likely attributable to the relative low dose of LPS and limited hypoperfusion due to the prehydration protocol. Future studies are therefore needed to establish a gut-protective effect of enriched nutrition in man.

CCK-mediated activation of vagal afferents plays a dominant role in nutrient-induced digestive, metabolic and immunologic feedback [19, 42, 43]. Intestinal release of CCK is predominantly triggered by the luminal presence of lipid and protein [20, 44], while termination of nutrient exposure results in a rapid drop of CCK levels [44]. Taking these considerations into account, we chose to continuously administer nutrition enriched with lipids and proteins to induce a prolonged stimulation of the CCK-mediated anti-inflammatory pathway. Our nutritional intervention resulted in detectable circulating CCK levels during the entire endotoxin-induced inflammatory response. The fact that bolus administration of a lipid-rich milkshake containing 100 gram fat

prior to endotoxin challenge failed to affect the immune response [45], underlines the importance of continuous nutrient administration. In comparison, continuous infusion of enriched nutrition delivered approximately 60 gram fat in total. Although enriched nutrition displayed a more powerful anti-inflammatory effect than control nutrition, significant differences in CCK levels could not be detected in plasma. This might be explained by the fact that circulating CCK levels do not reflect local intestinal concentrations and subsequent activation of afferent vagal fibres in the gut. In this context, it is interesting that plasma concentrations of exogenous CCK have to be at least 10-fold higher compared with postprandial CCK levels to obtain a similar satiety effect [46]. Future studies using specific CCK-1 receptor antagonists, which are currently not available, should specify the role of local CCK levels. In addition, these studies should also focus on the role of other intestinal peptides, including glucagon-like peptide 1 (GLP-1). Recently, our group implicated GLP-1 as co-stimulatory peptide of the nutritional anti-inflammatory pathway in rodents, since administration of GLP-1 receptor antagonists partially reduced the inhibitory effect of lipid-rich nutrition on systemic inflammation [47].

In conclusion, the current proof-of-principle study demonstrates for the first time that: 1) short-term continuous administration of enteral nutrition immediately modulates inflammation in humans, and 2) enrichment of the nutritional composition with lipid and protein enforces this anti-inflammatory potential. Our findings show that the anti-inflammatory effects of enriched nutrition as previously observed in rodents also apply to the human situation. Taken together, the current study implicates continuous administration of enriched nutrition as a promising intervention to modulate inflammatory conditions in the clinical setting.

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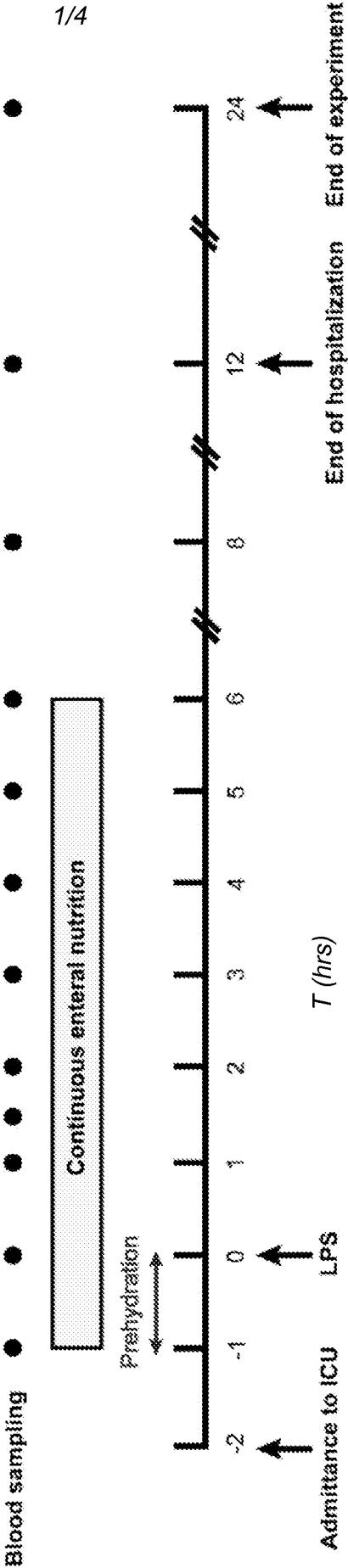
Claims

1. Use of a preparation in the manufacture of a liquid nutritional composition for mitigating, attenuating or preventing an acute inflammatory response during or after surgery of a patient undergoing said surgery, said composition comprising fat and proteinaceous matter, wherein said fat contributes for at least 41 En% and said proteinaceous matter contributes for at least 23 En% to the total energy content of said composition, wherein said composition is to be administered to said patient by intra-operative tube feeding.
2. Use according to claim 1, comprising between 23 En% and 59 En%, more preferably between 23 En% and 45 En%, most preferably between 23 En% and 40 En% of proteinaceous matter relative to the total energy content of said composition.
3. Use according to any one of claims 1 to 2, wherein the proteinaceous matter comprises a source of vegetable proteinaceous matter and a source of dairy proteinaceous matter.
4. Use according to any one of claims 1 to 3, wherein the proteinaceous matter comprises a hydrolysed protein, preferably an hydrolysate of soy, casein, whey or wheat protein.
5. Use according to any one of claims 1 to 4, wherein the proteinaceous matter comprises one or more of casein, whey, soy, pea and wheat protein, preferably casein and wheat protein.
6. Use according to any one of claims 1 to 5, comprising at least 1.5 gram, more preferably, 1.7 gram of L-glutamine (bound and/or free) per 100 ml of total liquid nutritional composition.
7. Use according to any one of claims 1 to 6, comprising between 41 En% and 77 En% of fat, relative to the total energy content of said composition.

- 8 Use according to any one of claims 1 to 7, wherein said fat comprises at most 25 weight% of medium chain triglycerides (MCTs), relative to the total weight of said fat.
- 5 9. Use according to any one of claims 1 to 8, wherein said fat comprises less than 10 weight% of phospholipids, or wherein said fat comprises less than 0.5 weight% of cholesterol, relative to the total weight of said fat.
- 10 10. Use according to any one of claims 1 to 9, further comprising at most 36 En% of a digestible carbohydrate, relative to the total energy content of said composition.
11. Use according to any one of claims 1 to 10, having a total energy content of less than 250 kcal, preferably less than 200 kcal, more preferably less than 160 kcal, most preferably about 125 kcal per 100 ml of said composition.
- 15 12. Use according to any one of claims 1 to 11, characterized in that it is in a sterilized or pasteurized form.
13. Use according to any one of claims 1 to 12, wherein the tube feeding is provided in a continuous way.
- 20 14. Use according to any one of claims 1 to 13, wherein the surgery is invasive surgery.
- 25 15. A liquid nutritional composition comprising fat, proteinaceous matter and digestible carbohydrates, wherein said fat contributes for at least 41 En%, said proteinaceous matter contributes for at least 23 En%, and said digestible carbohydrates contribute for at most 36 En% to the total energy content of said composition.

16. The liquid nutritional composition according to claim 15, further comprising at least 1.5 gram, more preferably, at least 1.7 gram of L-glutamine (bound and/or free) per 100 ml of said composition.
- 5 17. The liquid nutritional composition according to claim 16, comprising about 45 En% of fat, about 23 En% of proteinaceous matter, about 29 En% of digestible carbohydrates, and about 2 gram of L-glutamine per 100 ml of said composition.
- 10 18. The liquid nutritional composition according to any one of claims 15 to 17, and as described in any one of claim 1 to 14, in the form of a tube feed.
- 15 19. The liquid nutritional composition according to any one of claims 15 to 18 for mitigating, attenuating or preventing an acute inflammatory response during or after surgery of a patient.
- 20 20. The liquid nutritional composition according to any one of claims 15 for to 19, wherein the patient is a patient that is undergoing surgery, that has undergone surgery or that is a critically-ill patient.
- 25
- 30

Fig. 1



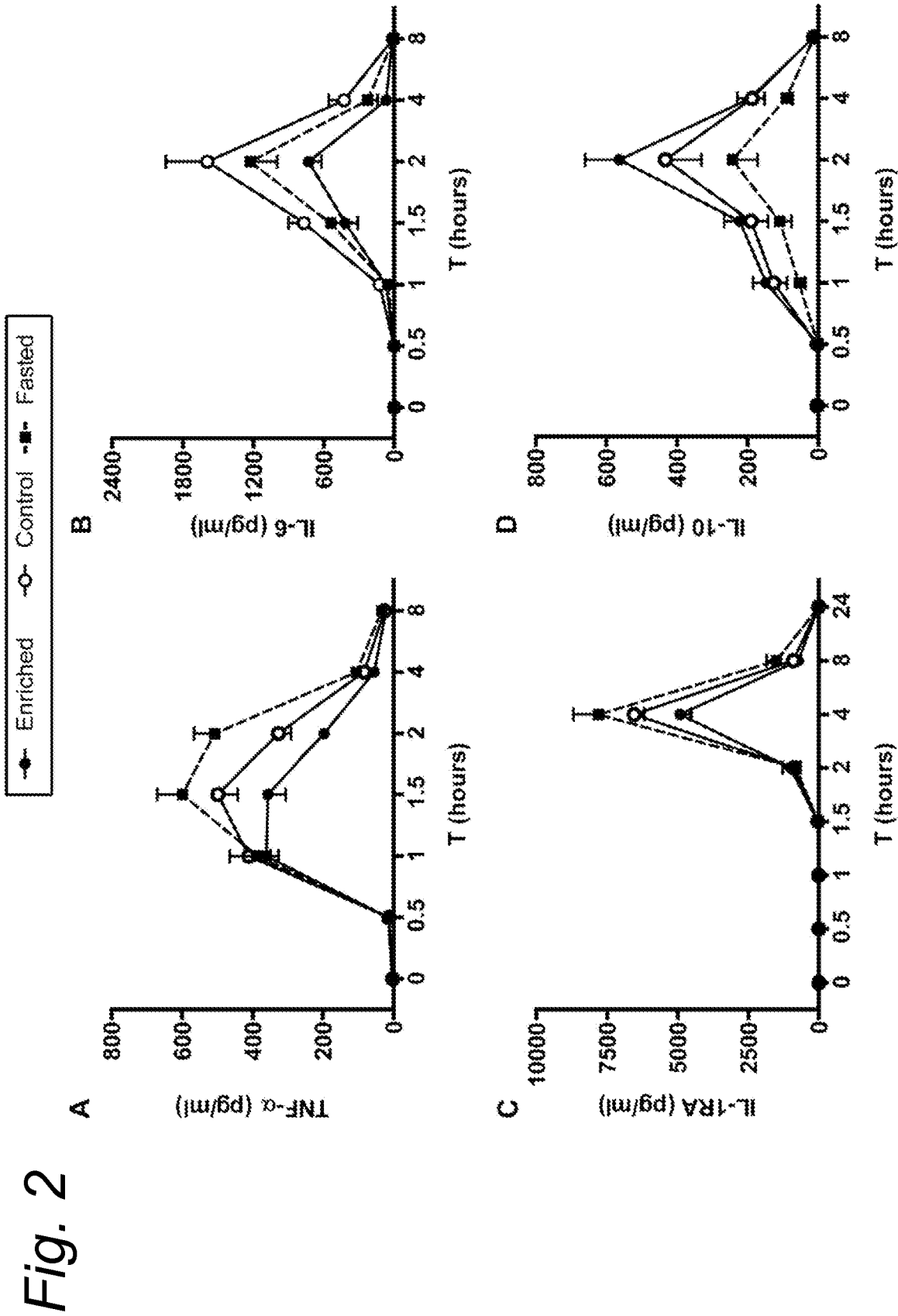


Fig. 3

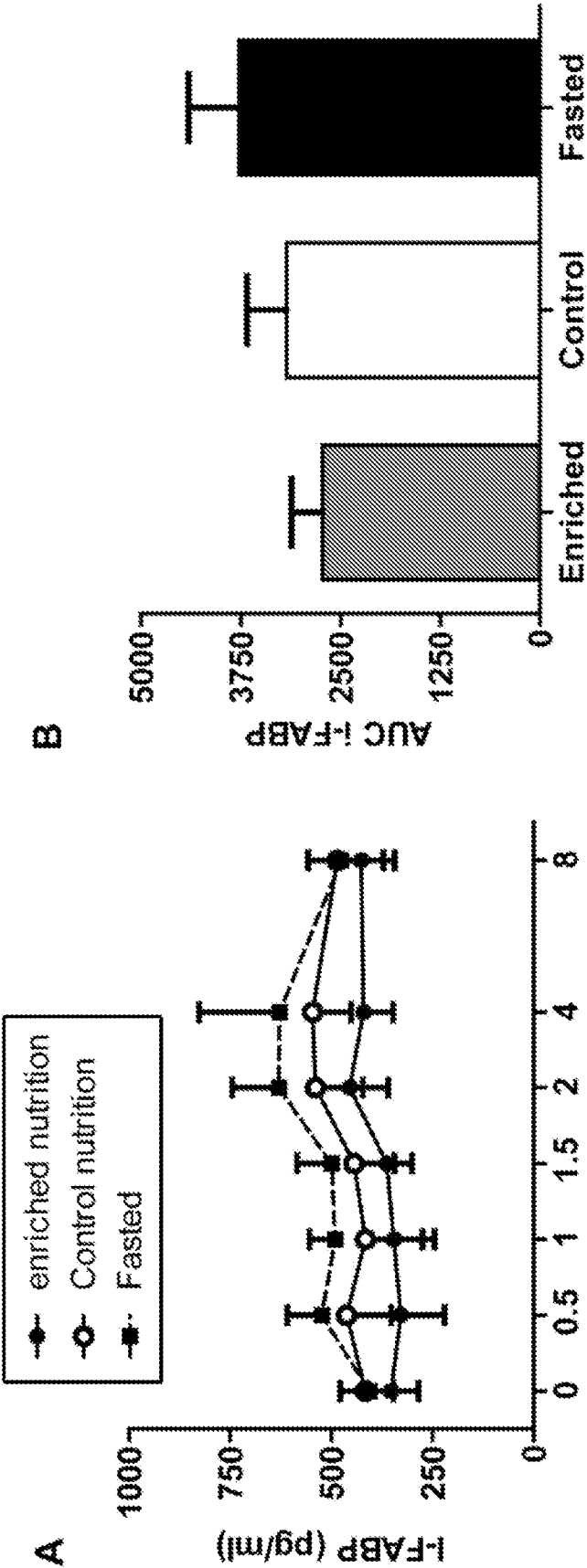
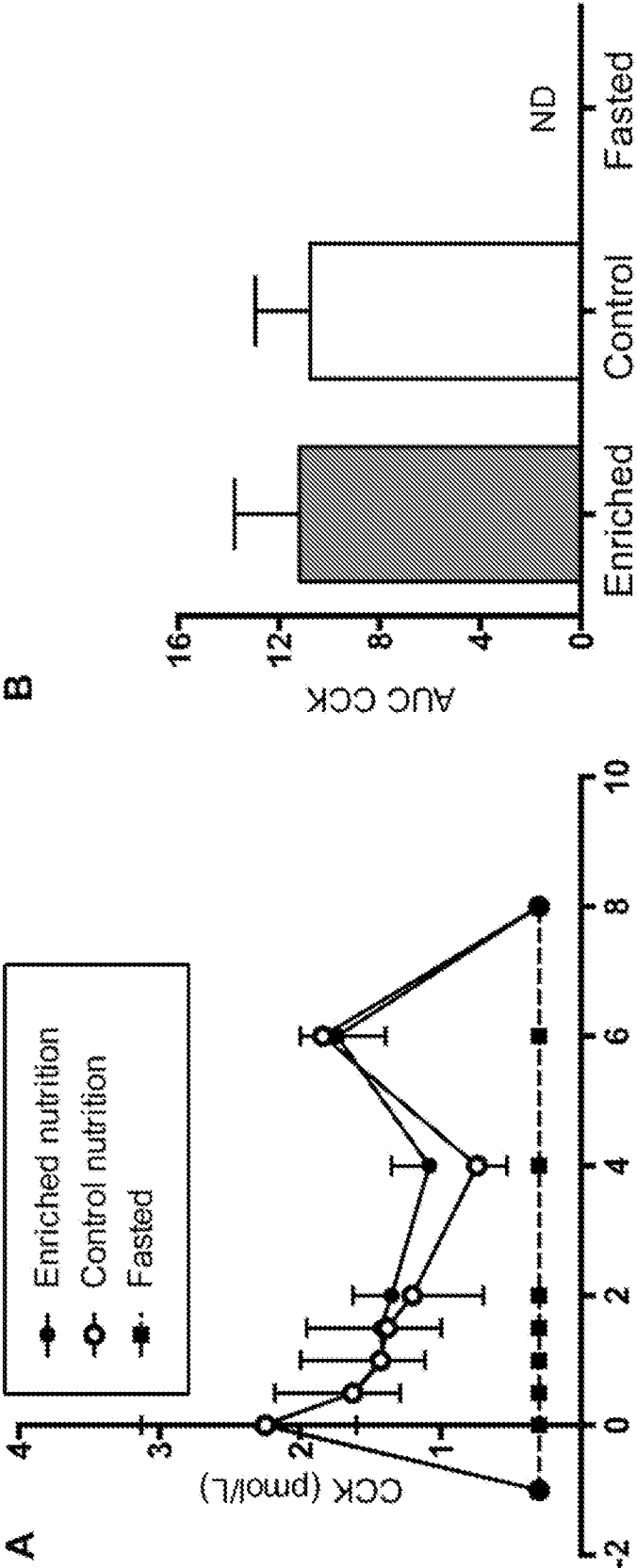


Fig. 4



INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2011/050231

A. CLASSIFICATION OF SUBJECT MATTER

INV. A23L1/30 A23L1/305 A61K45/06 A61P3/02 A61P41/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO 2010/033424 A2 (NESTEC SA [CH]; SCHIFFRIN EDUARDO [CH]; MILLER KEVIN BURKE [US]; BRASS) 25 March 2010 (2010-03-25) examples 4-8	1-20



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

27 December 2011

Date of mailing of the international search report

02/01/2012

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Estañol, Inma

INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2011/050231

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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