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REVIEW ARTICLE

Role of Glutamine Supplementation in Critically ill patients: A Narrative Review

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ABSTRACT:
Enteral nutrition has been known to bring about reduction in infectious complications in post major abdominal surgery. Previous systematic reviews and meta-analysis have suggested that immune nutrition in critically ill have been associated with reduced hospital stay, infection rate and inflammatory response. Glutamine is considered an essential amino acid during stress and critical illness. Parenteral glutamine supplementation in critically ill patients has been shown to improve survival rate and minimise infectious complications, costs and hospital length-of-stay. The purpose of this article is to provide a narrativereview of the current evidence and trials of enteral and parenteral glutamine supplementation in multipletrauma patients. A search in PubMed and EMBASE was conducted and relevant papers that investigated the effect of enteral or parenteral glutamine supplementation in patients with multiple trauma were reviewed. Although recent nutritional guidelines recommend that glutamine supplementation should be considered in these patients, further well-designed trials are required to provide a confirmed conclusion. Due to the inconclusive results of enteral glutamine supplementation trials in patients receiving enteral nutrition, future trials should focus on intravenous glutamine supplementation in patients requiring enteral nutrition and on major clinical outcome measures (e.g. mortality rate, infectious complications).

KEYWORDS: trauma, head injury, glutamine, alanyl-glutamine, supplementation, enteral, Parenteral.

INTRODUCTION:
Multiple traumas are very risky not only at the onset of the attack but also it leads to impairment in the immunological system but also leads to metabolic dysfunction. Major trauma is characterised by alteration and depression of the immune response along with increased infections, sepsis, multiple organ failure and also death. In fact, many critically ill patients die due to serious infectious complications.

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The role and effectiveness of glutamine supplementation in critically ill patients has been extensively studied and debated in literature for at least the 15 years [1]. A number of systematic reviews and Meta analyses have shed light on this interesting topic. The critically ill patient population is haemodynamically and immunologically different from the surgical population. [2] Furthermore, the critically ill patient population is clinically heterogeneous, hence results from one subgroup of patients cannot be generalised to the whole population, even in nutrition support interventions. Many of the studies that have investigated the effect of intravenous or enteral glutamine supplementation includes multiple trauma patients with other critically ill patients as one population group and have utilised many

different outcome measures,[3] not all of which are likely to be of clinical relevance.

The standard approach for this study is the meta-analysis approach, but the heterogeneity of this approach has decreased the usefulness of the approach and also the extensive studies done in this category has made it difficult to pool all the effects, hence we decided to do a narrative review. Therefore, the purpose of this narrative review was to focus on the trials conducted specifically to investigate the effect of glutamine or glutamine dipeptide as a single pharmaco nutrient. It is to critically appraise, and synthesize randomised clinical trial data evaluating the effect of enteral immuno nutrients in critically ill patients.

Search strategy and selection criteria:

The patient group in this review represents the critically ill patients with multiple trauma that require enteral or parenteral nutrition support. Pub Med and EMBASE from 1990 to 2011 were searched and was used to identify trials that evaluated enteral and parenteral glutamine supplementation in trauma patients. Search terms included "glutamine", "alanylglutamine" "Trauma", "injury" or "head injury". Papers that were written in English were only used for the review. [4,5] Search Parameters were limited to human clinical trials. Studies which had only glutamine supplementation were only used for the trial. If the trials were conducted with glutamine supplementations along with other immune nutrients then those trials were excluded. Also any kind of safety trials were also excluded. Additional articles were identified through searching the bibliography of practice guidelines, systematic reviews and meta-analyses of glutamine supplementation in critically ill patients.

BACKGROUND:

Immune and metabolic response to trauma and injury:

Multiple trauma and severe injury evoke reproducible immune and metabolic responses that

Correlate with the extent and duration of the injury. The immune (inflammatory) response starts within minutes and is characterized by increased release of pro-inflammatory cytokines. Alternatively, if the anti-inflammatory mediators predominate, this results in compensatory anti-inflammatory response syndrome. [6] In parallel, there is a concurrent production of anti-inflammatory cytokines. This response is required to restore homeostasis as soon as possible. In uncomplicated trauma and injury, there is an equilibrium between the pro and anti-inflammatory cytokines. However, if the pro-inflammatory mediators predominate, this results in a systemic inflammatory response syndrome. An imbalance between systemic inflammatory response syndrome and compensatory anti-inflammatory response syndrome,

The severity of the trauma and stress will lead to infectious complications and also increased multiple organ failure rate. [7] In conjunction, there is an escalated production of catabolic and counter-regulatory hormones. These neuroendocrine changes trigger the metabolic response that is characterised by hyper metabolism, insulin resistance associated with hyperglycaemia, increased fat breakdown (lipolysis) and accelerated protein catabolism (proteolysis). [8,9,10] Proteolysis, which may reach up to 16%, is mainly derived from the skeletal muscle and can last for up to 21 days. The synthesis of protein in the muscle also rises but it does not equal the proteolysis. In critically ill patient s, protein catabolism is elevated despite aggressive nutritional support and increased protein intake. Although muscle catabolism is important for providing substrates for acute phase protein synthesis and gluconeogenesisin the liver, severe and prolonged depletion of lean body mass has deleterious effects such as irreversible muscle wastage, impaired wound healing and delayed recovery from illness. Protein catabolism is also associated with the release of glutamine from the skeletal muscle and this result in a marked and prolonged depletion of glutamine levels in plasma and the skeletal muscle. [11]

Glutamine metabolism during stress and critical illness:

Protein energy malnutrition" a major problem in the management of post-operative patients was long recognized by Hiram, an American surgeon way back in 1936, as he observed that weight loss was as significant predictor of surgical risk among his patients suffering from peptic ulcer disease.[14] According to "gut origin of sepsis" hypothesis the leaky gut is an essential factor in developing septic complications with the concept of bacterial translocation as demonstrated *in vitro* and *in vivo* studies. In addition, nutritional depletion is associated with increased intestinal permeability and a decrease in villous height. Post-operative nutritional supplementation has been known to improve the quality of life, nutritional status, and morbidity of patients. Hence, "malnutrition matters" and "nutrition is the cutting edge in surgery."[12, 13] Enteral nutrition has been known to bring about reduction in infectious complications in post major abdominal surgery. Previous systematic reviews and meta-analysis have suggested that immune nutrition in critically ill have been associated with reduced hospital stay, infection rate, and inflammatory response.[15] Any catabolic stressful condition results in 50% loss of glutamine from the muscles and it is of utmost importance to deliver adequate amounts of glutamine to maintain the integrity

of intestinal mucosa, to preserve the muscle glutamine pool and to improve overall nitrogen economy during conditions of stress.

Glutamine is the most abundant amino acid in the body and is synthesised in sufficient amounts under normal physiological conditions, and therefore has been considered as a non-essential amino acid for decades. It is involved in a wide range of metabolic and biochemical processes in the body.

Glutamine is known to be a precursor of protein synthesis and the mucosal and the immune cells in the body utilize this particular immunonutrient as an energy source in almost all the tissues. Furthermore, glutamine is involved in a large number of metabolic pathways. One of the major procedures which result in severe depletion of glutamine from the skeletal muscles, bringing about muscle loss immunosuppression thus resulting in increased risk for post-operative infection and sepsis is surgery. [16]

These functions are summarised in Table 1. As the preferred fuel for enterocytes, it has been suggested that glutamine may have a role in reducing bacterial translocation across the gastrointestinal tract and thus reduce the risk of infections and sepsis.[17] In fact, enteral glutamine administration has been associated with reduced intestinal permeability and bacterial translocation in some animal studies. Also, some clinical trials showed that glutamine supplementation maintained gastrointestinal structure in critically ill patients and was associated with reduced intestinal permeability. However, other trials could not reproduce this finding.

Table 1:
Glutamine functions in the human body:

- Fuel for immune cells (lymphocytes and macrophages)
- Arginine synthesis in the kidney (being a precursor for citrulline)Fuel for enterocytes
- Glutathione synthesis (antioxidant defence)
- Enhance heat shock protein expression (prevent apoptosis)
- Enhance insulin sensitivity
- Nitrogen transport
- Acid-base homeostasis
- Gluconeogenesis

Under catabolic conditions, such as critical illness, glutamine is released from the skeletal muscle in large quantities. Although glutamine synthesis is not impaired during critical illness, plasma and intramuscular glutamine levels are severely depleted in conditions such as major surgery, burn injury and multiple trauma because of increased demand. Therefore, glutamine has been proposed as an essential amino acid in these situations.

Clinical trials of glutamine supplementation in multiple trauma patients:
A number of trials have been conducted to investigate the effect of glutamine supplementation in a homogeneous group of multiple trauma patients. Table 2 and 3 summarise the trials of enteral and parenteral glutamine supplementation in traumapatients, which are subsequently discussed.

Clinical trials of enteral glutamine supplementation in multiple trauma patients:
The use of glutamine supplementation in people following enteral nutrition after surgery is a controversial topic. Research indicates that initiation of early enteral nutrition (i.e. within the first 24–48 hours following intensive care unit admission) in critically ill patients, including trauma patients, is recommended when the gastrointestinal tract is functioning as it is associated with decreased infectious morbidity, hospital length of-stay and improved overall clinical outcome. Therefore, the concept of enteral glutamine supplementation in multiple trauma patients is attractive and advocated when enteral nutrition is required. However, it has been documented that the systemic bioavailability of glutamine through the enteral route is lower than the parenteral route.

Also, glucose turnover, oxidation and recycling were not significantly different between the two groups. The same trial attempted to see the effect of glutamine supplementation on hypoaminoacidaemia, which results in increased in nonessential amino acids in the intracellular pool. However, it was reported that total essential amino acids concentration was significantly increased in both groups, while the nonessential amino acids concentration was increased significantly only in the control group. This increase was explained by the added amino acids to the control formula to make it is nitrogenous. [19] Plasma glutamine level was not influenced by supplementation.

Most enterally administered glutamine is utilised and oxidised by the splanchnic organs. Furthermore, before consideringglutamine supplementation via the enteral route, it is important to recognise that most enteraltrials failed to reach the target prescribed dose due to delayed feeding, feeding intolerance and interruption of feeding due to extubation or surgery. One of the early trials that have been conducted to investigate the effect of enteral glutamine supplementation in 30 trauma patients by Long et al found that there were no significant differences in outcomes including nitrogen balance, protein synthesis and breakdown, and muscle proteolysis

between the glutamine supplemented and the control groups. These results suggested that a short period of glutamine provision (i.e. three days) has no effect on nutritional or metabolic outcomes and a longer period is required. The authors explained the negative results by altered glutamine absorption in critically ill patients and glutamine being mostly oxidised by the gut and liver.

On the other hand, Houdik et al showed that enteral glutamine supplementation significantly increased plasma glutamine concentration, whichwas associated with an increased plasma arginine concentration suggesting that enteral glutamine stimulated renal production of arginine. Mortality as a primary outcome was investigated in one of the largest trials of enteral glutamine supplementation in trauma patients. The in-hospital mortality rate was higher in the treatment group compared with the control group, but the results were not significant (P=0.09), particularly after controlling for age and severity of illness ($P \leq 0.11$). This trial suggested that enteral glutamine might have negative effects with a trend toward increased mortality. [20]

The authors theorised that enteral administration of glutamine makes it available to the bacteria in thegastrointestinal tract. The effect of enteral glutamine supplementation on infectious morbidity was investigated in two main trials. Houdijk and colleagues reported that glutamine-enriched enteral feed resulted in a significant decrease in pneumonia (17 vs 45%; P <0.02), bacteraemia (7 vs 42%; P <0.005) and sepsis (4 vs 26%; P <0.02). Gram-negative bacteraemia occurred in 54% of the cases of bacteraemia in the control patients and was not reported in any of the glutamine supplemented patients, suggesting that glutamine might prevent bacterial translocation from the gut. In contrast, Schulman et al found that enteral glutamine had no significant effect on reducing infectious complications and the use ofantibiotics. In both trials there were no significant differences in mechanical ventilation days, intensive care unit and hospital length-of-stay between the supplemented and the control groups. In an attempt to explain the relationship between the reduction in infectious morbidity by enteral glutamine supplementation and endocrine responses.

Houdijk et al reported in a subsequent paper that enteral glutamine had no influence on metabolic and endocrine changes in trauma patients. Hyperglycaemia was sustained in both glutamine and control groups, and plasma levels of stress hormones (cortisol and glucagon) increased to high normal levels in both groups, but this was not significant. Growth hormone levels were within the normal range and did not differ between groups. In both groups there was a significant increase in α1-antitrypsin levels and the inflammatory marker C-reactive protein. [21, 22, 23] It was concluded that the reduction in infectious complications by glutamine supplementation was not related to the changes in the metabolic and hormonalresponses. In a pilot study, 20 patients with severe trauma were randomised to receive enteral glutamine or an isonitrogenous placebo during the first 24 hours of resuscitation, before even starting enteral feeding for ten days.

The supplementation was given as a bolus two to three times daily, dissociated from enteral feed as a pharmacological dose. The study demonstratedthat glutamine was well-tolerated during resuscitation with no adverse events. It was reported that the glutamine group had significantly fewer instances of high gastric output (5 vs 23, P=0.01) and abdominal distension (3 vs 12; P=0.021).

These results suggested that enteral glutamine can be safely given during active shock resuscitation and enhances gastrointestinal tolerance. However, this was a pilot study and a larger trial is required to investigate the effect of enteral glutamine administered to haemodynamically unstable patients on other clinical outcomes.

Table 2-Trials of enteral glutamine supplementation in trauma patients

Study	Design	Route	Commencement and duration
Houdijk et al 1998, 199965,69	DB RCT, n=72 (60 received feeding ≥5 d)	EN (NJ)	Within 48 h of trauma and until tolerating oral feeding (study period 15 d)
Long et al 1995, 1996	DB RCT, n=30	EN (NG)	Approximately 24 h after admission; 3 d
Boelenes et al 2002	DB RCT, n=108	EN (NJ)	Within 48 h of trauma and until tolerating oral feeding (pts fed at least 5 d enterally were included in results; study period 15 d)
Schulman et al 2005, 2006	Sequential rotating assignment, unblind, n=185 (175 trauma)	EN (NJ) and some converted to PEG	EN continued until oral diet was tolerated or TPN was required
Brantley et al 200083 (Abstract	RCT unblended (not mentioned in abstract), n=70	EN	7 d
McQuiggan et al	Pilot, unblinded RCT, n=20	EN (NG)	Start during the first 24 h of resuscitation; 10 d

Table 2 Continue…..

Intervention-gln	Intervention-control	Main outcomes
Gln-enriched EN provides 30.5 g Gln/ 100 g protein, n= 35	Isocaloric, isonitrogenous feed, n=37	Mean plasma levels of Gln, citrolline and arginine ↑↑ in Gln group Mean serum levels of TNF-receptors ↓↓ in Gln group ↓↓ pneumonia (17 vs 45%; *P* <0.02), ↓↓ bacteraemia (7 vs 42%; *P* <0.005), ↓↓ sepsis (3 vs 26%; *P* <0.02) in Gln group No gram-negative bacteraemia in Gln group vs 54% in control group. ND ICU or hospital length-of-stay, mechanical Ventilation days. Glucose levels above normal fasting levels in both groups Plasma levels of stress hormones (cortisol and glucagon) ↑ to high normal levels in both groups (*P*=NS) Growth hormone levels were in normal range throughout study and ND between groups α1-antitrypsin ↑↑ on day 2; *P* <0.05, days 3, 7 and 10; *P* <0.01 vs baseline in both groups CRP ↑↑ and reached peak levels on day 3 (*P* <0.05 vs baseline) in both groups
Gln-enriched EN, mean intake 0.35 g Gln/kg/d, n=16	Isonitrogenous, is caloric EN, n=14	ND NB, protein turnover, synthesis and breakdown ND glucose turnover, oxidation and recycling ND plasma Gln levels EAA conc. ↑↑ in both groups NEAA ↑↑ in control group
Gln-enriched EN; provides 30.5 g Gln/ 100 g protein, n=28	Isocaloric, isonitrogenous EN (control), n=27 Age-matched healthy people, n=53	On day 1 HLA-DR expression much lower in Gln and control groups compared to healthy volunteers group HLA-DR expression ↑↑ on day 5 (*P* <0.05), day 9 (*P* <0.05) and day 14 (*P* <0.05) in Gln group compared with day 1 but did not restore normal values FcγRI/CD64 expression in monocytes in Gln and control groups = expression in healthy volunteers
0.6 g/kg/d Gln + Standard EN (Group 2), n=59 0.6 g/kg/d Gln + Immune-modulated EN (Group 3), n=62	Isocaloric, isonitrogenous standard EN feed (Group 1), n=64	ND mean number of infections, incidence of infections, antibiotic use between groups ND mechanical ventilation days, ICU and hospital length-of-stay In-hospital mortality was 6.3% (Group 1) vs 16.9% (Group 2; P=0.09) and 16.1% (Group 3; *P*=0.09) ND in-hospital mortality between groups (after controlling for age and severity of illness, *P* ≤0.11)
0.5 g/ kg Gln + supplemented EN formula, n=32	Isocaloric, isonitrogenous formula, n= 38	Prealbumin ↑↑ in Gln group on day 7 NB balance better in Gln group (NS) ND infections, total costs, ICU and hospital length of-Stay
0.5 g/kg/d glutamine(boluses 2–3 times daily (NG) + immune enhancing EN (NJ) which started on post-injury day 1, n=10	0.5 g/kg/d isonitrogenous whey protein + immune enhancing, n=10	Gln well tolerated during resuscitation, no adverse events Gln group had ↓↓ instances of high gastric output (5 vs 23; *P*=0.01), abdominal distension (3 vs 12; *P*=0.021) and total instances of intolerance (8 vs 42; *P*=0.011) ND in CRP on day 4 between groups Total UUN ↑↑ in Gln group vs control (*P*=0.012)

Gln=glutamine, DB=double-blind, RCT=randomised clinical trial, EN=enteral nutrition, NG=nasogastric, h=hours, d=days, ND=no significant difference, NB=nitrogen balance,
EAA=essential amino acid, NEAA=non-essential amino acid, ↑↑=significant increase, NJ=nasojejunal, TNF=tumour necrosis factor, ↓↓=significant decrease, ICU=intensive care unit,
↑=increased, NS=not significant, CRP=C-reactive protein, HLA-DR=human leukocyte antigen DR, FcγRI/CD64=Fc receptor, PEG=percutaneous endoscopic gastrostomy, TPN=total
Parenteral nutrition, UUN=urinary urea nitrogen

Clinical trials of parenteral glutamine supplementation in multiple trauma patients:

Limitations of glutamine supplementation via the enteral route triggered researchers to investigate the effect of intravenous glutamine supplementation in patients receiving enteral nutrition. The effect of parenteral alanyl-glutamine on insulin resistance was investigated by Bakalar et al, who showed significantly improved insulin sensitivity and insulin-mediated glucose disposal in the glutamine supplemented patients [24]. There was no significant difference in the Sequential Organ Failure Assessment score between groups. The authors concluded that this trial should be considered as a pilot study and further trials are required to gain further understanding about the mechanisms by which glutamine improves insulin resistance. The effect of intravenous alanyl-glutamine supplementation in 46 patients with severe traumatic brain injury receiving total parenteral nutrition was investigated in a randomised trial.[25] The authors demonstrated that alanyl-glutamine supplementation resulted in a significant decrease in infectious complications (P <0.05). It was reported that glutamine supplementation was associated with a significant decrease in two-week mortality rate and alimentary tract haemorrhage (P <0.05). [26]There was a significantly shorter intensive care unit length-of-stay with glutamine supplementation (P <0.05). The rate of protein breakdown was not different between groups during the study, but hypermetabolism was attenuated in the glutamine supplemented patients by reducing energy expenditure. It was concluded that glutamine supplementation was associated with significantly better insulin sensitivity in trauma patients, offering a new approach to glycemic control in this group of patients. This study was the first to investigate the effects of glutamine supplementation in head injury patients. However, there are number of limitations of this paper. The results suggest that glutamine might play a role in prevention of alimentary tract haemorrhage but only if patients are not receiving standard management (i.e. stress ulcer prevention). Furthermore, this was a single trial and the number of recruited patients was relatively small, limiting the ability to make clear conclusions and recommendations. It is also important to mention that the dose used was relatively low (2 mg/kg) compared with other trials that found beneficial effects.[27] There is no evidence for beneficial effects of intravenous glutamine supplementation in trauma patients receiving enteral nutrition. In summary, from the previous trials, positive and consistent findings were demonstrated in patients receiving glutamine-supplemented parenteral nutrition and with higher doses. [28, 29, 30]

Table 3-Trials of parenteral glutamine supplementation in trauma patients

STUDY	DESIGN	ROUTE	COMMENCEMENT AND DURATION
Bakalar et al	Pilot, unblended RCT, n=40	IV	Started 24 h after injury for 7 d
Yang et al 2007	RCT	IV	Started within 24 h for 2 w TPN started on day 3 after injury, EN gradually replaced TPN in the first week
Eroglu 2009	DB RCT, n=40	IV	7 d
Perezéz-Bárcena 2010	SB RCT, n=43	IV	5 d

Table 3 Continue…

INTERVENTION-CONTROL	MAIN OUTCOMES
Isocaloric, isonitronegous amino acids control + PN or EN, n=20	ND protein breakdown between groups ND SOFA score Energy expenditure ↓ in Gln group Insulin-mediated glucose disposal ↑↑ in Gln group at day 4 (P=0.044) and day 8 (P <0.001) Endogenous insulin secretion was ↑↑ in control group on day 8 Gln group had a better insulin sensitivity (statistically significant)
Standard nutritional therapy, n=23	Mortality rate in first 2 w and ICU length-of-stay ↓↓ in Gln group ND GCS between groups Patients with lung infection and alimentary tract haemorrhage↓↓ in Gln group ND urinary tract infection between groups Total serum protein and total lymphocyte count ↑↑ in Gln group
Control (normal saline) + standard EN, n=20	Total plasma glutathione levels ↑↑ in Gln group on days 7 and 10 ND CRP, prealbumin, glucose levels between groups ND SOFA score ND infections, ICU length-of-stay between groups ND 1 m mortality rate between group
Isonitrogenous, isocaloric TPN, n=20	TLR4 levels were not different between groups before treatment (glutamine supplemented TPN doesn't improve the expression or the functionality of TLRs in peripheral blood monocytes)

Gln=glutamine, RCT=randomised clinical trial, IV=intravenous, h=hours, d=days, PN=parenteral nutrition, EN=enteral nutrition, ND=no significance difference, SOFA=sequential
Organ failure assessment, ↓=decrease, ↑↑=significant increase, w=weeks, TPN=total parenteral nutrition, ICU=intensive care unit, ↓↓=significant decrease, GCS=Glasgow Coma Score,

DB=double-blind, CRP=C-reactive protein, m=month, SB=single-blind, TLR=toll-like receptor.

Limitation of glutamine trials in multiple trauma patients:

Like other nutritional interventions, there are limitations in the existing trials of glutamine supplementation in trauma patients that make recommendations inconclusive. These are as follows:

- Some trials used a mixture of immunonutrients concurrently as an intervention, which makes it impossible to make a clear judgment about the exact beneficial effect of each nutrient.
- Other trials used a historical group as a control.
- In enteral feeding it is often difficult to deliver the supplemented feed effectively due to feeding intolerance, which is present in many critically ill patients.
- The quality of many trials was low and did not meet the CONSORT (consolidated standards of reporting trials) guidelines in terms of random allocation concealment, blinding of assessors or care-givers and presenting results in an intention to- treat analysis.
- Most trials had a small number of subjects and were not sufficiently powered to investigate major clinical outcomes such as mortality.
- The doses varied between trials which makes clear comparison between trials problematic.
- The period of supplementation was very short in some trials (e.g. three to seven days).

CONCLUSION:

There are many evidences that glutamine supplementation must be used in patients with multiple trauma but at the same time well-designed multi centre trials are very important to impart any sort of greater clinical evidences. The trials have been conducted only among limited number of patients hence the conclusions are not made clearly. The use of glutamine as an enteral supplementation is very difficult as well as uncertain; hence future trials must focus more on the use of glutamine intravenously.

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REFERENCES:

1. Faist E, Mewes A, Strasser T, Walz A, Alkan S, Baker C et al. Alteration of monocyte function following major injury. Arch Surg 1988; 123:287-292.
2. Ditschkowski M, Kreuzfelder E, Rebmann V, Ferencik S, Majetschak M, Schmid EN et al. HLA-DR expression and Soluble HLA-DR levels in septic patients after trauma. Ann Surg 1999; 229:246-254.
3. Napolitano LM, Faist E, Wichmann MW, Coimbra R. Immune dysfunction in trauma. Surg Clin North Am 1999; 79:1385- 1416.
4. O 'Mahony JB, Palder SB, Wood JJ, McIrvine A, Rodrick ML, Demling RH et al. Depression of cellular immunity after multiple trauma in the absence of sepsis. J Trauma 1984; 24:869-875.
5. García-de-Lorenzo A, Zarazaga A, García-Luna PP, Gonzalez-Huix F, López-Martínez J, Miján a et al. Clinical evidence for enteral nutritional support with glutamine: a systematic review. Nutrition 2003; 19:805-811.
6. Bone RC. Sir Isaac Newton, sepsis, SIRS, and CARS. Crit Care Med 1996; 24:1125-1128.
7. Moore FA, Sauaia A, Moore EE, Haenel JB, Burch JM, Lezotte DC. Postinjury multiple organ failure: a bimodal phenomenon. J Trauma 1996; 40:501-510.
8. Hoch RC, Rodriguez R, Manning T, Bishop M, Mead P, Shoemaker WC et al. Effects of accidental trauma on cytokine and endotoxin production. Crit Care Med 1993; 21:839-845.
9. Buckingham JC. Hypothalamo-pituitary responses to trauma. Br Med Bull 1985; 41:203-211.
10. Monk DN, Plank LD, Franch-Arcas G, Finn PJ, Streat SJ, Hill GL. Sequential changes in the metabolic response in critically injured patients during the first 25 days after blunt trauma. Ann Surg 1996; 223:395-405.
11. Black PR, Brooks DC, Bessey PQ, Wolfe RR, Wilmore DW. Mechanisms of insulin resistance following injury. Ann Surg 1982; 196:420-435.
12. K lein S, Peters EJ, Shangraw RE, Wolfe RR. Lipolytic response to metabolic stress in critically ill patients. Crit Care Med 1991; 19:776-779.
13. Beier-Holgersen R, Boesby S. Influence of postoperative enteral nutrition on postsurgical infections. Gut 1996; 39:833-5.
14. Sodergren MH, Jethwa P, Kumar S, Duncan HD, John T, Pearce CB. Immuno nutrition in patients undergoing major upper gastrointestinal surgery: A prospective double-blind randomized controlled study. Scand J Surg 2010; 99:153-61.
15. Fürst, P, Stehle P. Glutamine supplemented nutrition in clinical practice and use of glutamine-containing dipeptides. Infusionsther Transfusionsmed 1995; 22:317-24.
16. Morlion BJ, Stehle P, Wachtler P, Köller M, König W, Fürst P, *et al*. Total parenteral nutrition with glutamine dipeptide after major abdominal surgery: A randomized, double-blind, controlled study. Ann Surg 1998; 227:302-8.
17. Gamrin L, Andersson K, Hultman E, Nilsson E, Essén P, and Wernerman J. Longitudinal changes of biochemical parameters in muscle during critical illness. Metabolism 1997; 46:756- 762.
18. Finn PJ, Plank LD, Clark MA, Connolly AB, Hill GL. Progressive cellular dehydration and proteolysis in critically ill patients. Lancet 1996; 347:654-656.
19. Wolfe RR, Goodenough RD, Burke JF, Wolfe MH. Response of protein and urea kinetics in burn patients to different levels of protein intake. Ann Surg 1983; 197:163-171.
20. Streat SJ, Beddoe AH, Hill GL. Aggressive nutritional support does not prevent protein loss despite fat gain in septic intensive care patients. J Trauma 1987; 27:262-266.
21. Petersson B, Vinnars E, Waller SO, and Wernerman J. Long-term changes in muscle free amino acid levels after elective abdominal surgery. Br J Surg 1992; 79:212-216.
22. Jackson NC, Carroll PV, Russell-Jones DL, Sönksen PH, Treacher DF, Umpleby AM. The metabolic consequences of Critical illness: acute effects on glutamine and protein metabolism. Am J Physiol 1999; 276:E163-170.
23. Newsholme P. Why is L-glutamine metabolism important to cells of the immune system in health, postinjury, surgery or infection? J Nutr 2001; 131:2515S-2522S.
24. Boelens PG, Houdijk AP, Fonk JC, Nijveldt RJ, Ferwerda CC, Von Blomberg-Van Der Flier BM et al. Glutamine-enriched enteral nutrition increases HLA-DR expression on monocytes of trauma patients. J Nutr 2002; 132:2580-2586.

25. Jungas RL, Halperin ML, Brosnan JT. Quantitative analysis of amino acid oxidation and related gluconeogenesis in humans. Physiol Rev 1992; 72:419-448.
26. Houdijk AP, van Leeuwen PA, Teerlink T, Flinkerbusch EL, Boermeester MA, and Sauerwein HP et al. Glutamine enriched enteral diet increases renal arginine production. JPEN J Parenter Enteral Nutr 1994; 18:422-426.
27. Melis GC, Boelens PG, van der Sijp JR, Popovici T, De Bandt JP, Cynober L et al. 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 2005; 94:19-26.
28. Fläring UB, Rooyackers OE, Wernerman J, Hammarqvist F. Glutamine attenuates post-traumatic glutathione depletion in human muscle. Clin Sci 2003; 104:275-282.
29. Bakalar B, Duska F, Pachl J, Fric M, Otahal M, Pazout J et al. Parenterally administered dipeptide alanyl-glutamine prevents worsening of insulin sensitivity in multiple-trauma patients. Crit Care Med 2006; 34:381-386.
30. Grau T, Bonet A, Minambres E, Pineiro L, Irles JA, Robles A et al. The effect of L-alanyl-L-glutamine dipeptide supplemented total parenteral nutrition on infectious morbidity and insulin sensitivity in critically ill patients. Crit Care Med 2011; 39:1263-1268.