International Journal of Prevention and Treatment 2015, 4(2): 34-39
DOI: 10.5923/j.ijpt.20150402.03

Therapeutic Targets of Glutamine in Parenteral Nutrition: A Medical Science Review

Alberto Leguina-Ruzzi

Hematology and Oncology, Faculty of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile

Abstract Glutamine is the most abundant free amino acid with multiple biological functions. Under hypercatabolic conditions, its levels are considerably depleted a condition that correlates with pathological severity and has been suggested as an independent predictor of mortality in intensive care unit patients. The supplementation of this amino acid to parenteral nutrition has been widely used for the management of intensive care complication. However, controversial clinical reports have generated reluctance in the use of this pharmaco-nutrient. In this review, we address the molecular aspects of the reported beneficial effects of glutamine. From a basic science point of view considering *in vitro*, *ex vivo* and *in vivo* studies, the evidence describes various metabolic pathways in which glutamine plays beneficial roles. These pathways support the role of glutamine as an antioxidant, detoxicant, heat shock protein inductor, immune enhancer, nitrogen stabilizer and insulin sensitizer. We strongly believe that there is a mandatory need for more clinical trials, which could address the clinical concerns of glutamine supplementation to parenteral nutrition. However, from the molecular point of view and based on the current clinical studies, the use of glutamine is still a clinical and economically attractive management strategy.

Keywords Glutamine, Parenteral Nutrition, Pharmaco-nutrient

1. Introduction

Glutamine (Gln) is the most abundant free amino acid (AA) in the body with concentrations fluctuating around 500-900 μmol/L [1]. The biological functions of this AA have been widely studied, opening a whole new world of targets in which Gln could modulate physiological functions such as immune enhancer, muscular maintainer, nitrogen transporter, neuronal mediator, pH homeostasis, gluconeogenesis, aminosugar synthesis, among others [2].

For decades it has been used as a supplement of total parenteral nutrition (TPN) in its dipeptide Alanylglutamine form, because of its limited solubility and instability in aqueous solution [3].

In 1990 it was identified that Gln is one of the only conditionally essential AA, meaning that in hypercatabolic or stress conditions the body suffers depletion in the circulating levels [4]. This characteristic confers the option of Gln use as a pharmaco-nutrient, meaning that through its targets it could improve the outcome of patients that are suffering a hypercatabolic or hypermetabolic condition.

Studies have identified the patients in whom a depletion of Gln is correlated with severity of their pathological condition [5]. Furthermore, this phenomenon is an independent predictor of mortality in intensive care unit (ICU) patients [6].

A series of clinical trials, meta-analyses and systematic reviews have shown that supplementation of TPN with Gln improves three major clinical outcomes: 1) mortality, 2) infections, 3) length of stay (LOS) and 4) cost effectiveness [7-9].

Even though nutrition guidelines recommend its use in ICU patients with TPN requirement (Table 1), controversy has emerged after the publication of the REDOX study [10] causing distrust and fear in the use of this supplement.

Table 1. International Guidelines for Glutamine Supplementation

Year	Glutamine in Parenteral Nutrition	
	Guide	Recommendation
2009	ESPEN [11]	0.3-0.6 g/kg/day (dipeptide)
2009	ASPEN/SCCM [12]	0.5/ g/kg/day (dipeptide)
2011	ASPEN [13]	>0.2-0.5 g/kg/day (dipeptide)
2011	ACHINUMET [14]	0.3-0.6 g/kg/day (dipeptide)

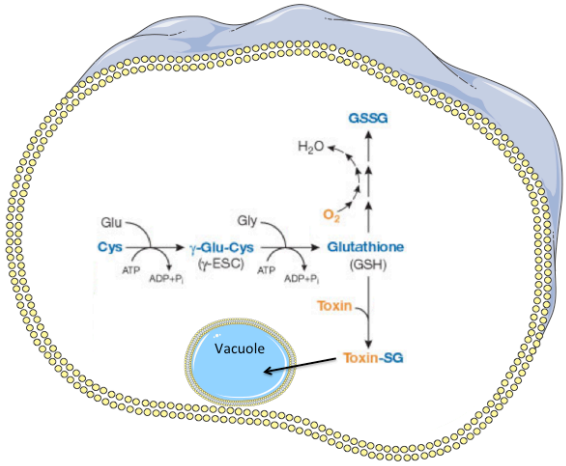
In this review we summarize the evidence provided by the basic science research that supports the beneficial effects of supplementation with Gln in main ICU patients outcomes. The literature searching was made in pubmed following the queries "glutamine" combined with "supplementation", "parenteral nutrition", "ICU" and/or "pharmaconutrient". Reports in English and from the last 3 decades were considered for this purpose.

* Corresponding author:
aaleguin@uc.cl (Alberto Leguina-Ruzzi)
Published online at http://journal.sapub.org/ijpt

2. Molecular Targets of Glutamine

2.1. Glutathione Biosynthesis

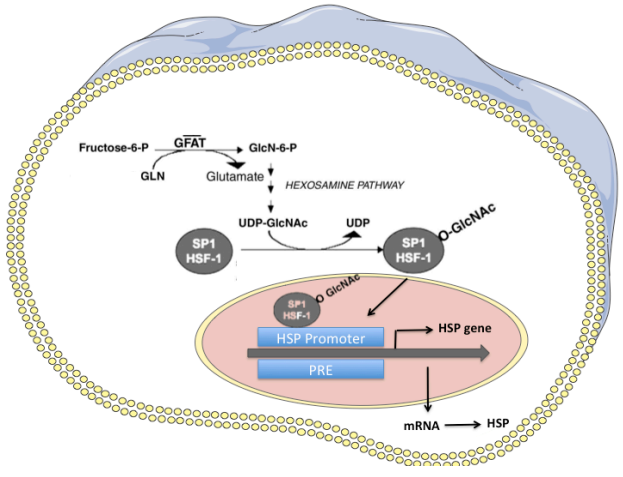
Glutathione (GSSH) is a reduced non-protein thiol, which is present in all mammalian tissues and has important antioxidant and detoxification functions [15]. Gln is a precursor of GSSH when associated with cysteine in the cytoplasmic compartment of the cell [16]. This reduced metabolite has strong affinity to free radicals and toxins, passing to oxidized glutathione disulphide (GSSG). GSSG can be converted again to GSSH or be translocated to the vacuole for degradation, conferring its beneficial capacities to the cells as shown in Figure 1 [17].



Cys: cysteine, ATP: adenosine triphosphate, ADP: adenosine diphospate, y-ESC: gamma glutaminecystein dipeptide, Glu: glutamine, Gly: glycine, SG: glutathione disulfide.

Figure 1. Glutathione antioxidant and detoxicant intracellular capacity

2.2. Heat Shock Proteins



GLN: glutamine, GFAT: glutamine fructose-6-phospate amidotransferase, GlcN-6-P: glucosamine-6-phospato, UDP-GlcNAc: uridine diphosphate N-acetylglucosamine, UDP: uridine di phosphate, SP1: specific protein 1, HSF-1: heat shock transcription factor 1, O-GlcNAc: O-linked N-acetylglucosamine, PRE: promotor regulatory elements

Figure 2. Enhancement of HSP synthesis by Gln and hexosamine cross talk

Heat shock proteins (HSP) (also known as stress response proteins) are highly conserved and present in all cells [18]. An important part of these molecules participate in protein folding, assembly and correct transport, enabling them to act as cytoprotective molecules [19]. It has been shown that in sepsis or in inflammatory response syndrome, there is a significant reduction in the intracellular levels of HSP72, which correlates with severity of illness and mortality [20].

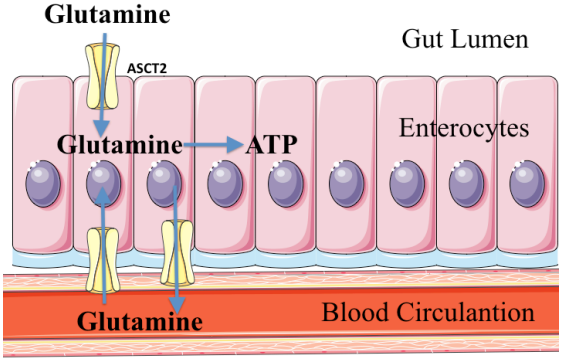
Hamiel et al. showed that Gln enhanced the HSP70 expression through the crosstalk with the hexosamine pathway [21]. Interestingly this process could ameliorate cell stress and protect cellular integrity, which in turn potentiates the regeneration.

2.3. Bacterial Translocation

This pathological condition is based in the passage of viable bacteria from the gastrointestinal tract to extrainstestinal sites, giving rise to a systemic infective condition [22].

ICU patients are at higher risk of bacterial translocation (BT), 15% of the ICU population is affected, particularly those with intestinal damage. This condition is one of the main causes of sepsis and multiorganic failure [23].

Interestingly, it has been reported that the supplementation of Gln to the TPN reduces the prevalence of BT and prevents inflammatory intestinal complications [24]. *In vivo* and *in vitro* studies have reported that the enterocyte uses Gln as its principal energy source [25], enhancing its growth and proliferation [26]. Moreover, the enterocyte is capable of transporting it to and from the intestinal circulation, creating a bidirectional supply of this AA [27]. This process uses a series of antiporters coupled to Na^+ and H^+ from the family ASCT2 [28]. On the other hand, a deprivation of this AA induces BT, which suggests the importance of Gln in the intestinal barrier integrity [29]. This suggests a protective role for Gln in intestinal integrity, providing fuel for the enterocyte and therefore as a preventive mechanism of sepsis.



ASCT2: amino acid transporter 2, ATP: adenosine triphosphate

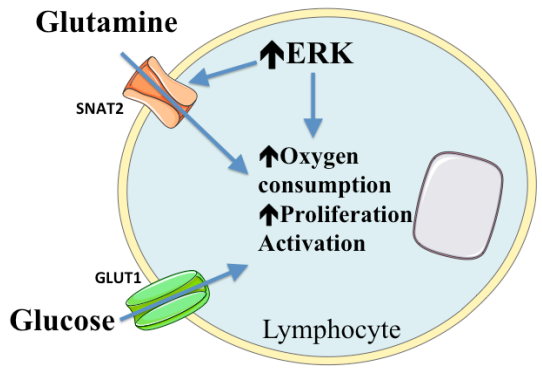
Figure 3. Glutamine transport and metabolism in the enterocyte

2.4. Lymphocytic Function

The activation of naïve T cells is a pivotal process for the

immune response and is a highly energetic event that requires an increase in nutrient metabolism [30]. Among the processes required, Gln uptake is regulated by the ERK/MAPK pathway and is fundamental for the activation of this cell type. See Figure 4. The Gln AA also modulates the proliferation of the Naive T cells [31-32]. *In vitro* studies have shown that extracellular Gln is essential as a respiratory fuel and not only has an impact on the lymphocyte, but also mediates the macrophage phagocytic and secretory function as well as the neutrophil bacterial killing [33]. *In vivo* studies have suggested that Gln in close interaction with glucose metabolism might be potential targets for the anti-inflammatory and immunomodulation effect of physical activity, which could be particularly relevant for patients with reduced mobility [34].

In relation to the inmunomodulatory effect of Gln, a clinical study showed that its supplementation significantly decreased nosocomical and bloodstream infections after surgery, suggesting a positive impact on surgical intensive care [35].



SNAT2: amino acid transporter 2, GLUT1: glucose transporter 1, ERK: extracellular signal-regulated kinases

Figure 4. Metabolic processes required for lymphocyte activation

2.5. Nitrogen Balance

The nitrogen balance (NB), measured as nitrogen input minus output, was the first approach used to study the utilization of nitrogen in the body. Even though this method has several limitations, it is still widely use in clinic [36].

The regulation of a relatively constant level of adult body protein is a physiologically favourable process to maintain the cellular integrity [37]. It is widely accepted that ICU patients with TPN present a negative NB that correlates with the clinical outcome [38-39]. Interestingly, Gln supplementation has shown the capacity to improve the NB from the third day of use [40]. Furthermore, the Gln supplemented diet did not affect portal ammonia concentration, showing that it does not affect the excretion pathway [41].

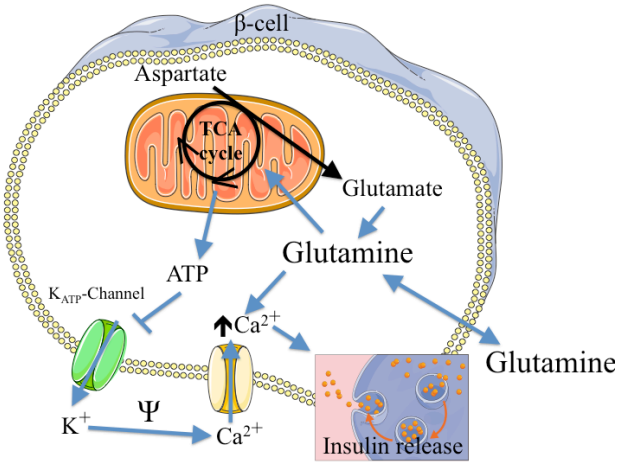
2.6. Insulin Sensitivity

Hyperglycaemic crises are metabolic emergencies commonly associated with uncontrolled diabetes mellitus, which may result in significant morbidity or death [42]. This complication is also common in critical illness, regardless of a diabetes history. The prevalence in UCI patients is around 40% [43] and classically was presumed to be an adaptive response to stress [44]. However, more recent reports have shown that hyperglycemia is associated with increased mortality and morbidity [45]. Guidelines for glycemic control have been suggested by the main organizations giving specific goals as shown in table 2.

Table 2. Guidelines for Glucose Blood Levels in Critically Ill Patients

Year	International Guidelines for Glycemic Control	
	Guide	Recommendation
2009	AACE/ADA [46]	140-180 mg/dL
2011	ACP [43]	140-200 mg/dL
2012	ADA [47]	140-180 mg/dL
2011	SCCM [48]	100-150 max. 180 mg/dL

The role of Gln in insulin sensitivity has been widely studied [49]. A recent randomized-controlled clinical trial demonstrated that the supplementation of Gln to the TPN for more than 7 days reduces significantly the hyperglycemic episodes and the insulin requirement in ICU polytrauma patients [50]. *In vivo* studies have demonstrated the Gln stimulates calcium dependent insulin secretion and beta-cell depolarization [51]. *In vitro,* it has been shown that Gln enhances the insulin glucose response. The process involves the metabolism of the gamma-glutamyl cycle, the glutathione synthesis and the mitochondrial function as shown in Figure 5 [52].



TCA: tricarboxylic acid cycle, ATP: adenosine triphosphate, K_{ATP}-Channel: ATP-sensitive potassium channel

Figure 5. Metabolic pathway in insulin release potentiation by Gln

3. When not to Use Glutamine?

Although Gln as a molecule seems promising for treatment of ICU patients, it is fundamental to identify when not to use it. Ironically, the biggest Gln clinical that opened the "can of worms" provided the most valuable information. The REDOX study reported that Gln did not confer any

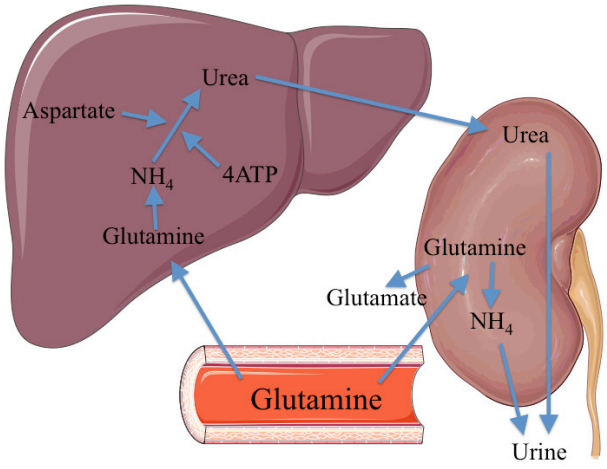
beneficial effect and increased mortality [10]. This conclusion was mainly because patients fulfilling contraindication parameters were included and an inappropriate dose was used. However, the report is telling us how not to use glutamine and this information is a valuable guide for the correct use of Gln, as shown in Table 3. Additionally, a recent report that had a great impact in the current Canadian Nutrition Guide supports the idea of the proper "time-frame" of supplementation [53].

Table 3. Contraindications of Glutamine

Impact	Parameters of contraindication	
	Condition	Values
1	Renal failure	Creatinine Clearance <25 ml/min
2	Liver failure	INR>1.5 and altered laboratory testing
3	Metabolic acidosis	Altered levels of arterial blood gas, serum electrolytes and urine pH
4	Short use	Less than 7 days
5	Use delay	More than 24 hours
6	Inappropriate dose	More or less than recommended
7	Protein misbalance	>30% of the total AA

Even when all of the above parameters of contraindication are equally important, we gave a greater impact to the kidney and liver function. It is important to recognize the cytotoxic effect of Gln. *In vitro* related species can participate in pathways that lead to apoptosis [54].

That is why the proper excretion of Gln is required for safety of patients. In the first step, in the kidney the AA passes through a metabolic transformation producing urea that is excreted by the kidney. Additionally, the kidney can metabolize Gln in a process called glutaminolysis. In a series of biochemical reactions the Gln is lysed to glutamate, aspartate, CO_2, pyruvate, lactate, alanine and citrate. See figure 6 [55].



NH_4: ammonium, ATP: adenosine triphosphate

Figure 6. Liver and kidney glutamine excretion through ureagenesis and glutaminolysis

4. Conclusions

Strong evidence emerges from the basic science showing the beneficial effects of Gln in the metabolism. Interestingly, *in vitro* is used in classical media ranges from 500 to 2000 µmol/L depending on the cell culture requirement, values that could represent a physiological state and AA supplementation. Gln pleiotropic functions make it a great candidate for the treatment of hypercatabolic conditions. However, important lessons have to be learned from the controversial evidence that impacts negatively on Gln use. The correct identification of patients for whom it is safe and the correct usage of the supplement are pivotal for its safe administration.

A critical and rigorous evaluation of the clinical trials is required to avoid misunderstandings and errors in the real properties of this AA. There is an urgent need for more clinical trials that could address the concerns of Gln use in the clinical field.

ACKNOWLEDGEMENTS

No sources of funding were used to assist in preparation of this manuscript. The author acknowledges that in figure 1 a different glutamine designation was used. This was intentionally made to maintain the fidelity to the cited reference.

The author has no conflict of interests that are directly relevant to the content of this review.

REFERENCES

[1] Brosnan JT. 2003, Interorgan amino acid transport and its regulation. J Nutr 133 (6 Suppl 1): 2068S-2072S.

[2] Newsholme P, Lima, Procopio MR, Pithon-Curi TC, Doi SQ, Bazotte RB, Curi R. 2003, Glutamine and glutamate as vital metabolites. Braz J Med Biol Res 36(2): 153-163.

[3] Berg A, Rooyacker O, Norberg A, Wernerman J. 2005, Elimination kinetics of L-alanyl-L-glutamine in ICU patients. Amino Acids 29: 221-228.

[4] Lacey JM, Wilmore DW. 1990, Is glutamine a conditionally essential amino acid?. Nutr Rev 48(8): 297-309.

[5] Vinnars E, Hammarqvist F, von der Decken A, Wernerman J. 1990, Role of glutamine and its analogs in posttraumatic muscle protein and amino acid metabolism. J Parenter Enteral Nutr 14(4 Suppl): 125S-129S.

[6] Oudemans-van Straaten HM, Bosman RJ, Tresken M, van der Spoel HJ, Zandstra DF. 2001, Plasma glutamine depletion and patient outcome in acute ICU admissions. Intensive Care Med 27(1): 84-90.

[7] Chen QH, Yang Y, He HL, Zie JF, Cai SX, Liu AR, Wang HL, Qiu HB. 2014, The effect of glutamine therapy on outcomes in critically ill patients: a meta-analysis of randomized controlled trials. Critical Care 18:R8

[8] Bollhalder L, Pfeil AM, Tomonaga Y, Schwenkglenks. 2013, A systematic literature review and meta-analysis of randomized clinical trials of parenteral glutamine supplementation. Clin Nutr 32(2): 213-223.

[9] Pradelli L, Povero M, Muscaritoli M, Eandi M. 2015, Updated cost-effectiveness analysis of supplemental glutamine for parenteral nutrition of intensive-care patients. Eur J Clin Nutr 69: 546-551.

[10] Heyland D, Muscedere J, Wischmeyer PE, Cook D, Jones G, Albert M, Elke G, Berder MM, Day AG. 2013, A randomized trial of glutamine and antioxidants in critical ill patients. N Engl J Med 368(16): 1489-1497.

[11] Braga M, Ljungqvist O, Soeters P, Fearon K, Weimann A, Bozzetti F. 2009, ESPEN guidelines on parenteral nutrition: surgery. Clin Nutr 28(2009): 378-386.

[12] McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Tylor B, Ochoa JB, Napolitano L, Cresci G, ASPEN Board of Directors, American College of Critical Care Medicine, Society of Critical Care Medicine. 2009, Guidelines for the provision and assessment of nutrition support therapy in the adult critical ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN). J Parenter Enteral Nutr 33(3): 277-316.

[13] Vanek VW, Matarese LE, Robinson M, Sacks GS, Kochevar M, Novel Nutrient Task Force, Parenteral Glutamine Workgroup, American Society for Parenteral and Enteral Nutrition (ASPEN), Board Directors. 2011, ASPEN position paper: parenteral nutrition glutamine supplementation. Nutr Clin Pract 26(4): 479-494.

[14] Galvez R, Hirsch S, Klaassen J, Papaprieto V, Reyes E, Ugarte S. 2011, Guías prácticas de soporte nutricional en unidades de cuidado intensivos e intermedio. (Online article), available from http://www.achinumet.cl/guias-soporte/Guias%20Soporte%20Nutricional%20UCI.pdf. Accessed on 14 august 2015.

[15] Lu SC. 2013, Glutathione synthesis. Biochim Biophys Acta 1830(5): 3143-3153.

[16] Amores-Sánchez MI, Medina MA. 1999, Glutamine as a precursor of glutathione and oxidative stress. Mol Genet Metab 67(2): 100-105.

[17] Wu G, Fang YZ, Yana S, Lupton JR, Turner ND. 2004, Glutathione metabolism and its implications for health. J Nutr 134(3): 489-492.

[18] Liz Z, Srivastava P. 2004, Heat-shock proteins. Curr Protoc Immunol doi: 10.1002/0471142735.ima01ts58.

[19] Feder ME, Hofmann GE. 1999, Heat-shock proteins, molecular chaperones, and the stress response: evolutionary and ecological physiology. Annu Rev Physiol 61: 243-282.

[20] Apostolou K, Vardas K, Briassouli E, Psara K, Goukos D, Mageira E, Nanas S, Routsi C, Briassoulis G. 2015, Early heat shock protein 72 and 90α intracellular and extracellular responses in patients with severe sepsis or systemic inflammatory response syndrome. Critical Care 19 (Suppl 1): P41.

[21] Hamiel CR, Pinto S, Hau A, Wischmeyer PE. 2009, Glutamine enhances heat shock protein 70 expression via increased hesoxamine biosynthetic pathway activity. Am J Physiol Cell Physiol 297(6): 1509-1519.

[22] Berg RD. 1999, Bacterial translocation from the gastrointestinal tract. Adv Exp Med Biol 473: 11-30.

[23] McFie J. 2004, Current status of bacterial translocation as a cause of surgical sepsis. Br Med Bull 71(1): 1-11.

[24] Gatt M, Reddy BS, MacFie J. 2007, Review article: bacterial translocation in the critically ill-evidence and methods of prevention. Aliment Pharmacol Ther 25(7): 741-757.

[25] McCauley R, Kong SE, Hall J. 1998, Glutamine and nucleotide metabolism within enterocytes. J Parenter Enteral Nutr 22(2): 105-111.

[26] Yang H, Soderholm JD, Larsson J, Pernert J, Lindgreen J, Wirén M. 2000, Bidirectional supply of glutamine maintains enterocyte ATP content in the in vitro using chamber model. Int J Colorectal Dis 15(5-6): 291-296.

[27] Yi D, Hou Y, Wang L, Ouyang W, Long M, Zhao D, Ding B, Liu Y, Wu G. 2015, L-Glutamine enchances enterocyte growth via activation of the mTOR signaling pathway independently of AMPK. Amino Acids 47(1): 65-78.

[28] Pochini L, Scalise M, Galluccio M, Indiveri C. 2014, Membrane transporters fro the special amino glutamine: structure/function relationships and relevance to human health. Front Chem 2:61 doi: 10.3389/fchem.2014.00061.

[29] Clark EC, Patel SD, Chadwick PR, Warhurst G, Curry A, Carlson GL. 2003, Glutamine deprivation facilitates tumor necrosis factor induced bacterial translocation in Caco-2 cells by depletion of enterocytes fuel substrate. Gut 52(2): 224-230.

[30] Carr EL, Kelman A, Wu GS, Gopaul R, Senkevitch E, Aghvanyan A, Turay AM, Frauwirth KA. 2010, Glutamine uptake and metabolism are coordinately regulated by ERK/MAPK durng T lymphocyte activation.cJ Immunol 185(2): 1037-1044.

[31] Chang WK, Yang KD, Shaio MF. 1999, Lymphocyte proliferation modulated by glutamine: involved the endogenous redox reaction Clin Exp Immunol 117(3): 482-488.

[32] Yaqoob P, Calder PC. 1997, Glutamine requirement of proliferating T lymphocytes. Nutrition 13(7-8): 646-651.

[33] Newsholme P. 2001, Why is L-Glutamine metabolism important to cells of the immune system in health, postinfury, surgery or infection?. J Nutr 131(9): 2515S-2522S.

[34] Wasinkski F, Gregnani MF, Ornellas FH, Bacurau AV, Camara NO, Araujo RC, Bacurau RF. 2014, Lymphocyte flucose and glutamine metabolism as targets of the anti-inflammatory and immunomodulatory effects of exercise. Mediators Inflamm ID 326803.

[35] Estivariz CF, Griffith DP, Luo M, Szeszycki EE, Bazargan N, Dave N, Daignault NM, Bergman GF, McNally T, Battey CH, Furr CE, Hao L, Ramsay JG, Accardi CR, Cotsonis GA, Jones DP, Galloway JR, Ziegler TR. 2008, Efficacy of parental nutrition supplemented with glutamine dipeptide to decrease hospital infections in critical ill surgical patients. J Parenter Enteral Nutr 32(4): 389-402.

[36] Tomé D, Bos Cecile. 2000, Dietary protein and nitrogen utilization. J Nutr, 130(7): 1868S-1873S.

[37] Young VR. 1986, Nutritional balance studies: indicators of human requirements or of adaptive mechanisms?. J Nutr 116: 700-703.

[38] Pitkanen O, Takala J, Poyhonen M, Kari A. 1991, Nitrogen and energy balance in septic and injured intensive care patients: response to parenteral nutrition. Clin Nutr, 10(5): 258-265.

[39] Cheatham ML, Safcsak K, Brzezinski S, Lube M. 2007, Nitrogen balance, protein loss and the open abdomen. Crit Care Med 35(1): 127-131.

[40] Morlion BJ, Stehle P, Wachtler P, Siedhoff HP, Koller M, Konig W, Furst P, Puchstein C. 1998, Total parenteral nutrition with glutamine dipeptide after major abdominal surgery: a randomized, double blind controlled study. Ann Surg, 227(2): 302-308.

[41] Brown MG, Campbell GR, Rowlands BJ. 1991, Glutamine-enhaced enteral diet improves nitrogen balance without increasing portal ammonia. Br J Surg 78(11): 1305-1306.

[42] Van Ness-Otunnu, Hack JB. 2013, Hyperglycemic crisis. J Emerg Med 45(5): 797-805.

[43] Qassem A, Humphrey LL, Chou R, Snow V, Shekelle PC. 2011, Use of intensive insulin therapy for the management of glycemic control in hospitalized patients: a clinical practice guideline from the American Colleges of Physicians. Ann Intern Med 154(4): 260-267.

[44] Van den Vergue G. 2004, How does blood glucose control with insulin save lives in intensive care?. J Clin Invest 114(9): 1187-1195.

[45] Krinsley JS. 2003, Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc 78(12): 1471-1478.

[46] Moguissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, Inzucchi SE, Ismail-Beigi F, Kirkman MS, Umpierrez GE.2009, American Association of Clinical Endocrinologist and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Cares 32(6): 1119-1131.

[47] American Diabetes Association. 2012, Standards of medical care in diabetes-2012. Diabetes Care 35(suppl1): s11-s63.

[48] Jacobi J, Bircher N, Krinsley J, Agus M, Braithwaite SS, Deutschman, Freire AX, Geehan D, Kohl B, Nasraway SA, Rigby M, Sands K, Schallom L, Taylor B, Umpierrez G, Mazuski J, Schunemann H. 2012, Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. Crit Care Med 40(12): 3251-3276.

[49] Molfino A, Logorelli F, Muscaritoli M, Cascino A, Preziosa I, Fanelli FR, Laviano A. 2010, Metabolic effects of glutamine on insulin sensitivity. Nut Therapy Met 28(1): 7-11.

[50] Grintescu IM, Vasiliu IL, Badica IC, Mirea L, Pavelescu D, Balanescu A, Grintescu IC. 2015, The influence of parenteral glutamine supplementation on glucose homeostasis in critically ill polytrauma patients- A randomized-controlled clinical study. Clin Nutr 34: 377-382.

[51] Li C, Buettger C, Kwagh J, Matter A, Daikhin Y, Nissim IB, Collins HW, Yudkoff M, Stanley CA, Matschinsky FM. 2004, A signaling role of glutamine in insulin secretion. J Biol Chem 279(14): 13393-13401.

[52] Brennan L, Corless M, Hewage C, Malthouse JP, McClenaghan NH, Flatt PR, Newsholme P. 2003, 13C NMR analysis reveals a link between L-glutamine metabolism, D-glucose metabolism and gamma-glutamyl cycle activity in a clonal β pancreatic cell line. Diabetologia 46: 1512-1521.

[53] Perez-Barcena J, Marse P, Zabalegui-Perez A, Corral E, Herrán-Monge M, Cervera M, Llompart-Pou JA, Ayestarán I, Raurich JA, Oliver A, Bruño A, García de Lorenzo A, Frontera G. 2014, A randomized trial of intravenous glutamine supplementation in trauma ICU patients. Intensive Care Med 40:539-547.

[54] Matés JM, Segura JA, Alonso FJ, Márquez J. 2006, Pathways from glutamine to apoptosis. Front Biosci 1(11): 164-180.

[55] Weiner D, Mitch WE, Sands JM. 2014, Urea and ammonia metabolism and the control of renal nitrogen excretion. Clin J Am Soc Nephrol 10(8): 1444-1458.