Egyptian Journal of Anaesthesia (2016) **32**, 415–420

HOSTED BY

ELSEVIER

Egyptian Society of Anesthesiologists

Egyptian Journal of Anaesthesia

www.elsevier.com/locate/egja
www.sciencedirect.com

Research Article

Studying the effect of parenterally administered L-alanyl L-glutamine dipeptide in diabetes and new onset diabetes in liver transplantation

Alaa el-Din A. Korraa *, **Heba A. Labib, Dina Salah**

Department of Anesthesiology, Intensive Care, and Pain Management, Faculty of Medicine, Ain Shams University, Egypt

Received 23 December 2015; accepted 27 December 2015
Available online 29 January 2016

KEYWORDS

Diabetes;
New onset diabetes;
Liver transplantation;
L-alanyl L-glutamate

Abstract *Objective:* The objective of this study was to evaluate the efficacy of using alanine–glutamine (Aln–Gln) dipeptide as a supplement to control diabetes in liver transplanted patients.
Patients and methods: Eighty patients aged >18 yr admitted to ICU after receiving right lobe living donor liver transplantation (LDLT), had a previous history of diabetes or had a new onset diabetes (NODM) were enrolled in this prospective randomized double blind study. Patients were randomized into two groups and assigned to receive parenterally an equal dose of amino acids either with alanyl-glutamine dipeptide in the dose of 0.5 g/kg/d (group AG) or without alanyl-glutamine dipeptide (control group C). This regimen started at day 1 postoperative in diabetic patients or when new onset diabetes has been diagnosed in non-diabetic and continued till day 9 with measuring the incidence of hyperglycemia, hyperglycemic episodes, total insulin requirements/day, infectious episodes, ICU and hospital length of stay, and 6 month mortality rate.
Results: The hyperglycemic episodes were significantly less in AG group patients than in control group patients (29 vs 38). Hyperglycemia requiring insulin therapy in AG group was significantly less (22 vs 28 patients). Also those who required decreasing TPN requirements were significantly lesser in the AG group (7 vs 11 patients). Insulin requirements per day in the AG group were significantly lower (53 ± 11 vs 78 ± 9 IU). The number of episodes of nosocomial infection per patient was lower in the AG group than in the control group (20 vs 28). The decrease in nosocomial infections in patients receiving AG was related mainly to a decrease in the incidence of pneumonia (7 vs 11). The ICU length of stay (LOS) was significantly lower in the AG group than in the control group (7.81 ± 2.98 vs 10.43 ± 4.67 day)
Conclusion: Our study showed that using AG supplementation in liver transplanted patients who have either a history of diabetes or NODM, reduces the insulin requirements, hyperglycemic episodes, infectious events and ICU stay.

* Corresponding author at: 8595 EL Reda and Nour St. Mokattam.
Tel.: +20 123606450.

Peer review under responsibility of Egyptian Society of Anesthesiologists.

http://dx.doi.org/10.1016/j.egja.2015.12.002

1. Introduction

Diabetes is a common complication of liver transplantation increasing the risk of infection and mortality. New onset diabetes (NODM) accounts for nearly 15% of liver transplant recipients and a similar proportion of patients have diabetes prior to transplant thus increasing the magnitude of the problem [1]. Diabetes may develop from either impaired glucose tolerance, insulin resistance associated with impaired liver function, or a result of corticosteroids treatment post transplant [2]. A proper tight glycemic control reduces morbidity and mortality and requires multiple therapies.

Glutamine (Gln) is the most abundant free amino acid in the extracellular and intracellular compartments, accounts for approximately 6% of bound amino acids [3], and plays an important role as immune function regulator and modulation of cell metabolism [4]. Gln enhances glucose-stimulated insulin secretion via the metabolism of the gamma-glutamyl cycle, glutathione synthesis and mitochondrial function [5]. In conditions of excessive organ or tissue demand of glutamine during episodes of sepsis, after trauma, major surgery, and other catabolic stress situations, endogenous glutamine production may not be sufficient to meet the increased requirements.

Several studies have shown that alanine–glutamine (Aln–Gln) dipeptide added to parenteral formulas improves nitrogen balance; increases protein synthesis; ameliorates immune function; preserves intestinal barrier permeability; and can reduce morbidity, length of stay, and mortality in critically ill patients [6–8]. Furthermore, glutamine can modify fatty acid oxidation and attenuates hyperglycemia and insulin resistance [9].

The aim of this study was to evaluate the efficacy of using Aln–Gln as a supplement to control diabetes in liver transplanted patients.

2. Patients and methods

After obtaining institution ethical board approval and written informed consent from patients, eighty patients were enrolled to this randomized double blind prospective, controlled study conducted between February 2012 and August 2015 in liver transplant unit in Ain Shams University Specialized Hospital. Patients included in the study were adults >18 years, admitted to ICU after performing right lobe living donor liver transplantation (LDLT), had a previous history of diabetes or had a new onset diabetes (defined as symptoms of diabetes plus casual plasma glucose $\geqslant 200$ mg/dl or fasting plasma glucose $\geqslant 126$ mg/dl on more than 2 occasions) [10].

Preoperative exclusion criteria were persistent hemodynamic failure (systolic blood pressure <80 mmHg), severe renal insufficiency (serum creatinine level $\geqslant 2.8$ mg/dl and (or) creatinine clearance <40 ml/min), and severe or uncontrolled sepsis. The following criteria may lead to the exclusion of a patient even after inclusion in the study period: necessity to perform major non-scheduled procedures within the study with subsequent total parenteral nutrition (TPN) discontinuation for more than 24 h, intolerable or serious adverse event, any inter-current disease likely to interfere with the study, or withdrawal of patient's consent.

All patients were assessed and received the standard preoperative care for patients undergoing liver transplantation according to our unit protocol. Standard anesthetic and surgical techniques for hepatic transplantation were performed by the same anesthesia and surgical team who were blinded to study medication. At the end of surgery patients were transferred to the ICU intubated and mechanically ventilated until fully conscious, good muscle power together with the standard acceptable ventilatory and hemodynamic parameters of weaning. Demographic data were obtained including age, sex, BMI, history of diabetes and APACHE Π score [11]. Fluid administration in intensive care unit was adjusted to maintain central venous pressure approximately 5–8 cmH_2O, mean arterial pressure >70 mmHg, urine output >1 ml/kg per hour. All patients received similar postoperative intensive care with a routine double immunosuppressive regimen including corticosteroids, and FK506 (tacrolimus) or cyclosporine. Mycophenolate with basiliximab are used instead of using tacrolimus or cyclosporine if serum creatinine rise after 48 hours.

Intravenous methyl-prednisolone 500 mg was given intraoperative after declamping. Maintenance dosage of methylprednisolone was 1 mg/kg, to be tapered rapidly over the next 7–10 days. Maintenance prednisone 0.25 mg/kg/d was continued for 3 months then steroid therapy was stopped. Cyclosporine was used for immunosuppressive therapy for all patients except hepato-cellular carcinoma (HCC) patients, and starting dose tacrolimus 0.5 mg was used instead. Maintenance dosages of tacrolimus were adjusted to maintain a level of 10–12 ng/mL during the first 2 months. For cyclosporine maintenance dosages to achieve trough levels of 150–250 ng/mL were prescribed in the first 2 months. Mycophenolate was used postoperative in the presence of preoperative renal impairment (cr.cl. 40–60) or postoperative renal dysfunction (rise in serum creatinine level >0.3 mg/dl in less than 48 h) instead of calcineurin inhibitors. Basiliximab was also used (day 0 and day 4) in the presence of preoperative renal impairment.

Postoperative prophylactic antibiotic treatment included piperacillin-tazobactam and Metronidazole for 10 days. All patients received sulfamethoxazole/trimethoprim for prophylaxis against Pneumocystis carinii on day five for 6 months. Fluconazole for prophylaxis of fungal infection was used for specific cases such as severely malnourished patients, prolonged treatment with antibiotic, fulminant hepatic failure, preoperative diabetic patients, re-exploration for surgical causes, biliary leak and small for size liver transplant.

This study began at day 1 postoperative in diabetic patients or when new onset diabetes has been diagnosed in non-diabetic patients. Partial TPN was started at day one as the standard protocol in our ICU. Non-protein energy requirements were calculated using the usual body weight and set at 25 kcal/kg/d. Protein requirements were set at 0.25 g N/kg/d. Patients were randomly assigned on a basis of 1:1 by means of a computer program into two groups AG group and control group. Protein + Ala–Gln and Protein containing TPN were labeled identically and the two solutions were indistinguishable. All patients, investigators, and coworkers were unaware of treatment allocation and remained blinded to the treatment allocation until the final statistical evaluation was completed. Patients in the Ala–Gln AG group (40 patients) received 0.5 g/kg/d of Ala–Gln dipeptide (AG) (Dipeptiven, Fresenius Kabi Spain, SA) plus 1.0 g/kg/d of a standard admixture of

amino acids (Aminosteril N hepa). The control group C (40 patients) received 1.5 g/kg/d of the same standard amino acids admixture. The calorie/nitrogen ratio and glucose–lipid ratio were, respectively, set at 100 and 64/36. Vitamins, trace elements, and electrolytes were administered according to the usual practice of our ICU. The Spanish Pharmacy Registry limits the use of Ala–Gln dipeptide to a maximum of 9 days [12]. If patients needed to be treated after 9 days with TPN, Ala–Gln dipeptide was discontinued, and they received the admixture of amino acids used in the control group.

Regular insulin administration was started if the blood glucose level exceeds 150 mg/dl. Adjustments of the insulin dose were based on measurements of the whole blood glucose in undiluted arterial blood at 1- to 4-h intervals with a glucose analyzer. The following protocol for tight glycemic control was used: if the blood glucose exceeds 200 mg/dl despite an insulin administration of a maximum of 10 IU during 3 consecutive hrs, the TPN infusion was decreased by 50%. If the blood glucose exceeds 200 mg/dl, despite the 50% decrease of TPN infusion with an insulin administration of 10 IU during 3 consecutive hrs, the TPN infusion was stopped (when the blood glucose is between 120 and 200 mg/dl, the TPN infusion was started again). If after restarting, despite a maximal insulin administration, the blood glucose exceeds 200 mg/dl during 3 h, the TPN was definitively stopped and patient is withdrawn from the study. Hourly glycemia and the hourly insulin dose were recorded at least 15 times a day (see Table 1).

2.1. Outcome assessment

The primary outcome was the incidence of hyperglycemia, hyperglycemic episodes that require insulin infusion, and episodes with 50% decrease of TPN as well as insulin needs to assess the effect of glutamine on insulin resistance. For hyperglycemia, only one episode was considered for each patient even if hyperglycemia was prolonged for several days.

Secondary outcomes were the incidence of nosocomial infections acquired throughout the stay in ICU in patients who received at least 4 days of treatment.

Nosocomial pneumonia was defined as follows: new onset of purulent sputum; change in character of sputum, respiratory secretions, or suctioning requirements; or worsening gas exchange (e.g., $PaO_2/FIO_2 < 240$, increasing O_2 requirements, or increased ventilation demand) plus two or more serial chest radiographs with new or progressive and persistent infiltrates; consolidation or cavitation; and at least one of the following laboratory findings: positive growth in blood culture not related to another source of infection, positive growth in culture of pleural fluid, positive quantitative culture from minimally contaminated lower respiratory tract specimen (e.g.: broncho-alveolar lavage or protected specimen brushing) or >5% broncho-alveolar lavage obtained cells contain intracellular bacteria on direct microscopic examination (e.g., Gram-negative stain). Other nosocomial infections were defined according to the Centers for Disease Control and Prevention guidelines [14]. Two investigators blinded to the treatment allocation validated the diagnosis of infection, and each infection at each site was considered as a separate infectious complication. Other secondary outcomes are length of ICU, hospital stay and 6 month mortality rate.

Table 1 Proposed insulin infusion method based on hourly measurement of capillary blood glucose level [13].

Glucose level (mg/dl)	Insulin infusion (IU/h)
151–200	1.5–2.0
201–250	2.5–3.0
251–300	3.5–4.0
>300	5.0–6.0

2.2. Sample size calculation

Sample size calculation was based on a power of 80% in detecting a 25% reduction in the occurrence of hyperglycemic episodes when the significance level is $\alpha = 0.05$ with two sided testing and previous experience showing normally distributed data. With equal allocation ratio, it was estimated that each group would include 35 patients. We included 40 patients in each group for possible dropouts.

2.3. Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 18.0. Data were tested for normality using Kolmogorov–Smirnov test. Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. The following tests were done: Independent-samples *t*-test was used when comparing between two means and Chi-square (X^2) test or Fisher exact test was used as appropriate in order to compare proportions between two qualitative parameters. *P*-value < 0.05 was considered significant.

3. Results

Between February 2012 and August 2015, 80 patients who underwent LDLT were enrolled in this study after admission to the ICU. They were randomized into AG group ($n = 40$) and control group C ($n = 40$). These patients either have a previous history of diabetes (21 patients in control group vs 23 in AG group) with no significant difference between the two groups or suffered from NODM (19 patients in control group vs 17 in AG group) with no significant history between the two groups. On admission, there were no significant differences between the two groups regarding patients' characteristics and severity of illness score (APACHE II) (Table 2).

Table 2 Patients characteristics and APACHE II at study admission.

	Group (C) ($n = 40$)	Group (AG) ($n = 40$)	*P*-value
Sex [M/F]	22/18	24/16	0.821
Age (years)	53 ± 6	55 ± 7	0.124
BMI (kg/m_2)	26.0 ± 19	24.9 ± 2.6	0.061
History of DM	21 (52.5%)	23 (57.5%)	0.880
NODM	19 (47.5%)	17 (42.5%)	0.822
APACHE II	16 ± 4	15 ± 3	0.421

Data are presented as number, percent and mean ± SD.

Table 3 Incidence of hyperglycemia and total insulin requirements per day.

	Group (C) (n = 40)	Group (AG) (n = 40)	P-value
Hyperglycemia episodes	38 (95%)	29 (72.5%)	**0.013***
Requiring insulin	28 (73.68%)	22 (75.86%)	**0.023***
Requiring insulin + TPN volume reduction	11 (28.95%)	7 (24.14%)	**0.039***
Total insulin req. IU/day	78 ± 9	53 ± 11	**<0.001***

Data are presented as number, percent and mean ± SD.
* p-Value < 0.05 significant difference.

Table 4 Adverse events.

	Group (C) (n = 40)	Group (AG) (n = 40)	P-value
Infectious episodes	28 (70%)	20 (50%)	**0.016***
Pneumonia	11 (39.3%)	7 (35%)	**0.039***
Surgical wound infection	3 (10.7%)	2 (10%)	0.876
Septic shock and sepsis	4 (14.3%)	3 (15%)	0.778
Urinary infection	5 (17.9%)	5 (25%)	1.000
Intravenous catheter infection	5 (17.9%)	3 (15%)	0.543

* p-Value < 0.05 significant difference.

Table 5 Secondary outcomes.

	Group (C) (n = 40)	Group (AG) (n = 40)	P-value
ICU LOS (days)	10.43 ± 4.67	7.81 ± 2.98	**0.033***
Hospital LOS (days)	35.11 ± 1444	31.62 ± 11.47	0.235
Mortality	5 (12.5%)	4 (10%)	0.855

LOS: length of stay.
* P value < 0.05 significant difference.

Both groups had similar caloric requirements which they received equally across the study period.

3.1. Primary outcome

The hyperglycemic episodes were significantly less in AG group compared to C group. They were reported to occur in 29 AG group patients and in 38 in control group patients (P value < 0.05). Hyperglycemia requiring insulin therapy in AG group was significantly less (22 vs 28 patients) (P < 0.05). Also those who required decreasing TPN requirements were significantly less in the AG group (7 vs 11 patients). Insulin requirements per day in the AG group were significantly lower (53 ± 11 vs 78 ± 9 IU) (Table 3). No withdrawals were reported throughout the study period of 9 days.

Regarding secondary outcomes, each nosocomial episode corresponds to a single patient. Patient can have more than one episode of infection. The number of episodes of nosocomial infection was lower in the AG group than in the control group (P value < 0.05). The decrease in nosocomial infections in patients receiving AG was related mainly to a decrease in the incidence of pneumonia (Table 4; P < 0.05), whereas no significant differences were found among the two groups regarding the other types of nosocomial infections (surgical wound infection, septic shock and sepsis, urinary tract infection, intravenous catheter infection). Three patients in the AG group and seven patients in the control group had two different types of infectious episodes, such as pneumonia and wound infection or pneumonia and septic shock.

There was significant difference between the two groups in ICU length of stay (LOS), as it was significantly lower in the AG group than the in control group (7.81 ± 2.98 vs 10.43 ± 4.67 days), but the hospital LOS and 6 month mortality rates showed no significant difference between the two groups (Table 5). All patients completed the study period and mortalities occurred after 9 days in both groups. Although there was no significant difference between the two groups in mortality rates, deaths due to infection were more in control group (four patients) compared to the AG group (one patient).

4. Discussion

In this prospective controlled randomized study, AG dipeptide supplemented TPN decreased incidence of hyperglycemia, hyperglycemic episodes, insulin requirements, infectious episodes and ICU stay in diabetic patients who had LD liver transplantation.

AG is a non-essential or conditionally essential amino acid that plays an important role in maintaining and promoting the function of many cells and tissues. AG enhances glucose-stimulated insulin secretion via the metabolism of the gamma-glutamyl cycle, glutathione synthesis and mitochondrial function [5]. It is known that AG modulates the glucose induced loss of maximal insulin responsiveness [15]. AG, together with insulin and glucose, increases the activity and mRNA levels of pyruvate kinase involved in glucose metabolism [16]. Experimental data on overweight hyperglycemic mice showed that AG supplementation decreased weight gain, hyperglycemia, and hyperinsulinemia but the actual mechanism is still unknown [17]. Another animal study hypothesized that AG needed ß cell depolarization and intracellular calcium to act as a signaling molecule in amino acid and glucose stimulated insulin secretion [18].

In a clinical study on type 2 diabetes patients who were given oral AG supplementation, AG increased circulating glucagon-like peptide 1 (GLP-1), glucose dependent insulinotropic polypeptide, and insulin concentration [19]. An experimental study showed that insulin and AG attenuate the expression of inflammatory cytokines such as tumor necrosis factor-α and interleukin-8, and reduce the oxidative stress of hyperglycemia concentration [20]. Our study showed that AG supplementation decreased total insulin requirements per day with a decrease in hyperglycemic episodes indicating a better control of diabetes and thus decreasing insulin resistance commonly seen in stressful conditions as in postoperative periods. This is consistent with a study done by Déchelotte et al. on critically ill patients stating that AG by decreasing

hyperglycemic episodes has a specific effect on insulin sensitivity [21]. Also it was found that administration of AG attenuates insulin resistance in trauma patients [22].

In the present study, administration of AG was associated with less infectious episodes. This reduction is mainly due to a decrease in incidence of pneumonia only and without any significant reduction in other types of infectious episodes between the two groups. These results are in accordance with the decrease in infectious events when AG-enriched enteral nutrition was supplemented to trauma patients [23] and parenterally supplemented to enterally feed severely burned patients [24] and critically ill patients [21] and in patients with peritonitis [25]. Also in another meta-analysis [26], AG decreased risk of infection episodes. In contrast, Griffiths et al. [27] observed no significant reduction in infectious episodes in critically ill patients receiving AG supplementation but reported that there were reduced severity scores and ICU death rates among the AG supplemented group stating that parenteral nutrition containing glutamine may not reduce the overall incidence of ICU acquired infection, but it may reduce the risk of dying from acquired infections. The improved survival seen at 6 month appeared related mostly to reduced mortality in the intensive care unit from multiple organ failure in those patients in whom acquired infections are common.

In the current study, there was no significant difference between the two groups in mortality rates but deaths were caused by infectious vs non-infectious complications in (four vs one respectively) patients in the control group, whereas an opposite pattern (one vs three) was observed in the AG-treated group suggesting that AG supplementation may reduce the severity of infectious episodes which is in accordance with other studies [21,27]. Other studies revealed a decrease in mortality rates among AG supplemented groups [24,28,29] or a trend toward reduction [30]. As infection is one of the leading causes of morbidity and mortality in liver transplant recipients and the release of cytokines during the infection can have other indirect and negative effects, including allograft injury, opportunistic super-infection, and malignancy especially during the first month immediately after transplantation [31], this may be attributed to the recipients' general poor preoperative clinical condition, immunosuppressive therapy, the extensive surgical field, and lengthy operating times, so that postoperative respiratory disorders are very common after liver transplantation and significantly contribute to the related morbidity and mortality, both in the acute postoperative stage and in the long term course. AG supplementations seem beneficial to be used in liver transplanted patients to decrease the rate of infection especially pneumonia which was common in liver transplanted patients as Pirat et al. [31] reported an incidence of 22.7% and a mortality rate of 40% and Xia et al. [32] showed that the overall incidence of severe pneumonia was 18.2%, with an associated mortality rate of 37.5%. These authors found that individuals who developed pneumonia had longer times to extubation and higher mortality.

In the present study, AG enriched TPN had a significant effect on the ICU LOS but not on hospital LOS which is mainly attributed to the decreased incidence of infectious episodes and better control of diabetes in liver transplanted patients. The difference in the hospital LOS among the two groups in our study reflects the multi-factorial determinants of LOS in hospitals among which infection is only one aspect. This was not in accordance with other studies done on critically ill patients which showed no significant effect on both the ICU and the hospital LOS [21,28].

Other explanation for improved clinical outcome may be due to other mechanisms that explain the effects of AG by its influence on intestinal and immune function as it decreases intestinal permeability in stressed patients [33–35]. Experimental studies reported that AG modulates inflammatory cytokine production by gut mucosa, decreases pro-inflammatory cytokines such as interleukin 8 [36,37] or increases anti-inflammatory cytokines such as interleukin 10 [38,39]. In addition, AG maintained intestinal and pulmonary IgA levels in rats [37,38]. AG also modulates heat-shock protein expression [39,40] and improves intestinal protein metabolism [41,42]. In addition, AG maintains or restores immune defenses [43–45]. As this study was designed to show the effect of using AG supplementation for 9 days on control of diabetes in liver transplanted patients, Hb A_1C was not assessed.

5. Conclusion

Our study showed that using AG supplementation in liver transplanted patients who either have a history of diabetes or NODM, reduces the insulin requirements, hyperglycemic episodes, infectious events and ICU stay.

Conflict of interest

There is no conflict of interest.

References

[1] Heisel O, Heisel R, Balshaw R. New onset diabetes mellitus in patients receiving calcineurin inhibitors: a systematic review and meta-analysis. Am J Transplant 2004;4:583–95.
[2] Yoo HY, Thuluvath PJ. The effect of insulin – dependent diabetes mellitus on outcome of liver transplantation. Transplantation 2002;74:1007–12.
[3] Newsholme P, Procopio J, Lima MM, et al. Glutamine and glutamate: their central role in cell metabolism and function. Cell Biochem Funct 2003;21:1–9.
[4] Molfino A, Logorelli F, Muscaritoli M, et al. Metabolic effects of glutamine on insulin sensitivity. Nutritional Ther Metab 2010;28(1):7–11.
[5] Brennan L, Corless M, Hewage C, et al. ^{13}C NMR analysis reveals a link between L-glutamine metabolism, D-glucose metabolism and gamma-glutamyl cycle activity in a clonal pancreatic ß cell line. Diabetologia 2003;46:1512–21.
[6] Cynober L. Glutamine as an activator of immune cells: how does it work? Nutrition 1997;13:688–9.
[7] Morlion BJ, Stehle P, Wachtler 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.
[8] Mertes N, Schulzki C, Goeters C, et al. Cost containment through L-alanyl-L-glutamine supplemented total parenteral nutrition after major abdominal surgery: a prospective randomized double-blind controlled study. Clin Nutr 2000;19:395–401.
[9] Opara EC, Petro A, Tevrizian A, et al. L-glutamine supplementation of high fat diet reduces body weight and attenuates hyperglycemia and hyperinsulinemia in C57BL/6J mice. J Nutr 1996;126:273–9.

[10] Tueche SG. Diabetes mellitus after liver transplant new etiologic clues and cornerstones for understanding. Transplant Proc 2003;35:1466–8.
[11] Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818–29.
[12] Grau T, Bonet A, Minambres E, Pineiro L, 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(6):1263–8.
[13] American Diabetes Association. Hyperglycemic crises in patients with diabetes mellitus. Diabetes Care 2001;24:154–61.
[14] Horan TC, Gaynes RP. Surveillance of nosocomial infections. In: Mayhall CG, editor. Hospital epidemiology and infection control. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 1659–702.
[15] Marshall S, Bacote V, Traxinger RR. Discovery of a metabolic pathways mediating glucose-induced desensitization of the glucose transport system: role of hexosamine biosynthesis in the induction of insulin resistance. J Biol Chem 1991;266:4706–12.
[16] Traxinger RR, Marshall S. Insulin regulation of pyruvate kinase activity in isolated adipocytes: crucial role of glucose and the hexosamine biosynthesis pathway in the expression of insulin action. J Biol Chem 1992;267:9718–23.
[17] Opara EC, Petro A, Tevrizian A. L-glutamine supplementation of a high fat diet reduces body weight and attenuates hyperglycemia and hyperinsulinemia in C57BL/6J mice. J Nutr 1996;126:273–9.
[18] Li C, Buettger C, Kwagh J, et al. A signaling role of glutamine in insulin secretion. J Biol Chem 2004;279:13393–401.
[19] Greenfild JR, Farooqi IS, Keogh JM, et al. Oral glutamine increases circulating glucagon-like peptide 1, glucagon, and insulin concentrations in lean, obese, and type 2 diabetic subjects. Am J Clin Nutr 2009;89:106–13.
[20] Muniandy S, Qvist R, Yan GO, Bee CJ, Chu YK, Rayappan AV. The oxidative stress of hyperglycemia and the inflammatory process in endothelial cells. J Med Invest 2009;56:6–10.
[21] Déchelotte P, Hasselmann M, Cynober L, et al. L-alanyl-L-glutamine dipeptide-supplemented total parenteral nutrition reduces infectious complications and glucose intolerance in critically ill patients: the French controlled, randomized, double blind, multicenter study. Crit Care Med 2006;34:589–604.
[22] Bakalar B, Duska F, Pachl J, et al. Parenterally administered dipeptide alanyl-glutamine prevents worsening of insulin sensitivity in multiple-trauma patients. Crit Care Med 2006;34:381–6.
[23] Houdijk AP, Rijnsburger ER, Jansen J, et al. Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. Lancet 1998;352(9130):772–6.
[24] Wischmeyer PE, Lynch J, Liedel J, et al. Glutamine administration reduces gram negative bacteremia in severely burned patients: a prospective, randomized, double blind trial versus isonitrogenous control. Crit Care Med 2001;29:2075–80.
[25] Fuentes-Orozcoa C, Anaya-Pradoa R, González-Ojedaa A, et al. L-alanyl-glutamine-supplemented parenteral nutrition improves infectious morbidity in secondary peritonitis. Clin Nutr 2004;23:13–21.
[26] Griffiths RD, Jones C, Palmer TE. Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. Nutrition 1997;13(4):295–302.
[27] Griffiths RD, Allen KD, Andrews FJ, et al. Infection, multiple organ failure, and survival in the intensive care unit: influence of glutamine-supplemented parenteral nutrition on acquired infection. Nutrition 2002;18:546–52.
[28] Novak F, Heyland DK, Avenell A, et al. Glutamine supplementation in serious illness: a systematic review of the evidence. Crit Car Med 2002;30:2022–9.
[29] Goeters C, Wenn A, Mertes N, et al. Parenteral L-alanyl-L-glutamine improves 6-month outcome in critically ill patients. Crit Care Med 2002;30:2032–7.
[30] Powell-Tuck J, Jamieson CP, Bettany GE, et al. A double blind, randomised, controlled trial of glutamine supplementation in parenteral nutrition. Gut 1999;45:82–8.
[31] Pirat A, Ozgur S, Torgay A, et al. Risk factors for postoperative respiratory complications in adult liver transplant recipients. Transplant Proc 2004;36:218–20.
[32] Xia D, Yan LN, Xu L, et al. Postoperative severe pneumonia in adult liver transplant recipients. Transplant Proc 2006;38:2974–8.
[33] Van der Hulst RR, van Kreel BK, von Meyenfeldt MF, et al. Glutamine and the preservation of gut integrity. Lancet 1993;341:1363–5.
[34] Zhou YP, Jiang ZM, Sun YH, et al. The effect of supplemental enteral glutamine on plasma levels, gut function, and outcome in severe burns: a randomized, double-blind, controlled clinical trial. JPEN J Parenter Enteral Nutr 2003;27:241–5.
[35] De Sousa DA, Greene LJ. Intestinal permeability and systemic infections in critically ill patients: effect of glutamine. Crit Care Med 2005;33:1125–35.
[36] Ameho CK, Adjei AA, Harrison EK, et al. Prophylactic effect of dietary glutamine supplementation on interleukin 8 and tumour necrosis factor alpha production in trinitrobenzene sulphonic acid induced colitis. Gut 1997;41:487–93.
[37] Fukatsu K, Kudsk KA, Zarzaur BL, et al. TPN decreases IL-4 and IL-10 mRNA expression in lipopolysaccharide stimulated intestinal lamina propria cells but glutamine supplementation preserves the expression. Shock 2001;15:318–22.
[38] Lai YN, Yeh SL, Lin MT, et al. Glutamine supplementation enhances mucosal immunity in rats with gut-derived sepsis. Nutrition 2004;20:286–91.
[39] Wischmeyer PE, Riehm J, Singleton KD, et al. Glutamine attenuates tumor necrosis factor-alpha release and enhances heat shock protein 72 in human peripheral blood mononuclear cells. Nutrition 2003;19:1–6.
[40] Coëffier M, Le Pessot F, Leplingard A, et al. Acute enteral glutamine infusion enhances heme oxygenase-1 expression in human duodenal mucosa. J Nutr 2002;132:2570–3.
[41] Coëffier M, Claeyssens S, Hecketsweiler B, et al. Enteral glutamine stimulates protein synthesis and decreases ubiquitin mRNA level in human gut mucosa. Am J Physiol Gastrointest Liver Physiol 2003;285:G266–73.
[42] Le Bacquer O, Nazih H, Blottiere H, et al. Effects of glutamine deprivation on protein synthesis in a model of human enterocytes in culture. Am J Physiol Gastrointest Liver Physiol 2001;281:G1340–7.
[43] Ockenga J, Borchert K, Rifai K, et al. Effect of glutamine-enriched total parenteral nutrition in patients with acute pancreatitis. Clin Nutr 2002;21:409–16.
[44] Melis GC, Wengel N, Boelens P, et al. Glutamine: recent developments in research on the clinical significance of glutamine. Curr Opin Clin Nutr Metab Care 2004;7:59–70.
[45] Boelens PG, Houdijk AP, Fonk JC, et al. Glutamine-enriched enteral nutrition increases HLA-DR expression on monocytes of trauma patients. J Nutr 2002;132:2580–6.