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Chien-Wei Hsu (cwhsu2003@yahoo.com)
Shu-Fen Sun (sfsun.tw@yahoo.com.tw)
Shoa-Lin Lin (sllin@vghks.gov.tw)
Hsiu-Hua Huang (hhhuang888@gmail.com)
Kam-Fai Wong (wongkf@nuk.edu.tw)

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Moderate Glucose Control Results in Less Negative Nitrogen Balances in Medical Intensive Care Unit Patients – A Randomized, Controlled Study

Chien-Wei Hsu[1,2], Shu-Fen Sun[2,3], Shoa-Lin Lin[1,2], Hsiu-Hua Huang[4], Kam-Fai Wong[5]

[1] Intensive Care Unit, Department of Medicine, Kaohsiung Veterans General Hospital, 386 Ta-Chung 1st Road, Kaohsiung City, 813, Taiwan

[2] Medicine Department, School of Medicine, National Yang-Ming University, 155 Sec. 2 Linong street, Taipei City, 112, Taiwan

[3] Department of Physical Medicine and Rehabilitation, Kaohsiung Veterans General Hospital, 386 Ta-Chung 1st Road, Kaohsiung City, 813, Taiwan

[4]Department of Food and Nutrition, Taipei Veterans General Hospital, 201 Sec. 2 Shipai Road, Beitou District, Taipei City, 112, Taiwan

[5]Institute of Statistics, National University of Kaohsiung, 700 Kaohsiung University Road, Nanzih District, Kaohsiung City, 811, Taiwan. (WKF)

Correspondence: Chien-Wei Hsu, MD

Kaohsiung Veterans General Hospital, 386 Ta-Chung 1st Road, Kaohsiung City, 813, Taiwan

Telephone: 886-7342121-2081

FAX: 886-73420243

E-mail: cwhsu2003@yahoo.com

Abstract

Introduction: Hyperglycemia and protein loss are common in critically ill patients. Insulin can be used to lower blood glucose and inhibit proteolysis. The impact of moderate insulin therapy on protein metabolism in critically ill patients has not been evaluated. We compared urinary nitrogen excretion, nitrogen balance, serum albumin concentrations, prealbumin concentrations, and clinical outcomes between patients receiving moderate insulin therapy (MIT) and conventional insulin therapy (CIT) in a medical intensive care unit (ICU).

Methods: Patients were randomly divided into groups and treated with MIT (glucose target: 120–140mg/dL) or CIT (glucose target: 180–200 mg/dL). Calories and protein intake were recorded each day. On the third, seventh and fourteenth day, 24-h urinary nitrogen excretion, nitrogen balance, serum albumin and prealbumin concentrations were measured. Clinical outcomes data were collected.

Results: A total of 112 medical ICU patients were included with 55 patients randomized to the moderate insulin therapy group and 57 patients randomized to the conventional insulin therapy group. Patients treated with MIT showed a trend towards increased nitrogen balance (P=0.070), significantly lower urinary nitrogen excretion (P =0.027), and higher serum albumin (P =0.047) and prealbumin (P =0.001) concentrations than patients treated with CIT. The differences between the 2 groups were the most significant on day 3 when all factors showed significant differences (P <0.05).

Conclusions: Moderate glucose control results in less negative nitrogen balances in medical ICU patients. Differences are more significant in the early stages compared with the late stages of critical illness.

Trial registration: ClinicalTrial.Gov NCT 01227148

Introduction

Hyperglycemia, which is common in critically ill patients, occurs even in those patients who have not previously had diabetes [1, 2]. Critical illness is associated with the increased circulating concentrations of proinflammatory cytokines, such as tumor necrosis factor - α, interleukin (IL)-1, and IL-6, which may be important mediators of insulin resistance and hyperglycemia [3]. Altered glucose metabolism results from the release of counter regulatory hormones. Epinephrine and cortisol oppose the normal action of insulin, leading to increased adipose tissue lipolysis and skeletal muscle proteolysis [4]. It has been reported that pronounced hyperglycemia may lead to complications or a poor clinical outcome in such patients [5, 6]. The maintenance of normoglycemia using insulin therapy has been shown to significantly reduce morbidity and mortality in critically ill patients [5, 7, 8]. However, some of the studies failed to demonstrate improved outcome [9- 12], even a higher mortality rate was found [13]. Intensive insulin therapy has been associated with a significantly higher risk of hypoglycemia [5, 7], resulting in concern regarding the safety of intensive insulin therapy. Glycemic control to a moderately tight range is not inferior to euglycemia and clearly safer in critically ill patients [14]. Patients with glucose levels of 130 mg/dL were reported to have a significant lower incidence of infection, sepsis and mortality rate [15].

Protein loss, which is also common in critically ill patients, is thought to arise from both

increased proteolysis [16] and diminished protein synthesis [17]. Protein wasting can negatively affect patient outcome [18]. The use of insulin to promote an anabolic response during critical illness is a promising therapeutic approach. Animal studies have shown that strict insulin therapy normalizes organ nitrogen contents in diabetic rats [19]. Woolfson et al. demonstrated that insulin has important protein-sparing effects in severely ill trauma patients [20]. Shiozaki et al. showed that burn patients who received higher doses of insulin maintained a better nitrogen balance than a lower-dose group [21].

The purpose of this study was to investigate the differences in urinary nitrogen excretion, nitrogen balance, serum albumin and prealbumin concentrations, and clinical outcomes between moderate insulin therapy (MIT) and conventional insulin therapy (CIT) in critically ill patients.

Materials and methods

Study Design

This was a prospective, randomized, and controlled trial that was conducted in an adult medical ICU of a tertiary medical center which has totally 1235 beds with 59 adult ICU beds in them. Trial and consent forms were approved by the Institutional Review Board of Kaohsiung Veterans General Hospital. The study was carried out between January 2006 and December 2006. Procedures were in accordance with the Helsinki Declaration.

Subjects

Patients aged 18 or over who were admitted to the medical ICU with blood glucose concentrations over 180 mg/dL were eligible for inclusion. The criteria for exclusion included prior surgical treatment, pregnancy, participation in another study, patients with chronic renal loss and patients who were expected to require treatment in the ICU for less than 4 days. Chronic renal loss was defined as persistent acute renal failure with the complete loss of kidney function for more than 4 weeks [22]. HCW enrolled participants. A total of 283 patients were evaluated and 171 patients were excluded. The remaining 112 patients were eligible for the study (Figure 1).

Insulin Therapy

After informed consent was obtained from patients or the next of kin, patients were randomly assigned to receive either MIT or CIT using software-generated simple randomization procedures (computerized random number) without blocking. Except for the interventionists (nurses and doctors), patients and other staff members were not informed of the group assignments. In the MIT group, continuous insulin infusion was started when the blood glucose concentrations exceeded 140 mg/dL in order to maintain a blood glucose concentration between 120 and 140 mg/dL. The insulin dose was adjusted using a

neuro-fuzzy method; the insulin protocol is shown in Additional file 1. In the CIT group, continuous insulin infusion was delivered when blood glucose concentrations exceeded 200 mg/dL; the insulin dose was then adjusted to maintain a blood glucose concentration between 180 and 200 mg/dL.

All patients were fed either intravenously (total parenteral nutrition) or enterally starting the day after ICU admission. Enteral feeding was attempted as early as possible at the discretion of the attending physician. Once enteral feeding were started, patient were administered full-strength isotonic commercial formula Jevity (Abbott laboratories, Ontario Canada) commencing at 20 mL/h, and increased by 20 mL/h every 4 hours to satisfy energy and protein requirements recommended by clinical dietitian following the Canadian clinical practice guideline for critically ill patients[23]. All patients did not receive albumin infusion during study period.

Data Collection

At the time of randomization, demographic data and clinical characteristics were obtained. Blood glucose concentrations were measured upon admission and, subsequently, every 1 to 4 h in all patients. Baseline serum albumin concentrations, prealbumin concentrations (Hitachi 7600, Tokyo, Japan), serum creatinine and 24-h urinary urea nitrogen (UUN) levels were collected and evaluated after beginning the study, and these data were collected and

evaluated on the third, seventh, and fourteenth days of the study. Additionally, we used full 24-h urine collection rather than spot urine samples to determine the UUN. Blood cultures were obtained whenever the central body temperature exceeded 38.5°C or other clinical signs of sepsis were present. Blood transfusions were conducted according to the protocol when hemoglobin levels decreased to below 7 g/dL and were continued until target hemoglobin levels of 7–9 g/dL were attained. A higher hemoglobin level was required in patients with special circumstances, e.g. myocardial ischemia, severe hypoxemia, acute hemorrhage, or lactic acidosis [24].

From the time of randomization to the time of discharge from the ICU, daily caloric and protein intake, all blood glucose measurements, doses of insulin, red-blood-cell transfusions, blood cultures that were positive for pathogenic organisms, renal function, gastrointestinal bleeding, moderate hypoglycemia, and severe hypoglycemia were recorded.

Definition

Patients were classified as having diabetes on the basis of their medical history. Previous treatment with corticosteroids was defined as treatment with systemic corticosteroids for 72 h or more immediately before randomization. Sepsis was defined by the presence of both infection and a systemic inflammatory response [25]. Acute renal injury was defined when serum creatinine concentrations increased by 2.0 times or the glomerular filtration rate

decreased by more than 50% [22]. Creatinine clearance was calculated using the Cockcroft-Gault equation: (140-age in years) x body weight in kg x 0.85 (if female)/ 72 x serum creatinine in mg/dL [26]. Bloodstream infection was diagnosed when 1 of the following criteria was met: 1. A recognized pathogen was isolated from a blood culture; or 2. The presence of 1 of the following: fever (>38°C), chills, or hypotension, and any of the following: A. A common skin contaminant was isolated from 2 blood cultures that were drawn on separate occasions. B. A common skin contaminant was isolated from the blood culture of a patient with an intravascular access device, and the physician instituted appropriate antimicrobial therapy; or C. A positive antigen blood test [27]. Gastrointestinal bleeding was defined as the presence of hematemesis, melena, bright red blood per rectum, or a coffee grounds-like substance that was aspirated from the feeding tube. Patients with hypoglycemia were defined as those who developed at least 1 episode of hypoglycemia. A moderate hypoglycemic event was defined as a blood glucose concentrations ≤ 60 and > 40 mg/dL. A severe hypoglycemic event was defined as a blood glucose concentrations ≤ 40 mg/dL.

The 24-h nitrogen balance was calculated using the following formula [28]: Nitrogen balance = (protein intake ÷ 6.25) - (UUN + 4). The difference in daily insulin dose between the 2 groups was the total mean insulin dose of the MIT group – the total mean insulin dose of the CIT group on the same day.

Outcomes

Primary outcomes included 24-h UUN levels, nitrogen balance, serum albumin concentrations, and prealbumin concentrations. Secondary outcomes included ICU days, ventilator days, hospital days, acute renal injury, bloodstream infection, blood transfusions, gastrointestinal bleeding, moderate hypoglycemia, severe hypoglycemia, and hospital mortality rate.

Statistical Analysis

All data were analyzed by SPSS version 12.0 (SPSS, Inc., Chicago, IL). Data are presented as the mean ± SD, medians (with interquartile ranges), or number and percentages. All data were analyzed according to the intention-to-treat principle. To detect differences of nitrogen balance using a two-sided 5% significance level and a power of 85% when the difference and standard deviation were equal to 0.80 and 1.97, a sample size of 55 patients per group was necessary. This was based on previous studies involving nitrogen balance and different doses of insulin treatment in a burn ICU [21]. Primary outcomes, such as 24-h UUN levels, nitrogen balance, serum albumin concentrations, and prealbumin concentrations were analyzed with a generalized linear model for repeated measures using dummy variables. Student's t test was used to compare continuous variables with normally distributed data.

Wilcoxon's Rank-Sum tests were used to compare continuous variables with nonnormally distributed data. Chi-square tests were used to compare dichotomous variables. All *P* values were two-tailed. A *P* value < 0.05 was considered significant.

Results

Patient Characteristics

All participants were recruited from April 2006 to December 2006. This trial ended when it reach the sample size goal. Of the 112 patients randomized to the study, 55 patients received MIT, and 57 patients received CIT. All patients were available for the intention-to-treat analysis (Figure 1). Table 1 shows the patient baseline characteristics of all the patients enrolled in the study. Demographic data at the time of randomization showed no significant differences in any of the parameters. Figure 2 showed serum creatinine, creatinine clearance and urine output during study period between 2 groups, there were no significant differences. The 2 groups shared similar background characteristics.

Nutrition and blood glucose control

Actual daily protein (grams per day and per kilogram of body weight) and caloric (calories per day and per kilogram of body weight) intake, blood glucose concentrations, and insulin dose (per h corrected for caloric intake) are shown in Figure 3. Daily protein and caloric

intake progressively increased until day 5, but then fluctuated after day 5 in both groups. The 2 treatment groups had similar protein and caloric intakes. The mean blood glucose concentration was 125.3 ± 2.4 mg/dL in the patients of the MIT group and 199.9 ± 4.0 mg/dL (P <0.01) in the patients of the CIT group. The median daily insulin dose was 82 (69-111) units/day in the patients of the MIT group and 37 (26-43) units/day (P <0.01) in the patients of the CIT group (Table 2). In order to maintain the low blood glucose concentrations, patients in the MIT group were administered a significantly higher insulin dose than patients in the CIT group. The insulin requirement per calorie decreased each day in both groups (Figure 3). The difference in mean daily insulin doses between the 2 groups ranged from 58 IU/day on day 1 to 43 IU/day on day 14. The difference in insulin requirements per day between the 2 groups decreased each day (Figure 4).

Primary outcomes

Both groups showed a trend of decreasing levels of excreted urinary nitrogen, better nitrogen balance and increasing serum albumin and prealbumin concentrations during their hospital courses. A generalized linear model for repeated measurements using dummy variables revealed that there were significantly lower 24-h urine nitrogen excretion (P = 0.027) (Figure 5), and higher serum albumin (P = 0.047) and prealbumin (P = 0.001) (Figure 6) concentrations during the study period in the MIT group. The MIT group

exhibited a higher nitrogen balance than the CIT group; however, this difference was not statistically significant ($P = 0.070$). Differences in 24-h urine nitrogen excretion, nitrogen balance, serum albumin concentrations, and prealbumin concentrations between the 2 groups were most significant on day 3 when all factors showed significant differences ($P < 0.05$). These differences decreased after day 3.

Secondary outcomes

There were no statistically significant differences in ICU, ventilator and hospital day, and rate of acute renal injury, bloodstream infection, red-blood-cell transfusion and gastrointestinal bleeding in two groups (Table 2).

Moderate hypoglycemia (blood glucose levels ≤ 60 mg/dL and > 40 mg/dL) occurred more often in the MIT group than in the CIT group, but this difference was not statistically significant (18.2 % vs. 10.5 %, $P = 0.10$; 2.4 episodes vs. 1.5 episodes per 100 treatment days, $P = 0.18$) (Table 2). The CIT group also exhibited a lower rate of severe hypoglycemia (blood glucose levels ≤ 40mg/dL), but the difference was not significantly (3.6 % vs. 1.8 %, $P = 0.53$; 0.3 episodes vs. 0.2 episodes per 100 treatment days, $P = 0.44$). No hemodynamic deterioration, convulsions, or neurological sequelae were noted in association with any hypoglycemic event in either group.

Patients with MIT had a trend of lower hospital mortality rate than that of patients with

CIT, but they did not reach statistically significant difference.

Discussion

The results of this study showed that MIT could significantly improve nitrogen balance in the early stages of critical illness. Patients treated with MIT had significantly lower urinary nitrogen excretion and higher serum albumin and prealbumin concentrations than patients treated with CIT.

In this study, both groups showed a negative nitrogen balance during the study period. Although the nitrogen balance was negative, both groups showed improvement during the study period. Protein is rapidly broken down in critically ill patients who are subjected to high stress [18]. Hypermetabolism in patients under stress is associated with an increased negative nitrogen balance, and a positive nitrogen balance is difficult to attain in hypermetabolic patients [29]. Equilibrium between energy intake and energy expenditure, early feeding, and a high-protein diet may improve nitrogen balance [30-32]. In this study, nitrogen balance was improved using moderate glucose control. This improvement may have arisen from higher dose insulin administered to the MIT group during the hospital course. Higher infused doses of insulin can result in a marked reduction in UUN excretion and a better nitrogen balance [21].

Differences in nitrogen balance between the 2 treatment groups were significant in the

early stages of critical illness, but decreased over time. This observation may be related to insulin dose. Differences in insulin dose between the 2 groups were more significant in early stages than in late stages.

The effect of insulin on protein metabolism appears primarily to be due to inhibition of proteolysis [33-35], although increased protein synthesis has been reported [36]. In healthy subjects, insulin inhibits proteolysis in a dose-dependent manner [37]. Insulin binding to its receptors activates the insulin receptor substrate pathway, leading to activation of protein kinase; protein kinase B modulates enzyme activities that affect nitric oxide generation and control protein metabolism [38].

Insulin also has an anabolic effect that is beneficial to critically ill patients; it may increase levels of insulin-like growth factor (IGF)-1, a mediator of anabolic growth hormone action, and decrease hepatic synthesis of IGF-1 binding protein, leading to the increased bioavailability of IGF-1 [39]. In a study involving rats, IGF-1 administration significantly improved nitrogen balance [40].

Critical illness is characterized by hypermetabolism and catabolism, leading to peripheral protein waste [41, 42]. Pro-inflammatory mediators enhance catabolism and hypermetabolism by the inhibition of the growth hormone-IGF-I-insulin axis [43- 45]. Insulin improves hypermetabolism by affecting pro-inflammatory cytokine production and hepatic signal transcription factor expression [46]; it attenuates the inflammatory response

by decreasing the pro-inflammatory and increasing the anti-inflammatory cascade. By decreasing pro-inflammatory mediators, liver constitutive proteins such as albumin and pre-albumin are increased [47]. Inflammation reduces albumin concentration by decreasing its rate of synthesis and increased transfer of albumin out of the vascular compartment [48].

Although our data and previous studies showed that insulin benefits protein metabolism, the extent to which the benefit is derived from the correction of hyperglycemia as opposed to the direct effects of insulin remains unclear [49]. Van den Berghe et al. revealed that the lowering of blood glucose levels rather than the amount of infused insulin is related to the effects of insulin therapy on morbidity [7]. Acute hyperglycemia enhances proteolysis in the entire body during hyperinsulinemia in normal men [50]. Additionally, Whyte et al. demonstrated that the administration of insulin that resulted in supraphysiological concentrations did not attenuate protein breakdown and had no effect on net protein balance in critically ill patients [51].

For patients receiving total parenteral nutrition, glucose and lipid ratios influence nitrogen balance. A previous study showed that total parenteral nutrition at a glucose/lipid ratio of 50/50 induced a significantly higher nitrogen balance than an 80/20 ratio with an isocaloric isonitrogenous parenteral nutrition formula [52]. In this study, few patients received total parenteral nutrition, and it was found that they had a similar glucose/lipid ratio; thus, the glucose/lipid ratio is not a confounding factor for maintaining nitrogen

balance.

A meta-analysis study showed that intensive insulin therapy has no advantage in reducing the mortality rate, but significantly increases the risk of hypoglycemia [53]. Our study demonstrated that most patients with hypoglycemia have moderate hypoglycemia; severe hypoglycemia was rarely observed. Target glucose levels in our study were 120–140 mg/dL, which was higher than those in intensive insulin therapy studies that had a target below 110 mg/dL [5, 8]. The rate of severe hypoglycemia in the intensive insulin therapy was ranged from 5.1% to 28.6 % [5, 9-13]. The rate of severe hypoglycemia was lower in our study (3.6 %) compared with previous studies that adopted intensive glucose control. Moderate glucose control was safer than intensive glucose control regarding severe hypoglycemia.

There are some limitations to our study. First, this was a single-center study that was limited to medical ICU patients without chronic renal loss. These results do not represent all critically ill patients. Second, our study was not double-blinded because safe insulin titration required the monitoring of blood glucose levels. Doctors and nurses should be aware of target glucose control levels. However, all patients followed the same protocol except for those following the glucose control protocol. Third, the study group was only moderately sized. Some parameters, such as clinical outcomes, did not show a significant difference due to the small sample size. Further studies are needed to examine larger sample sizes.

Conclusions

Patients treated with MIT had significant lower urinary nitrogen excretion and higher serum albumin and prealbumin concentrations compared with patients treated with CIT. Moderate glucose control can result in a less negative nitrogen balance in medical ICU patients. This difference was more significant in the early stages compared with the late stages of critical illness.

Key messages

- Patients treated with MIT had significantly lower urinary nitrogen excretion and higher serum albumin and prealbumin concentrations than patients treated with CIT.
- Moderate glucose control can result in a less negative nitrogen balance; this may be related to insulin.
- The difference of nitrogen balance between MIT and CIT was more significant in the early stages compared to the late stages of critical illness in medical ICU patients.

Abbreviations

CIT: conventional insulin therapy; ICU: intensive care unit; IL: interleukin; IGF: insulin-like growth factor; MIT: moderate insulin therapy; UUN: urinary urea nitrogen

Competing interests

The authors declare that they have no conflict of interest.

Authors' contributions

CWH was the main contributor to design of the study, interpretation of data and the drafting of the manuscript. SFS contributed to the acquisition and analysis of the data. SLL contributed to design of study and revision of manuscript. KFW contributed to statistical analysis of data. HHH contributed to the execution of the study. All authors read and approved the final manuscript.

Authors' information

CWH : Intensive Care Unit, Department of Medicine, Kaohsiung Veterans General Hospital, 386 Ta-Chung 1st Road, Kaohsiung City, 813, Taiwan, and Medicine Department, School of Medicine, National Yang-Ming University, 155 Sec. 2 Linong street, Taipei City, 112, Taiwan. SFS: Department of Physical Medicine and Rehabilitation, Kaohsiung Veterans General Hospital, 386 Ta-Chung 1st Road, Kaohsiung City, 813, Taiwan, and Medicine Department, School of Medicine, National Yang-Ming University, 155 Sec. 2 Linong street, Taipei City, 112, Taiwan. SLL: Intensive Care Unit, Department of Medicine, Kaohsiung Veterans General Hospital, 386 Ta-Chung 1st Road, Kaohsiung City, 813, Taiwan, and Medicine Department, School of Medicine, National Yang-Ming University, 155 Sec. 2 Linong street, Taipei City, 112, Taiwan. HHH: Department of Food and Nutrition, Taipei Veterans General Hospital, 201 Sec. 2 Shipai Road, Beitou District, Taipei City, 112, Taiwan. KFW: Institute of Statistics, National University of Kaohsiung, 700 Kaohsiung University Road, Nanzih District, Kaohsiung City, 811, Taiwan.

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References

1. Levetan CS, Passaro M, Jablonski K, Kass M, Ratner RE: **Unrecognized diabetes among hospitalized patients.** *Diabetes Care* 1998, **21**:246-249.

2. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE: **Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes.** *J Clin Endocrinol Metab* 2002, **87**:978-982.

3. Mizock BA: **Alterations in fuel metabolism in critical illness: hyperglycaemia.** *Best Pract Res Clin Endocrinol Metab* 2001, **15**:533-551.

4. Robinson LE, van Soeren MH: **Insulin resistance and hyperglycemia in critical illness: role of insulin in glycemic control.** *AACN Clin Issues* 2004, **15**:45-62.

5. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R: **Intensive insulin therapy in the critically ill patients.** *N Engl J Med* 2001, **345**:1359-1367.

6. McCowen KC, Malhotra A, Bistrian BR: **Stress-induced hyperglycemia.** *Crit Care Clin* 2001, **17**:107-124.

7. Van den Berghe G, Wouters PJ, Bouillon R, Weekers F, Verwaest C, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P: **Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose vs. glycemic control.** *Crit Care Med* 2003, **31**:359-366.

8. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R: **Intensive insulin therapy in the medical ICU.** *N Engl J Med* 2006, **354**:449-461.

9. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K;German Competence Network Sepsis (SepNet): **Intensive insulin therapy and pentastarch resuscitation in severe sepsis.** *N Engl J Med* 2008, **358**:125-139.

10. De La Rosa GC, Donado JH, Restrepo AH, Quintero AM, González LG, Saldarriaga NE, Bedoya M, Toro JM, Velásquez JB, Valencia JC, Arango CM, Aleman PH, Vasquez EM, Chavarriaga JC, Yepes A, Pulido W, Cadavid CA, Grupo de Investigacion en Cuidado intensivo: GICI-HPTU: **Strict glycaemic control in patients hospitalised in a mixed medical and surgical intensive care unit: a randomised clinical trial.** *Crit Care* 2008, **12:**R120.

11. Arabi YM, Dabbagh OC, Tamim HM, Al-Shimemeri AA, Memish ZA, Haddad SH,

Syed SJ, Giridhar HR, Rishu AH, Al-Daker MO, Kahoul SH, Britts RJ, Sakkijha MH: **Intensive versus conventional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients.** *Crit Care Med* 2008, **36:**3190-3197.

12. Preiser JC, Devos P, Ruiz-Santana S, Mélot C, Annane D, Groeneveld J, Iapichino G, Leverve X, Nitenberg G, Singer P, Wernerman J, Joannidis M, Stecher A, Chioléro R: **A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study.** *Intensive Care Med* 2009, **35**: 1738-1748.

13. Finfer S, Chittock DR, Su SYS, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ: **Intensive versus conventional glucose control in critically ill patients.** *N Engl J Med* 2009, **360**:1283-1297.

14. Bhamidipati CM, LaPar DJ, Stukenborg GJ, Morrison CC, Kern JA, Kron IL, Ailawadi G: **Superiority of moderate control of hyperglycemia to tight control in patients undergoing coronary artery bypass grafting.** *J Thorac Cardiovasc Surg* 2011, **141**: 543-551.

15. Jeschke MG, Kraft R, Emdad F, Kulp GA, Williams FN, Herndon DN: **Glucose control in severely thermally injured pediatric patients: what glucose range should be the**

target? *Ann Surg* 2010, **252:**521-528.

16. Hasselgren PO, James JH, Benson DW, Hall-Angerås M, Angerås U, Hiyama DT, Li S, Fischer JE: **Total and myofibrillar protein breakdown in different types of rat skeletal muscle: effects of sepsis and regulation by insulin.** *Metabolism* 1989, **38**:634-640.

17. Vary TC, Kimball SR: **Sepsis-induced changes in protein synthesis: Differential effects on fast- and slow-twitch muscles.** *Am J Physiol* 1992, **262**:C1513-1519.

18. Btaiche IF, Chan LN, Pleva M, Kraft MD: **Critical illness, gastrointestinal complications, and medication therapy during enteral feeding in critically ill adult patients.** *Nutr Clin Pract* 2010, **25**:32-49.

19. Almdal TP, Vilstrup H: **Strict insulin therapy normalises organ nitrogen contents and the capacity of urea nitrogen synthesis in experimental diabetes in rats.** *Diabetologia* 1988, **31**:114-118.

20. Woolfson AM, Heatley RV, Allison SP: **Insulin to inhibit protein catabolism after injury.** *N Eng J Med* 1979, **300**:14-17.

21. Shiozaki T, Tasaki O, Ohnishi M, Nishimura T, Hiraide A, Shimazu T, Yoshioka T, Sugimoto H: **Paradoxical positive nitrogen balance in burn patients receiving high-dose administration of insulin for nutritional care.** *Surgery* 1997, **122**:527-533.

22. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality

Initiative workgroup: **Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of Acute Dialysis Quality Initiative (ADQI) group.** *Crit Care* 2004, **8**:R204-212.

23. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P; Canadian Critical Care Clinical Practice Guidelines Committee: **Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adults patients.** *J Parenter Enteral Nutr* 2003, **27:**355-373.

24. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM; Surviving Sepsis Campaign Management Guideline Committee: **Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock.** *Crit Care Med* 2004, **32**:858-873.

25. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G; International Sepsis Definitions Conference: **2001 SCCM/EISCM/ACCP/ATS/SIS International Sepsis Definitions Conference**. *Intensive Care Med* 2003, 29:530-538.

26. Cockcroft DW, Gault MH: **Prediction of creatinine clearance from serum creatinine.** *Nephron* 1976, **16:**31-41.

27. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM: **CDC definitions for nosocomial infections.** *Am J Infect Control* 1988, **16**:128-140.

28. Blackburn GL, Bistrian BR, Maini BS, Schlamm HT, Smith MF: **Nutritional and metabolic assessment of the hospitalized patient.** *JPEN J Parenter Enteral Nutr* 1977, **1**:11-22.

29. Pingleton SK: **Nutrition in chronic critical illness.** *Clin Chest Med* 2001, **22**:149-163.

30. Japur CC, Monteiro JP, Marchini JS, Garcia RW, Basile-Filho A: **Can an adequate energy intake be able to reverse the negative nitrogen balance in mechanically ventilated critically ill patients?** *J Crit Care* 2010, 25:445-450.

31. Jivnani S, Iyer S, Umakumar K, Gore MA: **Impact of enteral nutrition on nitrogen balance in patients of trauma.** *J Emerg Trauma Shock* 2010, **3**:109-114.

32. Bellomo R, Seacombe J, Daskalakis M, Farmer M, Wright C, Parkin G, Boyce N: **A prospective comparative study of moderate versus high protein intake for critically ill patients with acute renal failure.** *Ren Fail* 1997, **19**:111-120.

33. Castellino P, Luzi L, Simonson DC, Haymond M, DeFronzo RA: **Effect of insulin and plasma amino acid concentrations on leucine metabolism in man. Role of substrate availability on estimates of whole body protein synthesis.** *J Clin Invest* 1987, **80**:1784-1793.

34. Fukagawa NK, Minaker KL, Rowe JW, Goodman MN, Matthews DE, Bier DM, Young

VR: **Insulin-mediated reduction of whole body protein breakdown. Dose-dependent effects on leucine metabolism in postabsorptive men.** *J Clin Invest* 1985, **76**:2306-2311.

35. Nair KS, Ford GC, Ekberg K, Fernqvist-Forbes E, Wahren J: **Protein dynamics in whole body and in splanchnic and leg tissues in type I diabetic patients.** *J Clin Invest* 1995, **95**:2926-2937.

36. Biolo G, Declan Fleming RY, Wolfe RR: **Physiologic hyperinsulinemia stimulates protein synthesis and enhances transport of selected amino acids in human skeletal muscle.** *J Clin Invest* 1995, **95**:811-819.

37. Tessari P, Inchiostro S, Biolo G, Trevisan R, Fantin G, Marescotti MC, Iori E, Tiengo A, Crepaldi G: **Differential effects of hyperinsulinemia and hyperaminoacidemia on leucine-carbon metabolism *in vivo*. Evidence for distinct mechanisms in regulation of net amino acid deposition.** *J Clin Invest* 1987, **79**:1062-1069.

38. Van den Berghe G: **How dose blood glucose control with insulin save lives in intensive care?** *J Clin Invest* 2004, **114**:1187-1195.

39. Brismar K, Fernqvist-Forbes E, Wahren J, Hall K: **Effect of insulin on the hepatic production of insulin-like growth factor-binding protein-1 (IGFBP-1), IGFBP-3, and IGF-1 in insulin-dependent diabetes.** *J Clin Endocrinol Metab* 1994, **79**:872-878.

40. Núñez M, Urdaneta E, Santidrián S: **Effect of insulin-like growth factor-I on nitrogen**

balance and intestinal galactose transport in rats with moderate liver cirrhosis. *Br J Nutr* 2003, **90**:929-937.

41. Rennie MJ: **Muscle protein turnover and wasting due to injury and disease**. *Br Med Bull* 1985, **41**:257-264.

42. Wilmore DW: **Catabolic illness. Strategies for enhancing recovery.** *N Eng J Med* 1991, **325**:695-702.

43. Van den Berghe G, de Zegher F, Veldhuis JD: **The somatotropic axis in critical illness: effect of continuous growth hormone (GH)- releasing hormone and GH-relaesing peptide-2 infusion.** *J Clin Endocrin Metab* 1997, **82**:590-599.

44. Frost RA, Lang CH, Gelato MC: **Transient exposure of human myoblasts to tumor necrosis factor-α inhibits serum and insulin-like growth factors-I stimulated protein synthesis.** *Endocrinology* 1997, **138**:4153-4159.

45. Timmins AC, Cotterill AM, Hughes SC: **Critical illness is associated with low circulating concentrations of insulin-like growth factors-I and –II, alterations in insulin like growth hormone factors binding proteins, and induction of an insulin-like growth factor binding protein 3 protease.** *Crit Care Med* 1996, **24**:1460-1466.

46. Jeschke MG, Einspanier R, Klein D, Jauch KW: **Insulin attenuates the systemic inflammatory response to thermal trauma.** *Mol Med* 2002, **8**:443-450.

47. Jeschke MG, Klein Dagmar, Herndon DN: **Insulin treatment improves the systmic inflammatory reaction to severe trauma.** *Ann Surg* 2004, **239**:553-560.

48. Don BR, Kaysen G: **Serum albumin: relationship to inflammation and nutrition.** *Semin Dial* 2004, **17**:432-437.

49. Wolfe RR: **Regulation of skeletal muscle protein metabolism in catabolic states.** *Curr Opin Clin Nutr Metab Care* 2005, **8**:61-65.

50. Flakoll PJ, Hill JO, Abumrad NN: **Acute hyperglycemia enhances proteolysis in normal man.** *Am J Physiol* 1993, **265**:E715-721.

51. Whyte MB, Jackson NC, Shojaee-Moradie F, Treacher DF, Beale RJ, Jones RH, Umpleby AM: **Metabolic effects of intensive insulin therapy in critically ill patients.** *Am J Physiol Endocrinol Metab* 2010, **298**:E697-705.

52. Boulétreau P, Chassard D, Allaouchiche B, Dumont JC, Auboyer C, Bertin-Maghit M, Bricard H, Ecochard R, Rangaraj J, Chambrier C, Schneid C, Cynober L: **Glucose-lipid ratio is a determinant of nitrogen balance during total parenteral nutrition in critically ill patients: a prospective, randomized, multicenter blind trial with an intention-to-treat analysis.** *Intensive Care Med* 2005, **31**:1394-1400.

53. Wiener RS, Wiener DC, Larson RJ: **Benefits and risks of tight glucose control in critically ill adults: a meta-analysis.** JAMA 2008, **300**:933-944.

Figure Legends

Figure 1 Assessment, randomization, and follow-up of the study patients. For detailed characteristics of randomized patients, see Table 1.

Figure 2 Serum creatinine, creatinine clearance and 24-hour urine output on day 0, 3, 7, 14. Serum creatinine is on the top panel, creatinine clearance is on the middle panel and 24-hour urine output is on the bottom panel. Filled bars represent patients receiving moderate insulin therapy (MIT group), and open bars represent patients receiving conventional insulin therapy (CIT group).

Figure 3 Daily protein, calories intake, mean blood glucose levels and insulin dose. Daily protein intake (top panel), daily caloric intake (second panel from top), mean blood glucose levels (second panel from bottom) and insulin dose (bottom panel) during the 2-week study period in the medical intensive care unit. Filled bars represent MIT group, and open bars represent CIT group.

Figure 4 Differences in mean daily insulin doses between the MIT and CIT group.

Figure 5 Course of 24-h UUN and nitrogen balance in patients receiving either MIT or CIT. 24-h UUN is on the top panel and nitrogen balance is on the bottom panel. Data represent mean ± SD. Generalized linear model of repeated measurements showed statistically significant differences (#$P = 0.027$ for entire study period, * $P < 0.05$ for day 3) between the 2 groups.

Figure 6 Course of serum albumin and prealbumin levels in patients receiving either MIT or CIT. Serum albumin is on the top panel and serum prealbumin is on the bottom panel. Data represent mean ± SD. Generalized linear model of repeated measurements showed statistically significant differences (#$P = 0.047$ for entire study period, ## $P = 0.001$ for entire study period, * $P < 0.05$ for day 3).

Table 1.Demographic data of all patients

Characteristic	MIT (N = 55)	CIT (N = 57)	*P* value
Primary ICU admitting diagnosis			
Sepsis	25	26	
Respiratory	11	12	
Neurologic	9	7	
Cardiovascular	3	5	
Gastrointestinal or liver	2	3	
Hematologic or oncologic	3	1	
Renal	1	2	
Metabolic	1	1	
Age	68.1 ± 16.3	70.4 ± 12.1	0.40
Body weight (Kg)	61.4 ± 9.6	62.5 ± 9.8	0.57
Gender (F/M)	16/39 (41)	16/41 (39)	0.90
BMI (kg/m^2)	23.6 ± 3.0	23.9 ± 3.8	0.72
History of diabetes (%)	19/55 (34.5)	22/57 (38.6)	0.67
Previous corticosteroid treatment (%)	14/55 (25.4)	16/57 (28.1)	0.77
Use of inotropes (%)	15/55 (27.3)	12/57 (21.1)	0.44
APACHE II score [median (IQR)]	20 (17–25)	21 (16.5–26.5)	0.94
Patients with TPN (%)	2/55 (3.6)	2/57 (3.5)	0.97
Intake of nutrients			
Carbohydrate (%)	54.3 ± 0.2	54.4 ± 0.2	0.84
Protein (%)	16.4 ± 0.1	16.4 ± 0.2	0.50
Fat (%)	29.3 ± 0.2	29.2 ± 0.8	0.55
At randomization			
Blood glucose (mg/dL)	229.2 ± 39.3	231.1 ± 52.1	0.93
Serum hemoglobin (g/dL)	10.9 ± 2.2	10.8 ± 2.3	0.80
Serum ALT (U/L)	59.1 ± 79.3	63.8 ± 83.0	0.76
Serum total bilirubin (mg/dL)	1.1 ± 0.4	1.2 ± 0.4	0.88
UUN (g/BSA/24 hours)	7.0 ± 3.7	6.7 ± 3.8	0.78
Nitrogen balance (g/BSA/day)	-4.8 ± 5.9	-4.7 ± 4.5	0.93
Serum albumin (mg/dL)	1949.9 ± 376.0	1955.4 ±506.5	0.95
Serum prealbumin (mg/dL)	11.3 ± 5.2	11.2 ± 4.5	0.87

Values in parentheses are percentages; MIT, moderate insulin therapy; CIT, conventional insulin therapy; ICU, intensive care unit; BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; IQR, interquartile range; TPN, total parenteral

nutrition; ALT, alanine aminotransferase; UUN, urinary urea nitrogen; BSA, body surface area

Table 2.Clinical outcomes

Outcome Variable	MIT (N = 55)	CIT (N = 57)	*P* value
Mean blood glucose (mg/dL)	125.3 ± 17.8	199.9 ± 30.2	< 0.01
Daily dose of insulin (unit/day) [median (IQR)]	82 (69–111)	37 (26–44)	< 0.01
ICU days [median (IQR)]	14 (9–19)	15 (11–26)	0.26
Ventilator days [median (IQR)]	20 (11–30)	23 (11–43.5)	0.19
Hospital days [median (IQR)]	27 (15–36)	32 (18.5–51.3)	0.052
Acute renal injury (%)	3/55 (5.5)	7/57 (12.3)	0.10
Bloodstream infection (%)	1/55 (1.8)	3/57 (5.3)	0.33
RBC blood transfusion (%)	12/55 (21.8)	15/57 (26.3)	0.74
GI bleeding (%)	7/55 (12.7)	7/57 (12.3)	0.83
Number of mild hypoglycemia (%)	10/55 (18.2)	6/57 (10.5)	0.37
Rate of moderate hypoglycemia per 100 treatment days	2.4	1.5	0.18
Number of severe hypoglycemia (%)	2/55 (3.6)	1/57 (1.8)	0.53
Rate of severe hypoglycemia per 100 treatment days	0.3	0.2	0.44
Hospital mortality rate (%)	18/55 (32.7)	28/57 (49.1)	0.08

Values in parentheses are percentages; MIT, moderate insulin therapy; CIT, conventional insulin therapy; IQR, interquartile range; ICU, intensive care unit; RBC, red blood cell; GI, gastrointestinal

Additional Files

Additional file 1: Appendix 1

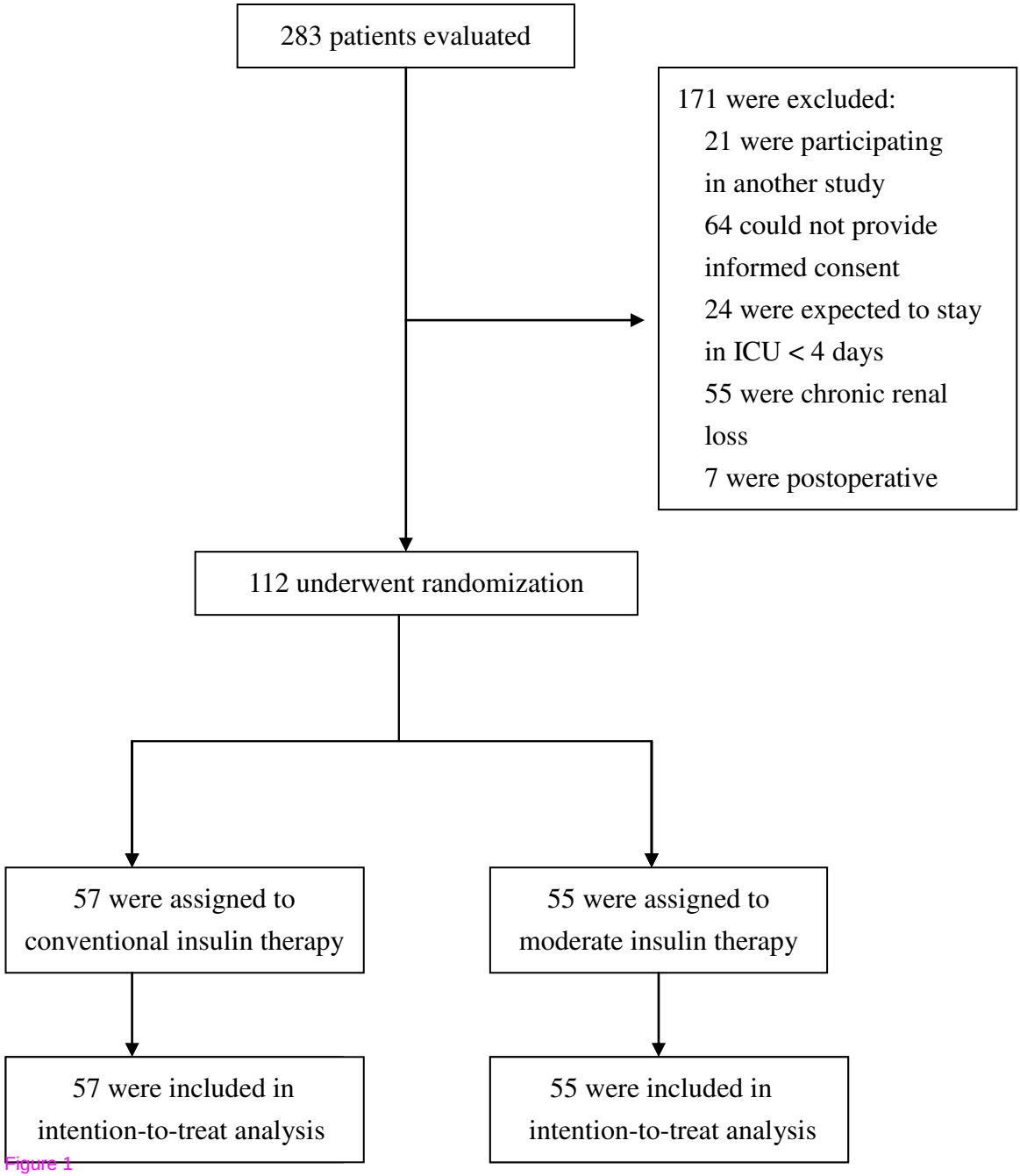

283 patients evaluated
171 were excluded:
21 were participating in another study
64 could not provide informed consent
24 were expected to stay in ICU < 4 days
55 were chronic renal loss
7 were postoperative
112 underwent randomization
57 were assigned to conventional insulin therapy
55 were assigned to moderate insulin therapy
57 were included in intention-to-treat analysis
55 were included in intention-to-treat analysis

Figure 1

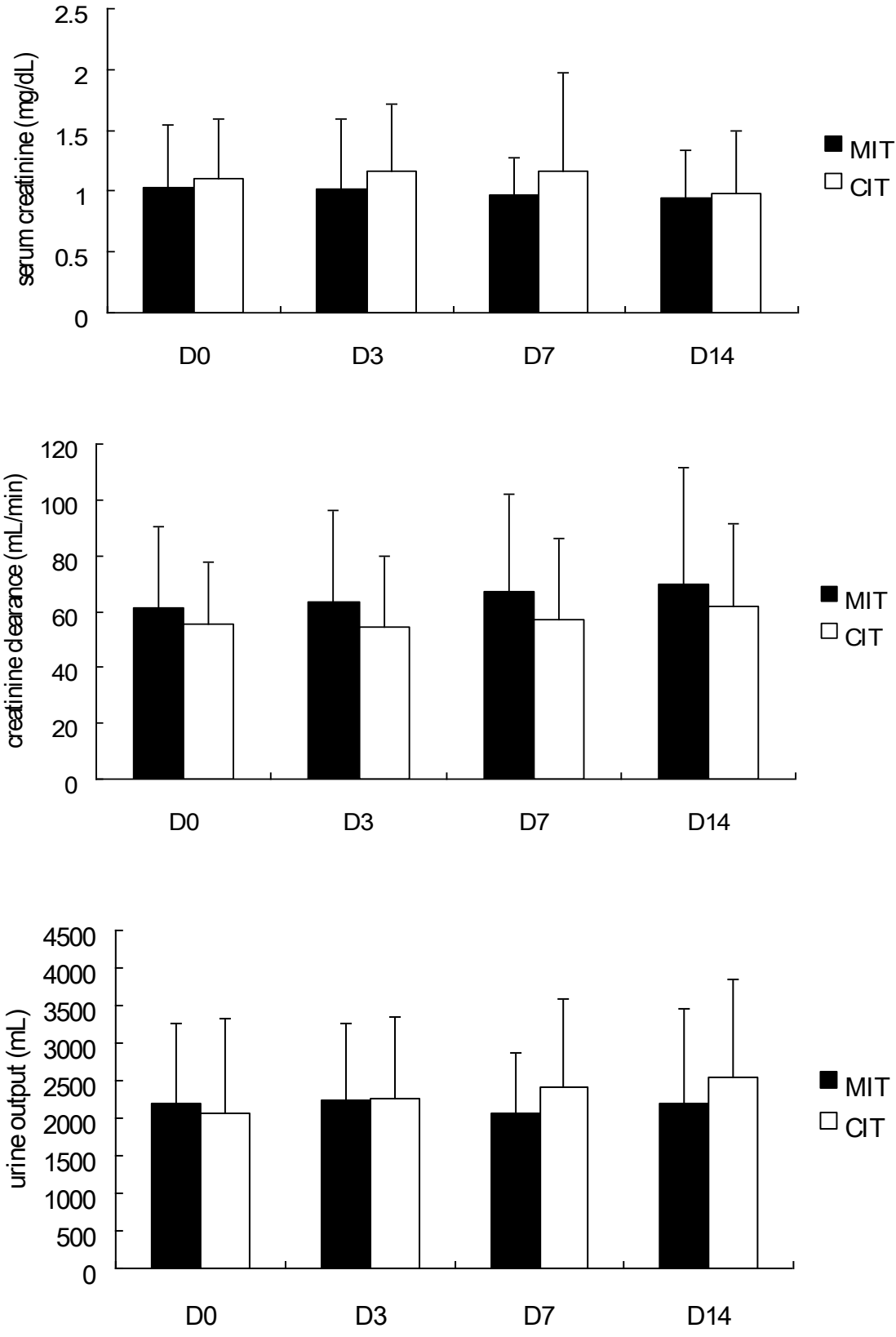
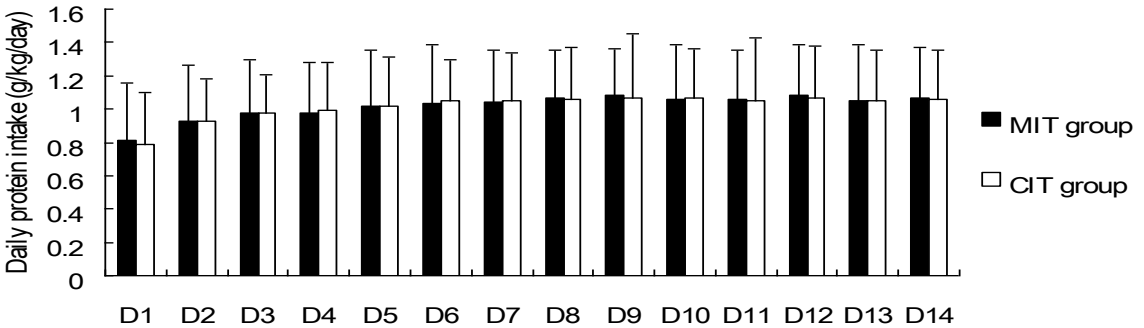
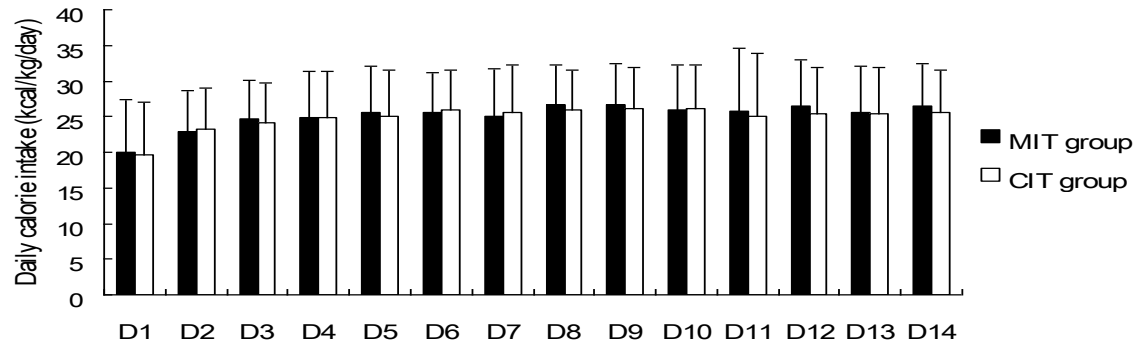
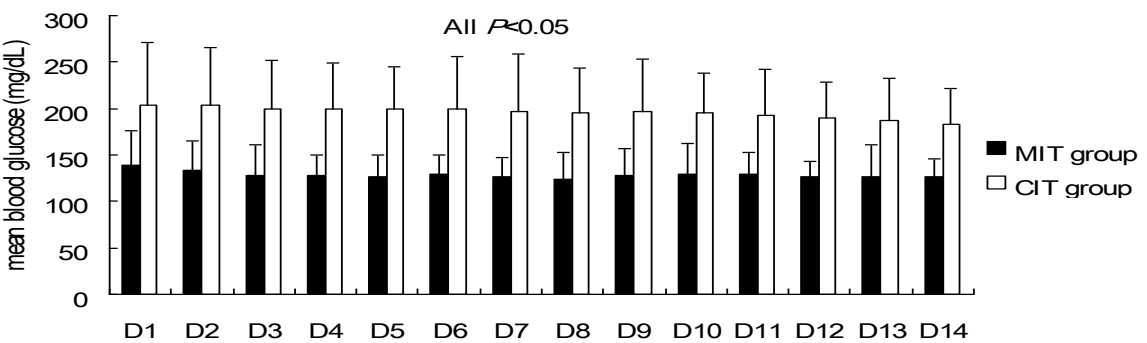

serum creatinine (mg/dL)
2.5
2
1.5
1
0.5
0
D0
D3
D7
D14
MIT
CIT
creatinine clearance (mL/min)
120
100
80
60
40
20
0
D0
D3
D7
D14
MIT
CIT
urine output (mL)
4500
4000
3500
3000
2500
2000
1500
1000
500
0
D0
D3
D7
D14
MIT
CIT

Figure 2


Daily protein intake (g/kg/day)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
D1 D2 D3 D4 D5 D6 D7 D8 D9 D10 D11 D12 D13 D14
MIT group
CIT group


Daily calorie intake (kcal/kg/day)
40
35
30
25
20
15
10
5
0
D1 D2 D3 D4 D5 D6 D7 D8 D9 D10 D11 D12 D13 D14
MIT group
CIT group


All P<0.05
mean blood glucose (mg/dL)
300
250
200
150
100
50
0
D1 D2 D3 D4 D5 D6 D7 D8 D9 D10 D11 D12 D13 D14
MIT group
CIT group

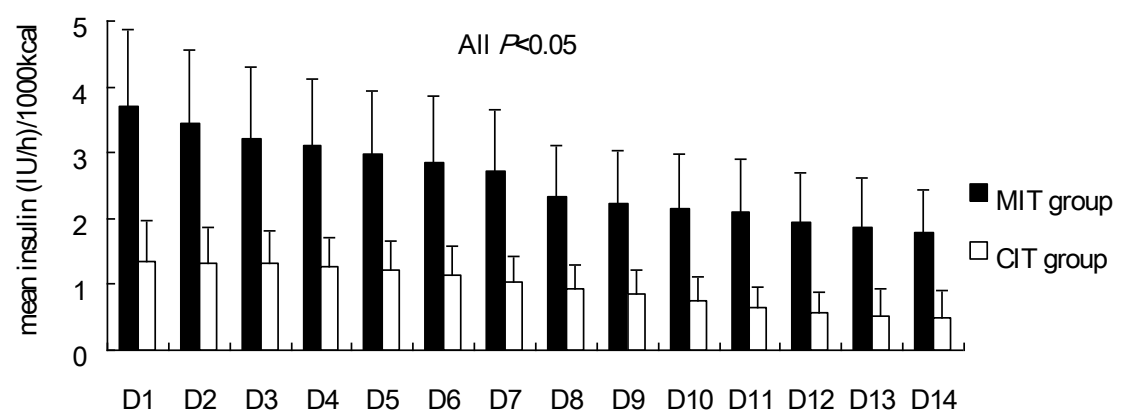

All P<0.05
mean insulin (IU/h)/1000kcal
5
4
3
2
1
0
D1 D2 D3 D4 D5 D6 D7 D8 D9 D10 D11 D12 D13 D14
MIT group
CIT group

Figure 3

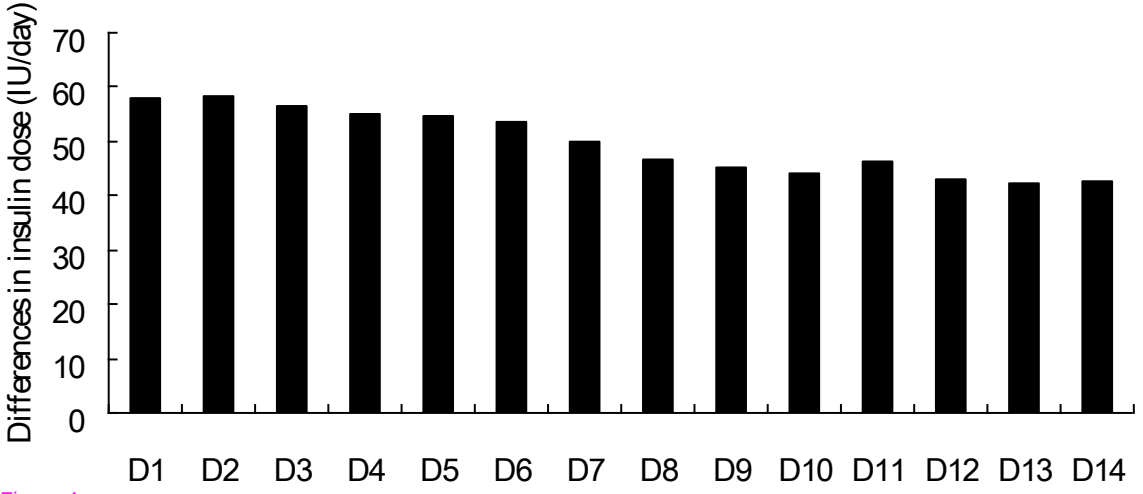
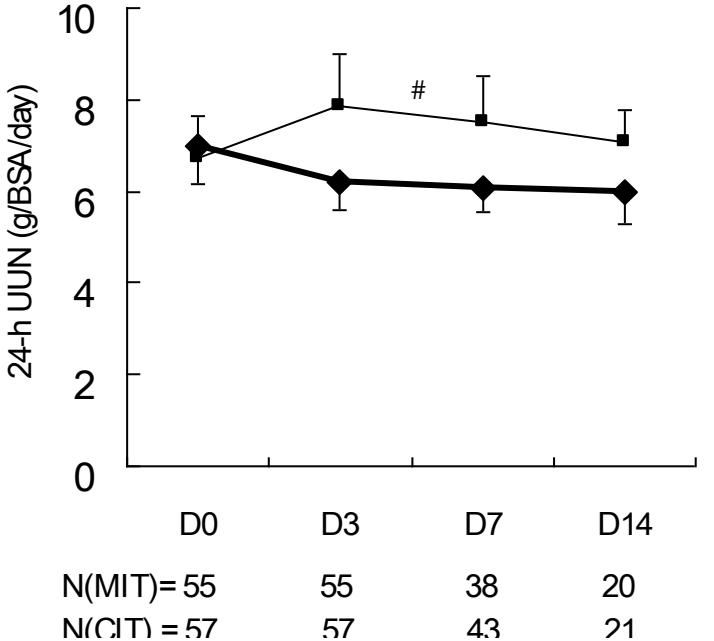

Differences in insulin dose (IU/day)
70
60
50
40
30
20
10
0
D1
D2
D3
D4
D5
D6
D7
D8
D9
D10
D11
D12
D13
D14

Figure 4


10
8
6
4
2
0
24-h UUN (g/BSA/day)
#
D0
D3
D7
D14
N(MIT)= 55
55
38
20
N(CIT) = 57
57
43
21
MIT group
CIT group

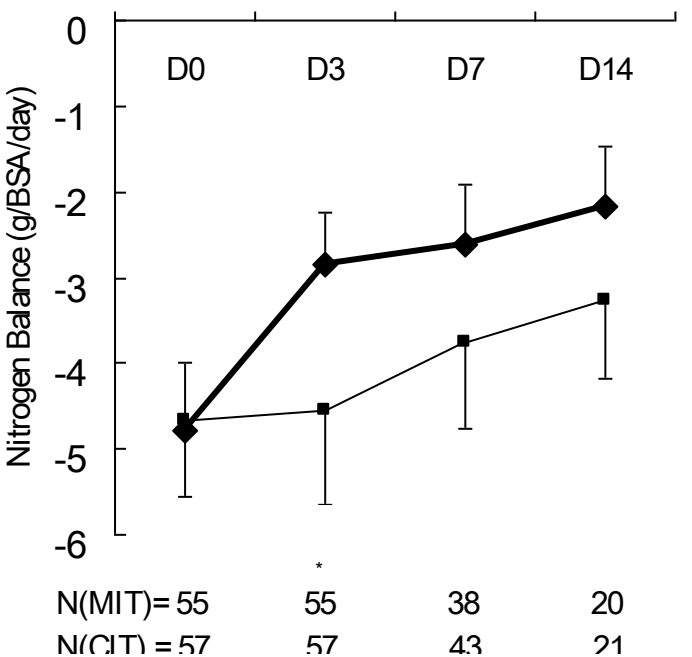
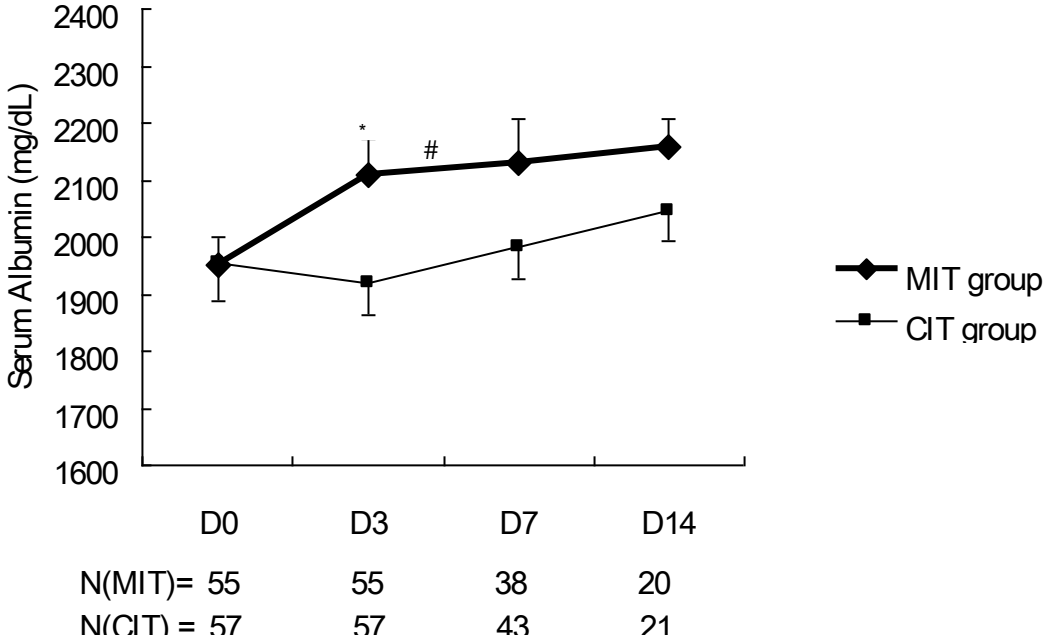

0
-1
-2
-3
-4
-5
-6
Nitrogen Balance (g/BSA/day)
D0
D3
D7
D14
*
N(MIT)= 55
55
38
20
N(CIT) = 57
57
43
21
MIT group
CIT group

Figure 5


2400
2300
2200
2100
2000
1900
1800
1700
1600
Serum Albumin (mg/dL)
*
#
MIT group
CIT group
D0
D3
D7
D14
N(MIT)= 55 55 38 20
N(CIT) = 57 57 43 21

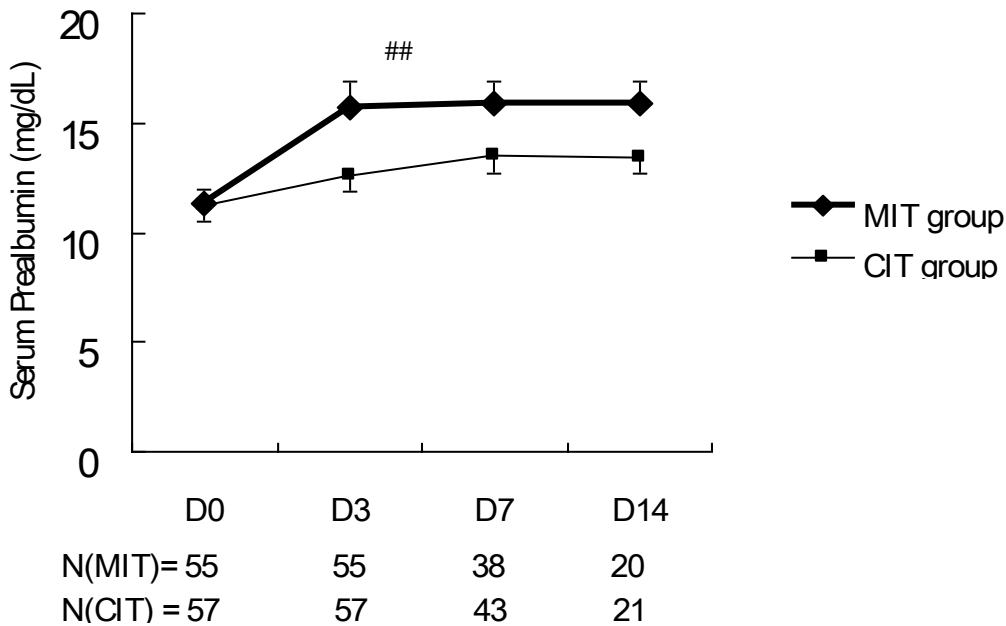

20
15
10
5
0
Serum Prealbumin (mg/dL)
##
MIT group
CIT group
D0
D3
D7
D14
N(MIT)= 55 55 38 20
N(CIT) = 57 57 43 21

Figure 6

Additional files provided with this submission:

Additional file 1: Additional files at the end of manuscript after the tables (Gluc, 89K
http://ccforum.com/imedia/1280631676700477/supp1.doc