Elevations in growth hormone and glucagon-like peptide-2 levels on admission are associated with increased mortality in trauma patients

Matthew P. Rowan1, Darrick J. Beckman2, Julie A. Rizzo1,3*, Claire L. Isbell4, Christopher E. White2, Stephen M. Cohn5 and Kevin K. Chung1,3

Abstract

Background: Burn and trauma patients present a clinical challenge due to metabolic derangements and hypermetabolism that result in a prolonged catabolic state with impaired healing and secondary complications, including ventilator dependence. Previous work has shown that circulating levels of growth hormone (GH) are predictive of mortality in critically ill adults, but few studies have examined the prognostic potential of GH levels in adult trauma patients.

Methods: To investigate the utility of GH and other endocrine responses in the prediction of outcomes, we conducted a prospective, observational study of adult burn and trauma patients. We evaluated the serum concentration of GH, insulin-like growth factor 1 (IGF-1), IGF binding protein 3 (IGFBP-3), and glucagon-like peptide-2 (GLP-2) weekly for up to 6 weeks in 36 adult burn and trauma patients admitted between 2010 and 2013.

Results: Non-survivors had significantly higher levels of GH and GLP-2 on admission than survivors.

Discussion: This study demonstrates that GH has potential as a predictor of mortality in critically ill trauma and burn patients. Future studies will focus on not only the role of GH, but also GLP-2, which was shown to correlate with mortality in this study with a goal of offering early, targeted therapeutic interventions aimed at decreasing mortality in the critically injured.

Conclusions: GH and GLP-2 may have clinical utility for outcome prediction in adult trauma patients.

Keywords: Biomarker, Burn, Hormone, Hypermetabolism, Trauma

Background

Severe trauma, burns, and critical illness affect millions of people every year and present a significant challenge to clinicians due to prolonged stays and metabolic derangements. Burns and other major traumatic injuries lead to a severe hypermetabolic response with elevated resting energy expenditure, insulin resistance, altered substrate use, elevations in protein synthesis and breakdown, and a negative nitrogen balance despite adequate nutrition [1]. The resulting catabolic state is characterized by impaired wound healing, muscle weakness, immobility, and prolonged ventilator dependence [2–5]. Current treatment approaches focus on managing the consequences of hypermetabolism through supportive therapy, but new approaches and advancements are needed to treat or attenuate the post-trauma hypermetabolic response.

The growth hormone (GH) axis is a key metabolic regulator that holds several potential targets for therapeutic intervention [5, 6]. Activation of the hypothalamus causes the release of growth hormone releasing hormone, which then activates the pituitary to release GH that acts on a number of targets, such as fat and liver, to increase the
concentration of glucose and free fatty acids and the production of additional hormones, including insulin-like growth factor 1 (IGF-1) [7], which is highly protein bound, most commonly to IGF binding protein 3 (IGFBP-3), but when free activates the Akt signaling pathway to induce cell proliferation and inhibit apoptosis. The GH axis response to critical illness is biphasic, with acute and chronic phases [8, 9]. The acute phase (5–10 days) is marked by an actively secreting anterior pituitary with an increase in GH levels and paradoxically decreased IGF-1 and IGFBP-3, secondary to GH resistance [9, 10]. Transition to the chronic phase is marked by a decrease in GH secretion, persistently low IGF-1 and IGFBP-3, and continued protein catabolism [9, 11–13].

Therapeutic interest has focused on targeting the chronic phase of the post-injury endocrine response, as ongoing catabolism is associated with increased morbidity and mortality [6, 14]. IGF-1 administration has been shown to improve patient outcomes, such as wound healing, muscle protein synthesis, and immune function [15–18]. Recombinant human growth hormone (rhGH) supplementation results in increased IGF-1 and positive nitrogen balance in patients with burns [19, 20], post-operative patients [21, 22], and the critically ill [23]. Additional studies with rhGH have shown improved morbidity and mortality in burn patients, including adolescents [24–30], and a recent Cochrane review of available randomized, controlled clinical trials of GH in patients with large burns concluded that GH treatment results in accelerated healing in both burn wounds and donor sites [31]. However, a large, multi-center, double-blind, placebo-controlled study showed that rhGH administration is associated with an increased risk of mortality in critically ill, non-trauma patients [32], suggesting that the target patient population may be an important caveat for rhGH intervention.

A clearer understanding of the timing and magnitude of the endocrine response to severe trauma would increase the likelihood of identifying targets for therapeutic intervention in order to minimize the impact of the hypermetabolic response. Few studies have examined the prognostic value of the GH axis in adult critically ill patients. Recent work showed no significant differences in GH levels among critically ill patients [33] whereas others have demonstrated that GH levels on admission were higher in non-survivors and were directly correlated with severity of sepsis and Acute Physiology and Chronic Health Evaluation II (APACHE II) score. Low IGF-1 levels were also associated with higher mortality [34], however IGFBP-3 was not correlated with APACHE II scores or mortality [35]. Furthermore, GH levels remained elevated after 24 h and at discharge or death in non-survivors and, along with IL-6 levels and APACHE II score, was an independent predictor of mortality [35]. To evaluate the prognostic value of other endocrine hormones, this study examined changes in the concentrations of GH, IGF-1, IGFBP-3, and glucagon-like peptide-2 (GLP-2) in adult burn and trauma patients with severe injury.

Methods

Subjects

This prospective, observational study was conducted under a protocol reviewed and approved by the Brooke Army Medical Center Institutional Review Board and in accordance with the approved protocol. Adults (≥18 years old) were eligible for the study if they were admitted to the Intensive Care Unit (ICU) at San Antonio Military Medical Center (trauma) or United States Army Institute of Surgical Research (burn) with a severe injury, defined as trauma with injury severity score (ISS) >15 or burn covering ≥20 % of the total body surface area (TBSA). Patients with known endocrine disorders other than diabetes mellitus were excluded. Delayed consent was used for subject enrollment in accordance with the approved study procedures. Additionally, five healthy subjects were selected as controls to establish uninjured values. Subject demographics, injury information, and clinical outcomes data were collected.

Sample collection

Blood samples were collected from existing central venous catheters, arterial lines, or intravenous lines for analysis of GH, IGF-1, IGFBP-3, and GLP-2 levels. A total of 4 mL of blood was collected twice (morning and evening) on admission (day 1) and on days 7, 14, 21, 28, 35, and 42, when possible. Samples were collected within 24 h of admission on all patients and for patients who proceeded to the operating room on the day of admission, samples were collected prior to the operation. Blood samples were centrifuged (1000 g, 15 min, room temperature) and the serum was separated within 90 min of collection and aliquoted for storage at −80 °C until analysis.

Hormone analysis

Serum samples were analyzed with commercially available ELISA kits for GH (DGH00, R&D Systems, Minneapolis, MN), IGF-1 (DG100, R&D Systems, Minneapolis, MN), IGFBP-3 (DBG300, R&D Systems, Minneapolis, MN), and GLP-2 (YK141, Yanaihara Institute, Shizuoka, Japan) according to manufacturer instructions.

Statistical analysis

Continuous variables were analyzed using either the Student’s t-test or Wilcoxon signed-rank test, based on the results of the Shapiro-Wilks test of normality. Log-
transformations were considered for right-skewed data, and log-normally distributed data is presented as geometric mean with 95 % confidence interval. Variables that passed or failed the test for normality are presented as mean (± standard deviation) or median (interquartile range), respectively. Categorical variables were compared using Chi-squared, Mann Whitney (when sample sizes were unequal), or Fisher’s exact tests, as appropriate. Linear regression was performed to determine an association between hormone levels over time and other factors. P-values and overall Pearson’s correlation coefficient were reported for all regression models. Statistical significance was accepted at $p < 0.05$. All data were analyzed with SAS 9.1 (SAS, Cary, NC).

Results
A total of 36 subjects were enrolled in this study. A summary of the different injuries are shown in Table 1; more detailed information on the subject demographics, detailed injury information and clinical outcomes are available (Additional file 1: Table S1). Subjects ranged from 18 to 74 years old (median 31.5) and were predominantly male (81 %) civilians (81 %). Body mass index values ranged from 19.4 to 42.2 (median 28.6). Subjects were most commonly injured in automotive crashes (14 motor vehicle and 3 motorcycle), assaults with or without gunshot wounds (5), explosions/blasts with or without burns (5), and burns (5). Average ISS was 29 ± 10.2 (range 9–57, median 27) and average APACHE II score was 22.7 ± 9.8 (range 6–44, median 25). Subjects averaged 26.1 days in the hospital (range 4–124, median 17), 14.9 days in the ICU (range 1–62, median 11), 9.3 days on a ventilator (range 0–43, median 6), and had an overall in-hospital mortality of 19 %. Samples were collected from all 36 subjects upon admission (day 1) but due to factors such as length of stay, study withdrawal, hospital discharge and mortality, weekly samples could not be collected for all subjects. Data was available from 21, 12, 9, 6, 4, and 2 subjects on days 7, 14, 21, 28, 35, and 42, respectively. Due to hormone variability and reduced power over time, no temporal trends were detected in any of the hormones evaluated. Likewise, subgroup analysis comparing burn patients with patients positive for traumatic brain injury (TBI) and non-TBI trauma patients revealed no significant correlations in hormone levels (Table 2). Age was inversely correlated with average levels of GH ($p = 0.016$, $R^2 = 16 \%$), IGF-1 ($p = 0.0001$, $R^2 = 35 \%$), and IGFBP-3 ($p = 0.003$, $R^2 = 23 \%$), and males had significantly higher levels of GLP-2 ($p = 0.049$) and IGF-1 ($p = 0.01$). Consistent with previous reports [35], non-survivors had significantly higher GH levels on admission than survivors (Fig. 1, $p = 0.038$). Furthermore, higher GLP-2 levels on admission were associated with higher mortality (Fig. 2, $p = 0.016$). As expected, ISS and APACHE II scores were significantly associated with increased mortality ($p = 0.035$ and $p = 0.004$, respectively). Comparison of burn/trauma ICU patients to healthy controls showed that, on average, ICU patients had higher levels of GLP-2 (Fig. 3, $p < 0.0001$) but lower levels of IGFBP-3 (Fig. 4, $p = 0.011$).

Discussion
Severe traumatic injuries, including burns, are a unique, complex challenge to clinicians. Patients often demonstrate

| Table 1 Injury information. Polytrauma patients experienced more than one type of injury, therefore the total number of injuries is greater than the number of patients |
| --- |
| Type of injury | Incidence (#) |
| Traumatic brain injury | 16 |
| Solid organ injury | 11 |
| Long bone fracture | 8 |
| Spinal cord injury/spinal fracture | 10 |
| Pelvic fracture | 3 |
| Rib fracture(s) | 5 |
| Burn | 6 |
| Othera | 13 |

aIncludes fractures other than long bones, pelvis or rib, pneumothorax, hollow viscous injuries and diaphragm injuries

| Table 2 Mean hormone levels comparing burn patients to non-burned trauma patients positive for TBI with non-TBI trauma patients |
| --- |
| Hormone | Burn | TBI | Non-TBI trauma |
| GHb | 3.22 | 2.76 | 2.84 |
| GLP-2c | 1.16 | 1.23 | 1.15 |
| IGF-1d | 2.06 | 1.77 | 1.87 |
| IGFBP-3d | 3.41 | 3.24 | 3.27 |

$^a p = 0.0625$, $R^2 = 10.9 \%$
$^b p = 0.293$, $R^2 = 21.6 \%$
$^c p = 0.052$, $R^2 = 10.9 \%$
$^d p = 0.252$, $R^2 = 8.85 \%$

Fig. 1 Growth hormone (GH) concentration on admission (day 1) in survivors and non-survivors of trauma. *, $p < 0.05$ by Mann-Whitney
major alterations in metabolic and endocrine responses that induce a host of physiological complications that often require intensive care and multiple organ support. In addition to established predictors of patient outcome, such as ISS and APACHE II scores, prognostic indicators of survival or disease progression could allow for earlier targeted intervention and improved patient outcomes. Furthermore, the ability to triage patients and focus care, when resources are limited, based on a combination of injury severity and outcome predictors could improve survival and functional recovery. In this study, the levels of GH, IGF-1, IGFBP-3, and GLP-2 were tracked in 36 burn and trauma patients over a 6 week period and compared with outcomes data (hospital days, ICU days, ventilator days, and survival). Non-survivors had significantly higher GH and GLP-2 levels, ISS and APACHE II scores on admission, and average GLP-2 levels than survivors. When compared with healthy controls, ICU patients had higher levels of GLP-2 and IGFBP-3.

Few studies have evaluated the prognostic potential of GH, IGF-1, IGFBP-3, or GLP-2 in trauma patients. A recent study of 103 critically ill patients found that survivors had significantly lower GH levels on admission than non-survivors, with or without sepsis, and that GH levels remain elevated in non-survivors after 24 h and at discharge or death [35]. Similarly, dichotomizing patients into low (<25) and high (≥25) risk based on APACHE II score revealed elevated GH levels in high risk patients. In fact, elevated GH at admission was identified as an independent predictor of mortality, and improved the prognostic accuracy of the APACHE II score when used in combination. These data are in agreement with the elevated GH levels seen in the 36 burn and trauma patients in the present study, and increase the potential of GH as an indicator of mortality in critically ill patients.

Therapeutic interest in attenuating the hypermetabolic response after injury has led to evaluating the effect of different therapies, such as insulin [9, 36], propranolol [37], and IGF-1 [15–18], which has been shown to improve patient outcomes such as wound healing, muscle protein synthesis, and immune function. Significant differences in IGF-1 levels between survivors and non-survivors were not detected in this study, but this is likely because of several limitations, including reduced power from small sample size and patient attrition throughout the 6 week study. The high patient attrition rate also impairs the ability to reliably correlate the measured values with parameters such as length of stay, ICU days, ventilator days and perhaps even survival. Studies
have also explored supplementation with rhGH which has been shown to increase IGF-1 levels, accelerate healing, and improve morbidity and mortality in burn patients in several studies [31].

The present study is in agreement with previous work [35] that shows higher GH levels in critically ill trauma patients than uninjured controls. Furthermore, GH levels on admission are correlated with outcome (Fig. 1) and serve as an independent predictor for mortality [35], which suggests that GH supplementation could be unnecessary or potentially dangerous in some critically ill patients. This could at least partly explain the results of a large multicenter trial that showed an increased risk of mortality with rhGH administration in non-trauma patients [32]. Additional side effects of GH supplementation have been noted to include hyperglycemia [31], sodium retention leading to an increase in extracellular water [35], hypercalcemia and hypercalciuria [38, 39]. More work is needed to identify the target patient population for rhGH administration in order to maximize any potential benefit and minimize potential complications of GH therapy in critically ill patients.

**Conclusion**

The treatment of severe trauma, burns, and critical illness remains a challenge to clinicians, but the ability to predict patient outcomes has impacted patient care to allow for early intervention and improved outcomes. New markers are needed to allow for more accurate, earlier predictions of patient outcome, and to improve the delivery of precision medicine. To our knowledge, this is the first study to identify GLP-2 as a novel prognostic indicator in trauma patients. Additional work is needed in larger patient populations across multiple centers to increase the impact of GLP-2, GH, and other clinically relevant hormones as potential indicators of clinical outcome.

**Additional file**

**Additional file 1: Table S1.** Patient demographics, injury information, and clinical outcomes. APACHE II = Acute Physiology and Chronic Health Evaluation II, Civ = civilian, GSW = gunshot wound, IED = improvised explosive device, ISS = Injury Severity Score, MCC = motorcycle crash, Mil = military, MVC = motor vehicle collision, N = no, TBI = traumatic brain injury, TBSA = total body surface area, Y = yes. (DOCX 23 kb)

**Abbreviations**

APACHE II: Acute Physiology and Chronic Health Evaluation II; GH: Growth hormone; GLP-2: Glucagon-like peptide 2; ICU: Intensive care unit; IGF-1: Insulin-like growth factor 1; IGFBP-3: Insulin-like growth factor binding protein 3; IL: Interleukin; ISS: Injury severity score; rHGH: Recombinant human growth hormone; TBI: Traumatic brain injury; TBSA: Total body surface area; USAMRMC: United States Army Medical Research and Materiel Command

**Acknowledgements**

We would like to thank Jay Aden for statistical analysis, Victoria Hatem for research coordination, and the rest of the Clinical Trials in Burns and Trauma team at ISR for their help in conducting this study. This work was supported in part by an appointment (MPR) to the Postgraduate Research Participation Program at the U.S. Army Institute of Surgical Research administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and USAMRMC.

**Funding**

This work was supported in part by an appointment (MPR) to the Postgraduate Research Participation Program at the U.S. Army Institute of Surgical Research administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and USAMRMC.

**Availability of data and materials**

Data supporting the findings are presented in the manuscript.

**Authors' contributions**

CLI, CEW, SMC, and KKC participated in the design of the study and patient recruitment. MPR and JAR collected and analyzed patient data and demographic information. MPR, DJB and JAR wrote the initial draft of the paper, with CLI and KKC providing edits during early review. All authors participated in data analysis and interpretation, and in the final manuscript review, providing edits and additions. All authors read and approved the final manuscript.

**Competing interests**

The authors declare that they have no competing interests.
Consent for publication
Not applicable

Ethics approval and consent to participate
As mentioned in Methods, this prospective, observational study was conducted under a protocol reviewed and approved by the Brooke Army Medical Center Institutional Review Board and in accordance with the approved protocol. Delayed consent was used for subject enrollment in accordance with the approved study procedures. Additionally, five healthy subjects were selected as controls to establish unjured values.

DOD Disclaimer
"The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Author details
1United States Army Institute of Surgical Research, 3689 Chambers Pass, JBLSA, Fort Sam Houston, San Antonio, TX 78234, USA. 2Brooke Army Medical Center, 3855 Roger Brooke Drive, JBLSA, Fort Sam Houston, San Antonio, TX 78234, USA. 3Uniformed Services University of the Health Sciences, 4301 Jones Bridge Rd # A34007, Bethesda, MD 20814, USA. 4Baylor Scott and White Memorial Hospital, 2401 S. 31st St, Temple, TX 76502, USA. 5Staten Island University Hospital, 475 Seaview Ave, Staten Island, NY 10305, USA.

Received: 11 May 2016 Accepted: 27 September 2016
Published online: 04 October 2016

References
1. Preiser JC, Ichai C, Orban JC, Groeneveld AJ. Metabolic response to the trauma of sepsis. Arch Surg. 1987;122(1):61–66. 
2. Arnold J, Campbell IT, Samuels TA, Devlin JC, Green CJ, Hipkin LJ, Rowan DA, Kell MC, Green DJ, Senger P, et al. The use of insulin-like growth factor I in sepsis. Am J Clin Nutr. 1993;57(3):489–495. 
3. Dempsey DT, Muller JL, Buzby GP. The link between nutritional status and clinical outcome: can nutritional intervention modify it? Am J Clin Nutr. 1998;67(2 Suppl):352–360.
4. Rennie MJ. Muscle protein turnover and the wasting due to injury and infection. Curr Opin Crit Care. 2008;14(4):388–394.
5. Taylor BE, Buchman TG. Is there a role for growth hormone therapy in the treatment of sepsis? Clin Sci (Lond). 1993;84(6):655–61.
6. Dempsey DT, Muller JL, Buzby GP. The link between nutritional status and clinical outcome: can nutritional intervention modify it? Am J Clin Nutr. 1998;67(2 Suppl):352–360.
7. Lang CH, Frost RA. Role of growth hormone, insulin-like growth factor-I, and insulin-like growth factor binding proteins in the catabolic response to injury and infection. Curr Opin Clin Nutr Metab Care. 2002;5(3):271–279.
8. Velloso CP. Regulation of muscle mass by growth hormone and IGF-I. Br J Pharmacol. 2008;154(3):557–68.
9. Baxter RC. The insulin-like growth factor (IGF)-IGF-binding protein axis in critical illness. Growth Horm IGF Res. 1999;9 Suppl A:57–68.
10. Gielen M, Messoren D, Brugts M, Coopmans W, Van Herck E, Vanhorebeek I, Baxter R, Lamberts S, Janssen JA, Van den Berge G. Effect of intensive insulin therapy on the somatotropic axis of critically ill children. J Clin Endocrinol Metab. 2011;96(8):2558–66.
11. Ross RJ, Chew SL. Acquired growth hormone resistance. Eur J Endocrinol. 1995;132(6):655–60.
12. Messoren D, Van den Berge G. Changes within the GH/IGF-I/IGFBP axis in critical illness. Curr Care Clin. 2006;22(1):17–28.
13. Giansotti L, Stella M, Boller D, Broglio F, Lanfranco F, Aimaretti G, Destefanis S, Casati M, Magliacani G, Ghigo E. Activity of GH/IGF-I axis in burn patients: comparison with normal subjects and patients with GH deficiency. J Endocrinol Invest. 2002;25(2):116–24.
14. Jeffries MK, Vance ML. Growth hormone and cortisol secretion in patients with burn injury. J Burn Care Rehabil. 1992;13(4):391–5.
15. Plank LD, Hill GL. Sequential metabolic changes following induction of systemic inflammatory response in patients with severe sepsis or major blunt trauma. World J Surg. 2002;26(4):630–8.
16. Bondy CA, Underwood LE, Clemmons DR, Guler HP, Bach MA, Skarulis M. Clinical uses of insulin-like growth factor I. Ann Intern Med. 1994;120(7):593–601.
17. Steenfos HH. Growth factors and wound healing. Scand J Plast Reconstr Surg Hand Med. 1994;28(2):95–105.
18. Stock LL, Singh H, Abdullah A, Miller JA, Herndon DN. The effect of insulin-like growth factor I on postburn hypermetabolism. Surgery. 1990;108(2):161–4.
19. Beldner HJ, Mercer D, Judkins KC, Shalaby S, Wise S, Marks V, Tanner NS. Biosynthetic human growth hormone in burned patients: a pilot study. Burns. 1989;15(2):99–107.
20. Herndon DN, Barrow RE, Kunkel KR, Broemeling L, Rutan RL. Effects of recombinant human growth hormone on donor-site healing in severely burned children. Ann Surg. 1990;212(4):424–9. discussion 30–1.
21. Jiang H, Sun MW, Hefright B, Chen W, Lu CD, Zeng J. Efficacy of hypocaloric parenteral nutrition for surgical patients: a systematic review and meta-analysis. Clin Nutr. 2011;30(6):730–7.
22. Ward HC, Halliday D, Sim AJ. Protein and energy metabolism with biosynthetic human growth hormone after gastrointestinal surgery. Ann Surg. 1987;206(1):56–61.
23. Douglas RG, Humberstone DA, Hoystead A, Shaw JH. Metabolic effects of recombinant human growth hormone: isotopic studies in the postabsorptive state and during total parenteral nutrition. Br J Surg. 1990;77(7):895–900.
24. Knox J, Demling R, Willmore D, Saraf P, Santos A. Increased survival after major trauma: the effect of growth hormone therapy in adults. J Trauma. 1995;39(3):526–30. discussion 30–2.
25. Losada F, Garcia-Luna PP, Gomez-Cia T, Gambino M, Pereira JL, Marin F, Astorga R. Effects of human recombinant growth hormone on donor-site healing in burned adults. World J Surg. 2002;26(12):1–8.
26. Micak RP, Suman OE, Murphy K, Herndon DN. Effects of growth hormone on anthropometric measurements and cardiac function in children with thermal injury. Burns. 2005;31(1):56–60.
27. Przkora R, Herndon DN, Suman OE, Jeschke MG, Meyer WI, Winkles DL, Micak RP, Huang T, Barrow RE. Beneficial effects of extended growth hormone treatment after hospital discharge in pediatric burn patients. Ann Surg. 2006;243(6):796–801. discussion –3.
28. Ramirez RJ, Wolf SE, Barrow RE, Herndon DN. Growth hormone treatment in pediatric burns: a safe therapeutic approach. Ann Surg. 1998;228(4):439–48.
29. Singh KP, Prasad R, Chari PS, Dash RJ. Effect of growth hormone therapy in burn patients on conservative treatment. Burns. 1998;24(8):733–8.
30. Suman OE, Thomas SJ, Wilkins JP, Mlcak RP, Herndon DN. Effect of exogenous growth hormone and exercise on lean mass and muscle function in children with burns. J Appl Physiol (1985). 2003;94(6):2273–81.
31. Breedervoeld RS, Tumeinbreier WE. Recombinant human growth hormone for treating burns and donor sites. Cochrane Database Syst Rev. 2014;CD008990.
32. Takala J, Ruokonen E, Webster NR, Nielsen MS, Zandstra DF, Vundellinnick G, Hinds CJ. Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med. 1999;341(11):785–92.
33. Kyle UG, Jollitt P, Genton L, Meier CA, Menis N, Graf JD, Chevrolet JC, Pichard C. Clinical evaluation of hormonal stress state in medical ICU patients: a prospective blinded observational study. Intensive Care Med. 2005;31(12):1669–75.
34. Shanhat T, Bastuji-Garin S, Polito A, De Jonghe B, Stevens RD, Maxime V, Rodriguez P, Ceuf C, Outin H, Touraine P, Laborde K. Hormonal status in protracted critical illness and in-hospital mortality. Crit Care. 2011;15:R47.
35. Schuetz P, Muller B, Nusbaumer C, Wieland M, Christ-Canin M. Circulating levels of GH predict mortality and complement prognostic scores in critically ill medical patients. Eur J Endocrinol. 2009;160(2):157–63.
36. Diaz EC, Herndon DN, Porter C, Sidossis LS, Mlcak RP. Beneficial effects of extended growth hormone treatment in pediatric burn patients: a pilot study. Burns. 1994;20(2):95–104.
37. Jeschke MG, Finnerly CC, Kulop GA, Przkora R, Micak RP, Herndon DN. Combination of recombinant human growth hormone and propranolol decreases hypermetabolism and inflammation in severely burned children. Pediatr Crit Care Med. 2008;9(2):209–16.
38. Ho KY, Weissberger AI. The antiinflammatory action of biosynthetic human growth hormone in man involves activation of the renin-angiotensin system. Metabolism. 1990;39(2):133–7.
39. Knox JB, Demling RH, Wilmore DW, Sanaf P, Santos AA. Hypocalcemia associated with the use of human growth hormone in an adult surgical intensive care unit. Arch Surg. 1995;130(4):442–5.