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Original Article

Albumin synthesis rates in post-surgical infants and septic adolescents; influence of amino acids, energy, and insulin

Sascha C. Verbruggen [a,b,c], Henk Schierbeek [a], Jorge Coss-Bu [b,c], Koen F.M. Joosten [a], Leticia Castillo [d], Johannes B. van Goudoever [a,e,f,*]

[a] Department of Pediatrics, Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands
[b] Children's Nutrition Research Center, USDA, Houston, TX, USA
[c] Critical Care Section, Department of Pediatrics, Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA
[d] Division of Critical Care Medicine, Children's Medical Center Dallas, University of Texas Southwestern, Dallas, TX, USA
[e] Department of Pediatrics, VU University Medical Center, Amsterdam, The Netherlands
[f] Department of Pediatrics, Emma Children's Hospital, Amsterdam Medical Center, Amsterdam, The Netherlands

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SUMMARY

Background & aims: To investigate the effects of glucose, parenteral amino acids, and intravenous insulin on albumin synthesis rates in critically ill children.
Methods: Two studies were performed in 8 post-surgical infants (age 9.8 ± 1.9 months; weight 9.5 ± 1.1 kg) and 9 septic adolescents (age 15 ± 1 yr; BMI 23 ± 4 kg m^{-2}), respectively. All received a primed, constant, tracer infusion with [1-^{13}C]Leucine. The infants in study 1 were randomized to receive low (2.5 mg kg^{-1} min^{-1}) and standard (5.0 mg kg^{-1} min^{-1}) glucose intake in a cross-over setting of two periods of 4 h each. The adolescents in study 2 were randomized to receive total parenteral nutrition with standard (1.5 g kg^{-1} day^{-1}) and high (3.0 g kg^{-1} day^{-1}) amino acid intake in a two day cross-over setting. On both study days, during the last 3 h of the tracer study, they received insulin infused at 80 mU m^{-2} min^{-1}.
Results: The post-surgical infants and the septic adolescents were mildly hypoalbuminemic (~2.5 g dL^{-1}) with high synthesis rates, which were not affected by different intakes of glucose, amino acids, or insulin infusion.
Conclusions: Albumin synthesis rates in hypoalbuminemic critically ill children are high but were not upregulated through nutrient supply, and in septic adolescents are unaffected by insulin.

1. Introduction

Albumin is the most abundant protein in human plasma with a normal plasma concentration of around 4.0 g dL^{-1}, while about 60% of the total albumin pool is located in the interstitial space.[1] Albumin holds several important functions, both in health as well as in critically ill patients. It is the main preserver of colloid oncotic pressure (~75%), it functions as an anticoagulant and anti-oxidant and it is an important binding transporter of metabolites and drugs.[1,2]

Critically ill patients are often hypoalbuminemic, primarily due to dilution and redistribution secondary to an altered vascular permeability.[1] In critically ill patients hypoalbuminemia has been documented as a marker for disease severity, nutritional status, prolonged ventilator support and prolonged length of stay.[3,4] In critically ill adults and children, low albumin plasma levels (<3.3 g dL^{-1}) are inversely related to morbidity and mortality, where in adults each 1.0 g dL^{-1} drop in serum albumin raised the odds of morbidity by 87% and mortality by 137%.[3–5] However, plasma concentrations are static measurements. Dynamic measurements by means of albumin synthesis rates actually show a consistent increase in critically ill adults.[6,7]

Despite the clear association between hypoalbuminemia and poor outcome, there is still a debate on the benefits and safety of intravenous albumin administration, partially due to the increased risk of escape in the extravascular space and inflammation.[2,5] Therefore, stimulation of endogenous albumin synthesis seems an appealing alternative.

Abbreviations: PICU, pediatric intensive care unit; LG, low glucose intake; SG, standard glucose intake; SAA, standard amino acid intake; HAA, high amino acid intake; TPN, total parenteral nutrition; APE, atom percent excess; KIC, α-ketoisocaproate; Ra, rate of appearance; Rd, rate of disappearance.

* Corresponding author. Kamer 9D11, VU Medical Center, De Boelelaan 1117, Postbus 7057, 1007 MB, Amsterdam, The Netherlands.
E-mail address: S.verbruggen@erasmusmc.nl (S.C. Verbruggen).

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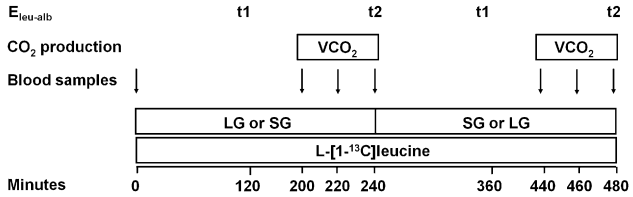

Fig. 1. Experimental design of study 1 in 8 post-surgical infants admitted to the pediatric intensive care unit receiving only parenteral glucose as nutrition, LG = low glucose intake (2.5 mg kg^{-1} min^{-1}), SG = standard glucose (5.0 mg kg^{-1} min^{-1}), $E_{leuc-alb}$ = Enrichment of [1-^{13}C]Leucine incorporated into albumin, VCO_2 = Carbon dioxide production.

Albumin synthesis can be stimulated by an increase in energy (glucose and fat) but is particularly responsive to amino acid intake.[8–10] Hyperinsulinemia has shown to increase albumin synthesis as well, with an additive effect of increased amino acids in healthy adults.[10] This latter intervention is of particular interest as insulin is more frequently used to treat hyperglycemia in critically ill adults and children.[11] Moreover, the increase in synthesis rates in response to these interventions is immediate and fast. Albumin synthesis rates increased by 40% within 2 h following intravenous endotoxin in healthy volunteers.[12] Furthermore, nutritional supplementation[13,14] and hyperinsulinemia[15] increased albumin synthesis rates, within 4, 6, and 3 h respectively.

The effect of various nutritional interventions on albumin synthesis rates have not been investigated in critically ill children, other than in premature infants.[16] Increasing amino acid availability resulted in higher albumin synthesis rates, although not as high as reached in utero.[16] Given the limited knowledge of albumin synthesis rates and the impact of nutrition in the critically ill pediatric population, we set out to ascertain these. We hypothesized that in critically ill children albumin synthesis rates are increased and responsive to nutrients and hyperinsulinemia. Therefore, our first objective was to quantify albumin synthesis rates in critically ill infants and adolescents. Our second objective was to determine the impact of nutrients on albumin synthesis rates in these children, with special emphasis on parenteral glucose and amino acids. Our third objective was to determine whether additional hyperinsulinemia in combination with parenteral glucose and amino acid intake would increase albumin synthesis rates through a synergistic fashion. The here described studies were part of two larger studies aiming to investigate the effect of reduced glucose intake on glucose homeostasis and protein catabolism (Study 1) and the effect and interactions of increased amino acid intake and hyperinsulinemia on substrate metabolism and insulin resistance (Study 2).

2. Methods

2.1. Patients

Study 1 was a one day study with infants (0.5–1.0 y) admitted after surgical repair of non-syndromal craniosynostosis to the pediatric intensive care unit (PICU) at Erasmus MC – Sophia Children's Hospital in Rotterdam, The Netherlands. Study 2 was a two day study in adolescents (13–18 y) who were admitted with a diagnosis of severe sepsis or Systemic Inflammatory Response Syndrome (SIRS), as defined by the criteria of the First International Pediatric Sepsis Forum[17] to the PICU at Texas Children's Hospital, Houston, Texas. All patients had drawing and infusing catheters in place for clinical purposes. Patients with metabolic diseases, diabetes mellitus, primary liver, or renal failure were excluded. The study protocols were approved, respectively by the Institutional Review Board of Erasmus Medical Center, Rotterdam, The Netherlands and by the Institutional Review Board of Baylor College of Medicine, Houston, Texas. Studies were carried out after written informed consent from the parents.

2.2. Study design and data collection

The experimental design of study 1 is shown in Fig. 1 and consisted of an 8 h glucose infusion in a randomized, cross-over design,

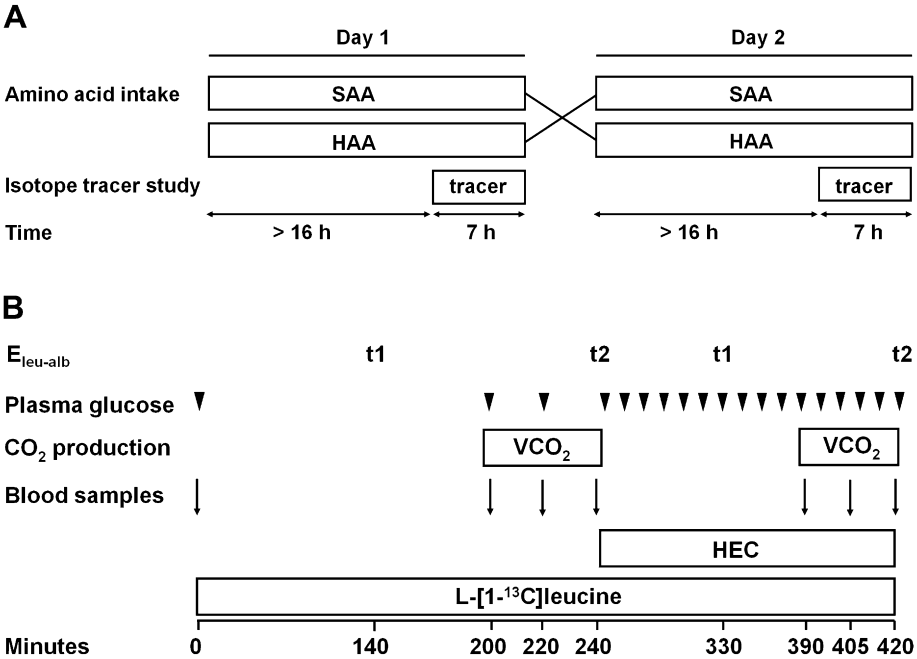

Fig. 2. Experimental design of study 2 in 9 adolescents admitted to the pediatric intensive care unit receiving full parenteral nutrition with two different amino acid intakes at baseline and during hyperinsulinemia, Panel A Two day study protocol with two different amino acid intakes in a randomized cross-over fashion, Panel B Isotope tracer infusion on both days during baseline and during hyperinsulinemia, SAA = Standard amino acid intake (1.5 g kg^{-1} day^{-1}), HAA = High amino acid intake (3.0 g kg^{-1} day^{-1}), $E_{leuc-alb}$ = Enrichment of [1-^{13}C]Leucine incorporated into albumin, VCO_2 = Carbon dioxide production.