Nutrition 29 (2013) 703–707

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review

Albumin synthesis in surgical patients

Ansgar Hülshoff Cand. med. [a], Thomas Schricker M.D., Ph.D. [b], Hamed Elgendy M.D., Ph.D. [c], Roupen Hatzakorzian M.D., M.Sc. [b,d], Ralph Lattermann M.D., Ph.D. [b,*]

[a] *Philipps-Universität Marburg, Germany*
[b] *Department of Anaesthesia, McGill University, Montreal, Canada*
[c] *Department of Anesthesia, Assiut University, Assiut, Egypt*
[d] *Department of Critical Care, McGill University, Montreal, Canada*

ARTICLE INFO

Article history:
Received 29 May 2012
Accepted 23 October 2012

Keywords:
Albumin synthesis
Surgery
Critically ill
Stable isotope tracers

ABSTRACT

Albumin plasma concentrations are being used as indicators of nutritional status and hepatic function based on the assumption that plasma levels reflect the rate of albumin synthesis. However, it has been shown that albumin levels are not reliable markers of albumin synthesis under a variety of clinical conditions including inflammation, malnutrition, diabetes mellitus, liver disease, and surgical tissue trauma. To date, only a few studies have measured albumin synthesis in surgical and critically ill patients. This review summarizes the findings from these studies, which used different tracer methodology in various surgical or critically ill patient populations. The results indicate that the fractional synthesis rate of albumin appears to decrease during surgery, followed by an increase during the postoperative phase. In the early postoperative phase, albumin fractional synthesis rate can be stimulated by perioperative nutrition, if enough amino acids are being provided and if nutrition is being initiated before the operation. The physiologic meaning of albumin synthesis after surgery, however, still needs to be further clarified.

Introduction

Plasma albumin plays an important regulatory role in body fluid distribution, acid–base physiology, and substrate transport. Assuming that the level of circulating albumin reflects its synthesis rate, plasma albumin also has been widely used as an indicator of nutritional status and/or hepatic function [1–4]. Although one may speculate that hypoalbuminemia in these patients is caused by impaired albumin synthesis, plasma albumin concentrations are not governed solely by synthesis and degradation. Changes in plasma volume and altered distribution between the intravascular and extravascular space also play a significant role. Hence, albumin levels are not reliable markers under a variety of clinical conditions, including inflammation, moderate malnutrition, hypertension, diabetes mellitus, liver disease, and surgical tissue trauma.

Because the quantitative assessment of albumin kinetics in the human body requires sophisticated methodology, data is scarce for surgical and critically ill patients. The purpose of this review is to summarize the present knowledge about absolute synthesis rates (ASRs) in this patient population and how they can be measured.

Physiology of albumin

Structure

Albumin is the most abundant protein in human plasma, representing 55% to 60% of the total serum protein. It consists of 585 amino acids, which are arranged predominantly into α-helices held together by 17 disulfide bridges. Three helices, arranged in parallel, constitute a subdomain and two subdomains facing each other in an antiparallel fashion constitute a domain. Three domains together form the complete molecule [2].

The outside of the structure, resembling a cylinder, is mainly polar, whereas the central part is mainly apolar, allowing the binding of hydrophobic substrates. A number of proline molecules permit the subdomains to move in relation to another, resulting in a change of their spatial orientation and consequently promoting or inhibiting potential binding sites.

All authors contributed significantly to the drafting and revision of the manuscript and have approved the final version.

* Corresponding author. Tel.: +1 514-9341934; fax: +1 514-8431723.
E-mail address: ralph.lattermann@muhc.mcgill.ca (R. Lattermann).

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http://dx.doi.org/10.1016/j.nut.2012.10.014

Pool

Albumin plasma concentrations typically range between 3.5 g/100 mL and 5 g/100 mL. The total body albumin pool contains about 3.5 g/kg to 5 g/kg (250–300 g for a 70–75 kg patient). Intravascular albumin reflects approximately 30% to 40% of the total body albumin, whereas 60% to 70% remains in the extravascular pool, with a transcapillary exchange rate between the two compartments of 4.5%/h.

The distribution of extravascular albumin varies among organs. Although skin and muscle contain 41% and 40%, respectively, of the total extravascular albumin pool, the liver accounts for only 1% to 3% [5]. About 27% of the extravascular albumin is tissue bound and the rest is exchangeable [6].

The extravascular compartment consists of two units each with its own rate of distribution of intravascular albumin into the compartment. The first is comprises tissues with discontinuous capillaries (liver, spleen, gut) with a fast rate of distribution and a half-life of about 6 h. The other compartment represents tissues with continuous capillaries (muscle, skin) with a distribution half-life of about 28 h.

Synthesis, degradation

In humans, albumin synthesis takes place exclusively in the liver. The average daily synthesis amounts to 12 g to 25 g, accounting for up to 50% of hepatic protein synthesis. This translates into a fractional synthesis rate between 6% and 12% (Table 1).

The principal regulator of albumin synthesis seems to be the oncotic pressure, as detected by osmoreceptors near the hepatocyte [7,8]. The ASR can be increased to only 2.0 times to 2.7 times normal, as most of the liver's synthetic capacity already is devoted to albumin under normal conditions [6].

The plasma half-life of injected albumin is about 24 h [9]. Approximately 4% to 5% (~ 14 g) of the total pool is degraded per d, which translates into a half-life of 17 to 19 d. Albumin depletion is not of localized entity, but seems to occur in all organs, with muscle and skin breakdown representing approximately 40% to 60%, the liver 15%, and the kidneys 10% of the total.

Measurement of albumin synthesis

In principle, the fractional synthesis rate (FSR; the percentage of the intravascular albumin pool synthesized per unit of time) can be measured from the change in incorporation of a labeled amino acid (e.g., l-[1-^{13}C]-leucine, L-[$^{2}H_5$]phenylalanine) into albumin over time, in relation to the labeling of the pool from which the amino acid is incorporated into protein. In practical terms, labeled amino acids are made available to the cellular machinery of protein synthesis by intravascular infusion or injection and samples of the protein are taken over time. This can be achieved by either a primed continuous infusion of a precursor or the use of the flooding dose technique.

In the primed continuous infusion method, a priming dose of a labeled amino acid is administered, followed by an infusion. After reaching steady state in the plasma pool, blood samples are drawn to calculate the FSR by measuring the enrichment of the tracer in albumin in the same period. One important determinant of the accuracy of measurement is knowledge of labeling at the site of the incorporation of the amino acid into protein (i.e., in the appropriate aminoacyl-tRNA pool). The enrichment in aminoacyl-tRNA is generally found in vivo to be between intracellular and the blood-free amino acid labeling. The measurement of the true precursor enrichment is difficult, making the use of a surrogate inevitable. α-Ketoisocaproic acid (KIC), a transamination product of leucine, approximating to within 10% of the labeling of the amino acid pool in human muscle, appears to reflect the intracellular pool in muscle. Even so, plasma α-KIC may not accurately reflect the hepatic precursor pool enrichment as necessary to determine albumin synthesis [10]. Alternatively, the enrichment of apolipoprotein B100 of very low-density lipoprotein, being a protein with high turnover rate and more than 98% of hepatic origin, reflects the enrichment of the precursor pool more precisely and, therefore should be used for the determination of hepatic protein synthesis [11,12].

The flooding dose technique has been developed to minimize differences between free amino acid pools, thereby avoiding the difficulty of correctly identifying the precursor labeling. A large quantity of labeled and unlabeled amino acid is administered with the aim of rapidly flooding all free amino acid pools to a similar value that can be measured easily after sampling the plasma-free pool. The FSR is calculated by comparing the incorporation of the tracer into albumin over the period of application with the average plasma amino acid labeling [13]. Typically, blood samples are taken every 10 min up to 90 min after the injection of the flooding dose.

The flooding technique appears attractive because only a short amount of time is needed to complete a study, as opposed to the

Table 1
Albumin synthesis rates in healthy subjects

Study	Method	Tracer	n	FSR (%/d)	ASR (mg/kg/d)
Cayol[37]	PCI	1-[^{13}C]leucine	5	7.2 ± 0.2	114 ± 9
DeFeo[38]	PCI	1-[^{14}C]leucine	7	12 ± 2	238 ± 24 (mg/kg LBM/d)
DeFeo[30]	PCI	1-[^{14}C]leucine	6	6.2 ± 0.6	
Jackson[39]	PCI	[$^{2}H_5$]phenylalanine	6	8.5 ± 0.96	151 ± 14
Mansoor[35]	PCI	1-[^{13}C]leucine	5	7.3 ± 0.4	91 ± 5
Martini[36]	PCI	[$^{2}H_5$]phenylalanine	5	4.1 ± 0.2	53 ± 5
	PCI	[$^{2}H_3$]ketoisocaproic acid	5	5.0 ± 0.5	65 ± 5
Olufemi[17]	PCI	[^{15}N]glycine	5	5.4 ± 0.9	271 ± 42
	PCI	1-[^{13}C]leucine	5	6.0 ± 1.1	267 ± 54
Rittler[24]	PCI	1-[^{13}C]leucine	5	6.7 ± 1.0	
Tessari[40]	PCI	1-[^{14}C]leucine	7	10.9 ± 1.5	
Ballmer[16]	FT	1-[^{13}C]leucine	7	7.2 ±1.3	157 ± 39
Barle[41]	FT	[$^{2}H_5$]phenylalanine	8	6.6 ± 0.6	132 ± 20
Hunter[42]	FT	[$^{2}H_5$]phenylalanine	12	5.8 ± 0.4	
	FT	[$^{2}H_5$]phenylalanine	12	7.1 ± 0.4	
Kleger[43]	FT	[$^{2}H_5$]phenylalanine	7	5.9 ± 0.9	96 ± 19
McMillan[44]	FT	[$^{2}H_5$]phenylalanine	6	10.3	208

PCI, Primed-continuous infusion; FT, Flooding technique; LBM, lean body mass