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Gratis

Review Article

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Where the Pendulum of Knowledge Stands Now: Is Circulating Albumin a Marker of Inflammation or of Malnutrition? How to Manage Hypoalbuminemia by Nutrition?

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Abstract

Low plasma albumin levels have been historically associated with insufficient nutritional nitrogen support. Recently, linked to the poor response of actual therapies and available supplements to manage this alteration, the role of this alteration has been attributed to the vast ensemble of modifications referred generally as consequent to inflammation. On the contrary, as recently it has been reported that life based on introduction of mainly essential amino acids is possible, and life span is improved when compared to standard diets, it is possible to hypothesize that by normal foods or by actually most widely diffused supplements insufficient amounts of essential amino acids to match with real needs of hypoalbuminemic patients are not provided. Peculiarly, some non essential amino acids provided in excess by diets may mislead clinicians by suggesting achievement of sufficient nitrogen intake if urea syntheses is used as reference of sufficient nutrition, while syntheses of liver proteins is not sufficiently implemented. Studies suitable to understand if some innovative therapy would be efficient in implementing albumin syntheses and thus prognosis in hypoalbuminemic patients are necessary.

Keywords: Nutrition, Albumin, Urea, Essential amino acids, Non essential amino acids, Arginine

Abbreviations: Essential Amino Acids: EAA; Non Essential Amino Acids: NEAA

Introduction

Since in 1979 Seltzen et al. [1] proposed albumin, in association to total lymphocytes count, as a marker of instant nutritional assessment and of malnutrition, since then a widely used way to screen patient for intensive nutritional care. But, many editorials and papers have been recently published questioning the interpretation of low levels of circulating albumin as primarily a marker of poor nitrogen intake.

Some authors, suggesting that low levels of albumin should be considered just a marker indicating and correlating with inflammation in both no diseased [2] and diseased patients [3], support the proposal that albumin concentration below normal should be considered mainly "a negative acute phase reactant".

On the other hand, to our knowledge, all authors agree that in presence of pathologies associated to hypoalbuminemia either mortality correlates with the dimensions of albumin lowering and quite obviously, that the best solution to restore normal values is to eliminate most efficiently the underlying pathology, a definitely embraceable purpose, unfortunately not often completely achievable.

Inflammation and plasma albumin levels

No one has supported that specifically targeting inflammation may have a sense to improve hypoalbuminemia. Other authors revising the argument have quite solomonically connected low levels of albumin to MIA (malnutrition, inflammation, atherosclerosis) syndrome [4], thus somehow recognizing that malnutrition per se may cause, or at least may contribute to inflammation. On the contrary, Lee et al. [2]. Recently stated "we hypothesize that low serum albumin and prealbumin levels, in contrast, identify a group of patients who will be unable to benefit from nutritional support", suggesting serum albumin totally useless as a marker of nutritional status. This is a very severe statement, and also, perhaps, this sentence indicates the near end of the run of the pendulum from the fully related to the fully unrelated side marking awareness of the connection between serum albumin and nitrogen intake. Indeed, the main point of those authors is empiric: usual nutritional intervention fails to correct hypoalbuminemia in different severe clinical situations, peculiarly in conditions where malnutrition is classically considered to play a central role as in advanced dementia, wasting illness, pressure ulcers, and cancer [2],[3]. But, can we accept passively the option in background to those failures: if those authors failed, nobody else and no different therapy can treat and improve hypoalbuminemia?

Thinking to some solution

In my opinion, one of the main points is the "measure", nitrogen balance based on urea syntheses, used to certify that any of those failures have been induced in spite of a most efficient nutritional approach. We have discussed elsewhere why urea synthesis is mostly dependent on arginine content of diets [5],[6] and discussed how arginine intake may influence both plasma and therefore urinary urea concentrations [7]. Thus, if nitrogen balance is used as the gold standard to certify sufficient quality of nitrogen intake, as we have observeded in animals [8] and paradoxically also in extreme human setting [9],[10] we may observe either a normalized nitrogen balance and the maintenance of clinical evidences of malnutrition comprehensive of unsuccessful treatment of hypoalbuminemia, unless we used very large doses of EAA as a major source of nitrogen. While nitrogen balance is used as a main standard to measure nitrogen intake, while in our opinion it certifies both dimensions of catabolic efflux of NEAA from wasting muscles and the excess nitrogen supplied by food to the body and potentially unsuitable to be fully used for maintaining adequate protein syntheses due to the reduced ratio (always < 0,9, but in beef, according cuts, may be near 0,7) among EAA and NEAA provided by food proteins [11]. and the ratios EAA/NEAA in animals have recently been found to correlate with a reduced life span [8].

On the contrary, if albumin is low as a consequence of inflammation, it would be low both if synthesis would be inhibited or catabolism would be increased and most reasonably if both conditions would be contemporarily present. Therefore, it remains to be solved the true question dealing with the balance among inflammation and albumin in plasma: is it adequate to promote increased syntheses of albumin the supply of EAA available by diets in patients who have enormously increased nitrogen needs? The question of adequacy of EAA supplied by diet is pivotal, since only EAA promote and maintains synthesis of proteins [12], they do not contribute immediately to urea synthesis as some of the NEAA most abundantly available in both dietary and structural human proteins, as arginine and glutamine [13], thus at least partially immediately flowing to and refueling urea metabolism [14].

On the contrary of NEAA, since EAA are the main promoters of protein syntheses and still antagonize cancer development in vitro [15], their sufficiently large availability condition evaluation of adequate nutritional supply [16] and only achieving a persistent success in normalizing liver syntheses of short lived circulating proteins (in progression of half life duration sequence: Retinol Binding Protein, Transthyretin/Prealbumin, Transferring) would be a necessary prelude to observe in time progression towards normality of albumin concentrations [17].

Failure to achieve short lived proteins normalization indicates that correction of a more long-lived plasma albumin would not be achieved, and this would indicate worst prognosis for that peculiar patient.

It should be remembered that low or very low protein diets were initially planned to delay uremic death in times where dialysis was an extremely demanding procedure for patients, and since some amino acids provided by food proteins feed directly urea pathway [18], cachexia accompanied this procedure, so that even in those pioneer studies the use of EAA as supplements were recommended [19].

The use of EAA as the only or main source of nitrogen has been rarely tested [12], more frequent is the use

of EAA based formulations as supplement to diets [20],[21],[22] and It is of notice that plasma urea never rises to pathological values in those studies, even if the amount of nitrogen supplied as EAA was extremely significant.

Alimentary proteins contain universally a smallest proportion of EAA and a largest of NEAA, and, as said, arginine and glutamine/glutamic acid, are preferred substrates and precursors of urea synthesis and most abundant in alimentary foods [23]. Certainly arginine and glutamine availability may become limited in plasma of patients with hyper-catabolic conditions and insufficient supply of nitrogen sources, but in front of health problems deriving by introduction of each of those amino acids [24],[25],[26] on the contrary, increasing supply of EAA as therapy, that is increasing EAA input as naturally occurring metabolic precursors of the NEAA arginine and glutamine/glutamic acid, is a solution that has never been fully explored. But, when supplementation with EAA has been done in small series of critically ill, results were exceptionally good [27]. Indeed, EAA based are both quite expensive formulations, and although easily available on different markets, have never been produced or tested by market leaders but for intravenous use. Parenteral route reduces the efficacy due both to poor solubility of key amino acids and to the excessive osmolarity of those solutions so requiring low concentrations, large volumes of liquid and long time for infusing adequate amounts of amino acids. Those chemical features of AA are limiting on the amounts that should be given on a daily base intravenously, and would not be able to create peak of plasma concentrations suitable to induce intra-cellular protein syntheses [28]. In author's opinion and based both on some animal and human studies [8],[9],[10],[29], a double blind controlled comparison of oral supply of any food protein versus an EAA formulation containing only free amino acids in stoichiometric ratios tailored on human needs [6] would be important to verify if EAA may match patient's needs at best. This study, if successful, would be seriously challenging for the use of less efficient but expensive supplements providing nitrogen as food derived protein or peptides, which indeed proved to be poorly effective on albumin syntheses [3].

Conclusions

There are different opinions about how to treat hypoalbuminemia, some authors consider no treatment of this evidence efficient. On the contrary, long term EAA supplementation to diet in large amounts, that is in amounts that empirically prove to be sufficient to improve and maintain elevate syntheses of short lived liver proteins should be necessary to safely achieve improved albumin syntheses and survival in responding patients.

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