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LETTER TO THE EDITOR

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Biochemical rationale for hypoalbuminemia in COVID-19 patients

To the Editor,

Recently, Huang et al.[1] have published an article in this journal, wherein they concluded that hypoalbuminemia is associated with the outcome of coronavirus disease (COVID-19). However, the mechanism for hypoalbuminemia in COVID-19 has not been explained. Considering the median onset time (time from the onset of illness to admission) of 3 days, and comparing with the half-life of albumin as 21 days, authors have suggested that hypoalbuminemia was less likely to be a result of decreased albumin synthesis for which I hereby express little disagreement and, through this letter, try to provide a biochemical rationale.

Let us calculate the energetic and nutritional burden, using the complete genome of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2; GenBank: MN988668).[2] To generate viral genomic RNA, ribonucleotides (NTs) are synthesized, each costing approximately 46 ATP (each ATP is considered here equivalent to one high energy phosphate bond).[3] Viral proteins viz spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins require AAs as mentioned (Table 1). Of 20 total, only 12 are synthesizable, each costs differently (Table 1).[4] Each virus has approximately 74 spikes, each of S proteins trimers, at least equal number of E proteins, 1,100M protein dimers, and minimum of 730N proteins.[5] Synthesis of RNA costs 2 ATP/NT, while protein costs 4 ATP/AA. If expenditure, exclusively toward the viral genome and structural proteins are accounted, then each virus costs minimum 1.7×10^7 ATP along with the nutritional load of EAAs (Table 1).

Even in mildly symptomatic patients, if the pharyngeal virus shedding on just 4th day of symptoms goes up to 7.1×10^8 virus per swab with shedding being detected up to 28 days,[6] then one can imagine the speed of replication, duration, and viral load in the entire body, and can envisage the energy burden on a human body to generate billions of SARS-CoV-2 along with EAAs load. COVID-19 spreads through respiratory droplets indicating that the virus gets continuously liberated, results in depletion of body AAs. This can change the whole equilibrium of the body, leading toward the consumption of protein stores. Also, the bioenergetic burden will not favor the use of energy resources to synthesize the 12 synthesizable AAs.

Albumin, a reservoir of excessive dietary AAs,[7] is exclusively synthesized in the liver, the synthesis being modulated by AAs and protein intake. Nutritional regulation of albumin synthesis occurs primarily at the transcriptional level, with hepatocyte nuclear factor 1 (HNF-1) as one of its strong transcriptional activators. AAs availability is suggested to be responsible for HNF-1-mediated transcriptional regulation. Supplementary branched-chain (BC) AAs, have been considered to induce mammalian target of rapamycin-mediated albumin translation.[8] With each virus liberated, the body is stripped of enormous amount of eight EAAs, of which BCAAs (valine, leucine, and isoleucine) account for 53.5% of the EAAs. Thus, continuous virus replication, and its shedding, can cause a considerable reduction in BCAA levels which can impact the albumin translation accordingly. Overall, these effects can only result in decreased albumin synthesis. The albumin levels are maintained due to a balance between the rate of albumin synthesis and albumin clearance, through the renal and gastrointestinal route, and catabolism. An increased breakdown of albumin with a subsequent decreased albumin synthesis can result in hypoalbuminemia.

The suggestion by Huang et al.,[1] based on the onset time of 3 days in comparison to 21 days of half-life of serum albumin, needs reassessment. During interpretation, it should be noted that the exchange of albumin between the plasma and the interstitium is a highly dynamic process where the albumin leaves the vascular compartment at a rate of 5% per hour and the circulatory half-life of albumin is just 16–18 h.[9] Additionally, in patients without pre-existing liver disease suffering from fever may have an albumin half-life reduced to about 7 days with serum albumin concentrations falling rapidly below 30 g/L, clearly suggesting a marked increase in albumin removal as well as inhibition of albumin synthesis.[10]

Moreover, the incubation period for COVID-19 can be up to 14 days, with a considerable percentage in presymptomatic stage, where the virus inside the body starts replicating and consuming AAs with no outward display of illness. The onset time thus has an onset of illness as a subjective component. Additionally, Huang et al.[1] have reported a higher onset time in the hypoalbuminemia group as compared to normoalbuminemia group. So. the general postulation of hypoalbuminemia not due to decreased albumin synthesis may be scientifically inappropriate. In fact, hypoalbuminemia appears due to increased catabolism to make the AAs available, with simultaneously decreased

TABLE 1 Distribution of amino acids in structural proteins of SARS-CoV-2, energy expenditure in terms of number of ATPs to synthesize viral RNA, viral proteins, and burden of eight essential amino acids on human body in generating virus

	Viral structural proteins				ATPs for each NEAA[4]	Nutritional burden of EAA per virus[a]	Viral genome[b]
	S	E	M	N			
Number of AAs per protein[b]							
NEAA							
Glycine	82	1	14	43	11.7	NA	NA
Proline	58	2	5	28	20.3	NA	NA
Alanine	79	4	19	37	11.7	NA	NA
Cysteine	40	3	4	0	24.7	NA	NA
Tyrosine	54	4	9	11	50	NA	NA
Histidine	17	0	5	4	38.3	NA	NA
Arginine	42	3	14	29	27.3	NA	NA
Glutamine	62	0	4	35	16.3	NA	NA
Asparagine	88	5	11	22	14.7	NA	NA
Glutamate	48	2	7	12	15.3	NA	NA
Aspartate	62	1	6	24	12.7	NA	NA
Serine	99	8	15	37	11.7	NA	NA
EAA							
Valine	97	13	12	8	NA	54736	
Leucine	108	14	35	27	NA	121722	
Isoleucine	76	3	20	14	NA	71314	
Methionine	14	1	4	7	NA	17092	
Phenylalanine	77	5	11	13	NA	51154	
Tryptophan	12	0	7	5	NA	21714	
Threonine	97	4	13	32	NA	73790	
Lysine	61	2	7	31	NA	51720	
Number of AAs or NTs per molecule	1,273	75	222	419	NA	NA	29,881
ATPs toward material	13,531	666	2,196	4,815	NA	NA	1,374,526
ATPs toward synthesis	5,092	300	888	1,676	NA	NA	59,762
Number of molecules per virus	222	74	2,200	730	NA	NA	1

Abbreviations: E, envelope protein; EAA, essential amino acid; M, membrane protein; N, nucleocapsid protein; NA, not applicable; NEAA, nonessential amino acid; NT, nucleotide; S, spike protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

[a]Burden of EAA on the human host is calculated in terms of number of EAAs stript per virus particle.

[b]Calculated from GenBank: MN988668.1 at https://www.ncbi.nlm.nih.gov/nuccore/MN988668.

albumin synthesis. The decreased albumin synthesis does play a significant role in hypoalbuminemia more so in the severe COVID-19 patients.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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