Vulnerabilities That Spread Systemically to Cause Complications

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COVID-19 and long COVID-19 vulnerabilities may be caused indirectly by albumin binding deficiency (ABD), which can be corrected by the correct administration of human serum albumin(HSA). The liver is the primary site of nutrient regulation and fluid volume maintenance; control of both is by changes to albumin concentration. In healthy subjects, the HSA lymphatic nutrient pump(HSALNP) ensures continual pumping of nutrients from the liver and that nutrients are appropriately distributed to organs. Nutrients are delivered to cells according to the availability of binding to HSA.The HSALNP, therefore, maintains the correct nutrient and colloidal pressure balance in all tissues independently. In unhealthy tissues, following COVID-19 infection, the passage of HSA/nutrients through the interstitial spaces and lymph will be impeded. Fluid therapy into the periphery leads to the dilution of essential nutrients attached to the protein carriers such as albumin. The levels of albumin being charged by the liver with nutrients is critical in maintaining immune stability by maintaining nutrient support and colloidal pressure of the cellular structures. The site of HSA binding by the liver is of great importance, and direct infusion of albumin into the hepatic portal vein is the most appropriate method of maintaining colloid pressure and cellular nutrient levels.

Keywords: human serum albumin ; COVID-19 vulnerabilities ; fluid therapy ; albumin binding deficiency ; lymphatic nutrient pump

1. Albumin-Binding Deficiency

COVID-19 virion increase, and antibody immune response depends upon factors that affect immune response such as vaccination status or health issues. However, the timing always produces a decrease in albumin binding. All three types of ligands—virions, antibodies, and waste—compete for transport with the protein carrier system, the most abundant of which is HSA. As the levels of ligands increase the albumin-binding potential is reduced for the nutrient ligands such as glycolates that maintain the integrity of the endothelial capillaries [1][2]. As competition increases between different ligands and HSA binding sites in the plasma, interstitial fluids, and lymph, the intracellular concentration of ligands also changes. These changes in ligand-nutrient concentration are a result of the different binding opportunities afforded by ligands during capillary exchange when albumin binding becomes deficient and has implications for patients with COVID-19 vulnerabilities. This capillary exchange may also affect colloidal pressure. Albumin-binding deficiency can occur because of insufficient albumin and/or insufficient binding sites; both are relevant to COVID-19 and long COVID-19. Albumin binding deficiency has been shown in chronic kidney disease [3]. Oxidative damage may also impair the binding properties of albumin. In advanced liver disease, a reduced binding capacity of albumin site II has been found mainly related to impaired liver function [4].

2. Common Damage to Epithelial Cells

The layer provides the integral support mechanisms for cellular adhesion, while a decrease will lead to cellular instability. Endothelial permeability appears quite early in the progress of aging. Aortas of 30-month-old rats had a two-fold increase in endothelial permeability to albumin compared with 10-month-old rats [5]. Endothelial cells lining blood vessels form a continuous layer that constrains proteins and blood elements to the vascular lumen. An increase in endothelial cell isometric tension (contraction) may disrupt the continuous endothelial barrier, leading to an increase in permeability and development of oedema, a hallmark of acute and chronic inflammation [6]. Recently, a comprehensive COVID-19 treatment protocol has been suggested involving the need to preserve the glycocalyx involving *N*-acetylcysteine (NAC) and other sulphur donors by optimising inorganic sulphate availability and, therefore, sulfation [7]. During COVID-19, any albumin-nutrient deficit may result in weakening of the endothelial cells, for example due to dissolution of the glycocalyx layer [1][2]. This leads to infection across barriers such as the gut and blood–brain barriers. The glycocalyx layer also becomes undersulphated in COVID-19. “The undersulphated glycocalyx may not only increase susceptibility to SARS-

CoV-2 infection, but would also result in a hyperinflammatory response, vascular permeability, and shedding of the glycocalyx components, giving rise to a procoagulant and antifibrinolytic state and eventual multiple organ failure" [8]. Once the barrier function is compromised, large molecules such as albumin pass through, changing both pressure and nutrient support. The weakening of this layer changes cellular structural integrity, leading to secondary infections, loosening of intercellular adhesion, and direct changes to the nutritional medium of the cell and thrombosis. The effects of sepsis are, therefore, cellular in nature and are dependent on the type of cell and function not necessarily organ based. That many organs are affected concurrently indicates the common factor of albumin binding deficiency (ABD) and is linked to the lymph nutrient–albumin pump.

3. The Lymphatic System and Plasma–Lymph Nutrient–Albumin Pump

The lymphatic system is conventionally regarded as part of the immune system, in part because of the changes that take place during infection. A closer look reveals a system that can be considered being made of channels starting as the leakage of fluid from capillaries through endothelial cell gaps into interstitial spaces. This fluid initially resembling plasma and containing the full protein–ligand complements of plasma infuses the interstitial spaces around cells, providing membrane surface area access to cells. Flow is determined by the mechanical action of movement and muscle rather than from cardiac activity, with the lymph formed flowing back into the venous system and eventually the vena cava and heart. The circulation of albumin is complementary to the cardiac circulatory system to which it returns extracellular fluids [9]. Transport of nutrients in the blood, therefore, follows a separate circulatory pattern to that of the gaseous respiratory system, and rather than a few minutes, it may take hours or weeks for an albumin molecule to circulate in a normal healthy subject due to the half-life of albumin within the interstitial fluid.

Nutrients enter through the stomach and are transferred via the hepatic portal vein (HPV) into the liver. Hepatocytes in the liver perform an enzymatic modulation of HPV and hepatic arterial plasma, responding to hormones such as insulin to maintain glycogen. The liver can store and metabolise molecular structures. It can both metabolise and manufacture albumin according to pressure. Organ body fluid concentrations of nutrients and colloidal pressure are, therefore, moderated and controlled by the liver. Both released and circulating albumin bind to the moderated concentrations of molecular nutrients until equilibrium is formed by mixing. Nutrient bound albumin then passes through the heart to the lungs.

In the lungs, 60–80% of the nutrient–albumin complex passes into the interstitial spaces and remains there for many hours before returning to the vena cava through the lymph, the rest remaining in circulation. Only about 10% will be recharged by the liver. In the lungs, some nutrients on the albumin complex are exchanged for waste products because of metabolism. In healthy patients, the moderation of nutrients with albumin is assumed to be minimal; however, any illness or damage to the lungs will cause this equilibrium to change. In COVID-19-infected lungs, COVID-19 virion antibodies and waste replace nutrient ligands, changing both nutrients and colloidal pressure [10]. The aerated plasma is then pumped by the heart to the organs and periphery. Only about 10% of the lymph returns to the liver to be recharged with ligands. In a healthy subject, the continual mixing and rapid supply of re-bound albumin through the capillary circulation is enough to prevent albumin-binding deficiency. During COVID-19 infection in the lungs, there will be a rise in COVID-19 virions, corresponding antibodies, and detritus. In addition, secondary infections will have the additive effect of creating further antibodies.

4. Liver

The liver is the main control of nutrient ligands and waste in the body and the site of albumin synthesis [11]. The feedback process to evaluate nutrients and controlled supply is indirectly provided by the ligand–albumin complex. Albumin synthesis is directly linked to the reduction in pressure in hepatocytes caused by insufficient HPV blood pressure. Albumin provides 80% of oncotic pressure and the addition of albumin increases blood volume and pressure in the hepatocytes self-regulating overall blood volume and pressure and concurrent nutrients. A lack of nutrients in the periphery changes colloidal pressure by changing the binding of nutrients [10], metabolism, and hydration, thereby reducing the amount of albumin in the blood because of low lymph flow and metabolism of albumin. When nutrients are bound to albumin, they are removed from solution but maintain most of the hydrogen bonds responsible for their oncotic pressure. Bound albumin removes ligands from solution but retains the ligand's hydrophilic ability, increasing osmotic pressure. This causes low pressure in the hepatocytes and instigates the production of albumin. Oncotic pressure reduction will occur across the system, including on the hepatocytes, which produce more nutrient bound albumin.

5. Obesity

The most prevalent vulnerability to COVID-19 is obesity. Obesity is a worldwide major public health problem affecting many organs, including the heart, where it can cause heart disease, stroke, high blood pressure, diabetes, cancers, and dermatological complaints. Obesity has metabolic effects, such as causing hyperandrogenism and gout, which in turn are associated with cutaneous manifestations [12]. Dermatological manifestations of a systemic disease, such as gout, must have a systemic common factor.

Fatty acid concentrations in the plasma, interstitial fluids, and lymph have been shown to reflect the concentrations in adjacent fat cells. More fat in cells create a corresponding higher level of fatty acids in the interstitial spaces [13]. Fatty acids are transported by albumin, and greater obesity leads to a higher concentration of fatty acids in the blood and bound to albumin, causing binding deficiency. As fatty acids rise in the interstitial fluids, lymph, and plasma, more remain bound to albumin in circulation. This reduces the number of available binding sites on albumin for other nutrients to supply endothelial and cellular structures. A reduction in binding sites sufficient to affect nutrients eventually destabilises cell integrity.

6. Diabetes

Both insulin and glucose are transported by albumin as well as competing fatty acids. Restricting insulin access to albumin-binding sites in COVID-19 reduces the concentration of insulin concentration delivered to the liver with the subsequent elevation of glucose. This excess glucose may result in glycosylation of albumin further reducing binding sites. A reduction in albumin predicts type 2 diabetes [14]. This process is promoted by the presence of elevated blood glucose concentrations in diabetes and occurs with various proteins [15]. Glycated albumin also suppresses glucose-induced insulin secretion by impairing glucose metabolism in rats [16] and pancreatic β-cells dysfunction through autophagy [17].

Glycated albumin has a greater affinity for virions than albumin, and the ability of bacteria and viruses to surround themselves with serum proteins is a recognised immune evasion and pathogenic process [18]. SARS-CoV-2 spike binding protein binds to glycated serum albumin [18]. Long-term binding of virions in interstitial spaces would slow the flow and isolate COVID-19 virions shielded by albumin for many weeks and may be an explanation for Long-COVID-19.

7. Arthritic Pain

Biological activity regulation by protein post-translational modification (PTM) is critical for cell function, development, differentiation, and survival. Dysregulation of PTM proteins is present in various pathological conditions, including rheumatoid arthritis (RA) [19]. A decreased albumin/globulin ratio in RA patients significantly correlates with dyslipidemia and ARDs, implicating the albumin binding limits of fats concurrently changing [20].

8. Lungs

An unusual feature of the COVID-19 disease is microthrombosis and localised disruption of the osmotic potential with pulmonary microvascular dilation, a commonality in sepsis-induced ARDS [18]. In COVID-19, there is a greater risk of thrombosis [21] and coagulation [22]. Most patients are asymptomatic, with only a few patients severely affected. The resultant stagnation of HSA and ABD will reduce the levels of waste and distort the action of cellular structures, providing a possible mechanism for the “ground glass lung opacity”, seen in COVID-19.

9. Heart

The risk of cardiovascular problems, such as a heart attack or stroke, remains high even many months after a SARS-CoV-2 infection clears up [23] and can affect even those with mild symptoms. The heart is a dynamic organ in continuous movement regulating pressure and flow of blood to the whole body; importantly, the movement of the heart also determines heart lymph flow, determining the amount of nutrients transported to essential heart cells. In disease, the first limiting factor is usually oxygen supply, where deprivation can produce stress within seconds; for medical practitioners, this is usually the first concern. Secondary to this, to maintain functional stability, the heart cells must be infused with nutrients. This occurs over a longer time-period, with albumin-charged nutrients lining the endothelial glycocalyx, protecting the stability of both capillary walls, and maintaining the correct supply of nutrients. This is dependent upon the albumin lymphatic pump over a much longer timescale, as heart movement and lymphatic flow become restricted and nutrients slowly cease to be delivered. As discussed above, the heart is secondary to the lungs; a change in nutrient

metabolism due to lung disease, producing a deficit in nutrients over time, will inevitably lead to further degradation of the heart and its function.

10. The Blood Brain, Placental Barriers, and Albumin Transport in the Kidney

A common factor for the blood–brain barrier (BBB), the placental barrier (PB), and the kidney is that normal movement of albumin is restricted, and in each case, albumin is controlled by clathrin enabled endocytosis [24][25]. Infection with COVID-19 leads to a reduction in albumin binding sites, including that used by clathrin to initiate endocytosis of the albumin–nutrient complex. This blocks the albumin from entering the cell and passing the barrier in each case.

11. The Central Nervous System and the Blood–Brain Barrier (BBB)

Severe COVID-19 and long COVID19 are both associated with cognitive defects [26]. In healthy subjects, both nutrients and pressure are kept stable within the cerebral spinal fluid (CSF) by the action of the blood–brain barrier, which stabilises and regulates albumin, intercranial pressure, and bound nutrients. Both pressure and nutrient support are therefore maintained within controlled limits within the CSF in a separate environment to the cardiac circulation. In the CSF, where 95% of amyloid b is bound to albumin [27], any decrease in binding levels will have a direct effect on amyloid beta (Aβ) concentration, potentially increasing plaque formation [28]. Studies have shown that the possibility that patients with COVID-19-associated neurological syndromes exhibit impaired amyloid processing [29]. There is therefore evidence of a connection between neurological damage due to plaque formation, with a direct link to the control of Aβ by albumin and albumin binding levels [27].

During initial COVID-19 systemic infection, COVID-19 virions interfere with entry of a proportion of the albumin by occupying the binding site for clathrin. This leads to gradual nutrient deficit within the CNS. There will also be weakening of the capillary walls due to lack of glycolates [9], thrombosis [30], and disturbances of synapse connectivity as transmitter vesicles decay. As the disease progresses the blood–brain barrier becomes weaker, and rupture may ensue, allowing larger bacteria, in addition to viruses, to enter from the systemic system leading to meningitis. There may, therefore, be more than one action occurring during COVID-19 infection in the brain in regard to albumin:

(I) Virions attached to HSA may affect the transport of vital nutrients across the BBB. This nutrient deficit will depend upon the state of has-binding deficiency. This level of binding deficiency will alter the levels of transmitter and affect transmission of action potential affecting cognition.

(II) Depletion of nutrients will also affect the capillaries of the brain, for example, the endothelial glycocalyx layer (EGL) already described [1][13]. A reduction in the EGL will eventually cause leakage, thrombosis [30], and rupture. Rupture may promote secondary infection, leading to symptoms of meningitis [31].

12. Kidney

Pathology of COVID-19 in the kidney indicates symptoms of nephrotic syndrome, numerous glomerulonephritides, microscopic polyangiitis vasculitis and collapsing glomerulopathy, and thrombotic microangiopathies, such as atypical haemolytic uremic syndrome (aHUS) [32].

In healthy individuals, there is minimum albumin loss from the kidneys and any albumin is reabsorbed by the peritubular capillaries by phagocytosis [33][34]. The glomerulus, the filtering unit of the kidney, is a unique bundle of capillaries lined by delicate fenestrated endothelia [35]. A large percentage of COVID-19 affected patients present with acute kidney injury (AKI); most cases of CoV-AKI are driven by a form that can cause impairment in tubular reabsorption of filtered proteins [36]. Reabsorption of albumin is usually by clathrin-mediated endocytosis, as described above. This necessitates the binding of albumin to clathrin. Any ligand that competes with clathrin will change this equilibrium and permit albumin to pass into the urine. This also correlates with evidence that urinary excretion of uric acid is negatively associated with albuminuria in patients with chronic kidney disease [37]. The association between albuminuria and serum uric acid may not be interrelated via renal handling of uric acid [37] but by the levels of albumin-binding available [37].

13. Pregnancy

Previously [38], researchers noted that albumin is entirely metabolised by the foetus and is not therefore circulated by the liver. Pregnancy therefore removes bound albumin–nutrient complexes for the metabolism of the foetus, leaving a deficit

that may be one cause of the adverse symptoms in preeclampsia [38]. A lack of albumin due to metabolism by the foetus is a plausible explanation for the stresses some pregnant women have experienced in the third trimester. For the same reason, in COVID-19, both the foetus and mother may experience reduced albumin-binding caused by both the permanent exclusion of returning albumin from mother to foetus and COVID-19 disease.

14. Skin: Distribution of Albumin in the Adult and Child and Infant Body

The human foetus metabolises albumin passed from the mother in the form of the albumin–nutrient complex. In the young child, albumin is concentrated in the periphery and the muscle and skin; this may be caused by children having a larger surface area to volume ratio. In the adult, the lungs and organs contain relatively larger proportions. There are great variations between individuals and ages. There have been many reported instances of dermatologically significant issues [39], including, thrombosis, chilblains [30][39][40][41][42], mucocutaneous disease [43], purpura [44], and rashes. The frequency and timing of cutaneous manifestations of COVID-19 are difficult to ascertain; also unclear is the association of certain skin manifestations with the illness severity. Moreover, it cannot be excluded that, in some patients, the observed skin findings may represent cutaneous reactions to the treatments used for COVID-19.

Obese COVID-19 patients have a high occurrence of dermatological problems. Increased body mass index affects skin physiology, skin barrier, collagen structure, and wound healing. Obesity also affects sebaceous and sweat glands and causes circulatory and lymphatic changes. Furthermore, obesity is associated with an increased incidence of bacterial and Candida skin infections, as well as onychomycosis; inflammatory skin diseases; and chronic dermatoses such as hidradenitis suppurativa, psoriasis, and rosacea. Obesity is also related to rare skin conditions [12]. Obese children have a higher prevalence of skin lesions than normal weight children [45].

In COVID-19 infection, the dermatological signs are diverse and the timing is irregular. There is a greater resting pool of albumin during COVID-19, remaining in the interstitial spaces for longer; a lack of movement during illness reduces the activity of the HSALNP HSA lymphatic nutrient pump, isolating the stagnating albumin and causing albumin binding deficiency in associated areas depending upon flow. For the skin of a child, therefore, dermatological nutrients bound albumin and, therefore, nutrients will be decreased in relation to the percentage of albumin flow, with changes in colloidal pressure. The timing of this is dependent upon the nutrient-bound albumin flow into the interstitial spaces. The pooling of albumin may be provoking dermatological reactions independently from the COVID-19 infection sites. Dermatological conditions, therefore, will vary according to localised albumin pooling, timing, and binding deficiency. A lack of available albumin binding may therefore instigate systemic nutrient deficiency, leading to symptoms of multisystem inflammatory disease, where apart from obesity (25.3%), comorbidities are rare [46].

Hypercortisolaemia is a condition involving prolonged excess serum levels of cortisol that can develop as a result of disregulatory abnormalities in the hypothalamic-pituitary–adrenal axis or from exogenous-source steroids. Hypercortisolaemia induces a state of immunocompromise that predisposes the patient to various bacterial, viral, fungal, and parasitic infections [47]. Low serum albumin levels in patients with ischemic stroke are associated with higher serum cortisol levels and predisposes to hypercortisolaemia [48]. High serum total cortisol concentrations are associated with high mortality from COVID-19 [49].

Inflammatory markers and acute phase reactants (“markers”) are also associated with COVID-19 infection and may be able to predict disease severity [27][50][51]. Negative acute phase reactants are downregulated, and their concentrations decrease during inflammation. Positive acute phase reactants include procalcitonin, C-reactive protein, ferritin, fibrinogen, hepcidin, and serum amyloid A. Negative acute phase reactants include albumin, prealbumin, transferrin, retinol-binding protein, and antithrombin. A reduction in albumin binding will have a concurrent effect on marker concentration.

15. Fluid Therapy

The use of fluid therapy is ubiquitous in medicine, with all medical staff, doctors, nurses, and many ancillary staff trained in infusion techniques. “Intravenous fluid therapy is one of the most common interventions in acutely ill patients. Each day, over 20% of patients in intensive care units (ICUs) receive intravenous fluid resuscitation, and more than 30% receive fluid resuscitation during their first day in the ICU. Virtually all hospitalized patients receive intravenous fluid to maintain hydration and as diluents for drug administration. Until recently, the amount and type of fluids administered were based on a theory described over 100 years ago, much of which is inconsistent with current physiological data and emerging knowledge. Despite their widespread use, various fluids for intravenous administration have entered clinical practice without a robust evaluation of their safety and efficacy. The belief that dehydration and hypovolaemia can cause or worsen kidney and other vital organ injury has resulted in liberal approaches to fluid therapy and the view that fluid overload and

tissue oedema are ‘normal’ during critical illness; this is quite possibly harming patients. Increasing evidence indicates that restrictive fluid strategies might improve outcomes.” [52]. Attempts at albumin infusion have been inconclusive [53][54], but there is ongoing discussion of its merits [52][55].

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