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PRE-ECLAMPSIA, HYPOALBUMINAEMIA AND ALBUMIN THERAPY.

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ABSTRACT

Albumin is a transport protein for other ligands: its presence in the plasma modulates nutrient supply to tissues. During pregnancy the foetus metabolises albumin passed across the placenta causing a depletion that cannot always be maintained by the maternal pool of albumin. In cases of poor nutrition, a cellular nutrient crisis may occur during fast foetal growth leading to maternal albumin deficiency and consequent nutrient loss throughout the systemic system. We suggest that to correct this loss and provide properly ligand-charged nutrients albumin should be infused into the portal vein system of the liver and not the periphery ensuring that new albumin is passed through the liver before entering the systemic system.

Pre-eclampsia affects from 3% to 14% of pregnancies worldwide and is a major cause of maternal and perinatal morbidity and mortality. There is already considerable evidence that pre-eclampsia may be intensified by a decrease in human serum albumin (HSA) (Gojnic et al 2004, Martell-Claros et al 2019). We have shown in recent review articles (Johnson and Winlow 2020,Johnson and Winlow 2021) that levels HSA and other ligand binding proteins in blood plasma are intrinsically linked to the levels of nutrients provided to the cells of epithelia where most damage occurs (Johnson and Winlow 2020) during the systemic stages of COVID-19 infection.

In applying our hypothesis on transport proteins from our work on albumin and COVID-19, a mechanism for the causation of the symptoms of pre-eclampsia became apparent. We provide evidence that pre-eclampsia is probably due to a crisis of hypoalbuminaemia caused by foetal metabolism – HSA produced by the mother's liver is metabolized by the foetus, but none is returned to the maternal circulation. Although HSA and its binding properties have been known for many years a full consideration of how binding proteins, such as HSA, transport vital nutrients systemically is not often considered, except as markers for illnesses like cancer. There is now considerable evidence to suggest that HSA levels are critical in maintaining the nutrient balance and concentrations in the target cells (Rabbani et al 2021, Johnson and Winlow 2020).

In the pregnant female a crisis of severe hypoalbuminaemia can occur due to the mechanisms of HSA maintenance between the mother and foetus. To supply the foetus with nutrients the HSA-complex does not pass the placental barrier (PB) but is envisicled by attachment to the protein clathrin (Lambot et al 2006). HSA is not returned by the foetus and not returned to the pool of the mother. The mother's liver therefore must provide the bulk of foetal HSA for the plasma and free-body-fluid pool where most HSA resides.

The foetus metabolizes HSA completely not returning it to the placenta or the mother's vena cava, foetal pool HSA is then circulated through the foetal liver and placenta. This may produce hypoalbuminaemia especially during rapid growth of the foetus, or poor nutrition of the mother or illness. Diet and nutrition are known risk factors for preeclampsia (Cao et al 2020). We submit that it is probably hypoalbuminaemia caused by foetal oversupply at a time of nutrition deficit that causes the symptoms and presentation of pre-eclampsia.

We hypothesise that low levels of pool HSA binding, caused for whatever reason, affect the performance of HSA as a carrier protein (CP) reducing the availability of nutrients. HSA is created in the liver of the mother where it is bound to the suitable nutrients to supply the plasma. It is unclear whether the foetal liver supplies any of its albumin requirements – the regulation is therefore determined by the mothers' liver. The clinical implication is that attempts made to return HSA to clinical levels must be directed at the portal system of the liver or must have HSA already bound to the appropriate proteins. Our hypothesis involves considering albumin and other binding-proteins as being part of the liver

circulatory system. In this model the regulation of albumin is defined mainly by the oncotic pressure within the portal vein of the liver. Albumin formation in the liver is formed in equilibrium with its precursors by the hepatocytes, the levels of albumin and corresponding precursors varying according to concentrations of precursor components that are catalysed by the correct portal vein pressure. It has long been known that portal vein oncotic pressure is related to HSA concentrations which in turn defines fluid volume. This process is reversible with the liver able to use and re-metabolize components for storage and other protein synthesis. In turn the availability of albumin permits the free control of essential components to the cellular structures (Johnson and Winlow 2020, Johnson and Winlow 2021). This produces an immediate hypoalbuminaemia, especially when the patient is low on pool HSA with subsequent collapse of the systemic system. Therapeutic albumin is usually given peripherally, and most preparations are unbound to ligands. Therefore, we suggest that a clinical trial of HSA therapy via the hepatic portal vein should be considered and studies should be performed to evaluate better preparations of HSA. HSA and other carrier proteins are intrinsically implicated in the systemic spread of COVID-19 (Johnson and Winlow 2020, Johnson and Winlow 2021) but protecting the body against the vulnerabilities of pre-eclampsia by using the portal structure is a new untried technique, which, if it works, should reduce harm directly.

We conclude that the reason infusion of HSA has historically led to unpredictable results is that using a peripheral point of entry leads directly to unbound-HSA lingering in the HSA pool. Addition of HSA must be given to the portal system so that nutrients and colloidal pressure may be correctly maintained within the systemic transport system. This area of research has been neglected and we feel very strongly it should be included in further research on pre-eclampsia. It is our hypothesis that properly increasing available pool HSA will eliminate many symptoms of pre-eclampsia. This can be achieved by pre-binding the carrier protein HSA before addition or adding to the portal vein instead of a peripheral vein to enable the natural binding of liver ligands to HSA to occur and for correct modulation of colloidal pressure. Infusion of HSA from a peripheral vein should take place through the portal system to ensure correct management both of nutrients but colloidal pressure.

Author contributions

ASJ conceived this work based on our previous reviews on Covid-19. We designed, refined and approved the submitted version of the manuscript together.

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Conflicts of interest

The authors declare no conflicts of interest.

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