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Factors that affect albumin concentration in dialysis patients and their relationship to vascular disease

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Introduction. Hypoalbuminemia is a powerful risk factor for cardiovascular mortality in hemodialysis patients (HD). Inflammation causes a decrease in albumin synthesis and an increase in albumin fractional catabolic rate, providing two mechanisms for hypoalbuminemia. The inflammatory response alters the endothelium and plasma protein composition in ways that favor vascular injury. Plasma volume is expanded in HD patients, providing another mechanism for hypoalbuminemia. Fibrinogen levels are an independent risk factor for cardiovascular disease (CVD) in HD patients, and fibrinogen levels are increased in HD patients. Plasma volume expansion is also an independent risk factor for CVD.

Methods. Albumin synthesis was measured in 74 HD patients as the disappearance of [^{125}I] human albumin over six weeks. Fibrinogen was measured in plasma. Plasma fibrinogen mass was the product of fibrinogen concentration and plasma volume.

Results. Albumin synthesis correlated positively with plasma volume ($P < 0.001$). Fibrinogen concentration and plasma fibrinogen mass both correlated positively with albumin synthesis ($P < 0.001$).

Conclusion. Albumin levels are reduced as part of the acute-phase response in HD. Plasma volume expansion also tends to decrease albumin concentration, but elicits an increase in its rate of synthesis, which, in turn, is associated with increased fibrinogen levels. Thus, both inflammation and plasma volume expansion factors that reduce albumin concentration and are independent cardiovascular risk factors, independently increase fibrinogen levels.

Serum albumin concentration is maintained in a narrow range in healthy subjects. Decreased albumin levels predict mortality in all populations, and are powerful predictors of CVD and all-cause mortality in HD patients [1, 2]. Factors determining albumin concentration are its synthesis rate, fractional catabolic rate-FCR [3], exogenous loss, redistribution into the interstitium, and changes in plasma volume. Volume expansion occurs commonly in chronic renal failure and is a cardiovascular risk factor in this population [4].

To understand the relationship between hypoalbuminemia and increased morbidity and mortality in HD patients requires the precise causes of hypoalbuminemia in dialysis patients be identified. Albumin synthesis is controlled in part by nutrition, especially protein intake [5]. However, malnutrition alone does not cause hypoalbuminemia unless patients are near starvation [6, 7]. For example, patients with anorexia nervosa have essentially normal albumin levels. Thus, hypoalbuminemia suggests additional processes, such as activation of the systemic inflammatory response [8] or albumin loss [9], may be present.

Albumin is a negative acute-phase protein [10]. HD patients with hypoalbuminemia have reduced albumin synthesis and increased levels of acute-phase proteins [11]. We evaluated the relationship between serum albumin concentration and cytokine, or acute-phase protein levels, as well as normalized protein catabolic rate (nPCR), cross-sectionally [12, 13] and longitudinally in HD patients. Cross-sectionally, albumin levels correlated inversely with markers of acute inflammation, including C reactive protein (CRP), or cytokines that control the acute-phase response, such as interleukin-6 (IL-6) [14]. Additionally, albumin concentration correlated inversely with nPCR, reflecting interaction between dietary protein and serum albumin levels [13]. Interestingly, while CRP levels correlated closely with contemporaneous values for serum albumin [13, 15], CRP levels did not predict future serum albumin levels [15, 16]. In contrast, serum levels of more long-lived acute-phase proteins, such as ceruloplasmin or α-1 acid glycoprotein, predicted future serum albumin [16]. Ceruloplasmin and α-1 acid glycoprotein levels correlated positively with albumin fractional catabolic rate (FCR) [17], suggesting that one way in which inflammation decreases serum albumin is by increasing its catabolic rate constant. Thus, the acute-phase response is one factor that strongly controls albumin levels both by decreasing albumin synthesis and increasing its FCR.

Key words: plasma volume, hemodialysis, albumin synthesis, fibrinogen, acute phase.

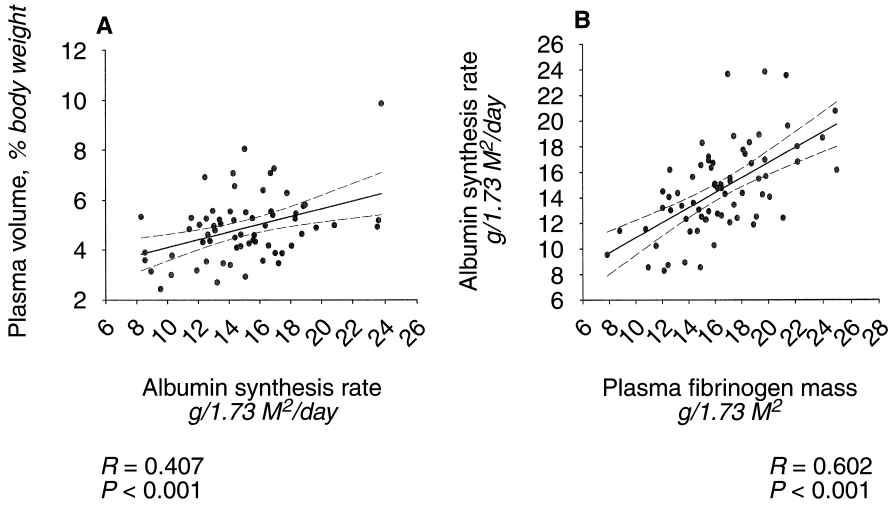

Fig. 1. Relationship between albumin synthesis rate, plasma volume, and plasma fibrinogen mass in 74 HD patients. (*A*, left panel) Albumin synthesis rate was measured as the turnover of [^{125}I] albumin over 6 weeks. (*B*, right panel). Fibrinogen mass was the product of plasma volume, measured as dilution of [^{125}I] albumin and average fibrinogen concentration in plasma measured during the 6-week period of measurement. Fibrinogen was measured nephelometrically. Data are from [42].

Table 1. Characteristics of the calcium-regulatory proteins MGP and Ahsg/fetuin

	MGP	Ahsg/fetuin
Molecular weight	10 kD	62 kD
Serum levels	60–130 U/L	0.5–1.0 g/L
Synthesis	Vascular smooth muscle cells, chondrocytes	Hepatocytes
Phenotype of knockout mice	Aortic media calcifications, cartilage calcifications, lethal due to aortic rupture	Diffuse metastatic soft-tissue and intra-arterial calcification, impaired survival
Properties	Vitamin K-dependent γ-carboxylation, necessary for activation	Negative acute-phase reactant TGF-β antgonist, inhibitor of insulin receptor tyrosine kinase activity

Abbreviations are: MGP, matrix Gla protein and Ahsg/fetuin, α_2-Heremans Schmid glycoprotein.

CRP levels predict cardiovascular risk both in the non-dialysis population [18] and in HD patients [2]. While acute phase protein levels may simply reflect vascular inflammation, the acute-phase response alters both the endothelium and plasma protein composition in ways that would promote vascular injury. Endothelial reactivity is decreased [19] in part from increased utilization of nitric oxide by myeloperoxidase (MPO) [20]. Vascular permeability is increased as are expression of specific receptors that bind leukocytes [21]. These release cytokines locally, as well as MPO. Low-density lipoprotein (LDL) is oxidized and high-density lipoprotein (HDL) that would normally reduce it, becomes dysfunctional by the replacement of apo A-I with serum amyloid A, an acute phase protein [22]. Lipoprotein (a) is a highly atherogenic lipoprotein whose level is usually genetically controlled [23], but is increased in patients with renal failure [24] and is associated with increased mortality in HD [25]. Lp(a) is increased in conjunction with acute-phase proteins [26].

Fibrinogen is another acute-phase protein. Fibrinogen levels are significantly greater ESRD patients compared with healthy subjects, and are an independent cardiovascular risk factor for ESRD patients [27, 28], for vascular access failure [29], and for the general population [30].

We determined the relationship between albumin homeostasis and fibrinogen levels in HD patients to gain insight into the mechanisms responsible for the very high levels of fibrinogen found. In the setting of external protein loss such as that which occurs in nephrotic syndrome [31, 32], or from transperitoneal albumin loss in peritoneal dialysis patients [33], albumin synthesis is increased probably in response to low oncotic pressure. Albumin synthesis is transcriptionally regulated in this regulatory loop [34, 35]. In nephrotic syndrome, fibrinogen synthesis and level is increased [35, 36]. In contrast to the acute-phase response, external protein loss is associated with increased synthesis and transcription of genes encoding both negative [37, 38] and positive acute-phase proteins, such as fibrinogen and albumin [37, 39]. This observation suggests that the genes encoding both positive and negative acute-phase proteins may be regulated so that they are expressed coordinately rather than reciprocally by conditions that tend to reduce plasma oncotic pressure. Thus, two separate and unrelated processes, inflammation and loss of albumin from the body, each have the potential to reduce albumin concentration and increase fibrinogen synthesis.

Plasma volume expansion should cause dilution of plasma proteins and a reduction in serum levels. The

decrease in serum albumin that should accompany dilution is offset in part by an increase in albumin synthesis [40, 41]. Similar to nephrotic syndrome, the increase in albumin synthesis observed with volume expansion is accompanied by increase in fibrinogen synthesis [40]. Similarly, when normal human subjects are brought to altitude, they sustain an increase in plasma volume, as well as an increased rate of synthesis of both albumin and fibrinogen [41]. Under this circumstance, the synthesis of a group of positive and negative acute-phase proteins is increased, including that of albumin and fibrinogen.

We measured the rate of albumin synthesis in 74 HD patients by injecting [^{125}I] albumin and measuring the disappearance kinetically [42]. We simultaneously measured plasma volume by isotope dilution and the average fibrinogen concentration in plasma during the six-week period. Albumin synthesis correlated positively with plasma volume (Fig. 1A), even after correction for age, sex, nPCR, and acute-phase proteins [42]. Fibrinogen concentration correlated positively with albumin synthesis rate [42], as did plasma fibrinogen mass (the product of plasma volume and fibrinogen concentration) (Fig. 1B). Fibrinogen levels also correlated with CRP and concentrations of the long-lived acute-phase proteins ceruloplasmin and α1-acid glycoprotein.

Thus, both the acute-phase response and plasma volume expansion, each individual risk factors for cardiovascular disease in HD patients, independently augment synthesis of fibrinogen, itself a risk factor for cardiovascular disease in this population. The combined effect of these two processes is likely to contribute to the significantly increased levels of fibrinogen in the dialysis population.

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