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Narrative Review

Human serum albumin in cardiovascular diseases

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ABSTRACT

Cardiovascular diseases are the leading cause of death worldwide. Endothelial dysfunction, inflammation and oxidative stress are at the forefront in the onset and development of atherosclerosis and many cardiovascular diseases. Epidemiological evidence is that low serum albumin levels are linked to incident ischemic heart disease, heart failure, atrial fibrillation, stroke and venous thromboembolism, independent of risk factors, body mass index and inflammation. Hypoalbuminemia has also emerged as an independent prognosticator in many cardiovascular diseases, such as coronary artery disease, heart failure, congenital heart disease, infective endocarditis and stroke, even after adjusting for usual causal factors and prognostic markers. Given physiological properties of serum albumin that include anti-inflammatory, antioxidant, anticoagulant and antiplatelet aggregation activity as well as colloid osmotic effect, hypoalbuminemia could act as an unrecognized modifiable risk factor. The purpose of this review is to provide an overview of the physiological properties of serum albumin, as well as prevalence, causes, prognostic value and potential contribution to the disease emergence and progression of hypoalbuminemia, and the resulting clinical implications.

Cardiovascular diseases are the leading cause of death worldwide. Conceptually, endothelial dysfunction, inflammation and oxidative stress, which are linked to many modifiable and non modifiable risk factors, are at the forefront in the onset and development of atherosclerosis and many cardiovascular diseases through a complex and not fully understood pathophysiological process [1–5]. Identifying unrecognized, potentially modifiable risk factors is essential in this setting, which is likely to improve outcome [6].

Albumin is a 69 kDa protein that accounts for more than half of the whole serum body's composition. It has long been well established that hypoalbuminemia is a powerful prognostic marker in the general population and many pathological settings, mainly as a result of malnutrition and inflammation [7,8]. However, evidence is growing that low serum albumin levels are linked to the emergence of several cardiovascular diseases, such as ischemic heart disease, heart failure, atrial fibrillation, stroke and venous thromboembolism, independent of traditional risk factors, body mass index and inflammation. Hypoalbuminemia has also emerged as a potent prognostic parameter in patients with many cardiovascular diseases, even after adjusting for causal factors and traditional prognostic markers. In light of these recent findings, and given physiological properties of serum albumin that include colloid osmotic effect and anti-inflammatory, antioxidant, anticoagulant and antiplatelet aggregation activity, hypoalbuminemia could act as a modifiable risk factor in patients with some cardiovascular diseases. The purpose of this review is to provide an overview of the physiological properties of serum albumin, as well as prevalence, causes, prognostic value and potential contribution to disease emergence and progression of hypoalbuminemia, and the resulting clinical implications.

1. Physiological properties of serum albumin

10 to 15 g of albumin is synthesized in the liver each day and released into the vascular space [9]. Its half-life averages 17 days. Exchanges between the intravascular and interstitial compartments are constant, with 40% of the total albumin pool remaining in the intravascular space. Albumin synthesis is stimulated by insulin, amino acids intake and low colloid osmotic pressure. Factors that decrease synthesis include high colloid osmotic pressure, malnutrition, inflammation, diabetes, liver disease and sepsis. The mechanisms of its degradation are poorly understood, but it is thought to occur mainly in the skin, muscles, liver and kidneys. The normal reference range for serum albumin in adults is 3.5 and 5 g/dl, but the threshold value defining a pathological level may vary from one test to another. Serum albumin concentration is physiologically slightly lower in women than in men and decreases slightly with age (Fig. 1).

Serum albumin has many physiological properties [9–15]. Serum albumin carries many endogenous and exogenous substances, such as inorganic ions, fatty acids, bilirubin, vitamins, hormones and steroids, and drugs. Serum albumin has anti-inflammatory activity that is not

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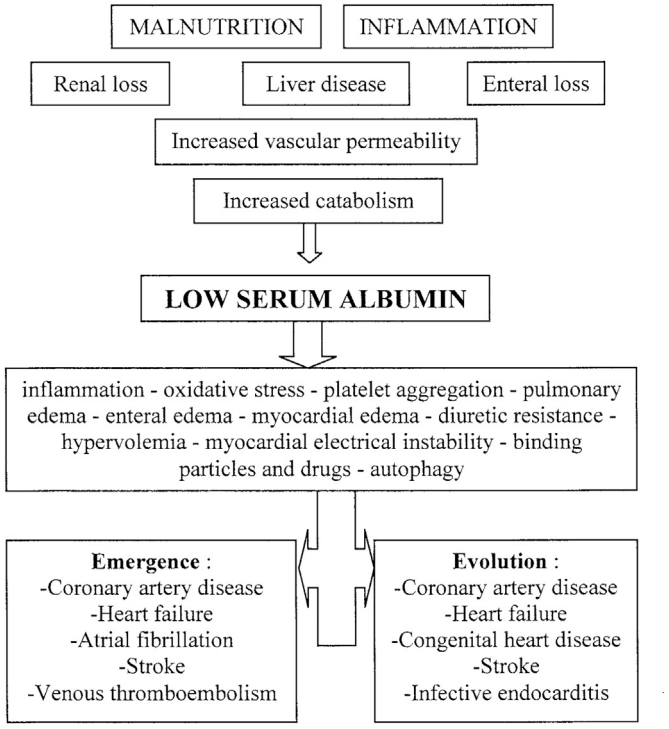

Fig. 1. Illustration of pathophysiological mechanisms involved in hypoalbuminemia and the emergence and evolution of cardiovascular diseases.

well understood [10,11]. On the contrary, serum albumin is viewed as the most important antioxidant in the whole blood [12,13]. Serum albumin contains abundant thiol groups which account for > 80% of total thiols in plasma scavenging reactive oxygen and nitrogen species. In addition, some substances such as nitric oxide and bilirubin are carried by serum albumin and provide additional protection against oxidative stress. Confirmatory evidence is that serum albumin exerts anticoagulant and antiplatelet aggregation activity [14,15]. Serum albumin also contributes to maintain capillary membrane stability and fluid balance across the capillary wall through its colloid osmotic effect and interaction with the endothelial glycocalix [9]. According to the Starling's modified equation, hydrostatic capillary pressure is the main force responsible for the fluid transfer from the intravascular to the interstitial space [9]. The plasma colloid osmotic pressure, of which approximately 80% of the effect results from serum albumin, is the main force opposing fluid extravasation outside the intravascular compartment. The imbalance of Starling's forces as a consequence of hypoalbuminemia induces a net extravasation of fluid to the interstitial space, leading to formation of interstitial edema, hypovolemia and fluid retention [9]. Pulmonary fluid homeostasis has specific characteristics that protect against an isolated decrease in serum colloid osmotic pressure, and increase in pulmonary capillary hydrostatic pressure, even moderate, is necessary for the development of pulmonary edema [9].

2. Prevalence and causes of hypoalbuminemia in cardiovascular diseases

There is no epidemiological data on the prevalence of hypoalbuminemia in patients with cardiovascular disease. However, its prevalence is reported as significant in many observational studies and varies from one to another. Prevalence of hypoalbuminemia ranges from 13% in stable coronary disease to 20–30% in acute coronary syndromes and myocardial infarction [16–19], from 20 to 25% in chronic heart failure to 90% in frail elderly patients with acute heart failure [9], and from 14% to 30% in congenital heart disease, stroke, transcatheter aortic valve replacement and infective endocarditis [20–22]. The prevalence of hypoalbuminemia in atrial fibrillation, essential and pulmonary arterial hypertension, as well as in venous thromboembolism, is unknown.

Hypoalbuminemia results from decreased liver synthesis, increased catabolism, increased vascular permeability and renal and enteral loss [9]. Relative contribution of these different mechanisms has not been investigated in patients with cardiovascular disease. However, malnutrition and inflammation are considered to play a major role in occurrence of hypoalbuminemia [8,9,23]. Fluid retention and increased vascular permeability, liver disease and enteral loss may account in part for hypoalbuminemia in patients with biventricular congestive heart failure [9]. Liver disease and enteral loss also contribute to this condition in patients with congenital heart disease [20,24]. The prevalence of nephrotic syndrome is unknown in cardiovascular diseases, however, macroalbuminuria was observed in 10% of patients with chronic heart failure in the CHARM study [9].

3. Value of serum albumin as an independent predictor of incident cardiovascular diseases

While the relative contribution of hypoalbuminemia to atherosclerosis has long been debated, recent evidence indicates that occurrence of ischemic heart disease, heart failure, atrial fibrillation, stroke, and venous thromboembolism is inversely related to serum albumin levels, even after adjusting for risk factors, body mass index and inflammation (Table 1).

In the ARIC study, 14,506 individuals were followed. Low serum albumin concentration was significantly linked to the emergence of ischemic heart disease in the category of smokers, independent of risk factors, inflammation and body mass index [25]. The association between serum albumin and active smoking has been consistently reported in another study [26]. In the “Framingham Offspring” study that included 4506 individuals followed for 22 years, serum albumin was an independent predictor of first myocardial infarction, after adjusting for risk factors [27]. In another recent study that involved 7647 individuals, low serum albumin level was strongly associated with occurrence of first or recurrent myocardial infarction, after adjusting for traditional risk factors [28].

There is also convincing evidence that hypoalbuminemia independently predicts incident heart failure [9,17,18,29,30]. In the Health ABC study, 2907 elderly individuals were followed for 9.4 years. Low serum albumin concentration was associated with the development of new onset heart failure, mainly with preserved ejection fraction, regardless of risk factors for heart failure, inflammatory markers, body mass index and coronary events [29]. These results were confirmed in a second study that included 5795 elderly individuals followed for 9.6 years. Occurrence of new onset heart failure was significantly related to low serum albumin concentration independent of risk factors, body mass index and inflammation [30]. Similar observation was made in 7192 patients with acute coronary syndrome ($p < 0.001$), after adjusting for age, ejection fraction, renal function, inflammation, blood pressure, diabetes and clinical presentation [17]. Further, adding both body mass index and inflammatory markers to usual risk factors in multivariate analysis did not alter the relevance of hypoalbuminemia in the prediction of incident heart failure in another study that included 1706 patients with acute myocardial infarction ($p = 0.003$) [18].

In the Copenhagen City Heart Study, 8870 individuals without cardiovascular disease were followed for 8 years. Lower serum albumin levels were significantly associated with occurrence of atrial fibrillation in women, independent of incident heart disease, new-onset heart failure, body mass index and inflammation [31].

In the Northern Manhattan Study that followed 2986 individuals free of stroke for 12 years, low serum albumin concentration was a predictor of incident cardioembolic and cryptogenic stroke, even after

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