Importance of serum albumin levels in cardiovascular events

Albumin and cardiovascular events

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Abstract

Cardiovascular diseases are among the leading causes of death worldwide. Inflammatory conditions, endothelial dysfunction and oxidative stress play a role in the onset and/or development of many cardiovascular diseases, especially heart failure and coronary artery disease. Serum albumin has many physiological functions, including anti-inflammatory, antioxidant, anti-platelet aggregation activity and anticoagulant. It is also critical for fluid exchange across the capillary membrane. Serum albumin performs binding and transport functions for many substances such as hormones, fatty acids, steroids, inorganic ions, vitamins and drugs. Albumin has important links with inflammation and cardiac events. Decreased SA levels are associated with myocardial infarction, atrial fibrillation, heart failure and coronary heart disease. This is because a decrease in serum albumin levels, i.e. hypoalbuminemia, plays a role in impairments in vasodilatory ability and anticoagulation, fibrinolysis, vascular permeability and increased blood viscosity. Hypoalbuminemia will lead to decreased antioxidant levels in plasma and trigger cardiovascular diseases due to decreased antioxidant levels. The aim of this review is to provide an overview of the relationship between serum albumin and cardiovascular diseases

Keywords

albumin, cardiovascular diseases and albumin, hypoalbuminemia

Introduction

Cardiovascular diseases (CVD) are among the leading causes of death worldwide. Inflammatory conditions, endothelial dysfunction and oxidative stress play a role in the onset and/or development of many CVDs, especially heart failure and coronary artery disease. Serum albumin (SA) has many physiological functions, including anti-inflammatory, antioxidant, anti-platelet aggregation activity and anticoagulant. It is also critical for fluid exchange across the capillary membrane.[1]

The most prominent known activities of SA include regulating fluid distribution between vascular compartments and maintaining plasma oncotic pressure. Albumin is the most abundant protein in the blood. It is not possible to isolate a single function of SA. Because most of its functions are interrelated and play a role in maintaining homeostasis. The reference range of SA in an adult human is 3.5-5 g/dl. However, the pathologic limit may differ according to the tests used. SA levels are lower in women than in men. It tends to decrease with age.[2]

Synthesis and Biological Functions of Albumin

Albumin is synthesized from hepatocytes. It is synthesized at a rate of almost 150 mg/kg/day.[3] Albumin synthesized in hepatocytes is transferred to the extracellular space by exocytosis. Approximately 2/5 is found intravascularly. 3/5 is transferred to the interstitial spaces of organs and tissues, especially muscle, connective tissue, adipose tissue and skin.[4] There is albumin activity between the interstitial-intravascular spaces via lymphatic vessels. Albumin concentration is high in plasma. The high concentration, together with a strong negative net charge, maintains the plasma oncotic pressure. Albumin in serum is higher than albumin in the interstitial space.[5] For example, concentrations of about 13 g/L in skeletal muscle and about 7 g/L in adipose tissue have been described.[6] The level of synthesis of albumin varies according to the osmolality of the hepatic extravascular space, differences in colloid osmotic pressure and the body's requirements (Table 1).[7]

SA performs binding and transport functions for many substances such as hormones, fatty acids, steroids, inorganic ions, vitamins and drugs.[8] It has also been reported to maintain the permeability of capillaries. Low albumin levels have been reported to impair the vasodilator response to nitric oxide. It has antioxidant functions against oxidative stress involved in the pathogenesis of atherosclerosis.[9]

Types of Albumin

Albumin can be obtained from many sources. These include rat serum albumin (RSA), human serum albumin (HSA) (Figure 1), bovine serum albumin (BSA) and ovalbumin (egg white, OVA). However, HSA[10] and BSA are the most preferred in drug delivery. Albumin is a negatively charged protein composed of 585 amino acids that form a single polypeptide chain with a molecular weight of 66.5 kDa (Figure 1). It is organized as a series of α-helices stabilized by 17 disulfide bonds. It consists of three homologous domains (I-III). These domains have two subdomains (A and B) and each domain consists of 4 and 6 α-helices. Albumin in solution is characterized by a flexible texture thanks to disulfide bonds. An unbound cysteine residue (Cys-34) in subdomain IA is a redox active thiol (-SH) group. The thiol moiety includes thiolation (HSA-SR), nitrosylation (HSA-S-

NO) and the ability to bind substances.[8] Albumin has an average half-life of 19 days. PH range is between 4-9. It can be heated at 60 °C for 10 hours.[10] BSA has a molecular weight of 69,323 kDa. It has an isoelectric point of 4.7 in water at 25 °C. This property makes it negatively charged at neutral pH and positively charged at acidic pH.[12] This creates binding conditions for both negatively and positively charged substances. BSA is generally preferred for drug delivery. Because it is cost effective, easy to control and purify. It can also bind hydrophobic and hydrophilic drugs, is water soluble and has the capacity to overload. The only possible undesirable situation is that it may cause an in vivo immunogenic response in humans.[13]

Albumin and Cardiovascular Disease

Albumin is believed to have important links with inflammation and cardiac events. It has also been suggested to have some commonalities with factors that aggravate CVDs.[14] Therefore, a number of studies have been conducted to fully explain the link between CVD and SA. SA reference range is 3.5-5 g/dl.[15] A value below 3.5 g/dl (< 3.5 g/dl) is called hypoalbuminemia. However, there is no clear definition to explain the relationship between SA level and the prediction of cardiovascular adverse events. Recent studies have shown that cardiovascular risks are increased even within the SA reference range (3.5-4.0 g/dL).[16] Furthermore, in patients hospitalized for acute myocardial infarction (AMI), a serum albumin level < 3.8 g/dl has been described as an independent predictor of cardiac events.[17]

Hypoalbuminemia is recognized as a new and critically important marker for coronary artery disease (CAD). Furthermore, hypoalbuminemia is associated with elevated total and low-density lipoprotein (LDL) cholesterol levels and increased risk of CVD mortality.[1] Hypoalbuminemia is also associated with impairments in vasodilatory ability and anticoagulation, fibrinolysis, increased vascular permeability and blood viscosity (Figure 2). Increases in these factors also increase the risk of CVD.[9]

Previous studies have shown that a decrease in SA levels is associated with myocardial infarction,[18] atrial fibrillation,[19] heart failure[20] and coronary heart disease (Figure 3).[21] This is because hypoalbuminemia will cause a decrease in antioxidant levels in plasma. It has been suggested that decreased antioxidant levels and CVDs are associated with each other.[2]

Ethics Approval

Not applicable. This article is a narrative review of previously published studies and does not involve new data collection from human participants or animals.

Table 1. Factors that decrease or increase albumin synthesis[9]

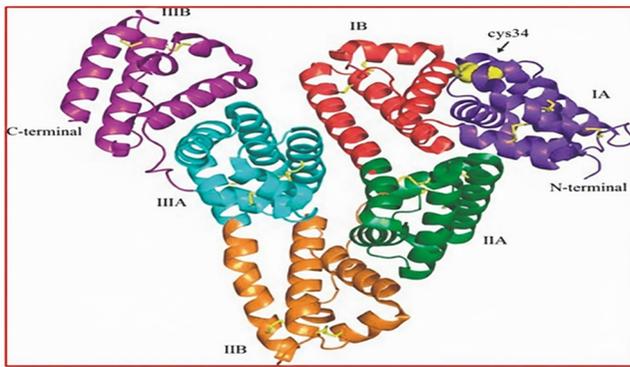| Factors that decrease	Factors that increase
Hepatic disease	Corticosteroids
Protein-deficient diet	Insulin
Diabetes	Growth hormone
COP↑	COP↓
Sepsis	High-protein diet
Fasting	High calories
COP colloidal oncotic pressure	

Figure 1. Structure of human serum albumin (A single polypeptide containing 585 amino acids)[11]
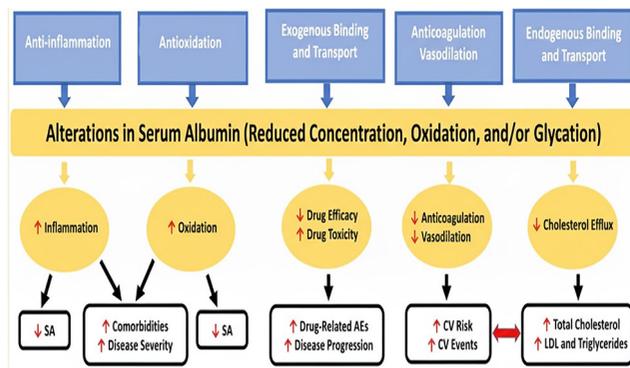

Figure 2. Demonstration of interactive effects between physiological functions of SA, except colloid oncotic pressure. AE, adverse event; CV, cardiovascular; LDL, low-density lipoprotein; SA, serum albumin.[9]
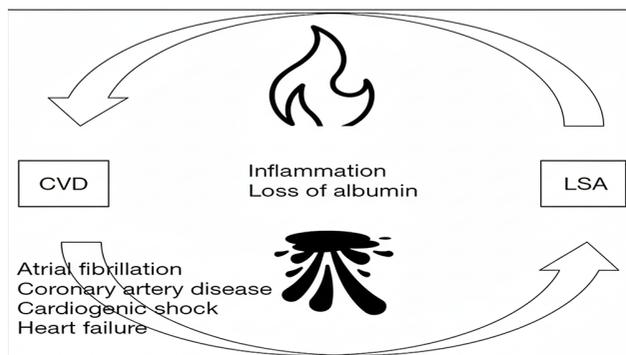

Figure 3. Association between low serum albumin and cardiovascular disease.[15]

Statistical Analysis

Not applicable. No new statistical analysis was performed in this narrative review.

Reporting Guidelines

This article is a narrative review of previously published literature. No specific reporting guideline was applicable.

Discussion

When the study data were evaluated, it was explained that, independent of inflammation and risk factors, hypoalbuminemia was linked to the occurrence of many CVDs, including heart failure, ischemic heart disease, AF and venous thromboembolism.[14] 8870 people without CVD were followed for 8 years. Hypoalbuminemia was linked to the occurrence of AF in women, independent of new-onset heart failure, heart disease and inflammation.[22] In a study of 12,833 individuals followed for 25.1 years to assess the prospective relationship between serum albumin and AF risk, it was concluded that the effect of serum albumin on AF is widespread. There is no evidence that increasing serum albumin levels (albumin infusion, dietary improvement, etc.) attenuates the clinical risk of AF. However, measurement of serum albumin is performed by an inexpensive and routinely available blood test. Therefore, if serum albumin is shown to contribute to the prevention of AF, a very important clinical benefit would be achieved.[23] Elevated serum albumin levels may be protective in cardiovascular events. In a study in which < 3.8 g/dL was considered a low SA level, among 289 AMI patients in the acute phase of AMI, 194 AMI patients improved in the chronic phase with SA levels ≥ 3.8 g/dL. This improved subgroup had better outcomes than the non-improved subgroup.[24] However, it remains unclear whether the higher the albumin levels, the better the prognosis for CVD.[15]

In a study of 352 patients with chronic heart failure, low serum albumin was associated with elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and increased long-term mortality.[25] Low serum albumin has also been shown to be an independent predictor of short- and long-term events in patients with acute heart failure. Another study for 546 patients with non-ischemic acute heart failure reported that low serum albumin on admission was an independent predictor of adverse cardiac events.[26] In a 708-day study of 204 patients with chronic coronary syndrome, they proved that low serum albumin predicts adverse cardiovascular events, including myocardial infarction (MI), all-cause mortality and stroke.[27] In a prospective study involving > 100,000 individuals, an inverse relationship between plasma albumin and CVD was reported, which was attributed to the fact that albumin is a negative acute phase reactant.[28] An albumin value ≤ 3.2 g/dL was found to be a critical predictor of in-hospital mortality in elderly patients hospitalized for acute HF.[29] A cross-sectional study described that SA density was inversely associated with the incidence of peripheral arterial disease (PAD) in hemodialysis patients.[30] In fact, results from the HEMO study, which enrolled 1411 hemodialysis patients, reported that CVD risk increased as albumin levels decreased in patients with SA concentrations ≥ 3.6 g/dL. For every 1 g/dL increase in SA, the odds ratio decreased by 68% for CAD, 67% for CVD, 61% for PAD and 77% for all atherosclerotic diseases.[31] In the Cardiovascular Health Study, 5450 healthy individuals aged ≥ 65 years were enrolled. Hypoalbuminemia has been shown to be significantly associated with HF within 10 years.[32]

Limitations

This narrative review is based on previously published studies and does not include a systematic search or quantitative synthesis. Therefore, the findings reflect associations reported in the literature and do not establish causality.

Conlusion

The SA level has evolved as an indicator of nutritional and

inflammatory status and has been described to predict CVD prognosis. Further and extensive studies on the pathophysiology of albumin levels are needed to fully explain the relationship between albumin levels and adverse events in CVD patients.[15]

Abbreviations
ACE: Angiotensin-Converting Enzyme
ACS: Acute Coronary Syndrome
AF: Atrial Fibrillation
AMI: Acute Myocardial Infarction
BMI: Body Mass Index
CAD: Coronary Artery Disease
CRP: C-Reactive Protein
CVD: Cardiovascular Disease
HDL: High-Density Lipoprotein
IL-6: Interleukin-6
LDL: Low-Density Lipoprotein
MI: Myocardial Infarction
NYHA: New York Heart Association
ROS: Reactive Oxygen Species
TNF-α: Tumor Necrosis Factor Alpha

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