Clinical Significance of Albumin: Structure, Function and Role in Different Pathophysiological States

Atiya Abbas and Zelle Humma*

Department of Biochemistry and Biotechnology, The Women University Multan, Pakistan
_____

ABSTRACT

Albumin is abundant protein in the human plasma. It is monomeric, multi-domain protein that causes oncotic pressure and involve in fluid distribution between the body compartments. It belongs to transport protein family and consist of single chain of 585 amino acids with molecular weight 66.5kDa. In healthy adults' its normal range is 3.5-5.5 g/dl mainly synthesize in hepatocytes. Its binding property impart significant role in the pharmacokinetics and pharmacodynamics of many drugs and important molecules. Alteration in blood composition reflect disease status mainly protein and nucleic acid (DNA or RNA) have used as a biomarker. Protein biomarker has significant importance due to small pool of protein, capitalize for diagnosis of disease by measuring these changing concentration. Albumin as a protein has the capacity to act as markers for the detection and monitoring of disease, its progression, prognosis, or assess the clinical status of patients. Hypoalbuminemia is observed in hypovolemic shock, burns, surgical loss of blood, trauma, hemorrhage, cardiopulmonary bypass, acute respiratory distress syndrome, hemodialysis, gastric tract disorder, acute and chronic liver diseases, chronic kidney disease and end stage renal failure. But hyeralbuminemia is only observed in dehydration. Hypoalbuminemia increases complications and long-term mortality in many diseases.

Keywords: Albumin, Hypoalbuminemia, Hyperalbuminemia, Physiologic, Pathologic.
_____

1. INTRODUCTION

1.1. Function of Human Serum Albumin

1.1.1. *Exert oncotic pressure*

Albumin is abundant protein in human blood plasma. It contributes PH maintenance and exerts oncotic pressure on plasma. It has direct osmotic effect and attracts negative charge sodium molecule and water

from intravascular compartment. Albumin has binding property with wide range of molecules both endogenous and exogenous molecules. It allows solubilisation, transportation to distant sites or organs. Albumin has high affinity with many metal cations such as cobalt, copper, zinc, nickel, fatty acid, metabolites such as bilirubin [1].

1.1.2. *Binding and transporting agent*

Albumin can bound and transport endogenous and exogenous molecule. In endogenous molecules include long-chain fatty acids, biliary products, steroids, hematin, L-thyroxine and vitamin D. While in exogenous molecules wide range of drugs that are cisplatin and N-acetyl-cysteine, salicylates, warfarin, penicillins, benzodiazepines, ibuprofen, furosemide and ketoprofen [2]. Due to this binding property of albumin toxicity of many drugs decreases and half-life increases because many drugs compete with binding to a specific site. So albumin has significant role in the pharmacokinetics and pharmacodynamics of many drugs [3].

1.1.3. *Antioxidant and antithrombotic agent*

Prevalent form of human plasma albumin is reduced state have free thiol group in the Cys-34 residue. It acts as extracellular antioxidant, potent for the capture of free radical for reactive oxygen and nitrogen species for example hydrogen peroxide and peroxynitrite [4]. Human serum albumin (HSA) in systemic or cellular inflammatory response and in organ dysfunction oxidation is significantly reduce by antioxidant actions. Albumin also has antithrombotic activity due to binding with nitric oxide (NO) and cystein-34. Nitric oxide has potential biological activity causing vasodilation and inhibition of platelet aggregation [1].

1.1.4. *Role in immune system*

Serum albumin has significance role in innate immune response, sepsis and systemic inflammatory reaction having binding affinity with inflammatory mediators, cytokines, factors toxins and bacterial antigens. Albumin selectively inhibits TNFa, vascular cell adhesion molecule-1 (VCAM-1) monocyte adhesion also has anti-inflammatory role just before endothelial cells [1].

1.1.5. *Structure of human serum albumin*

Three dimensional structural of albumin had been determined by crystallographic technique at resolution of 2.5A [5]. Albumin almost has 585 amino acids and a molecular mass of 66500 Da. X-ray crystallographic analyses of albumin, polypeptide chain or loops forming a heart-shaped protein about 67% a-helix but no b sheet [3]. Human serum albumin comprises a gene on chromosome 4 with almost great acidic amino acid having negative charge. HSA has tertiary structure like a heart-forming eight helices and having three domains (I, II, and III), with two subdomains (A and B). Due to stability and flexibility albumin change its structure that permit binding and transport property with widespread range of molecules and ligands [1].

1.1.6. *Properties of human serum albumin*

Binding studies of HSA shows that it has three domains I, II, III and two subdomains (A and B). Most important binding region that has been located in sub domain 11A and 111A.This binding locations are studied and determine by crystallographic technique at low resolution for many ligand. Most active binding site on HSA is 111A many ligands prefer to bind with that site for example digoxin tryptophan and ibuprofen. Aspirin and iodinated aspirin analogues show equal distribution between the binding site 11A and 111A. Warfarin binds with single site in 11A. These predicted locations have been observed on the bases of competition, inhibition and spectroscopic studies [1, 5].

1.1.7. *Synthesis of albumin*

Albumin is synthesized by hepatocytes in circular polysomes on the rough endoplasmic reticulum. In healthy adults, albumin is produce at the rate of 12 and 25 g per day [6]. Many stimuli such as injection of nutrient, insulin hormone, and oncotic pressure promote its synthesis. Serum albumin catabolism occur in all tissues, especially in skin, muscles and liver [7]. After synthesis by hepatocytes it discharged in intravascular space not store and about two third of it is transport into the body spaces, skin and muscles coming back widely by means of vessels and the lymphatic framework. 20-30% is only synthesized in hepatocytes. Half-life of albumin is almost 9-12 days but it may change in disease states. In healthy adult normal serum albumin is 3.5-5.5 g/dL while in children that are 3 years old has wide range 2.2 -5.5 g/dl. Production can be enhanced 3-4 times only on body function demands as liver has great reserve. Almost 40% albumin by weight is present in extravascular space while 60% interstitial space. Daily degradation of albumin is about 14g, 40-60% of which occur in muscles and skin [6-7].

2. ROLE OF ALBUMIN AS A BIOMARKER IN DIFFERENT PATHOPHYSIOLOGIC STATES

2.1. Biomarkers and their significance

Change in blood (plasma/serum) represents the physiological and pathological condition of human body. Variation in blood composition reflect disease status in different organ systems because of changes in proteomes, individually or collectively have the ability to act as biomarkers to detect and monitor disease, its progression, prognosis, or assess the clinical status of patients [8]. Variations that detect disease status are mainly proteins and nucleic acid (either DNA or RNA) fragments released in blood are mainly influence by disease induced changes or by malfunctioning of any body organ. These variations

do not cause any kind of illness, but act as markers that will improve diagnosis and risk factors. Gene expression and its level may signify a disease state. Constantly over expression or suppression of these genes in a certain clinical perspective, may be reflected as biomarkers. Gene expression can assess with various kind of different techniques for example real-time reverse transcription polymerized chain reaction (RT-PCR), microarray, blotting and gene profiling. Genetics studies divide the genetic diseases into two main categories monogenic and polygenic. These genes may be either monogenic or polygenic. Protein biomarker has significant importance due to pathophysiologic changes concentration of this small pool of protein, thus take advantage of diagnosis of disease by measuring these changing concentrations. Less abundant proteins are focus of investigation now as a serum biomarker [8- 9].

2.2. Albumin as a biomarker in physiologic stress

Alteration in albumin level is notified in pathophysiological states. Hyperalbuminemia is detected only in dehydration states. Hypoalbuminemia is frequently occur in hospitalized patients due to malnutrition, injury and stress condition. In starvation utilization of energy consumption decreases 80 percent to normal. Albumin level and survival of patients have direct relation there for hypoalbuminemia particularly, less than 2.2 g/dl is prognostic of infection and rate of mortality. Mortality rate increases 12 fold with hypoalbuminemia rater than normal albumin level. Frequency of highest death rates takes place in those patients having albumin levels less than 2 g/dL. Serum albumin level deceases in acute disease, inflammation and injury due to hormonal release in physiological stress that changes metabolic rate and energy utilization. Acute phase response includes blood clotting protein fibrinogen, ceruloplasmin,

gamma globulins, complement C3, as the acute phase response increases albumin synthesis decreases. Hyperalbuminemia is observed only in dehydration states [10].

2.3. Role of Albumin in Pathological States

2.3.1. Role in cardiac diseases

Cardiogenic shock the end- stage organ dysfunction initiated by hypoperfusion, low cardiac functions and reduces blood pressure. Hypoperfusion affect many organ system, resulting decreased in mental level, cool margin of periphery, and decreased urine output. Decrease cardiac index (2.2 L/min/m2) and prominent left ventricular filling pressures. Assuming pulmonary edema that causes changes by increased left ventricular filling or end diastolic pressure [11].

Cardiogenic Shock (SC) is circulatory failure with low cardiac output and inadequate cellular oxygen utilization resulting life threatening end organ hypoxia and hypo perfusion. Albumin has prognostic significant in cardiogenic shock. CS is most threatening event accompany with myocardial infarction. Acute myocardial infarction with cardiogenic shock (AMI-CS) is observed in 5% to 7% of patients. AMI-CS, has high hospital mortality rate of 35% to 40% instead of advancement in health sector. It is observed that men are more affected with CS than female, women are younger than male. Myocardial contractility reduce in cardiogenic shock (CS) is commonly due to the death in patients with acute myocardial infarction (AMI). Hypoalbuminemia is a recurrent finding early in cardiogenic shock and level of albumin is also reduce during hospital stay [12].

In a number of various ischemic conditions such as hypoxia, free radical injury and acidosis metals binding capacity of albumin altered which is commonly known as ischemic modified albumin (IMA). Reactive oxygen species (ROS) such as superoxide and hydroxyl free radicals that arises during myocardial ischemia alter N terminal of albumin that is involve in IMA formation. Raised serum IMA levels have been observed in deep vein thrombosis (DVT), cerebral infarct, diabetes mellitus, chronic liver disease (CLD), pulmonary and mesenteric infarct. Ischemic modified albumin (IMA) is use as a sensitive marker for the diagnosis of myocardial ischemia before the beginning of cardiac damage in patients with unusual chest pain. Higher serum IMA level used to evaluate the vascular disease in those patients having type 2 diabetes mellitus [13-14].

Heart failure both acute and chronic is increasing day by day and directly related with mortality. Acute mean dyspnoea identified by signs that are related to cardiogenic shock. In other words acute heart failure (AHF) is advice to precisely called cardiogenic shock or pulmonary edema [15]. Heart failure is pathophysiological state with abnormal cardiac function that is responsible for decrease blood pumping that not compete rate of inhalation. To define chronic heart failure is impossible because in many cases its diagnosis depends on clinical data such as patient history, physical examination and proper investigations. Heart failure patients have similar feature of symptoms, shortness of breath (SOB), ankle swelling fatigue, and rate of cardiac dysfunction even at rest [15].

Coronary slow flow (CSF) is another heart disease and incidence of CSF is 1% to 3% between those patients suffering from coronary angiography. Albumin is a major inhibitor of platelet activation, aggregation and mediator of platelet-induced coronary artery vasoconstriction [16]. Hypoalbuminemia has linked with increased cardiovascular mortality and morbidity shown in a number of studies conducted at different times [17-

18]. Coronary artery disease (CAD) and chronic heart failure (CHF) both are prominent reason of morbidity and mortality in diabetic patients. Microalbuminuria is defined as 20-200 mg/day albumin excretion in urine is marker of systemic vascular damage, renal functional diminishing and coronary artery disease. Microalbuminuria is about 19% in diabetic patients use as a predictive marker for renal, cerebral vascular and cardiac damage. Silent myocardial ischemia (SMI) is characteristically myocardial ischemia without ischemia symptoms. Microalbuminuria is use to predict silent myocardial ischemia (SMI) with type 2 diabetes in patients using myocardial perfusion imaging (MPI). Abnormal MPI outcomes have more significance in diabetic patients with microalbuminuria. Due to inexpensive and convenience it use as marker for estimation of SMI in diabetic individuals [19].

Incidence of hypoalbuminemia in patients of heart ranges from 18 to 49% and it act as prognostic marker of heart failure due to its unique properties of albumin. Hypoalbuminemia is associated with high mortality rate and predictor of adverse effects longer hospital stay after cardiac surgery renal dysfunction, and elevated inflammatory biomarkers poor exercise tolerance [20].

2.3.2. *Role of albumin in liver diseases*

In advance cirrhosis variety of many clinical manifestations that includes portal hypertension, ascites, hepatic encephalopathy and increased risk of infection. Progression of acute to chronic liver failure due to systemic inflammatory response commonly effect multiple organ dysfunction. Decrease in concentration of albumin has noticed in advance cirrhosis because of diminished synthesis could affect clinical and functional properties. But latest studies show that immunosuppression decompensated cirrhosis that is associated with hypoalbuminemia

and this may be improved by albumin replacement [1].

Altered in serum albumin level is mainly associated with liver disease due to acute-phase response is responsible for albumin levels reduction. Changing of albumin level with hepatic disease may change synthesis, degradation, and distribution between the intra- and extra vascular spaces [10]. Binding and other functions of albumin that had reduced in end stage liver disorder; it may be correlated to oxidative stress. It has been studied that albumin play significant role in the pathology of liver failure and in sepsis. In oxidative variation albumin losses its binding functions in advanced chronic liver failure and sepsis [4]. Progressive hypoalbuminemia is a common feature of cirrhosis. Previous research studies have revealed that function of albumin compromised in cirrhotic patients and associated with high death rate [21]. Infusion of serum albumin inhibits and recovers renal dysfunction in cirrhotic patients [22].

Ascites is common difficulties of cirrhosis, observed almost in 50% of patients within 10 years diagnosis of disease. Spontaneous bacterial peritonitis and the hepatorenal syndrome are complication in ascites develop in cirrhosis that severely affects patient's prognosis. In the pathogenesis of ascites two main factors involve is sodium retention, causing to extracellular fluid volume extension; and difference in liver sinusoids and splenic capillaries equilibrium of fluid from intravascular compartment to abdominal cavity [23].

In liver disease hepatic lymph leakage and imbalance lymph drainage function causes albumin accumulation in peritoneal cavity that causes portal hypertension due to reduce oncotic pressure which is most important factor of ascites. Both Plasma and ascetic fluid albumin has different gradient due to

liver disease. 95% patients with ascites has gradient of plasma to ascetic fluid albumin is more than 1 g/dL due to liver disease [10]. Long-standing infusion of albumin after first exposure to ascites considerably expands patients' survival and decline the risk of its recurrence [23].

2.3.3. In gastrointestinal tract disorders

Gastrointestinal disorder has little role in the breakdown of albumin while digestive tract disorder frequently causes major reduction in albumin level and it may adversely affect gut physiology.

Protein-losing enteropathy, albumin, globulins and other plasma proteins are excreted in the gut lumen. There are 90 different kind of gut diseases causes albumin loss may be due to lymphatic blockage and mucosal blockage. In majority of patient's albumin level less than 2.5 develop diarrhea high enteral osmotic load [10]. The Zollinger-Ellison (ZE) syndrome is characterized by symptoms of peptic ulcer disease, diarrhea, acid hypersecretion, and gastrin-producing tumors. Hypoalbuminemia is a main cause of gastrointestinal disease. Hypoalbuminemia may be due to low albumin synthesis and greater loss or degradation of albumin. Hypoalbuminemia or greater plasma protein loss is often an indication of gastrointestinal disease. Hypoalbuminemia in peptic ulcer disease may be the diagnostic clue of Zollinger-Ellison syndrome [24].

2.3.4. Importance of urinary albumin in renal disorders

Under normal circumstance kidney play small role in the degradation, synthesis and distribution of serum albumin. Normally little amount of albumin is filtered by renal tubules after degradation amino acid are return to amino acid pool. Kidney play significant role in the filtration and degradation of albumin in renal disorder. While in renal disorder kidney play important role in the degradation and filtration of albumin. In nephrotic syndrome, albumin catabolism increases by the renal cells. Measurement of urinary albumin excretion may be estimated via the kidney function, providing correlation of serum albumin and urinary albumin level [10]. In nephrotic syndrome glomerular permeability increases and loss of urinary albumin and many other plasma proteins having molecular weight similar to albumin increases. Severe hypoalbuminemia occur in nephrotic syndrome patient's urinary albumin loss almost as little as 3g/day. So high protein diets have been recommended to normalize plasma albumin level [25].

Proteinuria is currently considering prognostic and diagnostic marker of chronic renal Failure/disease (CKD) and end stage renal disease (ESRD). Microalbuminuria means moderate increase of albumin in urine when small amounts of albumin is excreted in urine by kidney while in other words, when permeability for albumin in the renal glomerulus abnormally high. Urinary albumin is use as marker of many different diseases such as diabetes, heart and renal disorder also associated with mortality [26]. Urine albumin to creatinine ratio (ACR) a prognostic marker of renal disorder effective by using to measure and monitor graft function after a kidney transplant with creatinine clearance. If ACR is more than 30 mg/day, almost 2 to 3 times greater than urine albumin level, indicates renal injury, risk of advancement of proteinuria increases and glomerular filtration rate decrease. The ACR predict graft failure and monitor patient disease/death status after transplant [26].

Diabetic neuropathy is the most common about 19% of diabetic patients have renal protein excretion. In different revisions risk of cardiovascular events in the patients with overt microalbuminuria. Microalbuminuria is signal of renal contribution and

entering diabetic nephropathy, so it is accurate and sensitive predictive indicator of end stage renal disease in diabetic patients. Microalbuminuria is marker of cardiac, cerebral vascular damage and renal damage in diabetic patients [27]. Hypoalbuminemia indicate nutritional status and strong predictor of deterioration and mortality in patients with renal insufficiency. In United States hemodialysis patients are monitored serum albumin levels monthly by the standardized method.

Podocytes (Bowman's capsule cells in kidney capillaries of glomerulus wrap around) have important role in glomerular filtration rate and albumin handling. Podocytes injury develops albuminuria and progressive kidney disease. Studies have shown that podocyte injury causes marked albumin excretion in urea and nephrotic syndrome, and it has confirmed that podocytes impart significant role in the maintenance glomerular filtration barrier [28].

2.3.5. Significance of albumin in bleeding disorder and erythrocytes morphology

Role of albumin has been notified in blood coagulation studies. Bleeding disorder associated with impaired platelet aggregation. Albumin has Heparin-like effects via neutralization of factor Xa by anti-thrombin III has important role in the synthesis of prostaglandin D2 and thromboxin. Albumin effects platelet function inhibition, platelet aggregation. The physiologic importance of albumin and its role on platelet function cleared in nephrotic syndrome thromboembolic complications in patients are related with hypoalbuminemia. Albumin synthesis may be increase as oncotic pressure markedly deceases but severe hypoalbuminemia may be noticed in patients of nephrotic syndrome with urinary loss. Peritoneal dialysis has significance and effectiveness rather than hemodialysis in reversing the effect of uremic platelet

disorder. Albumin level (hyper and hypoalbuminemia) in body also influence the erythrocytes morphology [10].

2.3.6. Significance of albumin in endocrine disorders

Endocrine disorders affect serum albumin level. Hypothyroidism decreases albumin synthesis, redistribution and degradation occur in extracellular space. While hyperthyroidism increase level of albumin synthesis occurs degradation has no overall effects on albumin pool. Thyroid level decrease in hospitalize children with severe protein malnutrition. Excess corticosteroids increases hepatic synthesis of albumin, while reduction in this hormone also reduces albumin level. In Hypoadrenal similar results related to the hypothyroid state has observed. In diabetes mellitus total hepatic protein synthesis decreases but albumin synthesis depressed in greater extent. Acute insulin insufficiency result decrease albumin synthesis rather than other hepatic proteins [29].

2.3.7. Role of hypoalbuminemia in other disorders

Albumin is main plasma protein that maintain oncotic pressure, microvascular permeability, acid–base function, and inhibit platelet aggregation [30]. Central nervous system disorders usually does not alter serum albumin level. While albumin level in cerebrospinal fluid (CSF) is most important than blood albumin. Integrity of blood - brain barrier has determined by measuring glucose and protein level of CSF. Hypoalbuminemia can easily notice and measure in patients with acute ischemic stroke and intracerebral hemorrhage (ICH) [10].

Low protein diet is also main cause of hypoalbuminemia. Kwashiorkor and marasmus, are diseases of protein-energy malnutrition differ from each other both clinically and bio chemically.

Hypoalbuminemia has been used as a marker to diagnose kwashiorkor because protein is markedly reduced in the plasma of kwashiorkor patients but is usually normal or low normal in cases of marasmus. With aging fall of albumin level is partially due to age dependent changes in clinical effects of different drugs. Decreases albumin level is seen in cigarette smoker, in pregnancy due to expansion of plasma level, lesser amount in oral contraceptive use [10]. Diabetes mellitus (DM) is epidemic chronic metabolic disease that is caused by reduced or absent of insulin secretion or may be due reduce tissue response or sensitivity to insulin secretion that causes hyperglycemia. For the diagnosis of diabetes most commonly use test in clinical laboratories are glycated hemoglobin (A1C), fasting blood glucose (FG) and random or two-hour plasma glucose (2hG) and oral glucose tolerance test (OGTT) for glycemic monitoring. Last decade's glycated albumin (GA) gain significance in laboratories for glycemic monitoring in DM. GA is one of the fructosamines, but it has benefit on other serum proteins for being effected by their concentration. Glycated albumin has many advantages on glycated hemoglobin A1C because no fasting is required for its measurement and reveals short-term glycemia due to the short half-life of albumin, not affected by hemolytic processes, abnormal hemoglobin, anemia and pregnancy. GA give the impression of better glycemic marker than A1C for the monitoring and screening of diabetes mellitus [31].

3. FUTURE PROSPECT

Albumin is an important protein that causes oncotic pressure, regulate osmotic balance has binding properties with molecules. It is use as a diagnostic marker in many diseases due to its unique properties. In diabetes urinary protein and microalbuminurea is use as diagnostic marker. In kidney disease protein creatinine (P/C) ratio, spot urine protein, 24-hour urinary protein and microalbuminurea are most important diagnostic test in chronic renal failure and end stage renal failure (ESRF). In chronic liver diseases albumin with other liver enzymes has significant role in diagnosis. Low albumin level is observed in cardiac disease, GIT, endocrine disorder, coagulation studies, hemorrhage, CSF, renal and hepatic disorder. After the study of this review it is observed that in future blood albumin or urinary albumin may be used as an important or compulsory marker both in prognosis and diagnosis of many physiologic and pathologic diseases.

4. CONCLUSION

It is concluded from the previous studies that albumin is an important protein that has significant role in prognosis and diagnosis of many diseases due to their unique properties and functions. Hypoalbuminemia is use as diagnostic marker in liver, cardiac, renal, endocrine, coagulation studies and other disorder such as cerebrospinal fluid (CSF) protein level has significant role to relate integrity of blood - brain barrier. Hypoalbuminurea is also observed in physiologic stress such as malnutrition, hospitalize patients and in stress condition including smoking, aging and pregnancy. In near future serum albumin and urinary albumin/protein use for the screening of many subclinical and pathologic disorders as a significant biomarker.

5. ACKNOWLEDGEMENT

6. CONFLICT OF INTEREST

7. SOURCE/S OF FUNDING

NA

8. REFERENCES

1. Spinella, R., Sawhney, R., & Jalan, R. (2016). Albumin in chronic liver disease: structure, functions and therapeutic implications. *Hepatology international*, *10***(1)**, 124-132.

2. Fasano, M., Curry, S., Terreno, E., Galliano, M., Fanali, G., Narciso, P., ... & Ascenzi, P. (2005). The extraordinary ligand binding properties of human serum albumin. *IUBMB life*, *57***(12)**, 787-796.

3. Kragh-Hansen, U., Chuang, V. T. G., & Otagiri, M. (2002). Practical aspects of the ligand-binding and enzymatic properties of human serum albumin. *Biological and Pharmaceutical Bulletin*, *25***(6)**, 695-704.

4. Oettl, K., Birner-Gruenberger, R., Spindelboeck, W., Stueger, H. P., Dorn, L., Stadlbauer, .. & Lackner, C. (2013). Oxidative albumin damage in chronic liver failure: relation to albumin binding capacity, liver dysfunction and survival. *Journal of hepatology*, *59***(5)**, 978-983.

5. Sugio, S., Kashima, A., Mochizuki, S., Noda, M., & Kobayashi, K. (1999). Crystal structure of human serum albumin at 2.5 Å resolution. *Protein engineering*, *12***(6)**, 439-446.

6. Rozga, J., Piątek, T., & Małkowski, P. (2013). Human albumin: old, new, and emerging applications. *Annals of transplantation*, *18*, 205-217.

7. Arques, S., & Ambrosi, P. (2011). Human serum albumin in the clinical syndrome of heart failure. *Journal of cardiac failure*, *17***(6)**, 451-458.

8. Colantonio, D. A., Dunkinson, C., Bovenkamp, D. E., & Van Eyk, J. E. (2005). Effective removal of albumin from serum. *Proteomics*, *5***(15)**, 3831-3835.

9. Gibbons, G. H., Liew, C. C., Goodarzi, M. O., Rotter, J. I., Hsueh, W. A., Siragy, H. M., & Dzau, V. J. (2004). Genetic markers: progress and potential for cardiovascular disease. *Circulation*, *109***(25)**, IV-47.

10. Doweiko, J. P., & Nompleggi, D. J. (1991). Reviews: The Role of Albumin in Human Physiology and Pathophysiology, Part III: Albumin and Disease States. *Journal of Parenteral and Enteral Nutrition*, *15***(4)**, 476-483.

11. Eve D. Aymong, MD, MSc, FRCPCa,b, *, Krishnan Ramanathan, MB, ChB, FRACP, FRCPCa,b,c , Christopher E. Buller, MD, FRCPC, FACCa, 2007.

12. Vahdatpour, C., Collins, D., & Goldberg, S. (2019). Cardiogenic shock. Journal of the American Heart Association, *8***(8)**, e011991.

13. Cakir, M., Karahan, S. C., Mentese, A., Sag, E., Cobanoglu, U., Polat, T. B., & Erduran, E. (2012). Ischemia-modified albumin levels in children with chronic liver disease. *Gut and Liver*, *6***(1)**, 92.

14. Mentese, A., Mentese, U., Turedi, S., Gunduz, A., Karahan, S. C., Topbas, M., ... & Eminagaoglu, M. S. (2008). Effect of deep vein thrombosis on ischaemia-modified albumin levels. *Emergency Medicine Journal*, *25***(12)**, 811-814.

15. Remme, W. J., & Swedberg, K. (2002). Comprehensive guidelines for the diagnosis and treatment of chronic heart failure Task force for the diagnosis and treatment of chronic heart failure of the European Society of Cardiology. *European Journal of Heart Failure*, *4***(1)**, 11-22.

16. Gresele, P., Deckmyn, H., Huybrechts, E., & Vermylen, J. (1984). Serum albumin enhances the impairment of platelet aggregation with thromboxane synthase inhibition by increasing

the formation of prostaglandin D2. *Biochemical pharmacology*, *33***(13)**, 2083-2088.

17. Phillips, A., Shaper, A. G., & Whincup, P. (1989). Association between serum albumin and mortality from cardiovascular disease, cancer, and other causes. *The Lancet*, *334***(8677)**, 1434-1436.

18. Oduncu, V., Erkol, A., Karabay, C. Y., Kurt, M., Akgün, T., Bulut, M., ... & Kirma, C. (2013). The prognostic value of serum albumin levels on admission in patients with acute ST-segment elevation myocardial infarction undergoing a primary percutaneous coronary intervention. *Coronary artery disease*, *24***(2)**, 88-94.

19. Emami, T., Naeimei, Z., Salehifard, A., Azizmohammadi, Z., Iranpour, D., Kalantarhormozi, M., ... & Assadi, M. (2019). Significance of Microalbuminuria in Predicting Silent Myocardial Ischemia in Patients with Type 2 Diabetes Using Myocardial Perfusion Imaging. *Molecular imaging and radionuclide therapy*, *28***(2)**, 62.

20. Gopal, D. J., Hanff, T. C., Mazurek, J. A., Grandin, W. E., Howard, J., Forde-McLean, R., & Jessup, M. (2017). Prognostic implications of changes in albumin following left ventricular assist device implantation in patients with severe heart failure. *The American journal of cardiology*, *120***(11)**, 2003-2007.

21. Jalan, R., Schnurr, K., Mookerjee, R. P., Sen, S., Cheshire, L., Hodges, S., ... & Davies, N. A. (2009). Alterations in the functional capacity of albumin in patients with decompensated cirrhosis is associated with increased mortality. *Hepatology*, *50***(2)**, 555-564.

22. Garcia-Martinez, R., Noiret, L., Sen, S., Mookerjee, R., & Jalan, R. (2015). Albumin infusion improves renal blood flow autoregulation in patients with acute decompensation of cirrhosis and acute kidney injury. *Liver International*, *35***(2)**, 335-343

23. Romanelli, R. G., La Villa, G., Barletta, G., Vizzutti, F., Lanini, F., Arena, U., ... & Laffi, G. (2006). Long-term albumin infusion improves survival in patients with cirrhosis and ascites: an unblinded randomized trial. *World journal of gastroenterology: WJG*, *12***(9)**, 1403.

24. Lamers, C. B. H., Hafkenscheid, J. C. M., Yap, S. H., & van Tongeren, J. H. M. (1977). Serum Albumin Levels in Patients with the Zollingerellison Syndrome. *Gastroenterology*, *73***(5)**, 975-979.

25. Kaysen, G. A., & Al Bander, H. (1990). Metabolism of albumin and immunoglobulins in the nephrotic syndrome. *American journal of nephrology*, *10***(1)**, 36-42.

26. Lin, C. T., Chiang, Y. J., Liu, K. L., Lin, K. J., Chu, S. H., & Wang, H. H. (2019, June). Urine Albumin Creatinine Ratio May Predict Graft Function After Kidney Transplant. In *Transplantation proceedings 51***(5)**, pp. 1331-1336). Elsevier

27. Emami, T., Naeimei, Z., Salehifard, A., Azizmohammadi, Z., Iranpour, D., Kalantarhormozi, M., ... & Assadi, M. (2019). Significance of Microalbuminuria in Predicting Silent Myocardial Ischemia in Patients with Type 2 Diabetes Using Myocardial Perfusion Imaging. *Molecular imaging and radionuclide therapy*, *28***(2)**, 62.

28. Brinkkoetter, P. T., Ising, C., & Benzing, T. (2013). The role of the podocyte in albumin filtration. *Nature Reviews Nephrology*, *9***(6)**, 328.

29. Flaim, K. E., Hutson, S. M., Lloyd, C. E., Taylor, J. M., Shiman, R. O. S. S., & Jefferson, L. S. (1985). Direct effect of insulin on albumin gene expression in primary cultures of rat hepatocytes. *American Journal of Physiology-Endocrinology and Metabolism*, *249***(5)**, E447-E453.

30. Limaye, K., Yang, J. D., & Hinduja, A. (2016). Role of admission serum albumin levels in patients with intracerebral hemorrhage. *Acta Neurologica Belgica*, *116***(1)**, 27-30.

31. Freitas, P. A. C., Ehlert, L. R., & Camargo, J. L. (2017) Glycated albumin: a potential biomarker in diabetes. Arch Endocrinol Metab, *61:* 296–304.