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Structure and Functions of Human Serum Albumin in Normal Conditions and in Patients with Liver Cirrhosis

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The aim: to highlight the main points of albumin synthesis, posttranslational modifications and functions in normal conditions and in patients with liver cirrhosis.
Key points. Albumin is the most abundant protein in blood plasma. Along with oncotic properties, albumin performs transport, antioxidant, immunomodulatory and endothelioprotective functions. Serum albumin in patient with liver cirrhosis undergoes modifications, leeding to functional impairment. Human serum albumin is a compaund of human mercaptalbumin with cysteine residues having a reducing ability, and oxidized human non-mercaptalbumin. The proportion of irreversibly oxidized non-mercaptalbumin-2 with impaired functional activity increases in liver cirrhosis.
Conclusion. The conformational structure of the albumin molecule plays an important role in maintaining its non-oncotic functions. Non-oncotic fuctions depend on albumin conformation. Further investigation of albumin conformation and albumin functions in patients with hepatic insufficiency can serve as an additional criterion for assessing the severity of cirrhosis and predictor of complications may become an additional criterion to new clinical applications and treatment strategies of liver failure.
Keywords: albumin, posttranslational modifications, non-mercaptalbumin-2, liver cirrhosis
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Особенности строения и функций сывороточного альбумина в норме и у пациентов с циррозом печени

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Цель обзора: осветить основные моменты синтеза, посттрансляционной модификации и функции альбумина в норме и при циррозе печени.
Основные положения. В плазме крови альбумин находится в наибольшей концентрации. Наряду с онкотическими свойствами альбумин выполняет транспортную, антиоксидантную, иммуномодулирующую, эндотелиопротективную функции. При циррозе печени сывороточный альбумин подвергается посттрансляционной модификации, ведущей к нарушению его функции. Сывороточный альбумин человека состоит из меркаптальбумина человека с остатками цистеина, обладающими восстанавливающей способностью, и окисленного немеркаптальбумина человека. При циррозе печени доля необратимо окисленного немеркаптальбумина-2 с нарушенной функциональной активностью возрастает.
Заключение. Конформационная структура молекулы альбумина играет важную роль в поддержании его неонкотических функций. Изучение его структурных и функциональных свойств у пациентов с печеночной недостаточностью может служить дополнительным критерием для оценки выраженности цирроза и предиктором осложнений.
Ключевые слова: альбумин, посттрансляционные модификации, немеркаптальбумин-2, цирроз печени
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Introduction

Albumin (Alb) belongs to the group of globular and water-soluble proteins that are synthesized by the liver [1]. Vitamin-D-binding protein, α-fetoprotein, α-albumin (afamin) are also included in the Alb group [2, 3]. Albumin is a heart-shaped molecule with a molecular weight (mw) of 66.438 kDa [4] and a half-life about 19 days. It is stable in the pH 4–9 and can withstand heating up to 60 °C for 10 hours [1]. Serum albumin is presented in the blood plasma in the highest concentration (35–50 g/l) and, according to various data, accounts for 50–60 % of all proteins [5, 6].

Alb exists in other compartments in lesser concentration: in the lymphatic system — 15–36 g/l, in the intercellular fluid — 3–10 g/l, in the liquor — 0.3 g/l, in saliva — less than 0.5 mg/ml [5, 7]. Vessels contain approximately 120–140 g of albumin (30 %), there are around 300 g (70 %) in the interstitial. Therefore, typically there are 400–450 g of Alb in adult's body [5].

One of the earliest mentions of albumin precipitated in urine goes back to 1500 AD [8]. The first clinical use of purified human albumin took place during the Second World War. There were reported seven cases with severe burns during the Battle of Pearl Harbor [9] treated with human serum albumin (HSA) for 10 days. Despite extensive burns, reparative processes were increased and all patients survived [10].

Albumin structure

In 1959, it was found that the albumin molecule consists of an amino acid sequence connected by disulfide bridges and does not contain carbohydrate residues [11]. In 1975, the primary sequence of HSA was independently identified by J.R. Brown and B. Meloun [5, 12].

The primary sequence of the protein contains one tryptophan residue (Trp214) and several charged amino acid residues (arginine, lysine, glutamic and aspartic acids), they give a total negative charge to the protein at physiological pH, and provide Alb with hydrophilic properties [13, 14]. In 1989, Carter and colleagues first visualized the three-dimensional structure of an albumin molecule by multiple isomorphic substitution with a resolution of 6.0 angstroms (A) [15]. In 1999, a group of Japanese scientists led by S. Sugio determined the three-dimensional structure of albumin with a higher resolution (2.5 Å). Based on the presented data, it was established that HSA is a spiral protein in the form of an asymmetric heart [16].

There are three homologous α-helical domains in the albumin structure: I (residues from 1 to 195), II (196–383) and III (384–585), all they have a similar structure. These three domains consist of ten antiparallel spirals and are divided into two subdomains: subdomain A with six spirals (h1–h6) and subdomain B with four spirals (h7–h10). In addition, the albumin molecule consists of 35 cysteine residues, 34 of which are involved in the formation of 17 disulfide bonds that stabilize the structure of this spherical molecule. Thus, the spherical configuration gives allosteric properties to the monomeric protein, making it capable of binding to a variety of ligands [17].

Alb contains only one tryptophan residue Trp-214 (W214), located closely to the hydrophobic part of subdomain IIA (Fig. 1) [9, 18].

The surrounding area of W214 includes two high affinity drug binding sites (Sudlow I and II). Site I is in subdomain IIA, and site II is in subdomain IIIA [13], W214 also acts as a probe in spectroscopic studies [19, 20]. And just one of the 35 Cys residues does not participate in the formation of disulfide bonds and remains free at position 34 (Cys34) [14]. This single free Cys34 is observed in all mammals studied and determines the diversity of albumin isoforms. According to the Cys34 status, Alb can exist in three fractions [21]: mercaptalbumin with reduced Cys34 (contains a vacant sulfhydryl group [22]), non-mercaptalbumin-1, which forms disulfides with low molecular weight thiols like homocysteine, cysteine, glutathione; non-mercaptalbumin-2 with thiol Cys34 oxidized to sulfinic or sulfonic acid (Fig. 2) [21].

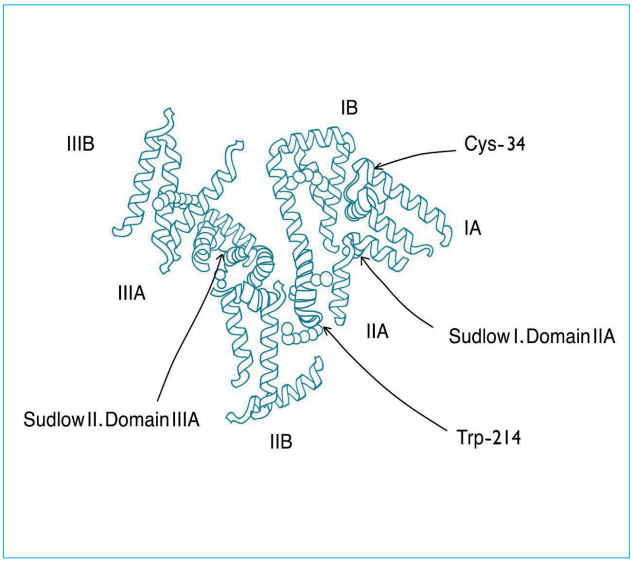

Fig. 1. Albumin structure. Three domains (I, II, III) are distinguished in the albumin molecule, which are subdivided into subdomains A and B. Free Cys-34 does not participate in the formation of disulfide bonds, and determines the heterogeneity of the albumin isoforms. The high-affinity drug binding sites Sudlow I and II are located in subdomains IIA and IIIA, respectively

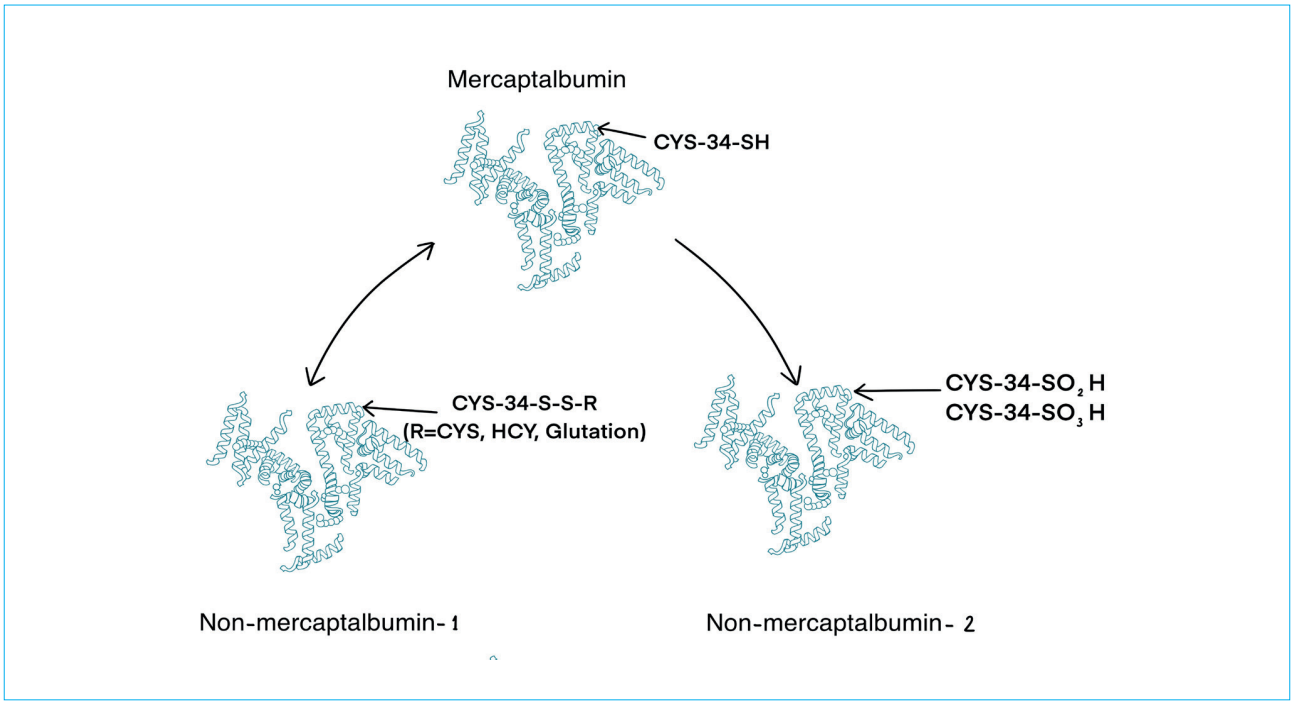

Fig. 2. Albumin fractions. Depending on the status of Cys-34, albumin may be in a free, non-oxidized form — mercaptalbumin (it accounts for more than 70 %), a reversibly oxidized form — non-mercaptalbumin-1 and irreversibly oxidized — non-mercaptalbumin-2 (CYS — cysteine; HCY — homocysteine; SO_2H — sulfinic acid; SO_3H-sulfonic acid)

Human serum mercaptalbumin (free sulfhydryl group) is the largest part of the three isoforms in healthy adults, comprising more than 70 % [23]. However, with the development of some pathological processes, the proportion of oxidized forms increases [22, 24]. The redox state of serum albumin has been extensively studied in patients with hepatic insufficiency. Its transition to an oxidized state has been reported in patients with chronic liver diseases [25]. Thus, with the progression of liver diseases, non-mercaptalbumin-2 (NMA-2) increases significantly [26]. This shift seems to be associated with impaired albumin circulation and oxidative stress as a result of impaired liver function [24, 27, 28].

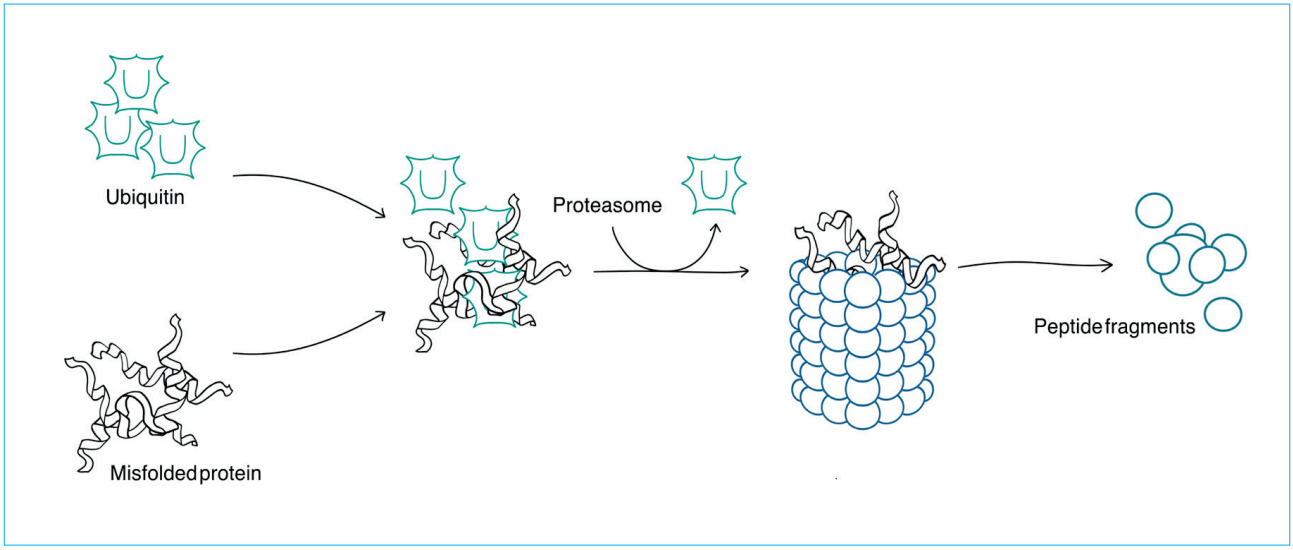

Fig. 3. Degradation of improperly folded protein in proteasomes. An incorrectly folded protein is labeled with a ubiquitin molecule for further destruction in proteasomes to amino acid residues

Transcription and translation

The human albumin gene is located on chromosome 4 q (11–22), and mutations of this gene lead to the synthesis of an abnormal protein. The Alb gene has 1691 nucleotides and contains 14 introns and 15 exons [29]. Every time during synthesis, due to unavoidable errors, several copies may form incorrectly. In this case, these defective copies covalently bind to ubiquitin molecules for further destruction in proteasomes [30] (Fig. 3).

Approximately 10–15 g of Alb is synthesized by liver daily, which is about 25–30 % of the total synthesized protein. At the same time, only 20–30 % of all hepatocytes are responsible for the synthesis of albumin [31]. The synthesized protein is not accumulated by the liver, but enters the portal circulation [14]. This process is regulated by the pH-dependent receptor of the neonatal crystallizing fragment (FcRn). FcRn binds albumin on the surface of hepatocytes and endothelial cells, redirecting albumin into the vascular bed, bypassing bile and extracellular space. Although epithelial cells of the renal tubules also express the FcRn receptor, albumin recycling and maintenance of its plasma level depend on the expression of FcRn by hepatocytes and endothelial cells, and the absence of the FcRn receptor on the surface of hepatocytes and endothelial cells leads to the development of hypoalbuminemia [32].

About 30–40 % of albumin stay in the plasma, remaining albumin is redistributing into the interstitial space at a rate of 4–5 % per hour. From the interstitial space albumin enters the lymphatic vessels and eventually returns to the systemic circulation [14]. The rate at which albumin leaves the plasma compartment is determined by Starling's law. In cirrhosis, the gradient value changes due to an increase in vascular permeability, which boosts the rate of its redistribution to 9–11 % per hour. Persistent sodium and water retention in patients with liver cirrhosis leads to hemodilution and a decrease in albumin concentration. These factors, combined with reduced protein-synthetic liver function in cirrhosis, lead to hypoalbuminemia [33].

Albumin synthesis also depends on hormones such as steroids, insulin and glucagon. In particular, steroids have been shown to enhance gene expression for albumin synthesis in animal models [34, 35]. Albumin catabolism occurs near the vascular endothelium, and its degradation is promoted by atrial natriuretic factor (peptide) [4]. Receptors gp18 and gp30 are expressed in many tissues and regulate albumin degradation and demonstrate a higher affinity for chemically modified albumin (oxidized albumin). Further this modified albumin is destroyed in lysosomes [32].

Albumin properties

Previously clinical effects of albumin were explained almost exclusively by its ability to increase the blood volume, thereby counteracting hypovolemia and related hemodynamic changes that are characteristic of progressive liver cirrhosis. Albumin is the main modulator of fluid distribution between the body compartments, it accounts for about 70–80 % of the oncotic plasma pressure. The oncotic properties of albumin are related to its molecular weight (about 2/3) and the Gibbs–Donnan effect (about 1/3). The Gibbs–Donnan effect is the ability of negatively charged albumin to attract positively charged molecules such as sodium, thus causing the movement of water from the extravascular to the intravascular space [36, 37]. However, in the last decade, experimental and clinical data have shown that a number of important functions of albumin are also due to the non-oncotic properties of the molecule and are related to the conformational structure. Albumin plays an important role in the binding, transport and detoxification of many endogenous and exogenous substances, modulates the inflammatory and immune response, stabilizes the endothelium, participates in the regulation of blood clotting and platelet function [38].

Antioxidant function of albumin. Antioxidant properties associated with ligand-binding ability

Albumin exhibits specific antioxidant functions due to its ability to bind multiple ligands and free radical inactivation, which depends on its structural configuration [39]. Transition metal ions (mainly copper and iron) act as a ligands in the direct or indirect oxidative reactions [40]. When interacting with hydrogen peroxide (H_2O_2), they initiate Fenton reaction, catalyzing the formation of reactive oxygen species (ROS) [41]. Free transition metals binding to albumin significantly limits their ability to participate in the Fenton reaction. Thus, albumin acts as a radical acceptor by a free thiol group on the Cys-34 residue [41–44]. M.Khosravifarsani et al. and co-authors confirm these data, suggesting that the antioxidant activity of albumin is associated with the simple reduction of sulfhydryl groups on Cys-34 as a in attempt to neutralize increased number of OH radicals produced by the Fenton system [45]. Other aspects of the antioxidant activity of albumin are due to its ability to bind bilirubin, homocysteine and lipids [39].

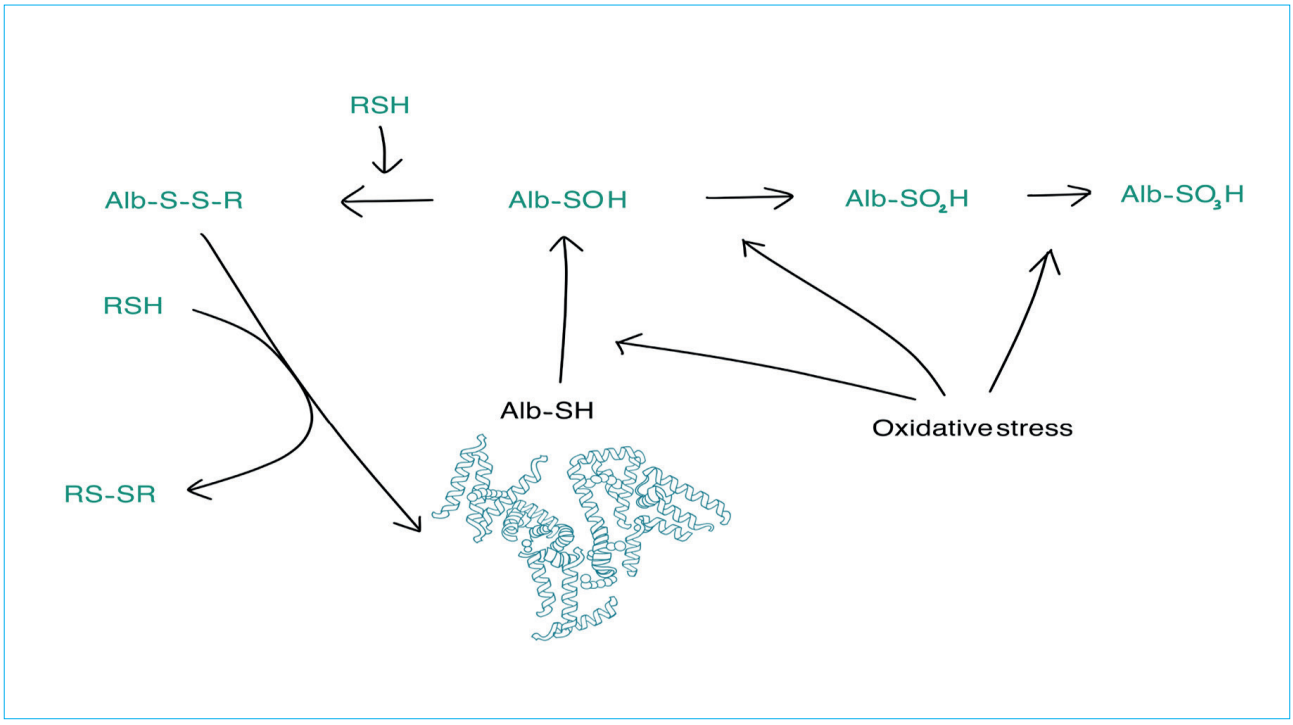

Fig. 4. Serum albumin molecule modifications in redox reactions. Under physiological conditions, 2/3 of the albumin molecules are in the reduced form with a free residue of Cys-34 (Als-SH) — mercaptalbumin. In oxidative stress, Cys-34 is oxidized to form sulfenic acid (Alb-SOH). Sulfenic acid can be oxidized to the final products — sulfinic (Alb-SO_2H) or sulfonic (Alb-SO_3H) acids, or converted into disulfide (Alb-SSR), followed by a return to the reduced form — mercaptalbumin (Als-SH)

Antioxidant properties of albumin are associated with inactivation of free radicals

Under physiological conditions, most of the albumin molecules (2/3) are in a reduced form with free thiol in the residue of Cys-34 (Alb-SH — human mercaptalbumin), which is capable of capturing several reactive oxygen and nitrogen forms such as hydrogen peroxide (H_2O_2), peroxynitrite (ONOO-), superoxide or hypochlorous acid (HOCl), performing the function of neutralization of free radicals [39, 40].

Under oxidative stress caused by interaction with peroxynitrite or hydrogen peroxide, thiol Cys34 passes into an open conformation and oxidizes itself, which leads to the formation of sulfenic acid (Alb-SOH). Sulfenic acid is a central intermediate in redox reactions. The final result of the oxidative process depends on whether the sulfenic acid is further oxidized or reduced to Alb-SH. Sulfenic acid can be oxidized to the final products — sulfinic (Alb-SO_2H) or sulfonic (Alb-SO_3H) acids. Sulfenic acid can also be converted to disulfide (Alb-SSR) by reactions with low molecular weight thiol (RSH, glutathione or free cysteine), which allows albumin to return to the reduced form of Alb-SH [46].

Participation of Alb in formation of disulfides supports the important function of Alb-SH as an extracellular redox regulator [39] (Fig. 4).

Alb as an inflammatory and immunological modulator is in focus of interest for researches. Some studies show that albumin is able to influence the redox state and bioavailability of many molecules involved in the processes of immune and inflammatory response. Examples of inflammatory activation are the binding of bacterial products (for example, lipopolysaccharide) [47, 48] or prostaglandin E2 (PGE 2) [49]. However, more recent data show that after capture by immune cells in early endosomes, albumin also reduces cytokine production by blocking the transmission of TLR3 and TLR4 signals [50]. In addition, albumin can actively participate in the immune response: one example is its ability to specifically bind the Clostridium difficile toxin in domain II in an experimental model of zebra embryos, so that albumin prevents the toxin entering the host cells.

Also, in this study, a correlation was obtained between hypoalbuminemia and the severity of the course of clostridial infection [51]. Finally, albumin regulates capillary permeability by binding the endothelial extracellular matrix, thereby modulating transcapillary fluid exchange. Hypothetically it binds to the subendothelium and interstitial

layers, modifying their permeability [52]. It is reported that Alb has a neuroprotective function and regulates brain blood circulation. Thus, based on the experimental model of ischemia and Alzheimer's disease, it can be assumed that the introduction of Alb has a neuroprotective function due to the antioxidant properties. Albumin also inhibits polymerization and increases the clearance of amyloid [53].

Post-translational modifications

The long half-life of serum albumin causes its high sensitivity to various posttranslational modifications, in particular to glycosylation. Serum albumin has 85 glycosylation sites, including 59 lysine residues and 24 arginine residues [54]. Glycosylation of albumin, like other proteins, begins with the addition of glucose to the N-terminal albumin residue (lysine or arginine residues). As a result of this interaction, a stable form (the Amadori form) is formed through an unstable intermediate compound called the Schiff base. Glycosylation of serum albumin changes its two- and three-dimensional structure, especially by the spiral formation of beta-leaf. A change in the conformational status of albumin leads to a decrease in antioxidant activity due to a decrease in the number of thiol groups and a change in the binding properties of albumin. The transport function is also reduced due to the difficulty for ligands to recognize and bind to albumin [55–57]. Glycosylation of albumin (gAlb) can have various effects on its ability to bind drugs. At the same time, binding affinity is usually reduced, for example, for sulfonylurea, salicylate and ibuprofen [58–60].

However, in some cases, the affinity of albumin remains unchanged for some other drugs, such as diazepam and naproxen [61]. After albumin glycosylation, gAlb acquires a pathological phenotype due to is functional impairment. It causes irreversible damage to organs and tissues and target organs with the development of complications of diabetes mellitus. For example, gAlb contributes to kidney damage by increasing the production of pro-oxidant molecules by epithelial and mesangial cells. As for cardiovascular conditions, gAlb predominantly reacts through the receptors activation of the end glycosylation products (RAGE receptor). It accelerates oxidation and plays an important role in platelet activation and aggregation, as well as stimulates the expression of adhesion molecules that contribute to the formation of atherosclerotic plaques [62]. gAlb also promotes insulin resistance by stimulating the production of intracellular reactive oxygen species, which, in turn, inhibit the transmembrane transport of glucose in muscle cells and adipocytes [63].

Glycosylated hemoglobin (HbA1c) serves as a reference essay for long-term monitoring of glucose levels. However, the use of HbA1c as a diagnostic marker of diabetes is not recommended for a number of conditions, such as hemoglobinopathies, pregnancy or chronic kidney disease. Quantitative determination of serum glycosylated albumin (gAlb) can serve as an alternative in these situations [63]. The results of recent studies show that posttranslational modifications of human serum albumin (HSA), such as oxidation, glycosylation, truncation, dimerization and carbamylation, are associated with certain types of diseases.

For example, a group of scientists led by Marco Domenicali conducted a study aimed at identifying structural changes in Alb that occur in cirrhosis and determining their relationship with specific clinical complications and patient survival [64]. One hundred and sixty-eight patients with liver cirrhosis were included in the study; 35 patients with stable condition and 133 patients with complications due to decompensation of cirrhosis; as well as 94 healthy participants of the control group. Using high-affinity liquid chromatography/ mass spectrometry with electrospray ionization, in addition to its own isoform of Alb, it was possible to identify seven isoforms with one or two modifications: truncation of the last two amino acid residues in the N-terminal part (HSA-DA); truncation of the last amino acid residue in the C-terminal part (HSA -L); cysteinylation of the Cys34 residue (HSA1CYS); sulfinylation of the Cys-34 residue ($HSA1SO_2H$); and glycosylation (HSA1GLYC). In addition, two additional isoforms of HSA were obtained from a combination of a cysteinylated with an N-terminal truncated form (HSA1CYS-DA) or a glycosylated form (HSA1CYS1GLYC) [64]. It was found that patients with liver cirrhosis have significant post-transcriptional changes in the Alb, affecting several molecular sites and increasing in parallel with the severity of the disease.

At the same time, these changes were rarely recorded in healthy individuals. There were significant depletion of native, non-modified isoforms in cirrhosis. The native Alb and most of the modified isoforms correlated both with Child-Pugh score and with the outcomes of the end-stage liver disease model. In hospitalized patients, oxidized and N-terminal truncated isoforms were independently associated with ascites, renal failure, and bacterial infection. Finally, native Alb and cysteinylated/shortened

isoforms at the N-terminus were predictors of one-year survival with greater prognostic accuracy than the total serum Alb concentration. The data obtained formed the basis of the concept of "effective albumin concentration", which implies that the global function of Alb is associated not only with its concentration in serum, but also with the preservation of its structural integrity [64].

At the same time, a small sample of patients and a large number of different modifications of albumin identified by researchers do not allow us to obtain reliable data on changes in the functional usefulness of albumin in various diseases; this requires further scientific research in this area.

It is noteworthy that the high level of humam non-mercaptalbumin (non-mercaptalbumin is an irreversibly oxidized form of albumin) is able to change the function of immune cells in patients with cirrhosis compared to healthy people [65]. In this group of patients, inflammation develops due to the production of proinflammatory cytokines (IL-6, IL-1, TNF-α and IL-8), and the subsequent cytokine storm is initiated by activated leukocytes. Further, Alb increases the level of inflammatory eicosanoids (prostaglandin E2, PG F2a, thromboxane B2 and leukotriene B4). The effect of Alb on immune cells during cytokine storm is caused by phosphorylation of p38 mitogen-activated protein kinase with subsequent activation of transcription factors, which ultimately leads to hyperproduction of proinflammatory cytokines [65].

The culmination of systemic inflammation is the development of bacterial peritonitis, complicated by decompensation of liver functions. In the laboratory parameters of this group of patients, more obvious signs of systemic inflammation are determined (high levels of C-reactive protein (CRP) in plasma; soluble inflammatory mediators (pro-inflammatory and anti-inflammatory cytokines and chemokines)) and also, indicators of oxidative stress (the irreversible form of human albumin — non-mercaptalbumin-2) are higher than in healthy individuals and patients with compensated cirrhosis [32].

Some recent studies demonstrated that there is a relation between hypoalbuminemia and high mortality rate in patients with *Covid*-19. According to a number of authors, monitoring and maintaining normal albumin levels can prevent the development of multiple organ failure in patients with *Covid*-19 [66–68], due to its ability to suppress ACE-2 receptor expression (target *Covid*-19 receptor) [69].

Conclusion

Albumin is the most common multifunctional protein in human plasma. Together with the violation of synthetic liver function, albumin not only decreases in quantitative ratio, but also undergoes molecular changes, inevitably leading to the suppression of its functional activity. Determination of effective albumin can serve as an additional criterion for assessing the severity of cirrhosis and predictor of complications [70].

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