Diabetes

Albumin

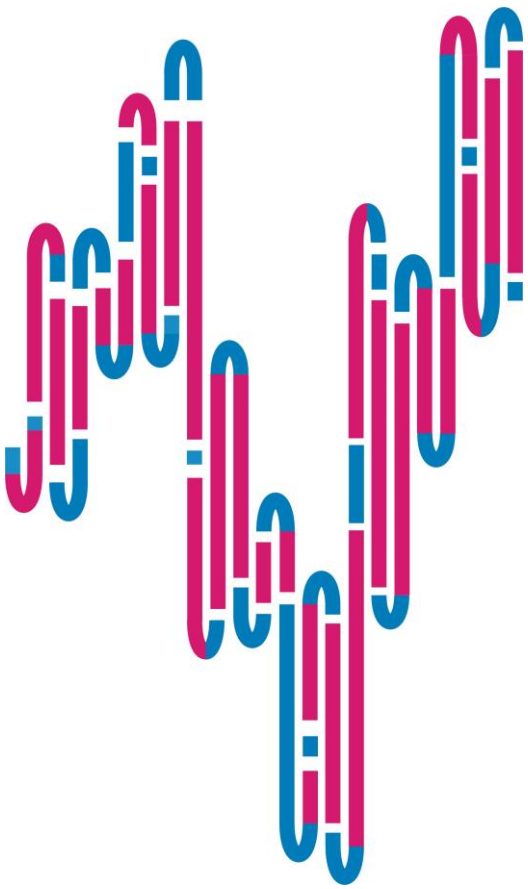
Analyte Information

Albumin

Introduction

Albumin consists of a single polypeptide chain of 585 amino acids with molecular weight of 66.5 kDa. The chain is characterized by having no carbohydrate moiety, a lack of tryptophan and methionine residues, and an abundance of charged residues, such as lysine, arginine, glutamic acid and aspartic acid. The mature, circulating molecule is arranged in a series of α-helices, folded and held by 17 disulphide bridges. The folding creates subdomains of three contiguous α-helices in parallel (Fig. 1). A pair of subdomains faces each other to form domains. These can be seen as cylindrical structures with polar outer walls and a hydrophobic central core. This structure enables albumin its function as a protein transporting and storing various molecules.

Fig.1: The albumin molecule reflecting the heart-shaped structure



Albumin represents the most abundant plasma protein, comprising 50 – 60% of the serum protein.

Albumin serves several functions. It provides the majority of intravascular osmotic pressure. Albumin is involved in the transport and storage of a wide variety of compounds, including bilirubin, calcium, long-chain fatty acids, toxic heavy metal ions, and numerous pharmaceuticals. Albumin also serves as a source of free amino acids for tissues.

Its structure is relatively resistant to denaturation. Other members of the albumin superfamily include vitamin-D binding protein (VDBP), α-fetoprotein (AFP) and afamin.

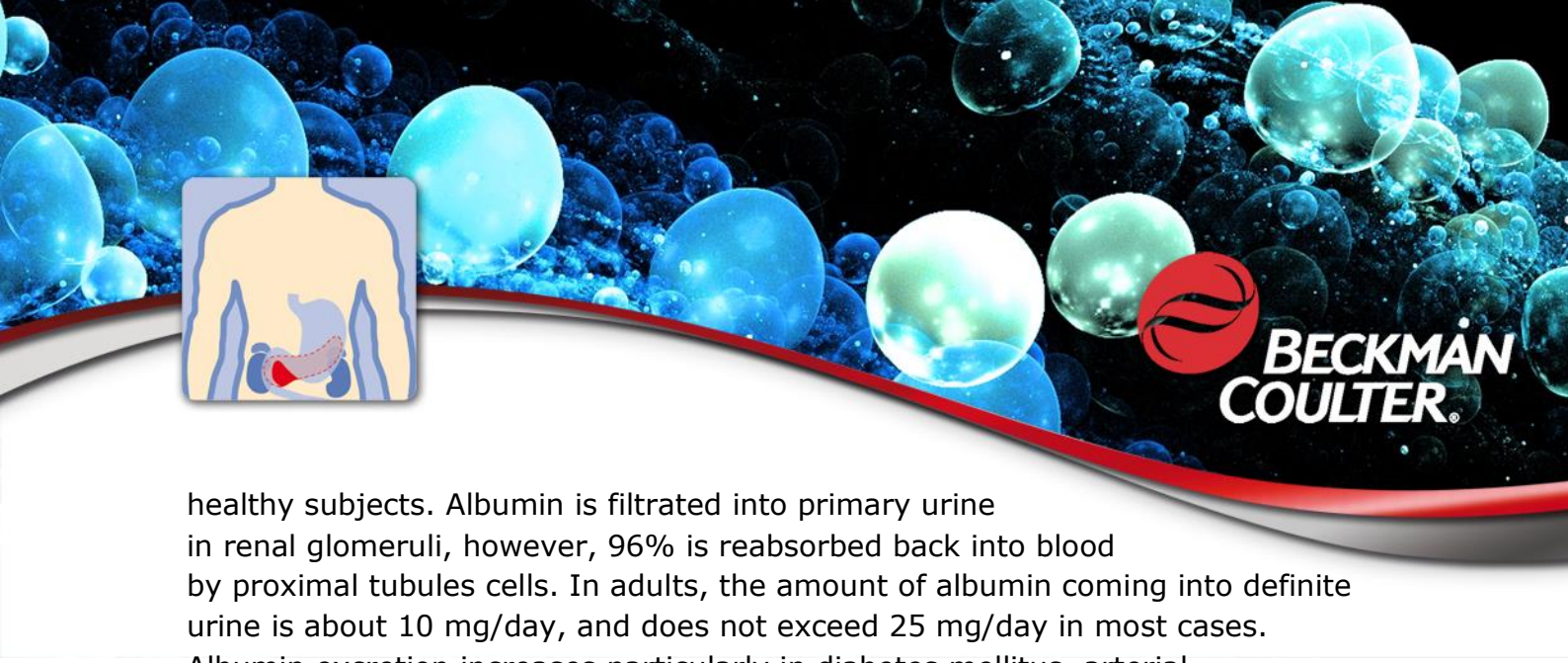
Biosynthesis

Albumin is synthetized exclusively by hepatocytes in the liver and is secreted into the portal circulation as soon as it is produced. Synthesis is primarily regulated by the colloid osmotic pressure of the interstitial fluid surrounding hepatocytes. Albumin is synthesized as preproalbumin, which has an N-terminal peptide that is removed before the nascent protein is released from the rough endoplasmic reticulum. The product, proalbumin, is in turn cleaved in the Golgi vesicles to produce the secreted albumin.

In healthy young adults, the rate of synthesis is 194 mg/kg/day, what is about 12 - 25 g of albumin per day in total. The rate of synthesis varies with nutritional intake, disease states and age. The liver can increase albumin synthesis to only 2 - 2.7 times than normal.

Metabolism

The serum albumin concentration is a function of its rates of synthesis and degradation and its distribution between the intravascular and extravascular compartments. The total body albumin pool represents about 3.5 - 5.0 g /kg of body weight (250 - 300 g for a healthy 70 kg adult). The plasma compartment holds about 42% of this pool, the rest is found in extravascular compartments. Some of this is tissue-bound and is therefore unavailable to the circulation. Each day, 120 - 145 g of albumin is lost into the extravascular space. Most of this is recovered back into the circulation by lymphatic drainage. Albumin is also lost into the intestinal tract (about 1 g each day), where digestion releases amino acids and peptides, which are reabsorbed. Urinary loss of albumin is minimal in



healthy subjects. Albumin is filtrated into primary urine in renal glomeruli, however, 96% is reabsorbed back into blood by proximal tubules cells. In adults, the amount of albumin coming into definite urine is about 10 mg/day, and does not exceed 25 mg/day in most cases. Albumin excretion increases particularly in diabetes mellitus, arterial hypertension, and in renal disorders.

Total daily albumin degradation in a 70 kg adult is around 14 g per day or 5% of daily whole body protein turnover. Albumin is broken down in most organs of the body. Muscle and skin break down 40 - 60% of albumin. The liver, despite its high rate of protein metabolism, degrades 15% or less of the total. The kidneys are responsible for about 10%, while another 10% leaks through the stomach wall into the gastrointestinal tract.

Albumin biological half-time is 21 days.

Physiological function

Albumin is essential for maintaining the osmotic pressure needed for proper distribution of body fluids between blood vessels and body tissues; without albumin, the high pressure in the blood vessels would force more fluids out into the tissues. In health people, albumin contributes up to 80% of the normal osmotic pressure. Albumin is present at a higher concentration than other plasma proteins and has the greatest osmotic significance. This direct osmotic effect provides 60% of the osmotic pressure of albumin. The remaining 40% is a result of its negative charge, providing an attractive force for the intravascular retention of positively charged solute particles.

It also acts as a plasma carrier. Albumin binds non-specifically several hydrophobic steroid hormones, thyroid hormones and serves as a transport protein for hemin and fatty acids. For instance, lipoprotein lipase activity in adipose tissue can be stimulated by the avidity of fatty acids to available albumin.

Albumin can stabilize some eicosanoids during metabolism, such as prostaglandin I2 and thromboxane A2.

Albumin also serves as a source of free amino acids in nearly all organs and tissues.

Under physiological conditions, albumin may have significant antioxidant potential. It can collect oxygen free radicals which have been implicated in the pathogenesis of inflammatory diseases.

Levels

Typical Albumin levels are given in table 1.

For each assay, relevant reference values are given in the appropriate Instructions for Use (IFU).

Tab.1: Typical Albumin levels

Specimen (serum)	**Reference range** (g/L)
0-4 days	28 – 44
4 days – 14 years	38 – 54
Adult	35 – 52
Adult, 60 – 90 years	32 – 46

Specimen (urine, 24 hours)	**Reference range** (mg/day)
	3.9 – 24.4

Diagnostic utility – prospects and possibilities

Albumin secretion into urine increases particularly in diabetes mellitus, arterial hypertension, and in renal disorders. According to the amount secreted, we can differentiate microalbuminuria (subclinical proteinuria) or macroalbuminuria (clinical proteinuria). Normoalbuminuria is defined up to 25 mg/day, microalbuminuria is between 25 – 250 mg/day, and macroalbuminuria is defined when secreted amount is higher than 250 mg/day. Detection of microalbuminuria by traditional method with sulphosalicylic acid is not possible.

There are many factors which should be considered in evaluations of **albuminuria** values. Albuminuria represents a rather variable parameter, varying in the course of several days. Albuminuria value is dependent on physical activity, diuresis, body position, diet, and it is higher at the day-time than at the night-time. Albuminuria rises in infections, at heart insufficiency, after sun exposure. Therefore, urine collection must be standardized, which is not easy to ensure in the 24 hour-variant, and this is why early morning urine collection after 8 hour-resting is preferred. In albuminuria evaluation the blood pressure values should also be known. Even so called microhypertension (135/90) is a factor contributing to pathologic changes in glomeruli, and thus affecting the microalbuminuria values. The renal disease progression leads to even higher quantitative albumin loss.

With liver disease, hypoalbuminemia is noted primarily in cirrhosis, autoimmune hepatitis, and alcoholic hepatitis. But in cirrhosis, hepatic synthesis of albumin may be decreased, normal, or increased.

In inflammatory conditions, Interleukin-6 (IL-6) inhibits albumin synthesis and induces synthesis of acute phase response proteins.

Elevated Albumin levels in serum

- any condition causing dehydratation
- congestive heart failure
- pregnancy
- oral contraceptives

Diminished Albumin levels in serum

- acute phase reaction and chronic inflammation:
  infection, surgery, trauma, chronic inflammatory disease, malignancy
- cirrhosis

Elevated Albumin levels in urine

- diabetic nephropathy
- renal nephrotic syndrome
- nephrosclerosis
- amyloidosis
- multiple myeloma
- glomerulonephritis
- pregnancy
- infection
- heart insufficiency
- after sun exposure

Diagnostic utility – practical applications

Diabetic nephropathy:

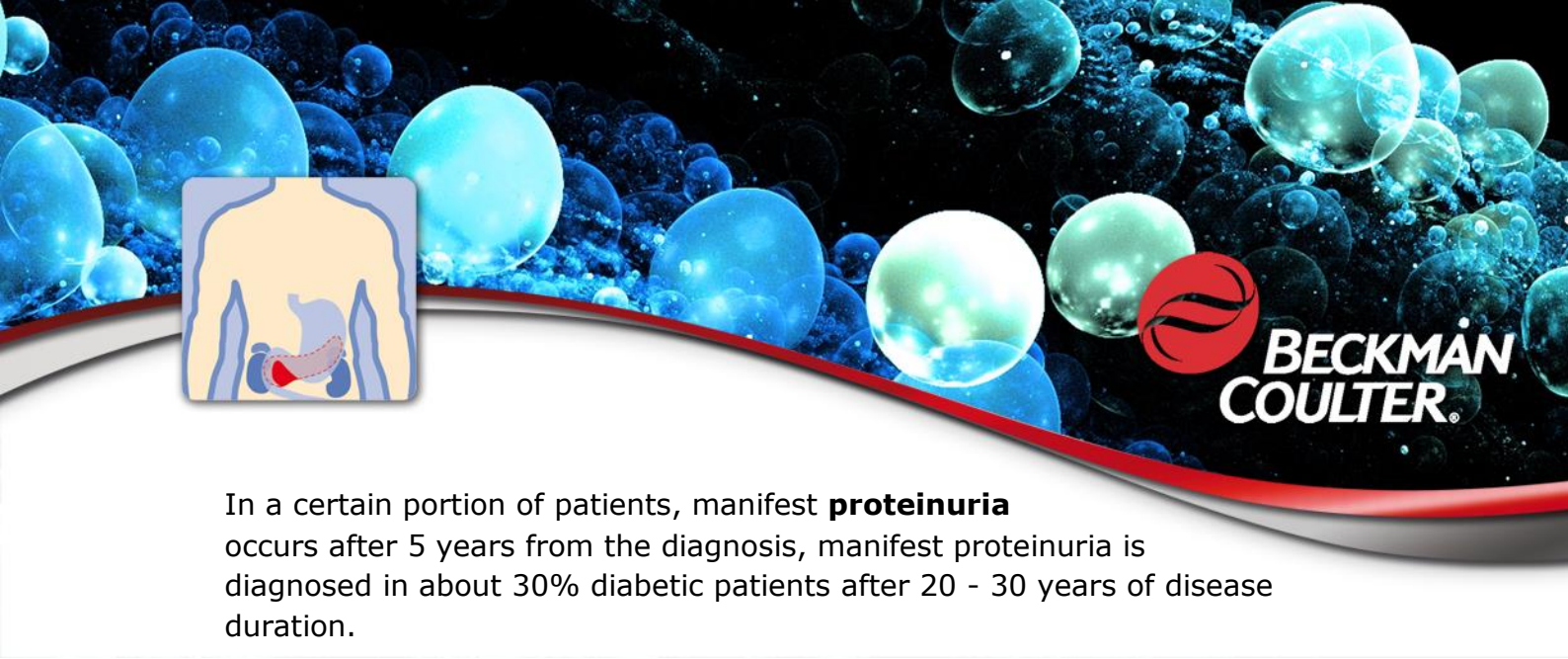
- **Early diagnoses of kidney involvement, mostly in DM type 1**
- **Monitoring of microalbuminuria in DM type 2**
- **Detection of proliferative diabetic retinopathy development**

Diabetic nephropathy is one of the most apprehensive diabetes complications. The early stages are connected with microcirculation changes in glomeruli (intra-glomerular pressure increase, hyper-filtration). These changes along with basal membrane negative charge loss result in increased albumin clearance - **microalbuminuria stage**. During the further disease progression, the basal membrane pore dilatations and other capillary glomeruli anatomic changes lead to increased penetration of plasma proteins from blood capillaries into renal tubules - **proteinuria stage**. Under this condition, the proteins are reabsorbed and deposited into tubuleinterstitium, where they initiate inflammation with successive fibrosis and nephron involution. Proteinuria contributes to renal insufficiency development. Follow-up of protein loss into urine enables to predict the rate of diabetic nephropathy progression. From the clinical point of view it is necessary to take into consideration that the **diabetic nephropathy course is frequently asymptomatic until the renal insufficiency stage.**

Therefore, the active follow-up of urine composition changes (and blood pressure changes) is very important for early detection of diabetic nephropathy.

Microalbuminuria development from normoalbuminuria is in particular connected with insufficient compensation of diabetes, and the presence of hypertension, smoking, and LDL cholesterol high levels are considered to be important risk factors.

Microalbuminuria occurs in about 8% patients within the first 3 years after DM type 1 diagnosis. The increased microalbuminuria values finding is usually reversible when full compensation of diabetes is reached. However, in certain number of patients with very good metabolic compensation microalbuminuria persists, indicating the significance and role of other factors in addition to hyperglycaemia. Microalbuminuria is found in 50 - 60% diabetic patients after 20 - 30 years of diabetes duration.



In a certain portion of patients, manifest **proteinuria** occurs after 5 years from the diagnosis, manifest proteinuria is diagnosed in about 30% diabetic patients after 20 - 30 years of disease duration.

The factors leading to microalbuminuria transferring into manifest proteinuria have not been fully explained yet, however, a long-term inappropriate diabetes compensation and early microalbuminemia manifestation after diagnosis are considered to be the most important ones.

Microalbuminuria detection always means presence of functional and anatomic changes in kidneys. Microalbuminuria represents an independent risk factor for diabetic nephropathy development in diabetic patients. It was also proved that microalbuminuria represent a risk factor for cardiovascular diseases and cardiovascular mortality even for non-diabetic individuals.

It is recommended to examine microalbuminuria at least once a year in all type diabetic patients over 50 years of age with diabetes duration over 5 years for screening reasons. In type 2 diabetic patients, microalbuminuria should be examined at the time of diabetes diagnosis and further once a year as a screening. At microalbuminuria positive findings, monitoring is indicated in 3 month intervals in both types of diabetic patients, eventually in the way corresponding with the clinical state of patient in order to reach normoalbuminuria by timely therapy onset.

Arterial hypertension

Microalbuminuria finding can help in detection of nephrosclerosis early stages.

Other renal diseases

The finding of microalbuminuria may be helpful in detection of the early stages and monitoring of therapeutic effect at:

- Primary glomerulopathy associated with minimum changes
- Secondary glomerular disorder, for example at systemic lupus erythematosus or at rheumatoid arthritis
- Renal impairment at so called nephrotoxic medicaments
- Renal disorders in pregnancy

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