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Transthyretin in the Evaluation of Health and Disease in Human and Veterinary Medicine

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Abstract

Transthyretin (also known as prealbumin) is an important transport protein, which plays an essential role in the binding of thyroid hormones and retinol with varying affinities in mammalian, as well as avian species. The determination of transthyretin concentrations may be used as a diagnostic tool for some disease conditions in humans, but is more often used as a nutritional marker to assess protein-calorie malnutrition and as prognostic indicator in critically ill patients. Transthyretin has shorter half-life (2–3 days) than that of albumin and belongs to negative acute phase proteins. This may complicate the use of transthyretin as a nutritional marker and the interpretation of results in the diagnosis of diseases. Although some studies have been carried out to determine the usefulness of transthyretin in selected disease conditions and disorders also in animals, it is a relatively rarely used parameter to evaluate health state and illness in veterinary medicine. The usefulness of transthyretin in the diagnosis of diseases and evaluation of nutritional status in humans and animals are reviewed in this article, including the laboratory assays available to measure its concentrations and the possible clinical application of the results, as well as its usefulness as a prognostic indicator in some disease conditions.

Keywords: disease marker, nutritional state, prealbumin, serum proteins, transthyretin

1. Introduction

Transthyretin is an important transport protein of the blood, which was originally named prealbumin because it migrates faster than albumin, and is visible as a band anodic to the main albumin fraction on electrophoretic gels [1]. According to Hamilton and Benson [2], this property is attributed to human prealbumin, not to bovine. Kaneko [3] reported that prealbumin is not always visualized on electrophoretograms and may not exist in all animal species. In the 1980s, the name was changed to transthyretin (TTR) describing its ability to bind both

thyroid hormones and retinol-binding protein (RBP) [4]. Moreover, transthyretin is one of the precursors, which may be found in amyloid deposits [5]. In humans, analyses of the concentrations of TTR in serum are recommended by some investigators as a screening marker for inflammation, malnutrition, or both [6]. In animals, there are only scarce literature data about this protein as a biomarker of health state and its use in the laboratory diagnosis [7].

2. Structure

Transthyretin is a small globular non-glycosylated tryptophan-rich protein of a homotetrameric structure, composed of four identical subunits with two thyroxine-binding sites per tetramer [8]. The binds for retinol-binding protein are placed at the surface of the molecule and do not interfere with thyroxine binding (**Figure 1**) [9]. Its molecular mass is of 54.98 kDa, which is small enough to penetrate the vascular wall and migrate into the extravascular space as easily as albumin or transferrin [10]. In some conditions, the transthyretin molecules may aggregate and form insoluble fibrillar deposits, which may be associated with amyloid diseases, predominantly senile systemic amyloidosis or neurodegenerative familial amyloidotic polyneuropathy [11, 12].

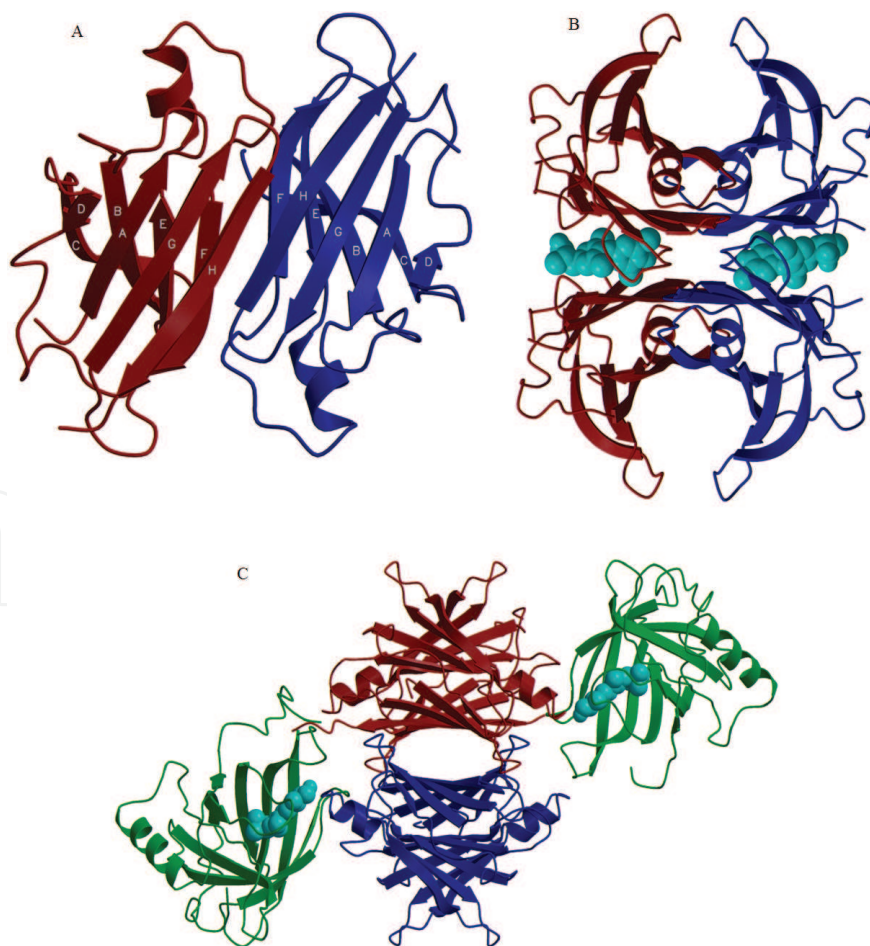


Figure 1. The three-dimensional structure of transthyretin displayed as a dimer (A) and a tetramer in complex with thyroxine (B) and retinol-binding protein (C) [103].

3. Functions

Transthyretin is a serum protein with multiple functional properties [13]. The main physiological functions of TTR include the carriage of thyroid hormone and indirectly vitamin A, which may promote the maturation of lymphocytes [14, 15]. Although each monomer of the TTR molecule has two binding sites for thyroid hormones, the binding of one molecule of T₃ or T₄ may reduce the binding affinity for the second site [6]. Moreover, the binding affinity for T₃ is lower compared with that for T₄. Transthyretin binds and transports approximately 15–20% of thyroid hormones circulating in the serum and up to 80% of thyroxine in the central nervous system (CNS) [16]. About 70% of thyroid hormones are transported by thyroxine-binding globulin (TBG), which is the major serum transport protein in humans [17]. The remaining part of thyroid hormones is transported by albumin. These proteins are responsible for the transporting of thyroid hormones to cells and maintaining a large store of these hormones in the blood in a non-diffusible form [2]. Among animal species, the concentration of TBG in the dog is only 15% of those observed in humans [18]. Cats do not appear to have a high-affinity thyroid-binding protein such as TBG, but have only transthyretin and albumin [19]. Some other small molecules may bind in the thyroxine-binding sites of TTR, including some natural products, drugs or toxicants [20]. These interactions with TTR may be important when TTR becomes a major circulating thyroxine-binding protein, for example, in humans with complete or partial TBG deficiency, or when the concentration of thyroxine in the serum is markedly increased [21].

In addition to the binding and carriage of thyroid hormones, transthyretin has a more important function, that is, the transport of retinol (vitamin A) through its association with retinol-binding protein (RBP) from its main storage site in the liver to target cells [22]. Retinol is bound to RBP, and then RBP binds to transthyretin. This binding of RBP to TTR was suggested to prevent the extensive loss of RBP, which is of low molecular weight and would be rapidly eliminated from plasma by glomerular filtration if it were not complexed to transthyretin [23, 24]. Although each of the four monomers has a binding site for RBP, the tetramer binds only one molecule of RBP with high affinity, and possibly a second with lower affinity [25].

Moreover, transthyretin acts as a negative acute phase reactant, serum concentrations of which fall due to decreased synthesis in inflammation, trauma, tissue injury or stress [26].

4. Synthesis

Transthyretin is synthesized mainly by hepatic parenchymal cells and in the choroid plexus of the brain, which has the highest concentration of TTR in the body [27, 28]. In cerebrospinal fluid, it is the second most abundant protein, which may be involved in the pathogenesis of Alzheimer's disease, depression and lead intoxication [29]. Other tissues have been reported also to produce TTR, but in much lower concentrations [30]. Small amounts of TTR are also produced by retinal pigment epithelium and the pineal gland [31]. Transthyretin has also been found in adult pancreatic islet cells, enterochromaffin cells in the gastrointestinal mucosa, as well as kidney cells [32, 33]. Neoplastic tissues, including choroid plexus papillomas,

glucagonomas and gut carcinomas, have been reported also to secrete transthyretin [33]. During fetal life, TTR is synthesized by the embryonic yolk sac endothelium [34]. Any alteration in energy-to-protein balance impairs the body mass reserves and causes early depression in the production of transthyretin [35].

The major sites of transthyretin degradation are the liver, muscles and skin, but a small amount of TTR may be catabolized by other tissues, including kidneys, adipose tissues, testes, as well as the gastrointestinal tract [36]. Transthyretin has a half-life in plasma of approximately 2 days, which is much shorter than that of albumin [37]. Transthyretin is therefore more sensitive to changes in protein-energy status, but its concentrations closely reflect the recent nutritional status rather than the overall nutritional support [38, 39].

5. Laboratory assays

Transthyretin is considered a more sensitive indicator of visceral protein status than albumin and transferrin because of its short half-life and low concentration in the body [40]. Conventionally, radial immunodiffusion and electroimmunodiffusion have been used for routine determination of transthyretin in humans [41]. Faster and more precise immunonephelometric and immunoturbidimetric assays have been developed also, which are easily applicable to many laboratory-automated equipments available in hospitals [6, 42]. Moreover, a sensitive enzyme immunoassay (enzyme-linked immunosorbent assay (ELISA)) for the determination of TTR values has been described, but this method is more time consuming and expensive compared with the above mentioned, and is more applicable, for example, for the estimation of TTR in the cerebrospinal fluid in nanogram amounts [43]. In veterinary medicine, species-specific ELISA is the most common analytical tool for the detection and quantification of transthyretin, utilizing monoclonal anti-TTR antibodies. In some avian species, for example, in budgerigars (*Melopsittacus undulatus*) transthyretin (prealbumin) constitutes as high as 75% of the total albumin concentration [44]. Therefore, it may be visualized and quantified easily by protein electrophoresis.

6. Factors influencing the concentrations of TTR

The concentration of TTR in serum is affected by many factors, including age, gender, as well as blood-drawing methods. In humans, the concentrations of transthyretin increase gradually after birth until they reached the adult values of 20–40 mg/dL [45]. A progressive increase of TTR concentrations with postnatal age was reported also by Kanakoudi et al. [46] in infants. Similarly, Cardoso and Falção [47] observed a marked increase of TTR concentrations in the period from birth till day 28 of age in preterm infants with very low birth weight. According to these authors, the serum concentrations of transthyretin in this important period of life are associated with the recent protein status, and reflect the balance between synthesis and degradation. Moreover, MacDonald et al. [48] stated that TTR values may predict future weight gain and concluded that if the serum concentrations of TTR remain stable or increase, it can

be expect that the newborn is in reasonable nitrogen balance and will gain weight subsequently. According to Benvenga et al. [49], the concentrations of TTR progressively decrease after 50–60 years. Approximately from the year 60 of age, muscle mass undergoes stepwise shrinking leading to sarcopenia, which may be responsible for the aforementioned decrease in the concentrations of TTR [50, 51]. In animals, the influence of age on the concentrations of TTR during the growth and development is not well described. A marked increase of TTR values from 72.9 to 251.4 mg/L was observed by Tóthová et al. [7] in calves 1 day after colostrum intake with a consecutive gradual decrease till the end of the third month of life. Rona [52] described that bovine colostrum contains among other bioactive molecules a small amount of prealbumin (transthyretin). Thus, the increase of serum TTR concentrations observed in calves after colostrum intake may reflect the adequate nutrition, as well as its hepatic synthesis due to adequate protein and energy intake [14]. In neonatal rats, low concentrations of TTR were found in the immediate postnatal period, which increases at the time when the concentrations of both thyroxine and corticosterone increase [53]. On the other hand, there were no significant differences in the serum concentrations of TTR in three different age groups of pigs from 10 to 25 weeks [54].

The concentrations of transthyretin linearly increase after birth without marked sexual differences during infant growth [55]. During human puberty, major hormonal and metabolic alterations occur, which result in increased height, weight gain and a substantial redistribution of body tissues. While androgens promote the development of muscle mass in male teenagers, oestrogens contribute to minimal enlargement of the female musculature and stimulate the accretion of subcutaneous fat depots [56]. These differences lead to higher concentrations of TTR in male adolescents compared with values recorded in teenage girls [57]. Higher concentrations of TTR in males compared with females were found also by Benvenga et al. [49] and Gaggiotti et al. [58]. Studies dealing with the evaluation of gender-related differences in the concentrations of TTR in animals were not found.

Pregnancy, hormonal changes, physiological status and stress are other factors that may influence the concentrations of transthyretin. In humans, the concentrations of TTR were evaluated by Zhu et al. [59] during normal pregnancy. The values of TTR increased significantly in the third month of gestation and rapidly decreased following 20 weeks of gestation. Transthyretin was measured also in females with severe preeclampsia, showing significantly decreased TTR concentrations in these patients compared with the control group. Transthyretin is synthesized also by placental trophoblasts, which are critical to the normal fetal development. Thus, disorders caused by the production of TTR may result in fetal distress [60]. The aforementioned results indicated that TTR may be a reliable biomarker for the diagnosis of severe preeclampsia [59]. Similarly, Kalkunte et al. [61] suggested a relationship between reduced TTR production and preeclampsia. The importance, functional role and alterations in the concentrations of TTR during pregnancy in animals have not been reported. Our findings suggest no significant changes in TTR concentrations during the last week of pregnancy and early stages of lactation in dairy cows (unpublished data). However, further evaluations are needed to establish the values of transthyretin and its possible changes in pregnant and lactating cows, which may be useful for veterinary practitioners in the early diagnosis, prevention and finding therapeutic solutions in periparturient dairy cows.

In humans, for the measurement of concentrations of TTR, it was recommended to take blood samples after 15–20 min in the sitting position [6]. Lower values are expected in bedridden patients, while standing position prior to blood sampling may result in higher concentrations.

7. The usefulness of transthyretin in the human clinical practice

7.1. Nutritional marker

Transthyretin may be used as important diagnostic tool for various disease conditions in humans, but is more often used as an indicator of malnutrition [62]. Several studies have shown a correlation between the concentrations of TTR and nutritional status [63, 64]. According to Ingenbleek and Young [14], low TTR concentrations are associated with inadequate protein calorie consumption or malnutrition. However, TTR may not serve as a reliable nutritional marker in patients with high concentrations of C-reactive protein (CRP), because of the activation of inflammatory responses [65]. This may complicate the use of TTR as an indicator of nutritional status, since inflammatory processes can lead to the decrease of serum TTR concentrations (negative acute phase protein) [66]. The CRP/TTR ratio may be a useful index in these cases to differentiate inflammatory states from protein malnutrition [67]. Very high ratios (>20) are indicative of acute phase response rather than protein malnutrition, while mild inflammatory processes may be accompanied by approximately a 10-fold increase in the concentrations of CRP and in CRP/TTR index values [6]. However, an inflammatory and nutrition index in animals was not yet established.

Surprisingly, extreme cases of starvation, including anorexia nervosa, have not been associated with a decrease of TTR concentrations. Nova et al. [68] reported normal values of transthyretin in patients with anorexia nervosa, which were comparable to values found in controls and did not differ after nutritional intervention. Barbe et al. [69] stated also that transthyretin concentrations in the majority of anorectic patients did not differ from those in control subjects, even in the presence of severe cachexia, but increased after weight gain. On the other hand, Gendall et al. [70] found lower concentrations of TTR in women with bulimia nervosa. These contradictory data indicate that further studies are needed to determine the effect of the aforementioned generalized malnutrition states on the values of transthyretin.

7.2. Disease marker

As transthyretin (prealbumin) belongs to negative acute phase proteins, its serum concentrations may be affected by many disease conditions, including trauma, inflammatory diseases, infections or malignancy (**Table 1**). Patients with severe sepsis or multiple injuries often have very low concentrations of TTR, related to severe acute phase response [71]. Studies have suggested that TTR may be a sensitive marker for the diagnosis of patients with liver cell damage, liver cirrhosis or hepatocellular carcinoma, reflecting the impaired liver synthetic function [72, 73]. Hutchinson et al. [74] and Yasmin et al. [75] found significantly lower concentrations of TTR in various types of chronic liver diseases when compared with controls with no impairment of liver functions. Moreover, Liu et al. [72] reported significantly lower

TTR values in patients who died compared to survivors suggesting its role in predicting the prognosis of patients with decompensated liver cirrhosis.

Pneumonia in children caused by *Mycoplasma pneumonia* was also associated with lower TTR concentrations compared to a healthy control group [76]. Similarly, Luo et al. [77] recorded reduced TTR values in patients with tuberculosis and lung cancer, while the serum concentrations of TTR were lower in patients suffering from tuberculosis than in patients with lung cancer. Moreover, the changes in TTR values were in accordance with the therapeutic effects of anti-tuberculosis drugs, which may be useful by the monitoring of therapy in these patients. However, seeing that nutritional imbalance is very common in patients with tuberculosis and after chemotherapy in subjects with lung cancer, poor performance status should be taken into consideration when interpreting serum TTR values in these patients and should be further investigated.

The concentrations of transthyretin may be altered also by thyroid diseases, especially endemic goitre [6]. Low concentrations of TTR were found by Vergani et al. [78] in patients with untreated thyrotoxicosis, but the values recorded in the majority of cases with untreated hypothyroidism were within normal range. The concentrations of transthyretin were measured also by Ishida et al. [79] in patients with various thyroidal states. In patients with untreated hyperthyroidism, markedly low serum TTR values were found, but were normalized by treating with anti-thyroid drug. Similarly, the aforementioned authors observed markedly low TTR concentrations in patients with subacute thyroiditis, but in patients with hypothyroidism the TTR values were within the normal range.

Changes in the concentrations of TTR were evaluated also in subjects affected by protein-losing enteropathy, which is characterized by marked losses of serum proteins through the bowel wall into the gastrointestinal tract resulting in hypoproteinaemia [80]. Despite hypoproteinaemia, Takeda et al. [81] observed TTR values within the normal range in patients with protein-losing gastroenteropathy. This phenomenon may be explained by the slightly increased production of rapidly turned-over proteins (including TTR) by the liver in response to the gastrointestinal losses.

Alteration	Associated disease condition
Decrease	Inflammatory diseases, infections, trauma, malignancy Severe sepsis, multiple injuries Liver cell damage, liver cirrhosis, hepatocellular carcinoma, chronic liver diseases Thyroid diseases, endemic goitre Protein-losing enteropathy Chronic malnutrition
Increase	Dehydration Chronic renal failure, renal insufficiency Anti-inflammatory therapy, anabolic steroids Acute alcohol intoxication Hodgkin's lymphoma, pancreatic cancer

Table 1. Abnormalities in the serum concentrations of transthyretin and associated diseases (adapted from Ref. [6]).

Increased serum concentrations of transthyretin are typically associated with chronic renal failure, presumably due to the decreased tubular uptake and degradation of RBP [82]. Cano [83] stated also that chronic renal failure may result in an increase of serum TTR concentrations, but these elevated TTR values during renal insufficiency are secondary to the lack of RBP degradation in renal tubules and to the subsequent increase in TTR. The concentrations of TTR may rise also during corticosteroid therapy and administration of anabolic steroids, as well as in patients using anti-inflammatory agents [6, 84]. Young et al. [85] found increased concentrations of TTR in ill-surgical patients receiving anabolic steroids, which may enhance amino acid and water uptake by tissues and increase the utilization of fat. Increased TTR concentrations may be seen in acute alcohol intoxication, caused by the leakage of proteins from damaged hepatic cells [86]. Transthyretin was shown to be upregulated also in Hodgkin's lymphoma and pancreatic cancer [11, 87].

7.3. Prognostic indicator

Several studies evaluated the significance of TTR as a prognostic biomarker and suggested that low concentrations may be associated with poor prognosis [88, 89]. Transthyretin was found as a prognostic factor for treatment outcomes and/or nutritional status of colon, oesophagus, ovarian and lung cancers [90–92]. In these studies, the concentrations of TTR correlated with response to treatment and clinical outcomes. Ho et al. [93] reported that low values of TTR may serve as prognostic factor for overall survival in cancer patients. However, the interpretation of its values in patients with systemic inflammatory response may be challenging. In these conditions, further clinical assessments and laboratory assays may be helpful, including markers of inflammation such as C-reactive protein, erythrocyte sedimentation rate or white blood cell number.

According to Cheng et al. [94], TTR has also been identified as a significant predictor of clinical outcomes after surgical intervention. Therefore, it may be used as part of the blood screening completed before surgery to determine pre-surgery health. Low TTR values before surgery may be associated with an increased risk of complications, including infections or pneumonia. Devakonda et al. [88] reported that surgery patients with low preoperative TTR values had significantly longer hospital duration of stay and longer intensive care unit duration of stay. Moreover, low concentrations of transthyretin were associated with higher rates of infectious complications, mortality and other surgical complications [95, 96].

8. The usefulness of transthyretin in veterinary medicine

Despite the physiological importance of transthyretin in health and as disease marker, there are only a few studies analysing its usefulness in the clinical and laboratory diagnosis of diseases in animals. Studies performed in dogs suggested that not only quantitative but also qualitative differences exist between human and canine TTR [97]. Transthyretin from dog plasma was of lower molecular mass compared to human TTR in samples subjected to sodium

dodecyl-polyacrylamide gel electrophoresis with subsequent Western blot analysis [98]. Piechotta et al. [99] investigated the serum concentrations of TTR in dogs with nonthyroidal illness (including neoplasia, allergy, cardiac disease, gastrointestinal disease, parasitism and hepatic disease) and low T4 concentrations compared with those in healthy dogs and dogs with primary hypothyroidism. They found significantly decreased serum concentrations of TTR in dogs with nonthyroidal illness (24.8 mg/L) compared with its concentration in hypothyroid dogs (41.1 mg/L). On the other hand, significant differences in TTR values were not found between hypothyroid and healthy dogs, or between dogs with nonthyroidal illness and healthy dogs. In the study presented by Raila et al. [100], low concentration of TTR was found in a young dog with chronic renal failure, probably caused by its increased urinary excretion. Changes in the serum concentrations of TTR were observed also in rats during protein-energy malnutrition [62]. The mean value of transthyretin in healthy pig serum obtained by Campbell et al. [54] was 302 ± 8 mg/L, but following *Streptococcus suis* type 2 infection the concentrations markedly decreased. In horses, transthyretin was identified using immunodiffusion technique, but the study was performed many years ago [101]. Establishing a quantitative method, such as an enzyme immunoassay, to measure the concentrations of TTR may be useful also in horses. In cattle, there are very little published reports about the usefulness of transthyretin in the diagnosis of diseases. Our preliminary results suggest lower concentrations of TTR in diarrhoic calves at the age of 1 month compared with healthy animals at the same age. Similarly, *Mycobacterium avium paratuberculosis* seropositive cows showed lower TTR values than those obtained in healthy cattle (unpublished data). Chang et al. [102] have isolated and sequenced transthyretin not only in humans and other mammalian species but also in birds, including emu, chicken, ostrich and pigeon. This study showed that TTR has greater than 98% homology and has a very similar binding pattern across species. However, additional studies should be done to determine the effect of various diseases on the serum concentrations of TTR in animals.

9. Conclusions

Presented data suggest that transthyretin may contribute to the evaluation of health state and diagnosis of some diseases also in animals. Changes in serum concentrations of TTR may be indicative of inadequate nutrient intake and may serve as an additional diagnostic tool for clinicians in the evaluation of some pathological conditions. It may be used as an integral part of the overall health assessment or in hospitalized animals to evaluate their nutritional status during the treatment and recovery. Low serum TTR concentrations may be considered a sign of increased risk of malnutrition, requiring further nutritional assessment.

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