Plasma Transthyretin as a Biomarker of Lean Body Mass and Catabolic States1,2

Yves Ingenbleek3* and Larry H Bernstein4

3Laboratory of Nutrition, Faculty of Pharmacy, University Louis Pasteur, Strasbourg, France; and 4Laboratory of Clinical Pathology, New York Methodist Hospital, Weill-Cornell University, New York, NY

ABSTRACT

Plasma transthyretin (TTR) is a plasma protein secreted by the liver that circulates bound to retinol-binding protein 4 (RBP4) and its retinol ligand. TTR is the sole plasma protein that reveals from birth to old age evolutionary patterns that are closely superimposable to those of lean body mass (LBM) and thus works as the best surrogate analyte of LBM. Any alteration in energy-to-protein balance impairs the accretion of LBM reserves and causes early depression of TTR production. In acute inflammatory states, cytokines induce urinary leakage of nitrogenous catabolites, deplete LBM stores, and cause an abrupt decrease in TTR and RBP4 concentrations. As a result, thyroxine and retinol ligands are released in free form, creating a second frontline that strengthens that primarily initiated by cytokines. Malnutrition and inflammation thus keep in check TTR and RBP4 secretion by using distinct and unrelated physiologic pathways, but they operate in concert to downregulate LBM stores. The biomarker complex integrates these opposite mechanisms at any time and thereby constitutes an ideally suited tool to determine residual LBM resources still available for metabolic responses, hence predicting outcomes of the most interwoven disease conditions.

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Introduction

Transthyretin (TTR)5 is a plasma protein endowed with multiple functional properties (1), which was proposed as an indicator of protein nutritional status in The Lancet in 1972 (2). From the beginning, the use of TTR as a biomarker has received strong support for assessing a broad array of diseases comprising metabolic and septic disorders (3–6) throughout the whole life span from birth (7) to old age (8). Some researchers have nevertheless cast doubt on the clinical reliability of TTR, which explains why the marker soon became a matter of persistent controversy. The most aggressive opposition came from members of the Division of Plasma Proteins of the International Federation of Clinical Chemistry (9). Their criticism has sown confusion in the minds of many clinicians, contributing to prognostic and therapeutic nihilism. The time is ripe to revisit some basic aspects of the physiopathology of TTR and to reconsider its nutritional merits in the light of recently published data showing that fluctuations in plasma TTR reflect the size of and alterations in LBM in humans (10, 11).

Plasma TTR in Healthy Subjects

TTR is a highly conserved protein in animal species, having been secreted by the choroid plexus (CP) and diffused within the cerebrospinal fluid (CSF) of reptiles for 300 million years (12). Liver synthesis of TTR occurred much later, 100 million years ago in most classes of vertebrates (birds, Diprotodont marsupials, eutherian mammals) but restricted to the developmental period in amphibians, reptiles, and Polyprotodont marsupials (13, 14). Using electrophoretic methods, researchers were able to identify TTR from members of the Division of Plasma Proteins of the International Federation of Clinical Chemistry (9). Their criticism has sown confusion in the
companion protein displaying a single binding site for 1 molecule of all-trans retinol (R-OH)—shown as retinol-binding protein (RBP) 4 (holo-RBP, 21-kDa MM) (19). The aggregation of holo-RBP to TTR occurs in the liver and stabilizes TTR before its extracellular export in the form of a retinol circulating complex (RCC) (20, 21), which has an MM of 76 kDa. Despite different biological half-lives \( T_{1/2} \) 2 d for TTR (22) and 0.5 d for RBP4 (23), both molecules remain attached at a close 1:1:1 stoichiometry (21). RBP4 is a member of the lipocalin superfamily thought to interact with specific receptors to deliver R-OH to target cells (24). In contrast, after having released its retinol ligand, apoRBP exhibits a significantly reduced TTR binding affinity and biological \( T_{1/2} \), undergoing rapid glomerular leakage, tubular disintegration, and subsequent recycling of the released AA residues (23). The data indicate that, within the RCC edifice, TTR protects RBP4 from premature urinary output and serves as a limiting factor for the delivery of retinoid compounds to peripheral tissues (25). The concept is supported by knockout mouse experiments showing rapid kidney clearance of RBP4 from plasma in TTR-deficient mice (26), although intrahepatic sequestration of native RBP molecules in TTR-mutant strains was also advocated (27). Under usual conditions, there exist large excesses of TTR (4.5 mM) over RBP4 (2 mM) in human plasma, which shows that virtually all RBP4 molecules are bound to TTR (21). In contrast, and depending on physiopathologic conditions, variable proportions of TTR may circulate in free and uncomplexed form. It has been shown that RBP4 may be overexpressed in obese and diabetic animals and humans, inducing a stage of insulin resistance (28). The pathway is mediated by a plasma receptor protein known as stimulated by retinoic acid 6 (STRA6), which governs the uptake of R-OH from holo-RBP and triggers a cytosolic cascade of functional abnormalities (29). Interestingly, TTR counteracts these molecular defects by blocking STRA6 receptor activities (29), suggesting that co-existing malnutrition, as assessed by lowered TTR plasma concentrations, would accentuate the STRA6-induced metabolic dysfunction generated by the burden of overweight.

TTR secreted by the liver is detected in the bloodstream as early as 8 wk after conception (30). At birth, plasma TTR concentrations are approximately two-thirds those in healthy mothers and thereafter increase linearly without sexual difference during infant growth (31). Human puberty is characterized by major hormonal and metabolic alterations leading to increased height, weight gain, and a substantial redistribution of body tissues (32). Androgens strongly promote the development of muscle mass in male teenagers, whereas estrogens contribute to minimal enlargement of the female musculature and stimulate the accretion of subcutaneous fat depots (32). As a result, a significantly higher S-shaped elevation of TTR is recorded in male adolescents compared with the blunted curve documented in teenaged girls (33, 34) (Figure 1). In healthy adults, the sex-related difference in plasma TTR and RBP4 concentrations is maintained and reaches a plateau during full sexual maturity (33, 34). Normal TTR plasma concentrations are maintained at ~300–330 mg/L in males and at ~250–270 mg/L in females (33, 34), whereas RBP4 plasma concentrations manifest a similar sexual difference at ~63 mg/L and 52 mg/L (34), respectively. Starting at ~60 yr of age, muscle mass undergoes stepwise shrinking leading to sarcopenia, with a steeper slope in elderly men (35, 36), accounting for the concomitant decline in TTR and RBP4 concentrations (34). Both TTR (15) and RBP (37) are synthesized by the CP and secreted in CSF following regulatory pathways distinct from those of the liver (38), which suggests that the brain might escape the harmful events affecting the overall body economy in the course of nutritional or inflammatory disorders. Moreover, intracerebral TTR and retinoids manifest a multitude of neuroprotective effects that sustain normal brain activities and contain the development of amyloidogenic processes (11). With increasing age, choroidal production rates of TTR (39) and RBP (40) reveal declining trends likely to be genetically programmed, which explains why elderly persons are no longer safeguarded against the risk of neural deterioration (11). The data suggest that the best physiologic way to prevent or delay the onset of neurodegenerative lesions is to promote nutritional rehabilitation and eradicate underlying co-morbidities, thus allowing maintenance of liver-derived RCC concentrations within normal ranges to compensate for CP-born involutive patterns (11).

**LBM in Healthy Subjects**

The most accurate method for assessing LBM size relies on the use of DXA. Ninety-five percent of body potassium is sequestered within metabolically active tissues; the

![Figure 1](image)

**Figure 1** Body accretion of TBK during the life span of healthy subjects. TBK compared with age on double-logarithmic ordinates is shown. TBK was determined by the measurement of \(^{40}K\) with the use of DXA. Averages of normal TBK values were obtained from the compilation of 7 different clinical investigations performed in healthy subjects aged 1 to 85 y. The data reveal that evolutionary patterns of lean body mass disclose linearly increasing, superimposable values from birth until the onset of adolescence and the occurrence of sexual dimorphism between teenaged boys and girls, then stabilization of TBK values until the age of 65 y. Elderly persons are characterized by gradual LBM downsizing in both sexes, with a more pronounced decline in male subjects in relation to more marked involutive trends toward sarcopenia. After the age of 65 y, the loss of TBK per decade is estimated at 5% in men and 3.5% in women. TBK, total body potassium. Adapted from reference 35 (Figure 5.5) with permission.
of resting energy expenditure, liver (2.6% of BW but oxygen turnover of the proteins in the body. The 2 main components in absolute terms an equivalent contribution to the daily represents almost half the total body weight (BW), reaching compartment. However, the size of the latter compartment are the fractional synthesis and renewal rates of visceral tissues Schematically, LBM may be subdivided into the visceral pro-

FIGURE 2 Evolutionary patterns of plasma TTR in healthy subjects from birth to age 100 y. Normal human TTR values measured in both sexes are shown. TTR concentrations were obtained from 68,720 healthy US citizens and measured by immunoturbidimetry with the use of monospecific goat anti-human TTR. Means and SDs stratified by age and sex are provided elsewhere (10). The results show that TTR values are low at birth, manifest a linear increase without sexual difference until the onset of puberty, followed by an increase in TTR values recorded in male teenagers and maintenance reaching a plateau during the period of full sexual maturity. Starting from age 60 y, TTR values show a stepwise decrease, with a steeper slope in elderly men, which reflects a relatively more rapid deterioration of their muscle mass. TTR, transthyretin. Adapted from reference 33 (Figure 4, chapter 9.01) with permission.

Importance of TTR in Protein-Depleted States Normal growth of neonates from birth to adulthood implies continuing accretion of body protein and is synonymous with positive nitrogen balance leading to LBM expansion, which is regarded as the major outcome measure of protein-related health (50, 51). These growth processes are tightly regulated and require the intake of appropriate energy and AA building blocks (52), in accordance with the concept that “protein synthesis occurs in the flame of sugar”, as expressed by the French physiologist Claude Bernard in 1865 (53). Plasma TTR is obviously situated on the cutting edge of the equilibrium between nutrient classes for which optimal requirements depend on age, physiologic status, and disease conditions. The restriction of dietary AA supply leads to curtailed nitrogen balance and to the concept of unachieved LBM replenishment (54). This is accompanied by depressed hepatic production of TTR mRNA (55), decreased abundance of TTR nuclear transcripts (56), and corresponding reduced exportation of mature TTR molecules in the bloodstream. The exquisitely sensitive response displayed by TTR is attributed to its small pool size, its short T1/2, and its high content of tryptophan (2, 17), which is known to constitute the narrowest of all indispensable AA pools in mammalian tissues (57). TTR has been used as an indicator of energy and protein adequacy in preterm, normal, and sick neonates (7, 58). TTR also proved useful for monitoring the dietetic management of anorexia nervosa (59) and weight-reduction programs (60). Likewise, the use of TTR is recommended for the nutritional follow-up of a variety of genetic and metabolic disorders such as uncontrolled diabetes (61), cystic fibrosis (62), drepanocytosis (63), Reye syndrome (64), inborn errors of AA metabolism (65), and defects of the urea cycle (66).

Protein malnutrition comprises a large spectrum of deficient states for which the extreme poles are frank kwashiorkor and emaciated marasmus. The former condition is characterized by swollen limbs, heavy liver steatosis (67), and very low plasma TTR concentrations (2). The latter condition is identified by borderline tissue overhydration, lesser hepatic fatty impregnation (68), and moderately depressed TTR concentrations (2). The flattened intestinal mucosa described in children with kwashiorkor (69) and its recovery under dietetic management recalls the malabsorptive events found in celiac patients that may be followed up by the serial measurement of plasma TTR concentrations (70). The same consumption of 44 mL O2/kg) and musculature (37% of BW and 2.3 mL O2/kg), contribute equally to basal metabolic activities, estimated at 26.4% and 25.6%, respectively (44). The data are in close harmony with a more recent clinical investigation showing that these chief organs together generate 50% of resting energy expenditure (45). In terms of specific fractional synthesis, the renewal rate of skeletal muscle mass is calculated at 1.7%/d (46), which is far below that of visceral tissues. Total liver proteins (stationary and exported) have a whole-body daily turnover reaching 25% of daily hepatic protein content (47), whereas the turnover of gut mucosa proteins (48) and lymphocytes (49) is estimated at 10% and 7%, respectively.
biomarker has been shown to be helpful for the detection and surveillance of elderly persons suffering from thymo-leukocytic disorders (71), likely resulting from a reduced dietary supply of protein resources combined with inadequate zinc intake (72). The data show that LBM stores are distributed into a composite agglomeration of various organs characterized by specific functional properties that are demonstrably interconnected to form an integrated system.

It becomes apparent that the intracellular protein content of each LBM component, taken separately, may undergo nitrogen depletion or recovery processes that can influence the hepatic amount of TTR production. Such coordinated linkages imply centrally mediated regulatory mechanisms governing the balance between protein accretion and protein breakdown as well as interorgan nitrogen fluxes between LBM components. The data provide a unifying concept of body nitrogen compartments for which adaptive alterations are reflected by the liver secretory rate of plasma TTR appearing as the ultimate indicator of LBM reserves. In malnourished children, a plasma TTR concentration of 65 mg/L indicates the upper limit below which the risk of lethality becomes likely (73). Surveys taking into account sex and age differences have shown that the TTR marker is distributed along Gaussian curves, paving the way for epidemiologic approaches seeking to compare protein-related health status in large population groups (74). Note also that, up to now, the synthesis of human TTR was not reportedly altered by ethnic differences or genetic deficiency, as described for TBG (75) and ALB (76). The data provide additional support for the universal reliability of TTR as a nutritional biomarker.

Importance of TTR in Stressful Disorders
Inflammatory disorders of any cause are initiated by activated leukocytes releasing a shower of cytokines working as autocrine, paracrine, and endocrine molecules (77). Pro-inflammatory cytokines stimulate the oversecretion of counter-regulatory hormones (glucocorticoids, catecholamines, glucagon, and growth hormone) opposing the hyperglycemic and anabolic effects of oversecreted insulin, thus creating a stage of insulin resistance in healthy tissues (78, 79).

Despite ambient hyperglycemia, the maintenance of low respiratory quotient values (of ~0.7) indicates that the energy economy is grounded on the mobilization of fat stores, which allows glucose and AA residues to be spared and preferentially redirected toward injured territories to uphold defense and repair purposes (79). During the course of any inflammatory disorder, cytokines reorganize overall protein metabolism, governing the overproduction of acute-phase reactants (APRs) that contribute in several ways to immune mechanisms using specific kinetic and functional properties (80). The severity and duration of bacterial and viral infections and parasitic infestations (81) or of multiple organ failure (82) lead to increased protein breakdown, which predominates over protein synthesis (82), and negative nitrogen balance; these developments support the concept of excessive LBM losses (54). The urinary leakage of nitrogen catabolites (mainly urea, ammonia, and creatinine) totaling 95% of output together with minor nitrogen compounds such as 3-methylhistidine, hydroxyproline, and AAs reveals that both visceral and structural compartments participate in the depletion of LBM stores of the whole body (43, 79). IL-6 is a key mediator in most chronic and acute inflammatory processes (77, 83), working through the mediation of a nuclear factor (NF) homologous with C/EBP-NF1 and competing for the same DNA-responsive element of the IL-6 gene (83). Stress-induced stimulation of IL-6 thus causes a dramatic elevation in APR values (80) together with reciprocal suppression of TTR synthesis as shown in animal (84) and clinical (85) experiments.

The burden of cytokines on protein metabolism is correlated with the severity and duration of initial impact. Patients afflicted with a combination of 2 distinct diseases or conditions exhibit accelerated LBM downsizing (86) identified by plasma TTR concentrations far worse than those recorded with a single disease (87). The data strongly support the view that the use of TTR enables monitoring of LBM depletion (10) and prediction of outcomes in critically ill patients (88). Clinical teams involved in the treatment of kidney failure (89), cardiac surgery (90), and ovarian cancer (91) have agreed in defining TTR concentrations of 180–200 mg/L as representing the boundary below which the likelihood of serious complications and increased mortality risk may be expected, whereas the threshold of 100–110 mg/L, presumably reflecting the exhaustion of LBM stores, suggests an ominous prognosis (92, 93). The decrease in plasma TTR in inflammatory states has fueled divergent debates. During the past 4 decades, researchers supporting the usefulness of the TTR biomarker had to face observations of its suppressed synthesis by nonnutritional factors (94, 95), which negated, ipso facto, TTR from any clinical relevance (9).

The recent demonstration that protein depletion and stressful disorders operate in concert to deplete LBM reserves along distinct and unrelated physiopathologic pathways helps to reconcile the diversity of opinions. Whatever the causal factors, the synthesis of TTR by the liver integrates opposing influences and yields as a net result a marker of LBM stores that remain available for metabolic processes. As a result, the TTR biomarker benefits from renewed reliability in identifying the most complex clinical situations characterized by the compounding effect of malnutrition and inflammation, as documented in hospitalized patients (4, 5), kidney failure (3), postoperative sepsis (96), cerebral infarction (97), head trauma (98), intensive care management (6, 99), organ transplantation (100), leukemia (101), and cancer (102).

Endocrine Implications
The abrupt decline in plasma TTR and holo-RBP concentrations in stressful disorders has major thyroid and retinoid implications (79, 103), but the importance of those implications is largely unrecognized by the scientific community. The liver serves as a large storage site for thyroxine and is capable of harboring as much as 40% of its total extrathyroidal body pool (104). The liver also secretes the 3 specific BPs ensuring
the normal transportation of total thyroxine (TT₄) in its intravascular space (5 L). Despite minor disagreements, it is generally held that TBG carries ~70% of TT₄, whereas TTR and ALB equally share the carriage of the remaining 30%. According to the free hormone hypothesis and the law of mass action (105), any endocrine ligand is metabolically inactive as long as it remains attached to the binding sites of specific carrier protein(s). This applies to T₄ because only minute fractions of its ligand are released in free form [free thyroxine (FT₄)] to exert hormonal activities (106).

The normal plasma concentration of TT₄ is 80 μg/L, whereas that of FT₄ is 20 ng/L, which indicates a free to bound ratio of 1:4000. In the case of acute inflammatory stress of medium severity, TTR plasma concentrations are usually decreased by 40% within 4 or 5 d, indicating that the 12 μg TT₄ transported by TTR should leak ~5 μg FT₄. The freed ligand diffuses uniformly in its normal distribution space (12 L) to reach throughout the critical stress period an estimated FT₄ concentration of 400 ng/L (~20-fold the normal FT₄ value). These hormonal alterations thus create a transient hyperthyroid state substantiated by the measurement of significantly higher plasma FT₄ concentrations in septic (107) and surgical (108, 109) patients. At least 3 other stress conditions may contribute to release freed ligands in the thyroxine distribution space, as follows: 1) bacterial infections, which cause a 4-fold accelerated peripheral turnover of both thyroid hormones (110); 2) anesthesia and surgery, which mobilize FT₄ sequestered in the hepatic parenchymal cells (111); and 3) cytokine-induced inhibition of TBG synthesis, which releases additional amounts of FT₄ (112). We conclude that the impact of the hyperthyroid stage associated with acute stress has been underdetermined as a result of ignoring the effect of increased tissue requirements and immediate cellular overconsumption. FT₄ molecules exceeding body tissue needs remain unmetabolized and are excreted by the kidneys (113), consistent with the view that increased amounts of thyroid hormones in the urinary output accurately reflect overall thyroid status (114). This hyperthyroid context has significant functional impact as disclosed by two-dimensional radioautographic experiments indicating that ~8% of the liver mRNA products (mainly enzymes, proteins, peptides, and components of energy metabolism) are stimulated under thyroid hormone influence (79, 115).

Holo-RBP is, in contrast with TTR, the sole conveyor of retinol, for which the normal concentration in adult humans (60 mg/L) ensures the carriage of ~500 μg R-OH/L with a free fraction [free retinol (FR-OH)] measured at 1 μg/L, yielding a normal free to bound ratio of 1:500. In the case of acute stress of medium severity, decreasing holo-RBP values by 40%, an estimated proportion of 200 μg retinol is released as FR-OH, which diffuses uniformly in a larger distribution space (18 L) than that of FT₄ and causes an augmented FR-OH concentration estimated at 10–12 μg/L or ~10 times the normal free value. To our knowledge, no study describing the sequential upsurge in plasma FR-OH is available, but there exists clear indirect evidence that this adaptive increase is validated by the recovery of an unexpected retinoluria after surgical stress (113), febrile rotavirus diarrhea (116), shigellosis (117), sepsis, and pneumonia (118). Healthy subjects do not excrete detectable amounts of retinol in the urine, indicating that stress-associated retinoluria, which has been shown to be correlated with the duration and severity of injury, results from an expanded extracellular free pool in which its unmetabolized fractions undergo, like FT₄, kidney overflow. The delivery of retinol targets a variety of cell-surface receptors that are unevenly distributed in body tissues, with high concentrations found in the epithelial cells of the CP and in organs belonging to the visceral compartment (liver, intestinal mucosa, bone marrow) (119). Cell surface receptors for holo-RBP operate the transmembrane uptake of the ligand, a process followed by cytosolic internalization (120), although nonspecific intracellular transfer of FR-OH was also documented (121).

Retinoid-induced reactions principally modulate cytokine activities, immune responses, and cellular components implicated in growth and repair processes (79). Taken together, the data show that the transitory hyperthyroid and hyperretinoid conditions created by abrogating liver TTR and RBP4 synthesis last as long as the decrease in both BPs continues. From a strictly mechanistic point of view, the currently used denomination of “negative APRs” applied to the suicidal behavior of TTR/RBP4 molecules is fully justified. From a physiopathologic point of view, this is a misnomer that denies the active participation of these BPs, which preferably deserve the designation of “acute-booster reactants” (57) to highlight the cascade of helpful events generated in the course of stress.

The clinical conditions described above apply to patients undergoing stressful disorders of medium severity. In the case of more grievous injuries (99, 122), the cytokine-induced decrease in TTR/RBP4 plasma concentrations entails longer slopes correlated with the magnitude and duration of the stress impact. The decrease in TTR/RBP4 is an obligatory process lasting some days, which is poorly responsive to dietetic manipulations and associated with culminating FT₄ and FR-OH plasma concentrations causing superactivated inflammatory responses. These inflammatory reactions aim at promoting the build-up of a second line of defense processes following that primarily initiated by cytokines (43, 123). Thermally injured patients affected by extensive tissue damage exhibit a decrease in TTR and RBP4 concentrations of 70% of starting concentrations, reaching a nadir on days 6–8 after initial impact (122). Critically ill subjects usually exhibit hyperglycemic status involving the flooding of poorly irrigated tissues via simple diffusion to locally promote anabolic drive and wound healing via anaerobic glycolysis (respiratory quotient ~1) (79). Serial TTR measurement performed on a daily basis in the most severely affected patients and twice or 3 times per week in illnesses of medium severity allows the identification of LBM stores that remain available to face further inflammatory conditions. Reaching the TTR nadir should initiate the prescription of aggressive
nutritional therapy. Two lines of response may develop during the ensuing days. The smallest and most gradual increase in TTR concentrations above nadir values indicate the reversal of nitrogen balance and the progressive restoration of LBM status, which predicts the best possible clinical recovery. It is worth noting that increases in TTR plasma concentrations occur when most other biological and clinical criteria remain silent, which pinpoints the unusual performance of the TTR analyte. In contrast, the maintenance of lowered TTR concentrations during days or weeks (124) indicates that catabolic and anabolic processes neutralize each other. The persistence of lowered TTR values likely indicates inappropriate nutritional management that misses the most effective protein-to-energy ratio and/or harmful effects generated by underlying comorbidities requiring specific therapeutic approaches. When an inflammatory burden is superimposed on pre-existing malnourishment, the secretion of cytokines by activated macrophages is depressed (125), entailing significantly reduced leakage of FT4 and FR-OH ligands whose boosting of TTR analyte. In contrast, the maintenance of lowered TTR concentrations during days or weeks (124) indicates that cat-
somatic burdens of hospitalization (131).

In sum, TTR appears to be a unique biomarker of acutely and chronically evolving disorders, hence fulfilling the scoring task claimed by recently published position papers (128, 129). The use of appropriate laboratory equipment for the routine measurement of the TTR indicator (130) allows for early detection and nutritional management of endangered patients, which leads to improved prognoses and alleviation of the financial burdens of hospitalization (131).

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