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Review

Is transthyretin a good marker of nutritional status?

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SUMMARY

The assay of plasma transthyretin (TTR), also known as prealbumin, is a key step in the assessment of nutritional status. However, it remains unclear whether it really is a useful nutrition marker, and when and how to use it and interpret TTR levels and variations. Risk of malnutrition, malnutrition severity, prognosis associated with malnutrition and effectiveness of refeeding are four parameters in nutritional assessment, and need clear separation to understand the associated utility of TTR. TTR does not have the same impact and potential on each of these parameters: it can be helpful but not essential for evaluating the risk of malnutrition, and it can diagnose malnutrition and its severity in patients with no inflammation syndrome. TTR is a good marker for prognosis associated with malnutrition, and is even better for monitoring refeeding efficacy despite inflammation. Thresholds depend on the purpose for which it is used. We propose a simple algorithm to guide the interpretation of TTR levels as a helpful tool for day-to-day practice.

1. Introduction

Assessment of nutritional status is central to current clinical nutrition practice [1,2]. However, there is still a lack of consensus, and no accessible gold standard to quantify protein energy malnutrition (PEM) or oversee the effectiveness of its treatment. The problem is worsened by the fact that under the term "assessment of nutrition status", there are in fact four different issues requiring different tools for their exploration: (i) risk of malnutrition, (ii) diagnosis of malnutrition and of its severity, (iii) prognosis associated with malnutrition, and (iv) effectiveness of refeeding [3]. Thus the often-used term "nutritional risk" is particularly confusing because it may refer to the risk of either malnutrition or complications related to nutritional derangements. Obviously, exploring these two items requires different approaches (e.g. decrease in food intake for the former, and albumin levels for the latter). Another example of a problem generated by this confusion is the Mini Nutritional Assessment test, very popular in geriatrics, which combines items predicting risk of malnutrition with others assessing severity of malnutrition. We focus here on transthyretin (TTR), not to argue for or against it, but rather to delimit its usefulness according to the issue at hand and the prevailing circumstances. This review thus seeks to clarify how and when TTR is well-suited to nutritional assessment, and offer guidance for its full use as a helpful tool in day-to-day practice.

2. Biological nutritional markers

Many markers have been used for nutritional purposes, but none have been found entirely satisfactory [4]. Albumin is impractical for assessment of acute changes in nutritional status because of its long half-life, but should perform better as an index of chronic malnutrition. Transferrin is dependent on iron status and so would be expected to decrease in malnutrition, but iron deficiency, which may be related to the nutritional derangements, increases its serum concentration. Its assay is thus no longer recommended for nutritional assessment [4]. Retinol binding protein (RBP) provides exactly the same information as transthyretin, but its assay costs more, and RBP is more sensitive to renal failure [4]. Insulin-like growth factor 1 (IGF-1) level is decreased in malnourished subjects, and its utility relies on its very short half-life of 6 h. It is theoretically a good nutritional marker, but peptic inhibitor levels rise during malnutrition, and these inhibitors can interfere with the plasma assay of IGF-1 [4]. In addition, this assay is time-consuming and costly. Plasma fibronectin has been mentioned in some studies, but it is insufficiently specific, and its broad variability influenced by inflammatory states precludes its use. Some studies have investigated the utility of markers such as

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sex hormone-binding globulin or serum pseudocholinesterase, but findings show them to be no better than any of the previous markers for nutritional assessment purposes [5,6]. At the present time, and until further biological markers are discovered, transthyretin (TTR) seems to be the most useful one.

3. General considerations on TTR

Knowledge of TTR goes back to 1942. Then called thyroxin-binding prealbumin (TBPA), or prealbumin, because of its electrophoretic migration just before albumin, TTR is a non-glycosylated protein that forms a complex molecule with RBP. The complex allows retinol and T4 thyroid hormone transport. TTR is mainly synthesized and catabolized by the liver and excreted by the kidney and gastrointestinal tract with a half-life of 1.9 days [7]. The small pool size of TTR, its short half-life and its unusual richness in the indispensable amino acid tryptophan makes TTR a potentially sensitive nutritional marker. In addition to hepatic production, TTR is also synthesized in the visceral yolk sac endoderm, retinal pigment epithelium and choroid plexus epithelium. However, these productions are regulated independently, especially during malnutrition and inflammatory processes, and do not influence serum TTR levels [7]. The reference interval is 0.20–0.40 g/L, but varies with age and gender (Table 1), and needs to be taken into account to interpret the result of an assay [8]. In healthy neonates it is approximately two-thirds of that found in healthy adults [9]. TTR gradually increases until age 20, reaching the reference interval for adults until age 60. Female values are slightly below male ones because TTR synthesis is controlled by sex steroid hormones. The lower range of values associated with elderly patients is more likely to be related to age and decreased IGF-1 [10].

TTR assay is inexpensive and easy to carry out in the laboratory, usually by immunonephelemetry or immunoturbidimetry. The former is the reference and yields more accurate results than other methods [11].

Serum concentration of TTR is influenced by many factors, including recent dietary intake. It is increased by severe renal failure, and by corticosteroids, non-steroidal anti-inflammatory agents and oral contraceptives [12]. It is decreased in liver disease, dialysis, hyperthyroidism, and significant hyperglycemia [12], but the most common cause of decrease is inflammation, which elicits an acute phase response. This process is mediated by pro-inflammatory cytokines (i.e. IL-6, IL-1, TNFα). It causes liver synthesis priority to favor inflammatory proteins such as c-reactive protein (CRP) and α2-macroglobulin at the expense of TTR. Although this synthesis priority hypothesis has been challenged [13] for albumin (i.e. increase in degradation and space of distribution rather than decrease in synthesis), no work has to our knowledge been done on that subject concerning TTR. Fluid distribution and hydrational changes also modify TTR serum concentration, increasing with acute dehydration and decreasing with hemodilution [12].

4. A complementary though not indispensable marker to assess risk of malnutrition

The pathway to diagnosing malnutrition begins with screening patients to identify those at risk of malnutrition. Some authors suggest, with rational arguments, that TTR could be a sensitive marker to identify patients at risk of malnutrition [14,15]. TTR concentration reflects recent dietary intake rather than overall nutritional status [14], independently of the presence of multiple-organ involvement and inflammation [16]. Hence it may characterize a patient at risk of developing malnutrition (e.g. due to decreased food intake) rather than a patient who is already malnourished. However, the simplest way to evaluate the risk of malnutrition is to use a questionnaire to ascertain only simple historical, environmental, and anthropometrical data, and more importantly recent food intake. Different screening tools such as MUST, NRI-2002 and MNA-SF have been designed for this purpose. Thus even though TTR could be a helpful tool, its cost (compared with that of filling out a questionnaire) and the need to take a blood sample argue against using it for systematic screening of hospital patients.

Table 1
TTR reference intervals by age and gender.

	Newborn	1–7 years	7–20 years	20–60 years	>60 years
Males	0.07–0.17	0.12–0.27	0.13–0.41	0.20–0.45	0.16–0.40
Females	0.08–0.17	0.12–0.28	0.13–0.38	0.18–0.38	0.14–0.37

Reference intervals are the 2.5th–97.5th centiles. Values in g/L adapted from Ritchie et al. [8].

5. A controversial marker for diagnosis of malnutrition and its severity

The first use of TTR as a malnutrition marker dates back to the 1970s, when low serum levels were found to be associated with malnutrition [17]. The assumption that a lower bioavailability of amino acids needed for TTR synthesis by the liver formed the rationale for its use as a nutritional marker. For the past decade, the use of TTR as a nutritional marker to diagnose malnutrition and assess its severity has been very controversial in the community of nutrition experts. Some reports claim that a reduced concentration of TTR indicates PEM [18], while others suggest that its specificity is too low for this purpose, considering the many circumstances inducing bias [19].

For now, the closest we have come to a gold standard to define malnutrition is estimated fat free mass (FFM) and fat mass (FM) by bioelectrical impedance [20] or, better, using dual-energy X-ray absorptiometry (DXA) [21]. Serum level of TTR is directly correlated with both bioelectrical impedance analysis [22] and DXA results [23], strongly suggesting a relationship between the visceral protein and the somatic proteins of FFM. A recent review [9] reconsiders the merits of TTR as a nutritional marker, with recently published data showing that fluctuations in plasma TTR reflect the amount of lean body mass and its alteration. As described above, many circumstances are associated with reduced serum TTR concentrations, of which the most common is acute phase response. Thus patients with multiple injuries and severe infections often have low or very low TTR plasma concentrations, negatively correlated with CRP plasma concentrations. Studies have sought to remove the confounding inflammation factor by using ratios including acute phase response proteins such as CRP [24]. However, in these ratios, the weight of CRP is much greater than that of TTR, and more likely to be indicative of acute phase response than PEM. Devoto et al. [25] surprisingly found an excellent correlation between TTR and Detailed Nutritional Assessment (DNA) as a diagnostic tool for diagnosing malnutrition, without assessing inflammation. However, when examined carefully, some of the items in DNA include inflammation variables, which explains why this correlation was found, while almost half the patients had an infection or had undergone trauma. Most studies before the 2000s using TTR as a nutritional marker for diagnosing PEM are outdated, given their failure to consider the possible influence of inflammation in the research design [26]. Even so, some recent studies [27] unfortunately still lack comparison of TTR data with inflammatory status, so perpetuating uncertainty about their interactions and casting doubt on the efficiency of TTR and its utility as a marker of nutritional status and of its severity.

Inflammation is today considered the main cause of reduced serum levels of TTR. Thus TTR should not be used for either

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