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Pediatric reference ranges for various laboratory markers as children's nutritional needs change: Review

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***Abstract*---**Background: Historically, serum visceral proteins like albumin and prealbumin have been used as indicators of patients' nutritional condition. Prealbumin is generally used over albumin since it has a shorter half-life, which means it reflects more fast changes in nutritional status. Recently, there has been increasing attention given to the need of doing a nutrition-focused physical examination and reviewing the patient's medical history in order to diagnose malnutrition. Additionally, there is a growing recognition of the role that inflammation plays as a risk factor for malnutrition. Inflammatory signals have a considerable inhibitory effect on the synthesis of visceral proteins. Aim of Work: The use of these proteins as indicators for nutritional status has been a subject of discussion since they are significantly impacted by inflammation and less affected by protein energy storage. Methods: Currently, it is widely agreed upon that laboratory markers may be used as a supplementary tool to a comprehensive physical examination. Additional indications of nutritional status, such as urine creatinine or 3-methylhistidine, have not been widely used to measure muscle protein breakdown. Serum IGF-1 is hardly affected by inflammation and decreases with starvation. Results: Nevertheless, the alterations in its concentration lack the necessary specificity to be therapeutically valuable as an indicator of malnutrition, and serum IGF-1 has been less often used in clinical studies. However, biomarkers like prealbumin that indicate malnutrition might be valuable in predicting surgical results and

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death rates in severe conditions due to their ease of measurement. Conclusion: The use of these proteins as indicators for nutritional status has been a subject of discussion since they are significantly impacted by inflammation and less affected by protein energy storage. Currently, it is widely agreed upon that laboratory markers may be used as a supplementary tool to a comprehensive physical examination.

***Keywords*---**Malnutrition, Inflammation, Nutritional Evaluation, Biomarkers, Albumin, Prealbumin, IGF-1, Old, Prognostic Signal.

Introduction

Malnutrition has significant clinical and economical importance as it leads to higher incidence of complications in hospitalized patients and increased healthcare-associated expenses. The incidence of this condition has been reported to range from 30-50% in hospitals in Western nations, and up to 85% in long-term care institutions, depending on the criteria and the specific group being investigated [1-3]. A challenge in identifying malnutrition is the absence of a consistent definition and standardized approaches for screening and diagnosis.

Malnutrition occurs when there is a discrepancy between the body's nutritional needs and the amount of nutrients consumed. Malnourished individuals often have disease-related inflammation, leading to an intricate interaction between these two factors. Inflammation affects both the nutritional needs and the amount of food consumed. It causes malnutrition and negative effects by inducing anorexia and changing metabolism via an increase in resting energy expenditure and muscle breakdown [4-8].

The recognition of the significant contribution of inflammation to the pathophysiology of malnutrition is often overlooked, and many doctors mistakenly believe that weight loss is the only crucial factor indicating malnourishment. As a result, the problem is often not recognized or acknowledged [8-12].

Aim of Work

The objective of this review is to analyze the existing literature on the use of laboratory biomarkers as a diagnostic tool for malnutrition, as well as for evaluating nutritional risk and monitoring nutritional intervention.

The Significance of Biomarkers in Screening Tools For Evaluating The Risk Of Malnutrition

Approximately 50% of the risk scores for malnutrition that have been published use blood laboratory indicators, such as visceral proteins, whereas the remaining scores do not [13-17]. The results of these screening tests exhibit significant variation, as shown in a research conducted in older individuals [18-21]. The authors discovered that the MUST assessment had the greatest validity

coefficient, whereas the NRS 2000 assessment, which is often used, had a lower specificity.

The European and US nutritional organizations (ESPEN and ASPEN) convened a consensus committee to establish three sub-definitions of malnutrition. "Starvation-related malnutrition" refers to the condition of chronic starvation without inflammation. "Chronic disease-related malnutrition" is defined as a condition where there is chronic and mild to moderate inflammation. "Acute disease or injury-related malnutrition" occurs when there is acute and severe inflammation. The diagnostic criteria for these sub-definitions included assessment of calorie intake, weight loss, body fat, muscle mass, fluid buildup, and grip strength, without the use of biomarkers [22]. Among other factors, serum visceral proteins were listed. However, it was suggested to use care when using them to diagnose malnutrition, since they mostly indicate the presence of inflammation.

A recent meta-regression analysis [23] examined the contribution of biomarkers in characterizing the extent of malnutrition using well-established and validated nutritional assessment techniques. The analysis comprised a total of 111 research, which consisted of observational and cohort studies. Unfortunately, there were no randomized controlled trials available for inclusion. The studies included a diverse range of clinical settings and involved a total of 52,911 people. The Body Mass Index (BMI) and levels of albumin, hemoglobin, total cholesterol, prealbumin, and total protein were considerably lower in persons at high risk of malnutrition, as judged by the Mini Nutritional Assessment (MNA), compared to those at low risk ($p < 0.001$ for BMI, albumin, hemoglobin, total cholesterol, and prealbumin; $p < 0.05$ for total protein). Comparable outcomes were seen for malnutrition ascertained by SGA and NRS 2002. The inclusion of individuals with acute diseases significantly reduced the predictive value of albumin and prealbumin, so validating the conclusion that these indicators are more indicative of inflammation rather than malnutrition. The researchers determined that BMI, hemoglobin, and total cholesterol were effective indicators of malnutrition in elderly individuals.

Serum Visceral Proteins Serve As Biomarkers for Assessing Nutritional Status

Visceral proteins are mostly produced in the liver. Inadequate consumption of protein and energy, together with reduced liver function and inflammation, lead to decreased levels of visceral proteins in the bloodstream. During periods of inflammation and heightened production of acute-phase proteins, the liver adjusts its protein synthesis priorities. It reduces the synthesis of visceral proteins to a level that corresponds to the severity of the damage.

Serum Albumin

Albumin is the predominant protein found in the serum of humans. For many years, it has been used as a marker of malnutrition in individuals who are in stable clinical circumstances (according to a review and meta-analysis [24]). As individuals age, the levels of serum albumin drop. The concentration of

hypoalbuminemia decreases by 0.1 g/L every year, however aging alone is not a direct cause of hypoalbuminemia.

A strong correlation exists between blood albumin levels and the risk of death from any cause in older individuals [25]. Patients who had a hip fracture and had albumin levels below 35 g/L had increased risks of post-operative complications, such as sepsis, and had a greater overall mortality. Elderly individuals with low levels of albumin have been shown to have substantial muscle mass depletion. High levels of the cytokines IL-6 and TNF-alpha, which are associated with inflammatory conditions, were identified as the primary variables contributing to decreased blood albumin levels [24]. Systemic inflammation has the dual effect of decreasing the production of albumin while increasing its breakdown and causing it to seep over blood vessel walls.

Furthermore, another research has shown demonstrated that this protein is a reliable indicator of surgical success [26,27]. Serum albumin emerged as the most powerful predictor among nine other risk indicators. The following research [26] supported similar results, however it did not provide clarification on whether hypoalbuminemia was caused by undernutrition or advanced illness in these trials.

In a research conducted in Spain, serum albumin was used as a biomarker to differentiate between unexplained weight losses (a loss of more than 5 kg in the last 6 months) in 306 referred patients. The study found that just over one-third of these patients were later diagnosed with a malignancy. Through multivariate analysis, it was shown that the most influential factors in predicting the presence of a neoplasm were those aged over 80 years, a white blood cell count over 12,000/mm3, and a serum albumin level below 3.5 g/dL [28].

Albumin has been criticism as a factor in nutritional evaluation since it lacks specificity and has a lengthy half-life of about 20 days [29]. Serum albumin concentrations may decrease not only due to reduced synthesis caused by inflammatory cytokines or hepatic insufficiency, but also due to renal losses in nephrotic syndrome and losses across the GI tract in protein-losing enteropathies [30].

Prealbumin in serum

Prealbumin, also known as transthyretin, is a protein that transports thyroid hormone. It is produced by the liver and partially broken down by the kidneys. Prealbumin values below 10 mg/dL are linked to malnutrition [31]. Prealbumin has been recommended as a nutritional indicator, especially in the context of refeeding and among older individuals [32]. Prealbumin has a shorter half-life (two to three days) compared to albumin, which makes it a better indicator of acute changes in nutritional status. Furthermore, the levels of prealbumin were not affected by intestinal protein losses in individuals diagnosed with protein-losing enteropathy [30]. Prealbumin levels may rise in the presence of renal failure, corticosteroid medication, or dehydration, whereas they may decrease during periods of physiological stress, illness, liver malfunction, and excessive hydration [34].

A newly suggested algorithm using prealbumin serves as a useful tool for clinicians to categorize general medical and critical care patients based on their risk of complications and outcome [34]. Prealbumin test should only be conducted after ruling out an acute inflammatory condition (CRP > 15 mg/L). A prealbumin level below 0.11 g/L was linked to higher death rates and longer hospital stays. Additionally, a rise of less than 0.04 g/L each week suggested that nutritional treatment was not successful.

Elevated C-reactive protein/prealbumin ratio in patients in the medical critical care unit has been linked to death [35], whereas a low C-reactive protein/prealbumin ratio in surgical patients has been shown to predict effective closure of gastrointestinal fistulas [36]. Regular assessment of prealbumin levels has been recommended as a valuable tool for evaluating nutrition and predicting outcomes in non-ICU patients who do not have inflammation [34]. Multiple articles have shown that prealbumin has a significant role in predicting prognosis, particularly survival rates, in different clinical circumstances such as gastric cancer [37], lung cancer [38], and cardiovascular illnesses [39].

Levels of albumin and prealbumin

A comprehensive study evaluated the significance of albumin and prealbumin in otherwise healthy individuals who experienced acute malnutrition as a result of limited food availability or a lack of appetite, mostly caused by anorexia nervosa [40]. The research demonstrated that serum albumin and prealbumin levels were stable despite significant weight loss, and were only reduced after severe fasting (BMI < 11 kg/m2). The authors' conclusion is that serum visceral proteins do not serve as a reliable indicator of nutritional deficiency and should not be used as a basis for guiding nutritional treatment in this particular patient population.

Transferrin

This protein serves as a carrier for iron during the acute phase response. With a half-life of around 10 days, this substance is often employed as an indicator of nutritional health. However, its levels may be affected by several variables such as iron levels, liver illness, and inflammatory conditions. Transferrin levels, similar to prealbumin, rise in the presence of renal failure [42]. While some writers regarded transferrin measures to be valuable for nutritional evaluation [43], others did not share the same view [44].

Transferrin levels are increased during iron-deficiency, whereas they are lowered under iron-overload conditions. During nutritional supplementation in critically sick children, there was a similar rise in serum transferrin and prealbumin levels [45]. Severe malnutrition causes a drop in serum levels. However, this indicator has been proven to be inaccurate when assessing moderate malnutrition and fat-free mass in a sample of elderly Italian patients [46].

Retinol-Binding Protein (RBP)

This protein is characterized by its low molecular weight and serves the specific function of transporting retinol from the liver to target tissues. This refers to the visceral protein that has the shortest duration of activity, with an approximate half-life of 12 hours [33]. Based on a study [47], it has been shown that it elicits comparable reactions to energy intake as prealbumin. However, measuring it is more challenging than prealbumin, and its levels are affected by the individual's vitamin A status. Due to these factors, the use of RBP measures has not been widely prevalent.

Alternative Laboratory Indicators of Malnutrition besides Visceral Proteins
Measurement of Creatinine in Urine

Creatinine is the last byproduct of creatine, a compound composed of three amino acids, mostly found in muscle tissue. If the kidneys are functioning properly, the excretion of creatinine reflects the generation of creatinine, which in turn is a reflection of the turnover of skeletal muscle. Each millimole (mmol) of creatinine present in urine originates from 1.9 kilograms (kg) of skeletal muscle, as stated in reference [47]. The drawbacks include a sluggish response to changes in nutritional status and a reliance on renal function, necessitating 24-hour urine collections.

Measurement of urinary 3-Methylhistidine

3-methylhistidine is a constituent of muscle fibers and is not recycled by the body. The urine excretion of a substance is indicative of the quantity of fat-free mass in the body and may serve as an indicator of the pace at which muscle protein is being broken down. It has a lower reliance on kidney function compared to creatinine; it is often measured per millimole of urine creatinine [47]. Both the measurement of urinary creatinine and 3-methylhistidine have not been widely used primarily because collecting urine samples may be inconvenient, their levels can rise after consuming meat, and they have limited sensitivity in monitoring changes in body protein levels.

Cholesterol in the Blood

Several nutritional screening procedures use total serum cholesterol as an indicator of malnutrition. There is a U-shaped association between serum cholesterol concentrations and mortality, meaning that both low and high levels are related with increased mortality. In particular, low levels of serum cholesterol have been linked to higher death rates [48]. Nevertheless, the ability to accurately detect and measure malnutrition is limited in terms of sensitivity and specificity.

Delayed Hypersensitivity and Blood Lymphocyte Count

The local inflammatory reaction to a subcutaneous injection. The administration of an antigen is hindered in cases of severe malnutrition. Simultaneously, malnourished individuals may have a decrease in the development of

lymphocytes, resulting in a total circulating lymphocyte concentration of less than 1500/mm3 (reference range 2000–3500) [47].

These anomalies may be considered as corroborating evidence for protein-energy malnutrition. However, they lack specificity and sensitivity, and other concurrent illnesses and a high stress response may also contribute to their presence. Both indicators exhibit a delayed response to the adjustment of the nutritional status. These factors restrict their use as diagnostic instruments for malnutrition.

IGF-1

IGF-1, formerly known as Somatomedin C, is a growth factor that is widely present in the body. The primary source of the circulating version of IGF-1 is the liver. The release of pituitary growth hormone is stimulated by itself. The serum half-life of the substance is rather brief, around 24 hours. Additionally, it is mostly bound to binding proteins in the plasma, with the primary binding protein being IGF BP 3. Fasting reduces plasma IGF-1 levels by more than four times, but IGF-1 concentrations rise with nutritional repletion. Previous research has shown a link between the amount of calories consumed and the levels of plasma IGF-1, with protein consumption having a lesser impact [49]. IGF-1 levels served as a dependable indicator of protein-energy undernutrition in older patients throughout the post-surgery healing phase for hip fracture. However, this study found that inflammation also had an impact on this marker [50]. However, inflammation did not have a significant impact on IGF-1 levels in other cohorts of postoperative patients [51,52].

Liver illness, renal dysfunction, and severe trauma such as burns may cause changes in IGF-1 concentrations [47]. However, IGF-1 was more effective in monitoring protein and energy status during nutritional rehabilitation compared to albumin or transferrin [53]. One drawback to measuring IGF-1 is that the levels in the blood might be affected by other variables, such as the acute-phase response. In recent times, there has been a growing interest in free IGF-I as a potential nutritional marker. However, despite previous encouraging findings, current papers have not recommended the use of IFG-1 measures.

Measurement of Leptin in the Blood Serum

A study found that malnourished hospitalized patients with end-stage liver disease had lower levels of leptin in their blood and higher prothrombin time [55].

The Serum Concentration of Nesfatin-1

Nesfatin-1 is a chemical that suppresses appetite and seems to be involved in regulating appetite and maintaining energy balance. Studies have shown that levels of nesfatin-1 in the blood are elevated in children who are chronically undernourished but otherwise in good condition [56].

Measurement of Zinc Concentration in the Blood Serum

Zinc is a trace element that is found in large amounts in the human body, second only to iron. It is present in all tissues and fluids and plays a vital role in the functioning of many enzymes. When there is a lack of zinc, it can lead to problems such as reduced ability to taste and smell, weakened immune system, and increased susceptibility to pneumonia. Severe zinc deficiency can cause skin lesions, anemia, diarrhea, loss of appetite, decreased function of lymphocytes, impaired vision, and mental retardation. Elderly individuals with zinc deficiency may also experience impaired psychological functions.

Zinc deficiency is due to low intake of zinc-containing foods such as meat and to decreased absorption caused by intestinal malabsorption [57]. According to a large sample of the TromsØ study, the risk of zinc deficiency was increased 3 fold in subjects at high risk of malnutrition, particularly in men [59]. Assessment of the zinc status carries the problems that only a small fraction of body zinc is circulating, and most serum zinc is bound to albumin. Therefore, albumin deficiency makes interpretation of serum zinc levels difficult. In spite of the widespread functions of zinc in the body and the potential importance replacing zinc in subjects with zinc deficiency, there is little high-quality evidence of the therapeutic benefit of zinc replacement in adult subjects. A randomized controlled trial in children with protein-energy malnutrition and zinc deficiency showed benefits of zinc replacement [60]. It is likely that zinc deficiency in subjects at risk of malnutrition remains often unrecognized.

Additional Crucial Micronutrients (Trace Elements and Vitamins)

The existing nutritional screening techniques do not particularly include laboratory testing of other trace elements such as iron. However, it is important to note that in situations when there is a clinical suspicion of micronutrient insufficiency, this procedure should still be carried out. The same may be said with laboratory testing for deficits in vitamins, namely vitamins A, B1, B6, B12, D, and folate.

Conclusion

The use of blood biomarkers in diagnosing or monitoring malnutrition is a subject of debate, especially in recent studies. This may be attributed to their relatively limited specificity and the impact of underlying illnesses, such as inflammation, especially on serum visceral proteins. Furthermore, the use of biomarkers to direct nutritional treatment has not been examined in extensive randomized controlled studies. In the near future, a randomized controlled multicenter study in hospitalized patients with malnutrition may address this gap. However, biomarkers like prealbumin are reliable predictors of illness prognosis and death in individuals who are at risk of malnutrition.

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