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Invited critical review

Diagnostic value of transferrin

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ABSTRACT

Despite the growing interest in hepcidin and other relatively new biomarkers, guidelines and clinical pathways continue to recommend traditional markers, such as serum transferrin (Tf) and ferritin, as laboratory tests for the diagnostic evaluation of iron-related disorders. In this study, we aimed to critically evaluate the diagnostic role of Tf relying on the highest level of available evidence by a comprehensive literature search. The role of Tf in iron deficiency (ID) and iron overload (IO) syndrome as well as a risk marker was evaluated. The low accuracy of Tf and Tf saturation (TS) in the diagnosis and management of ID conditions does not permit definitively recommending their use, even if recently published guidelines still consider the TS investigation as a complementary test for ferritin. If a tissue IO is suspected, TS is often used, even if it may not be the best test for detecting this condition. Nevertheless, clinical guidelines strongly recommend the use of TS as a first-level test for performing genetic diagnosis of hereditary hemochromatosis. Recently reported data indicating elevated TS as a risk factor for diabetes mellitus, cancer, and total mortality, may provide useful additions to the debate over whether or not to screen for IO using TS.

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Contents

1. Introduction

Iron is an essential micronutrient required for various biological processes, including erythropoiesis, oxidative metabolism, and cellular immune response [1]. At the same time, excess iron causes organ dysfunction through the production of reactive oxygen species (ROS) [2]. As a consequence, a strict regulation of iron homeostasis is mandatory, its maintenance being achieved by a sophisticated balance among mechanisms including iron absorption, transfer, utilization, storage, and loss. During the past few years, the understanding of molecular mechanisms controlling body iron metabolism has dramatically changed by the recognition of hepcidin as the main regulatory hormone of iron metabolism [3]. The introduction of hepcidin determination into clinical practice requires, however, further investigation [4]. Although a few commercial assays currently exist, the appropriate specimen type remains an unresolved issue [5,6]. In addition, excessive hepcidin

Abbreviations: AASLD, American Association for the Study of Liver Diseases; CHD, Coronary heart disease; CI, Confidence interval; CKD, Chronic kidney disease; DM, Diabetes mellitus; EASL, European Association for the Study of the Liver; ESA, Erythropoiesis-stimulating agents; FID, Functional iron deficiency; Hb, Hemoglobin; HH, Hereditary hemochromatosis; ID, Iron deficiency; IDA, Iron deficiency anemia; IO, Iron overload; KDOQI, Kidney Disease Outcomes Quality Initiative; NTBI, Non-transferrin-bound iron; OR, Odds ratio; ROS, Reactive oxygen species; Tf, Transferrin; TIBC, Total iron-binding capacity; TfR, Transferrin receptor; TS, Transferrin saturation; UIBC, Unsaturated iron binding capacity.

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production may occur in a number of acquired disease states, including infections, malignancies, and inflammatory conditions that makes its clinical assessment rather complex [7]. Although we can assume that hepcidin will very likely soon obtain an important role in the diagnostic evaluation of iron-related disorders, current guidelines and clinical pathways continue to recommend the measurement of more traditional biomarkers, such as serum transferrin (Tf) and ferritin. However, it is often difficult to understand if the clinical application of these markers is always evidence-based. The aim of this study was to conduct a comprehensive literature search regarding the diagnostic usefulness of Tf in iron-related disorders to derive available scientific evidence concerning the clinical role of Tf determination in serum. Particularly, we focused on meta-analyses and systematic reviews. Clinical guidelines were, although with precaution, also considered.

2. Role of transferrin in physiological iron homeostasis

The human body absorbs 1–3 mg/day of dietary iron balanced with losses via sloughed intestinal epithelial cells, menstruation, and other blood losses. These iron losing mechanisms do not provide an effective iron excreting system and thus the regulation of dietary iron absorption from the duodenum plays a critical role in iron homeostasis. Dietary iron is found in hem and non-hem forms and their absorption occurs in Fe^{2+} form at the apical surface of duodenal enterocytes via different mechanisms [8]. Once inside the intestinal epithelial cell, iron may remain in the cell for use or storage, never being absorbed but just lost when senescent enterocytes slough into the gut lumen, or it may be exported across the basolateral membrane of epithelial cells into the circulation [1]. When there is a body demand, iron is exported in reduced form through the basolateral membrane by ferroportin, then it has to be oxidized to Fe^{3+} by hephaestin before being bound by Tf. However, the Tf iron pool is replenished mostly by iron recycled from effete red blood cells. Besides dietary iron absorption, iron reutilization is indeed another elementary mechanism providing iron to the body. Senescent red blood cells are cleared by reticuloendothelial macrophages, which metabolize hemoglobin and hem, releasing iron into the bloodstream. By analogy to enterocytes, macrophages export Fe^{2+} via ferroportin in a process coupled by re-oxidation of Fe^{2+} to Fe^{3+} by ceruloplasmin and followed by the loading of Fe^{3+} to Tf [9].

Iron is transported in the circulation bound to Tf, which maintains iron in a redox-inert state and delivers it to tissues. Tf has multiple functions; first of all, it is the main plasma transport protein responsible for iron distribution and serves as a storage sink for sequestering iron extracellularly until iron is needed, then allowing it to reach target tissues [10]. On the other hand, Tf represents a protective mechanism against the presence of free-iron in the plasma, which could be extremely toxic to cells. This protective action is dependent upon two features of Tf: its high affinity ($Kd \approx 10^{-20}$ M) to Fe^{3+} and the fact that every Tf molecule has two iron binding sites and under physiological conditions transferrin saturation (TS) is only up to 30%–40% [11].

Developing erythroid cells, as well as most other cell types, acquire iron from plasma. Tf-bound iron enters target cells through receptor mediated endocytosis. Iron-loaded Tf binds with high affinity to Tf receptor (TfR) 1 and the complex undergoes endocytosis via clathrin-coated pits. The acidic pH of endosomes triggers the release of Fe^{3+} from Tf. Following the dissociation of iron, the affinity of Tf to TfR 1 dramatically drops resulting in the break-up of the complex and secretion of apo-Tf into the bloodstream to recapture Fe^{3+} [9].

The amount of iron bound to Tf (~3 mg) corresponds to less than 0.1% of total body iron, but it is highly dynamic and undergoes more than ten times daily turnover to sustain erythropoiesis [9]. In case of iron deficiency (ID), the concentration of Tf in plasma increases, but it reflects the iron status properly only when iron stores are exhausted and when serum iron concentration is <40–60 μg/dL, so it does not diagnose ID prior to ineffective erythropoiesis [12]. In iron overload (IO) states, when the whole iron binding capacity of Tf is saturated, an additional iron compartment called non-Tf-bound iron (NTBI) appears in the circulation. Unlike Tf-bound iron, the cellular uptake of NTBI is not dependent on TfR and NTBI is biologically toxic through the production of ROS to every tissue, especially liver, heart, and some endocrine tissues [2]. The activation of NTBI can be predicted by TS values and its increased levels may indicate developing organ toxicity in iron-overloaded patients [13].

3. Diagnostic role of transferrin determination

3.1. Background

Theoretically, the diagnostic gold standard for iron-related disorders is the technique that is able to estimate body iron stores most accurately. In this way, the bone marrow examination, establishing the absence of stainable iron, remains the gold standard for ID diagnosis. Bone marrow examination is, however, invasive, expensive, and requires technical expertise, and thus cannot be performed routinely in clinical practice [14]. In IO conditions, liver iron levels are considered to accurately reflect total body iron stores because liver is the dominant iron storage organ. Liver iron levels have also been used to estimate risk and predict outcomes, such as liver failure, diabetes mellitus (DM), heart failure, and death [13]. As with bone marrow examination, liver iron level quantifying methods, including liver biopsy and imaging techniques, are invasive and/or highly expensive, limiting their use in the screening and diagnosis of IO status. The use of surrogate biomarkers for evaluation of iron status is, therefore, inevitable, even if their diagnostic value can often be limited. Several serum markers are currently used to estimate the individual's body iron stores, including serum ferritin, iron, Tf, total iron-binding capacity (TIBC), and TS.

In clinical practice, both Tf and derived TS are widely used parameters in iron status evaluation. Screening for either ID or IO traditionally includes the determination of TS rather than a simple measurement of serum Tf concentrations [15]. The measurement of TS is widely available and cheap. Basically, there are two ways for TS determination, one based on TIBC estimate, the other employing the determination of Tf protein [16]. TIBC is the capacity of plasma proteins to bind iron. Although not the only iron-binding protein in the blood, Tf is the most important and TIBC can be utilized to indirectly determine serum Tf concentrations. In practice, TIBC is determined by the addition of sufficient iron to saturate iron-binding sites of serum proteins in the sample. After removing the iron excess, the assay for iron is performed. The ratio in percentage of serum iron and TIBC, in turn, indicates how much Tf is saturated by iron, so defining TS. As unsaturated iron binding capacity (UIBC) measurement is easily automatable, TIBC is often not directly measured as described above, but calculated by summing the results of serum iron and UIBC. UIBC assays add a fixed amount of iron to saturate iron-binding sites in the sample; the excess iron is not removed, but measured and UIBC is calculated as the difference of added and measured iron. Tf can also be directly determined as protein mass concentration using immunoassays and TS estimated on the results of serum iron and Tf measurements. In a head-to-head comparison by Hawkins [17], the diagnostic value of the immunologic measurement of Tf and of TIBC in the ID diagnosis was evaluated. By means of ROC curve analysis, no difference in the diagnostic performance was found between direct Tf measurement (immunoturbidimetry) and two commercial TIBC formulations.

Analytic, biologic, and pathologic factors may influence TS and limit its clinical utility. The within-subject biological variation of iron in serum is high (26.5% in average — http://www.westgard.com/biodatabase1.htm); furthermore, Tf may react as negative acute phase protein in acute inflammation. Additionally, the lack of

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