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The clinical value of serum transferrin measurements

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The dominating mechanism for iron delivery to tissues is the internalisation of the transferrin receptor-diferric transferrin complex. Other ways for iron to enter cells exist but do not contribute significantly to the cellular iron homeostasis in humans. Once the complex has been endocytosed, iron is released to the cytosol for further transport inside the cell, for example to the mitochondria. The receptor-apotransferrin complex recycles to the cell surface for a renewed round of iron uptake. A fraction of the transferrin receptors are cleaved inside the endocytotic vesicle and finally shed into the blood as truncated transferrin receptor monomers complexed with apotransferrin. The serum concentrations of these so called serum transferrin receptors (sTfR) correlate with erythropoietic activity and tissue iron demands. This review will focus on the clinical value of sTfR measurements.

Transferrin receptors

" Two different receptors for transferrin are known: transferrin receptor 1 and the newly discovered transferrin receptor 2. In this review transferrin receptor (TfR) alludes to transferrin receptor 1. "

The transferrin receptor is a type II transmembrane protein. It is a homo-dimer consisting of two identical monomers joined by two disulfide bindings at cystein residues 89 and 92 in the extracellular domain just outside the cell membrane (Jing and Trowbridge 1987). The monomer is a glycoprotein with molecular mass 90 kDa consisting of 780 amino residues. The protein have three domains: one 61-residue amino-terminal cytoplasmic region, a 28-residue transmembrane region and a 671-residue extracellular carboxyl-terminus (McClelland et al 1984, Schneider et al 1984). Each ectodomain can bind one molecule of transferrin and thus the transferrin receptor can bind two molecules of transferrin carrying in total four Fe3+. The ectodomain consists of three regions, each contributing to and critical for the transferrin binding (Lawrence et al 1999). The structure of the ectodomain has striking similarities to the membranebound carboxy peptidase II (Lawrence et al 1999), suggesting that they have evolved from a common peptidase (Bzdega et al 1997). The transferrin receptor however has no peptidase activity (Lawrence et al 1999, Bzdega et al 1997).

The transferrin receptor is glycosylated posttranslationally. One O-linked and three N-linked glycosylation sites are positioned on the extracellular domain (Omary and Trowbridge 1981). Receptors without the O-linked glycosylation are cleaved inside the cell with release of the extracellular domain. Mutations at the N-linked positions confers inability to bind to transferrin (Rutledge and Enns 1996, Williams and Enns 1991). Through acetylation with palmitate the transmembrane domain is also modified posttranslationally. (Omary and Trowbridge 1981, Schneider et al 1984). The cytoplasmic domain is necessary for clustering of the receptor-transferrin complex leading to the formation of coated pits in the cell membrane and subsequent endocytosis (Iacopetta et al 1988, Rothenberger et al 1987). Effective internalisation of the complex is initiated by phosphorylation and dephosphorylation in a conserved signal sequence, YTRF, in the cytoplasmic domain (Collawn et al 1990, 1993).

Almost all animal cells express the transferrin receptor, with the exception of terminally differentiated cells such as mature erythrocytes. In particular, the receptor is expressed, 10 000 to 100 000 molecules per cell, on the surface of proliferating cells (Gatter et al 1983, Chitambar et al 1983). Non proliferating cells have a very low or absent expression of the receptor. It has been suggested that the coupling between cell proliferation and expression of the transferrin receptor is mediated by the

enzyme ribonucleotide reductase. Epithelial cells in kidneys, cervix, breast, testicles, esophagus, stomach, endocrine pancreas, hepatocytes and the pituitary gland have a basal expression of the transferrin receptor. Besides vividly proliferating cells a high expression of the transferrin receptor is found on immature erythrocytes, placental syncytiothrophoblasts and in the liver (Iacopetta et al 1982, Loh et al 1980). The transport of iron into the brain is regulated by the expression of the transferrin receptor on capillary endothelial cells and on epithelial cells in the choroid plexus. Neurons also express the transferrin receptor.

The gene for the human transferrin receptor is 32 Kb long and located on chromosome 3. It shows some similarities to the gene for prostatic specific antigen. On chromosome 3 also reside the genes for transferrin and the transferrin like membrane bound paratransferrin. The transferrin receptor gene is transcribed into a 5 Kb mRNA with a large 3 ' region that is not translated. 100 base pairs upstream from the starting point for transcription lies the promoter region necessary for basal and activated transcription in proliferating non-erythroid cells. In this region the hypoxia responsive element is found among others.

In non erythroid cells the expression of the transferrin receptor is regulated by posttranscriptional stabilisation or degradation of mRNA. In the non-translated 3 ' region there are five iron responsive elements (IRE) to which iron regulatory proteins (IRP) bind when intracellular iron concentration is low. Bound IRP blocks the cleavage site from an endonuclease and stabilises mRNA thereby prolonging the half time from 30 minutes to six hours. The synthesis of ferritin and in some extension of transferrin is also regulated by the same IRPs. When they bind to a 5 ' IRE on ferritin mRNA translation is blocked and the synthesis of ferritin is diminished.

In erythroid cells the expression of transferrin receptor is regulated not by the intracellular iron concentration but by upregulated transcription during the differentiation of the erythroid cells.

The transferrin receptor binds diferric transferrin with high affinity but not apotransferrin at the pH found in blood. In the endosomal acidic milieu iron is released. The hemochromatosis gene product associates with the transferrin receptor and B 2 - microglobulin at the cell surface and remains associated with the receptor during the endo/ exocytotic cycle (Gross et al 1998). HFE participates in the control of cellular iron uptake and intracellular iron delivery; in the former case by decreasing the receptor ' s affinity for transferrin and abrogating transferrin receptor endocytosis (Feder et al 1998, Roy et al 2000, Salter-Cid et al 2000).

A second transferrin receptor (TfR2), predominantly expressed in the liver, has been described (Kawabata et al 1999) and the gene mapped to chromosome 7q22. The extracellular domain of TfR2 has 45% identity and 66% similarity with TfR. TfR2 mediates cellular uptake of iron and this mechanism is not regulated by iron (Fleming et al. 2000). A mutation in the TFR2 gene leading to hemochromatosis type 3 has been identified (Camaschella et al. 2000).

The serum transferrin receptor

A truncated form of the transferrin receptor can be found in serum (Kohgo et al 1986). This was first noted when reticulocytes maturing to erythrocytes were observed to lose their transferrin receptors by shedding them to the blood (Pan et al 1983). This serum transferrin receptor (sTfR), a 74-kDa monomer, is the extracellular domain of the transferrin receptor cleaved at Arg100-Leu101 inside the endosomes (Shih et al 1990, Baynes et al 1993). After exocytosis sTfR bound to transferrin circulates in blood in an amount proportional to cellular TfR (Beguin et al 1988). Elevated levels of sTfR may thus reflect increased erythropoietic activity or mass as seen in thalassemia and haemolytic anemias, whereas decreased levels are seen in for example aplastic anemia.

There is no difference in sTfr values for healthy adult men and women and no correlation of [sTfR] with the age of the subject (Skikne et al 1990, Flowers et al 1989). Black subjects have significantly higher concentrations than nonblacks, and people living at high altitude have higher concentrations (Huebers et al 1990, Flowers et al 1989, Allen et al 1998, Vernet et al 2000)

The sTfr-levels are higher in children, especially in infants, than in adults decreasing gradually from the neonatal period to adolescence (Anttila et all 1997, Virtanen et al 1999, Yeung et al 1997, Lonnerdal et al 1994, Choi et al 1999, Suominen et al 2001).

No gender differences in sTrf concentration exists for children except for neonates, where males have slightly higher concentrations (Choi et al 2000).

In the pregnant woman sTfR increases with gestational time and returns to normal 5 to 12 weeks after delivery (Choi et al 2001, 2000, Akesson et al 1998), but conflicting results have been reported (Carriaga et al 1991).

sTfr promises to be useful for detecting iron deficiency in pregnancy (Rusia et al 1999, Carriaga et al 1991).

In blood donors sTfR may be slightly elevated (Punnonen et al 1999, Vernet et al 2000, Bolton et al 2000).

The day-to-day intra-individual variation and the overall biological variation in sTfR is low (Cooper et al 1996)

sTfR increases when exogenous erythropoietin is administrated. Erythropoietin administration in patients undergoing hemodialysis or in healthy athletes increase sTfR significantly after one week of drug administration with a maximum 30-40 days later (Lorenzo et al 2001, Beguin et al 1995, Birkeland et al 2000, Parisotto et al 2000). .

Serum transferrin receptor in disease

Iron-deficiency anemia is associated with high concentrations of transferrin receptor in serum reflecting the degree of iron depletion. (Punnonen et al 1994, 1997, Suominen et al 1997, Chua et al 1999)

There is no advantage in using sTfR instead of other traditional parameters for detecting iron deficiency in uncomplicated anemia or as sole discriminator in unselected anemia (North et al 1997, Beguin et al 1993).

In non-anemic persons with functional iron deficiency, commonly seen in pregnancy, women of childbearing age, small children, adolescents and blood donors, sTfR is modestly increased and decreases with iron supplementation (Suominen et al 1998, Anttila et al 1997, Zhu et al 1998). It has been questioned if sTfR or the sTfR-ferritin ratio really contributes to the identification of sub clinical iron deficiency (Gimferrer et al 1997).

sTfR has been evaluated in masked iron deficiency in chronic renal failure patients. In patients on regular hemodialysis but not treated with erythropoietin sTfR is higher among those with iron deficiency than among those that are iron replete (Ahluwalia et al 1997, Fernandez-Rodriguez 1999).

The baseline sTfR before start of erythropoietin or the initial response in sTfR to an increased erythropoietin dose can predict a hemoglobin response in patients already on erythropoietin (Beguin et al 1993, Ahluwalia et al 1997). sTfR cannot reliably detect masked iron deficiency in anemic chronic hemodialysis patients on maintenance erythropoietin because of increased erythropoiesis, which itself raises serum TfR levels (Ahluwalia et al 1997, Hou et al 1998, Fernandez-Rodriguez 1999).

In chronic diseases serum ferritin is often increased irrespective of iron status and can thus not be used as a marker for iron deficiency. sTfR or sTfR-ferritin ratio have been shown to be of diagnostic value for detecting iron deficiency in rheumatoid arthritis patients (Suominen et al 2000, Zoli et al 1994, Nielsen et al 1994, Punnonen et al 2000). Other studies have not found any consistent deviations in sTfR or sTfR-ferritin ratio among patients with different chronic disorders an anemia (Junca et al 1998,

A slight decrease in sTfR and sTfR:ferritin has been reported in conditions with iron overload (Looker et al 1999, Khumalo et al 1998) but conflicting results have been obtained (Baynes 1994). Raised sTfR in Polycythemia vera and secondary polycythemia is an indicator of iron deficiency (Manteiga et al 1998).

sTfR is higher in heterozygous B-thalassemia patients than in healthy controls and does not differ significantly from sTfR in B-thalassemia concomitant with iron deficiency (Gimferrer et al 1997, Dimitriou et al 2000, Bianco et al 2000). In thalassemia intermedia no consistent patterns have been found (Camaschella et al 1996, Dore et al 1996). In sickle cell anemia sTfR correlates with the degree of erythropoetic expansion, i.e. hypersplenism (Singhal et al 1993).

sTfR assays

The sTfR assay has gone all the way from labour intensive RIA-methods to fully automated methods implemented on immunoassay analysers common in the clinical laboratory (Vernet et al 2000, Punnonen et al 2000, Suominen et al 1999, Hikawa et al 1996). The intra and interassay precision are good, about 5% coefficient of variation. The linear measuring interval covers the clinically important concentrations. But standardisation is lacking and there is a bias between all different assays (Cotton et al 2000,). No internationally accepted calibrator exists (Skikne 1998).

Where sophisticated instrumentation is not at hand, a technique for the measurement of the transferrin receptor/ferritin ratio on plasma spotted and dried on filter paper may be suitable for the identification of moderate to severe iron deficiency anemia (Cook et al 1998, Flowers et al 1999).

Perspectives

Transferrin receptor concentrations in serum increase with tissue iron deficiency and elevated erythropoiesis. Thus we now have an additional useful marker in addition to old and newer ones, for example reticulocyte maturation index and reticulocyte hemoglobin concentration, in the clinical work up of patients with suspected iron deficiency or erythroid hyperproliferative disorders. A major obstacle is the lack of standardization between different assay systems. The first step should be to agree upon an international calibrator followed by the establishment of appropriate reference intervals. Current assays have good precision, require only very small sample volumes and are fully automated and so have made it possible to introduce sTfR as a valuable diagnostic tool among the more conventional ones.

As sTfR does not increase in anemia of chronic disease per se, sTfR will help in the evaluation of anemic patients with normal or elevated serum ferritin values. sTfR also promises to be a marker of early functional iron deficiency, commonly seen in pregnant women, premenopausal women, adolescents and blood donors, among others. STfr measurements have a low total variation, biological and analytical, and hence the clinical value of serial measurements to assess the effect of treatment in the anemic or hyperproliferative patient should be investigated.

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