



THE SUPPLEMENT

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IRON AND CYSTIC FIBROSIS

Iron metabolism is a carefully choreographed dance involving dietary intake, digestion, absorption, transport, storage, and excretion. Any change can cause a misstep. The progression of iron status from normal, through iron deficiency (ID) to iron deficiency anemia (IDA) usually is gradual and subtle. (1,2) Interpreting the laboratory results of each change can be formidable. The role of infection to iron is complex and the reader is encouraged to obtain references 3 and 4 for background information.

In CF, this dance must be maintained in spite of dietary, GI, respiratory, and immunological challenges. Laboratory interpretation is confounded by chronic infection.

FEATURED PAPERS:

Keevil B. Rowlands D. Burton I. Webb AK. Assessment of iron status in cystic fibrosis patients. *Annals of Clinical Biochemistry.* 37(Pt 5):662-5, 2000 Sept.

Objective: To investigate the use of soluble transferrin receptor (sTfR), in addition to iron, transferrin and ferritin to assess iron status. **Subjects:** 70 adults with CF, 30 female, mean age 25 yrs, range 16–39. **Design:** Cross-sectional study. **Results:** 69% of subjects had ID as determined by transferrin saturation, but only 29% as determined by sTfR and 11% by ferritin. There was a significant positive correlation between C-reactive protein and ferritin and transferrin saturation.

Conclusions: In CF, transferrin saturation may be overestimating and ferritin underestimating ID. sTfR is unaffected by the acute-phase response and may be a more useful test for detecting iron deficiency in CF.

O'Connor TM. McGrath DS. Short C, O'Donnell MJ, Sheehy M, Bredin CP. Subclinical anaemia of chronic disease in adult patients with cystic fibrosis. *Journal of Cystic Fibrosis.* 1:31-34, 2002.

Objective: To determine the cause of "relative anemia" in patients with CF. **Subjects:** 15 adults with CF, mean age 24.6 yrs \pm 1.69, with mild to moderate dis-

ease and 17 healthy controls, mean age 26.1 yrs \pm 9.5.

Design: Cross-sectional study. **Results:** Hemoglobin (Hgb) and hematocrit (Hct) did not differ between groups; B12 and red cell folate were significantly higher in CF patients; serum iron, transferrin, and total iron-binding capacity were significantly lower in CF patients. There were no significant differences in serum ferritin, percentage transferrin saturation, serum erythropoietin or red cell volume. **Conclusions:** Normal Hgb and Hct in CF patients appear to represent a combination of the effects of arterial hypoxemia promoting polycythemia, counterbalanced by chronic inflammation promoting anemia of chronic inflammation (ACI).

Reid DW. Lam QT. Schneider H. Walter EH. Airway iron and iron-regulatory cytokines in cystic fibrosis. *European Respiratory Journal.* 24(2):286-91, 2004 Aug.

Objective: To determine the sputum levels of iron, ferritin, microalbumin, and total cell counts during and following exacerbation of CF lung disease. **Subjects:** 19 adults experiencing exacerbation, 5 female, mean age 26.5 yrs, range 18–40, 17 stable patients, 5 female, mean age 22 yrs, range 17–43, 8 stable patients with COPD and 6 normal controls. **Design:** Cross-sectional study. **Results:** Measures of iron status were significantly different in CF patients as compared to COPD and normal controls. There also was a difference in sick vs. stable CF patients. Sick CF patients treated with antibiotics showed some improvement in iron status, but not in all markers of inflammation. However improvement in markers of inflammation were related closely to changes in some markers of iron status and protein levels. **Conclusions:** Iron and iron-regulatory cytokines may play a role in CF lung disease and the increased iron content may even facilitate *Pseudomonas aeruginosa* infection.

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REVIEW

Iron status in the general population is affected by 1.) dietary intake, including: iron, copper, protein, vitamins A, E, C, pyridoxine, riboflavin, B12, and folic acid; 2.) blood loss; and 3.) medications, such as H2 blockers and antacids. In CF patients, all of these factors, plus malabsorption, hemoptosis, short bowel syndrome, bacterial overgrowth, liver and renal diseases, and chronic inflammation contribute to altered iron status. Additionally, the effect of supplemental pancreatic enzymes on iron absorption is unclear. Prior to the use of enteric-coated enzymes there were conflicting reports (5,6,7). Recently, one study indicated enteric-coated enzymes reduced iron absorption, (8) while others indicated that ID was unrelated to pancreatic supplementation (9,10).

Very little has been reported about the prevalence and mechanism of anemia in CF patients. Publications report a frequency of ID ranging from 33% to 66% of CF patients. (10,11,12). Ater (11) noted a “relative anemia” due to inadequate intake of iron and vitamin E, which could be improved by appropriate nutrient supplementation. Jaffe (13) found low iron concentrations in 58% of preschool patients tested, but only 12% had increased iron binding capacity. Pond (10) reported “functional iron deficiency” in 62% of 71 adult CF patients with 23% being anemic. The overall prevalence of true IDA in CF patients is thought to have decreased due to improved overall nutritional status and the increased use of nutrient supplements (O’Connor, 2002).

Assessing iron status via laboratory results in CF is complicated by chronic inflammation. In CF, chronic inflammation can mask IDA (Keevil, 2000). Ferritin, an

iron storage protein, indicates body iron reserve and thus is low in IDA. However, ferritin also is an acute-phase reactant and is elevated in ACI. Patients with ACI have sufficient body iron stores, but a defect in iron release from stores into the plasma results in ID (3). Pond (10) found significant variability in ferritin levels of CF patients and noted that patients with severe disease could have elevated ferritin levels even when other markers of iron nutrition indicate ID. Soluble transferrin receptor may be capable of differentiating between the anemias, but the test is not readily available (Keevil, 2000).

Polycythemia resulting from arterial hypoxia should be common in CF, yet it is not usually observed (11). The reason for this may be as O’Connor suggested, “normal hemoglobin values observed in patients with CF may result from the balance between chronic pulmonary inflammation, promoting ACI and hypoxemia, promoting polycythemia.”

Iron is a survival factor for bacteria. For example, it has been postulated that *Pseudomonas aeruginosa* has the ability to obtain extracellular iron from host tissues for growth and enhancement of virulence (14). Reid (9) suggested that the high rate of ID in CF patients is directly related to the severity of the underlying suppurative lung disease. However, this is controversial (15) and further research is needed.

“ASSESSING IRON STATUS VIA LABORATORY RESULTS IN CF IS COMPLICATED BY CHRONIC INFLAMMATION.”

CLINICAL APPLICATIONS

The RD plays a pivotal role in maintaining patients’ iron nutrition by focusing on dietary intake of iron and related nutrients. However, assessing iron status and defining the cause of ID is complex due to the multifactorial etiology of ID in CF and requires total team involvement. Assistance from a hematologist, familiar with CF, may be beneficial.

The CF Foundation’s Consensus Report on Nutrition for Pediatric Patients (16) suggests annual evaluation

of hemoglobin and hematocrit. The European Nutrition Consensus (17) statement suggests serum ferritin levels be used to monitor iron status when iron supplementation is given.

Mixed anemia (IDA with ACI) has to be considered in CF patients (Keevil, 2000, 10). Weiss (3) provides a comprehensive review of ACI. Suggestions are offered for differentiating between IDA and ACI. Proper diagnosis is both science and art. Because of this

CLINICAL APPLICATIONS (CONT.)

complexity, each CF Center may need to determine its own protocols for diagnosis and treatment. A sample method is the following. If a patient with low serum iron has a ferritin level below 20 ng/ml, the diagnosis is IDA. Ferritin levels above 200 ng/ml are more consistent with ACI. With IDA, iron supplementation is warranted. No iron supplementation is required in cases of ACI. Judgment becomes more challenging if serum iron is low and ferritin levels are normal (20-200 ng/ml). In such cases, IDA could be masked by ACI. Low ferritin levels caused by IDA will only rise moderately secondary to inflammation and yield a "normal" ferritin level. If in doubt or in case of mixed anemia, iron supplementation should be considered. Iron supplements may be better absorbed when taken with ascorbic acid and separate

MIXED ANEMIA (IDA WITH ACI) HAS TO BE CONSIDERED IN CF PATIENTS. (KEEVIL 2000)

from multivitamins containing competing minerals such as zinc and calcium. Adequate supplementation probably will result in a hemoglobin rise of 1-2 g/dl within approximately 4 weeks and might be diagnostic of IDA. If the anemia is refractory to oral iron supplementation, the patient may not have IDA, may not be taking iron supplements as prescribed, or may have other etiologies for the IDA. Oral iron can cause gastrointestinal irritation, discomfort, and constipation. In such situations, a different kind of supplement can be tried or the dosing schedule adjusted. If these modifications prove unhelpful, intravenous iron can be considered.

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REFERENCES

1. Gropper SS, Smith JL, Groff JL. Advanced Nutrition and Human Metabolism. Fourth edition. Thomson Wadsworth, 2005 pg 419 to 436.
2. Mahan LK, Escott-Stump S. Krause's Food, Nutrition, & Diet Therapy. 10th edition. W.B Saunders Company 2000, pg 125-131 and 781-800.
3. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med. 352:1011-23, 2005.
4. Groff JL, Gropper SS. Advanced Nutrition and Human Metabolism, Third edition. Wadsworth/Thomson Learning 2000, pg 469-70.
5. Tonz O, Weiss S, Strahm HW, Rossi E. Iron absorption in cystic fibrosis. Lancet. 2:1096-1099, 1965.
6. Davis AE, Biggs JC. The pancreas and iron absorption. Gut. 6:140-142, 1965.
7. Smith RS. Iron absorption in cystic fibrosis. Br Med J. 1:608-609, 1964.
8. Zempshy WT, Rosenstein BJ, Carroll JA, Oski FA. Effect of pancreatic enzyme supplements on iron absorption. Am J Dis Child. 143:969-972, 1989.
9. Reid DW, Withers NJ, Francis L, Wilson JW, Kotsimbos TC. Iron deficiency in cystic fibrosis. Relationship to lung disease severity and chronic pseudomonas aeruginosa infection. Chest. 121:48-54, 2002.
10. Pond MN, Morton AM, Conway SP. Functional iron deficiency in adults with cystic fibrosis. Resp Med. 90:409-413, 1996.
11. Ater JL, Herbst JJ, Landaw SA, O'Brien RT. Relative anemia and iron deficiency in cystic fibrosis. Pediatrics. 71:810-814, 1983.
12. Ehrhardt P, Miller MG, Littlewood JM. Iron deficiency in cystic fibrosis. Arch Dis Child. 62:185-187, 1987.
13. Jaffe A, Buchdahl, R. Bush A. Balfour-Lynn IM. Are annual blood tests in preschool cystic fibrosis patients

REFERENCES (CONT.)

- worthwhile? Arch D Childhood. 87:518-20, 2002.
14. Netlands JB. Microbial iron compounds. Annu Rev Biochem. 50:715-731, 1987.
 15. Kim EJ, Sabra W, Zeng AP. Iron deficiency leads to inhibition of oxygen transfer and enhanced formation of virulence factors in cultures of *Pseudomonas aeruginosa* PAO1. Microbiology. 149:2627-2634, 2003.
 16. Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. J Ped Gastro & Nutr. 35:246-259, 2002.
 17. Sinaasappel M, Stern M, Littlewood J, Wolfe S, Steinkamp G, Heijerman GM, Robberecht E, Doring G. Nutrition in patients with cystic fibrosis: a European consensus. J CF. 1:51-75, 2002.



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