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Iron status in the elderly

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ABSTRACT

Iron deficiency anaemia is prevalent in older age, particularly after the age of 80. Serum ferritin concentrations also decline, although there is no evidence to suggest that changes in iron stores are an inevitable consequence of ageing. Chronic inflammation is a common condition in older people, making the measurement of iron status difficult, and it is likely that elevated levels of circulating hepcidin are responsible for changes in iron metabolism that result in systemic iron depletion. Other contributory factors are poor diet and some medications, such as aspirin. Anaemia in older age has undesirable health outcomes, including increased susceptibility to falling and depression. However, there are concerns about possible adverse effects of iron supplements, either in relation to pro-inflammatory effects in the gut or inappropriate tissue iron deposition. Brain iron levels are increased with age-related degenerative diseases, but it is not known if this is the cause or a consequence of the disease, and genetic factors are likely to play a role. In order to maintain body iron within the normal range a personalised approach is required, taking into account all of the factors that may affect iron metabolism and the available strategies for preventing iron deficiency or overload.

1. Aim of this review

The objective of this narrative review was to summarise the latest information on changes in iron metabolism and status in the elderly population and consequent effects on health in order to provide the framework for studies on iron in an EC-funded project, NU-AGE (new dietary strategies addressing the specific needs of the elderly population for healthy ageing in Europe). Serum ferritin and soluble transferrin receptor will be measured in 1250 male and female volunteers between the ages of 65–79 y from five different European centres (UK, Italy, France, Netherlands, and Poland). Half of the volunteers have been randomly assigned to a one-year 'whole diet' intervention centred on dietary guidelines specifically tailored for elderly people with the aim of reducing age-related inflammation. The other half have been asked to maintain their usual diet for the year. Iron status is being measured at the beginning and end of the intervention to determine if a reduction in inflammatory status, resulting from the dietary changes, has an impact on iron metabolism. In addition, dietary intake data will be analysed to identify factors that explain the variance in iron status in elderly men and women, using both cross-sectional and longitudinal data.

2. Background

The adult human body contains 3–4 g of iron, approximately 70% of which is present in haemoglobin (Hb) in red blood cells and myoglobin in muscle. Iron is instrumental for the transport of oxygen around the body and is an essential component of many enzymes and cytochromes where it plays a role in electron transport, respiration and hormone synthesis. As a result of these multiple functions, iron is important for physical performance, immunity, cognitive development and function, thermoregulation, and thyroid metabolism. The body efficiently recycles iron from degraded red blood cells so the daily requirement to replace endogenous losses from the gastrointestinal tract, skin, hair, sweat and menstrual blood loss in women is relatively low, at about 1–1.5 mg/d.

Iron deficiency (ID) is the most common nutritional deficiency disorder in the world, defined as a lack of body iron stores, and usually caused by inadequate absorption and/or excessive iron losses. It is the result of an imbalance between iron supply and iron requirements of the erythroid bone marrow. The next stage of deficiency is iron-deficient erythropoiesis, characterised by reduced transferrin saturation. Finally, Hb concentrations fall and hypochromic, microcytic anaemia (IDA) is observed; this affects over 1 billion people worldwide (WHO, 2008).

3. Measurement of iron status

There are a number of biomarkers that reflect different aspects of iron metabolism and can be used singly or collectively to assess

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body iron status. An in-depth review of biomarkers of iron status is available on the Biomarkers of Nutrition for Development (BOND) website (www.nichd.nih.gov/global_nutrition/programs/bond).

1. Bone marrow grading is the gold standard method of assessing iron deficiency but is highly invasive so rarely used.
2. Serum iron concentration and transferrin saturation indicate the adequacy of the iron supply to developing red blood cells. Serum iron is less reliable as it is subject to diurnal rhythms and increases after the ingestion of iron-containing foods. A transferrin saturation of <15% generally indicates iron deficiency.
3. Zinc protoporphyrin (ZPP). When there is an inadequate supply of iron, zinc is incorporated into the protoporphyrin ring of the haem structure. An elevated ZPP is characteristic of iron deficient erythropoiesis.
4. Soluble serum/plasma transferrin receptor (sTfR). This binds diferric transferrin (Tf) on the cell surface. The main source of serum sTfR is bone marrow erythroid precursors (Flowers et al., 1989). When intracellular iron supply is reduced, cell surface TfR1 expression is up-regulated in order to acquire more iron, and it is down-regulated when there is sufficient iron. An elevated sTfR is a marker of tissue ID and increased bone marrow erythropoietic activity. The sTfR concentration increases in parallel with the severity of iron depletion and treatment of individuals with IDA results in a progressive fall in sTfR values (Skikne et al., 1990).
5. Serum/plasma ferritin concentration correlates closely with body iron stores, and values of <12 μg/L indicate absence of liver iron stores. However it is an acute phase protein and is elevated in people with infection or inflammation (see below). In order to identify raised ferritin values that do not accurately reflect body iron stores, C-reactive protein (CRP) or alpha-acid-glycoprotein (AGP) are determined and if these are above the normal cut-off, ferritin concentration is not used as a biomarker of iron status.
6. Body iron (Cook et al., 2003) is not a quantitative measure of iron in the body but is a sensitive index that is useful for monitoring changes in iron status, for example resulting from interventions. It is the ratio of serum transferrin receptor to serum ferritin concentration. It is a relatively new epidemiological technique for monitoring iron status in population groups susceptible to iron deficiency in which inflammation is uncommon or has been excluded by laboratory screening.
7. Hb concentration is a commonly measured biomarker but is not a specific measure of IDA as there are other causes of anaemia e.g. folate and B12 deficiency, and also the anaemia of chronic disease. It is not sensitive as the cut-off values and normal ranges vary according to sex, age, and ethnicity. Hypochromic microcytic appearance of red cells in blood film examination is used by clinician as suggestive of iron deficiency but requires a second biomarker (e.g. ferritin) to confirm the diagnosis of IDA.

4. Factors that affect biomarkers of status

Hb concentration has been reported to decline with advancing age, even in the absence of demonstrable disorders. In one report this was calculated to be 0.53 g/L/y in men and 0.05 g/L/y in women between the ages of 70 and 88 y (Nilsson-Ehle et al., 2000) and in another the decline was 0.1 g/L/y in men and 0.09 g/L/y in women between the ages of 70 and 80 y (Milman et al., 2008). The decline appears to increase after the age of 80, particularly in men. It has been shown that growth hormone and/or insulin-like growth factor-1 are positively and erythropoietin negatively correlated with Hb in elderly people (Nilsson-Ehle et al., 2005). Erythrocytes released from the bone marrow are less functional and partially damaged in aged individuals and as they are less able to protect themselves against stress this results in their early sequestration (Gershon and Gershon, 1988).

Differences in Hb concentration and ferritin levels have been noted between ethnicities (Patel et al., 2007). For example, anaemia is reported to be more common amongst black American compared to white American adults. However, there is evidence that the Hb distribution curve is shifted towards lower values in blacks (Perry et al., 1992) which has led to the debate about race-specific criteria for defining anaemia (Beutler and Waalen, 2006).

Cross-sectional data from the second National Health and Nutrition Examination Survey show that serum ferritin concentrations increase with age until the sixth decade of life at which time they reach a plateau (Yip, 1994). In a cross-sectional study of 441 men and women aged 60–93 y, serum ferritin concentration was reported to be positively associated with increasing age in women ($p = 0.0223$) but not in men. However, in a longitudinal study undertaken in a sub-set of 125 people there was no significant change in iron stores over the 10 y monitoring period (Garry et al., 2000), suggesting that changes in serum ferritin (and iron stores) are not an inevitable consequence of ageing.

Chronic inflammation, a common condition in older people, alters iron metabolism and haematopoiesis and can lead to anaemia (Lee, 1983), but it is difficult to determine whether or not the cause of anaemia is insufficient iron supply because indices of iron status (notably serum iron, ferritin and transferrin) are modified by the inflammatory state. It has been observed that malnutrition, not uncommon in the elderly, can exacerbate the effect of inflammation on biomarkers of iron status. Nevertheless, it is possible to differentiate between pure iron deficiency anaemia, anaemia of chronic disease, and anaemia of chronic disease with co-existing iron deficiency using the sTfR and sTfR/log serum ferritin index (Jain et al., 2010; Hanif et al., 2005). Rimon et al. (2002) undertook tests for anaemia in consecutive patients admitted to an acute geriatric ward who were older than 80 y. Bone marrow examination confirmed iron deficiency anaemia in 49 individuals but the routine laboratory tests identified only 8, whereas the transferrin receptor-ferritin index identified 35, demonstrating that this is a more sensitive and specific method for diagnosing iron deficiency anaemia in the elderly when bone marrow aspirates are not feasible. Karlsson et al. (2010) compared bone marrow iron status with various biomarkers of iron status in 50 elderly patients. The sTfR assay correctly identified 87% of iron deficient individuals; the specificity was 74%. With ferritin cut-offs of 20 μg/L for men and 7 μg/L for women this biomarker was 100% specific for iron deficiency but only 35% sensitive. When a ferritin cut-off point of 40 μg/L was used, the specificity fell to 88% but the sensitivity increased to 100%. The sTfR-ferritin index with a cut-off point of 3.0 gave a sensitivity of 100% and specificity of 43%.

Acute inflammation is another condition that affects iron metabolism. Cunietti et al. (2004) monitored changes in biomarkers through an acute inflammation episode identified by raised CRP (≥30 mg/L) in 39 older hospitalised patients (median age 79 y). All haematological indices measured, except for MCV and %transferrin saturation, were rapidly disrupted by the acute inflammation and followed differing time courses. ZPP and sTfR were not measured. The effects of a short period of inflammation (≤20 d) due to infection were similar to those observed in states of chronic inflammation.

The regular intake of aspirin, a commonly used antiplatelet agent in both primary and secondary prevention of cardiovascular diseases, is associated with lower serum ferritin. In 916 elderly people (aged 67–96 y) participating in the Framingham Heart Study, those who took > 7 aspirins/week has a significantly lower serum ferritin ($p = 0.004$), and the effect was more marked in diseased than healthy subjects (Fleming et al., 2001). The authors