In this issue of *Clinical Chemistry*, Ellervik et al. (1) report relationships between baseline ferritin concentrations and risk of all-cause and cause-specific mortality in 8988 individuals enrolled in the Copenhagen City Heart Study. Median follow-up was 23 years, during which 6364 individuals died. Multifactorially adjusted hazard ratios for total mortality in individuals with ferritin values below vs above 200 μg/L showed significantly lower mortality overall (P = 0.0008) and separately for men (P = 0.02) and women (P = 0.03) with lower ferritin concentrations. Cause-specific mortality below vs above the 200 μg/L threshold was significantly lower for cancer (P = 0.005), metabolic disease (P = 0.002) and cardiovascular disease (P = 0.00006). A highly significant progressive decrease in median survival occurred with increasing ferritin concentrations. The hazard ratio for total mortality increased by 13% for each 100 μg/L increase in ferritin concentration. The median survival was 79 years with concentrations <200 μg/L, 76 years with ferritin concentrations between 200 and 399 μg/L, 72 years with ferritin concentrations between 400 and 599 μg/L, and 55 years with ferritin concentrations in excess of 600 μg/L. A step-wise increase in mortality with increasing ferritin concentrations was found for each disease category. Adjusted hazard ratios for increased disease-specific mortality for ferritin concentrations above 600 μg/L vs below 200 μg/L were significant for malignant (P = 0.01), endocrine (P = 0.0001), and cardiovascular (P = 0.01) disease. The conclusion was that “increased ferritin concentrations represent a biological biomarker predictive of early death in a dose-dependent linear manner in the general population.” Increased ferritin concentrations were interpreted by the authors “as a biological marker of pathogenic processes that reflects severity and presence of a variety of disease states leading to premature death.” They stated that “causality may be difficult to claim in this study, since, unlike transferrin saturation, increased ferritin is associated with many diseases other than hereditary iron overload.”

Readers may be challenged by the interpretation of ferritin concentrations reported from this study. Ferritin values in the range of 200 μg/L, which were found to be disadvantageous, are common in practice. Reluctance to assign cause-and-effect relationships, or to test the relationship between ferritin concentrations and outcomes at all, may be based on the assumption that high ferritin values might in some sense be “nonspecific” (perhaps “acute phase”) in this context. It might also be thought that high ferritin concentrations occur too commonly and in too many different diseases to be useful in terms of determining diagnosis or prognosis or designing treatment strategies. The seemingly discontinuous association between increased ferritin concentrations and clinical outcomes for commonly observed increases in ferritin vs the larger increases seen with hereditary iron overload may lead to the presumption that iron is the culprit in the hereditary variety but may not be in the common variety.

Ferritin can be produced in apparently unlimited amounts by virtually all cells in response to excess intracellular iron (2) and augmented by inflammatory cytokines primed in a positive feedback manner by iron excess (3). Concentrations of the inflammatory markers interleukin-6 (IL-6) (4) and high-sensitivity C-reactive protein (hsCRP) are positively associated with ferritin values (4), and reduction of body iron concentrations by phlebotomy results in reduction of both ferritin and IL-6 values (3). Ferritin concentrations are used to diagnose both iron deficiency and excess and to monitor therapeutic iron unloading. Ferritin sequesters and detoxifies excess iron, functions that appear to be optimal to ferritin, the amount of transferrin available for binding...
ing iron is limited. Like ferritin, low %TS values reflect depleted iron stores. However, %TS values are a less reliable guide than ferritin for evaluation of increased body iron concentrations (8) or the adequacy of iron unloading (9). Transferrin carries essential iron to cells and also binds and detoxifies noxious redox-active iron (10). Concentrations reflect to a variable extent both transport and redox-active iron. In contrast to ferritin, concentrations of IL-6 and hsCRP are negatively associated with %TS values, indicating an important protective (antioxidant) function of transferrin (3, 4). Marked increases of %TS are associated with adverse disease outcome, as as cited by Ellervik et al. (1) However, Stack and colleagues (11) observed that both high %TS values (reflecting increased iron plus redox-active iron) and low %TS values, likely a result of high hepcidin concentrations rather than reduced iron concentrations per se (12), are associated with increased total and cardiovascular mortality. Outcome associations followed a J-shaped pattern, with intermediate levels between about 24%TS and 40%TS associated with lowest mortality (11). Such intermediate %TS levels, representing the “limits of normal,” occur commonly in practice (2), likely indicating successful compensation of potentially noxious redox activity.

Iron is essential for virtually all life forms because of its role in biological oxidation and energy production (13, 14). This abundant element is brought into the food chain cautiously, atom by atom, by plant and microbial siderophores and then handed off repeatedly en route to cells. Complex checks and balances, exemplified by ferritin and transferrin, supply essential iron while blocking noxious iron excess. The innate reactivity of iron supports life but only so long as stray atoms are ligand bound to prevent freewheeling oxidative stress. Humans are exposed chronically to nutritional iron excess (15) and no “ferrostat” exists to sense and excrete excesses. Thus, in cells and tissues iron may reach supraphysiologic concentrations that overwhelm protective mechanisms. Basic studies have shown direct links between iron-catalyzed oxidative stress and biochemical and cell biological changes leading to abnormalities characteristic of disease (13, 14). Ferritin may indeed have pathophysiologic roles apart from iron sequestration and transport, but its concentrations remain the most reliable measure of overall body iron burden (2) and damage from iron-catalyzed oxygen free-radical–mediated oxidative stress that leads to diseases of aging (4, 5). Several studies have identified a steep dose effect for outcomes with ferritin concentrations as low as about 70 µg/L to 150 µg/L in neoplastic, metabolic, cardiovascular, and other diseases (5, 6, 16, 17). Correspondingly, the “normal” reference interval for ferritin may be defined as that value associated with minimal disease risk and maximal longevity, with concentrations of about 70 µg/L to 100 µg/L representing the ideal upper limit from this perspective (5, 6, 16).

The findings of Ellervik et al. (1) may indeed reflect cause-and-effect relationships between iron excess represented by ferritin concentrations and disease. Among diseases of concern mentioned in this report are vascular (6), neoplastic (16), and metabolic (17) diseases, for which prospective randomized clinical trials of iron reduction have shown significantly improved outcomes indicating cause-and-effect relationships to iron-catalyzed oxidative stress. Other examples exist, including numerous well-designed cohort studies showing improvement of laboratory measures of disease activity with iron unloading in nonalcoholic fatty liver disease and observational studies showing a mean ferritin concentration of about 220 µg/L in fresh myocardial infarction. Obviously, knowledge of the relationship between concentrations of body iron and disease is far from complete. The term “ferrotoxic disease” has been proposed to describe the range of conditions for which body iron burden is a contributing factor (5, 16). Hereditary hemochromatosis should be considered a subtype of ferrotoxic disease.

Data reported so far suggest that increased ferritin concentrations, representing increased body iron burden, are common and not benign. Concentrations rise imperceptibly with aging, as influenced by hereditary and acquired (especially dietary) factors (15). Alteration of ferritin concentrations, as with blood transfusion or blood loss or ingestion of variable amounts of readily absorbable iron, modify disease risk (6, 15). Thus, iron concentrations can be modified readily and inexpensively by dietary iron restriction (15, 18) or by phlebotomy (6, 16, 17) to alter intermediate measures of disease and improve clinical outcomes. Laboratory testing for iron status, appreciation of the relationship between iron status and disease risk, and availability of inexpensive and nontoxic strategies for reducing risk by iron reduction herald the potential for fruitful clinical research and the prospect of unprecedented improvement in population health.

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