Should ferritin tests be added to routine screening: An integrative literature review

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Should ferritin tests be added to routine screening: An integrative literature review

Adebowale Adesuyi

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Dr. Kim Amer

DePaul University
Abstract

The purpose of this analysis was to explore the possible benefits of a blood screening to be coupled with the annual routine check-up. Blood screenings are only administered upon reasonable suspicion of pathology. Upon the examination of current research concerning ferritin levels within the blood, one can speculate the existence of strong correlations between ferritin levels, inflammatory disease and early mortality. Cause for concern stems from the fact that the ferritin levels of the vast majority of people in the US are completely unknown.

Ferritin levels are the most accurate marker for measuring the amount of iron being stored in the human body. Ferritin levels measured higher than 300 mcg/L for men and 200 mcg/L for women represent chronic iron toxicity (Schrier & Bacon, 2017). Although iron toxicity has been studied much less then iron deficiency, there has been some experimentation performed. This literature review will gather relevant works and will use the RE-AIM Framework to interpret the data compiled.

Results of the literature review reinforced the theory that there is a relationship between ferritin levels, inflammatory disease and early mortality. The inflammatory diseases studied include, but are not limited to cancer, endocrinological disease, cardiovascular disease and diabetes type II. The implications of these findings may potentially have a transformative effect on preventative care. A strong enough relationship between the variables suggest that high ferritin levels may either be a stark precursor to inflammatory disease, or conversely, an invaluable marker for it. Future research may be geared toward discovering which one of these two relationships best describe this correlation.
Part 1: Introduction

Background and Significance

Blood is the workhorse of the human circulation system. Blood provides transportation for oxygen to and from all of the living tissue dispersed throughout the entire body (Jarvis, 2015). This is accomplished by binding oxygen to a protein known as hemoglobin, which resides inside of the human cell. Every healthy red blood cell in the body is assembled with iron, which is an essential mineral. Iron is, in fact, imperative for the sustenance of life. Consuming an insufficient amount of iron can lead to iron deficiency anemia, the most common form of anemia in the world (Cafasso & Nall, 2015).

In response to concerns regarding iron deficiency anemia, global efforts have been concentrated on infusing larger amounts of minerals into flour and grains through a process called fortification. Fortification is used to augment oceans of products that people all over the world consume on a daily basis. The CDC Foundation is an independent nonprofit organization that was spawned from congress in the United Stated. Its mission is to mobilize resources in order to support the philanthropic goals of the CDC.

The Food Fortification Initiative, founded in 2004, builds alliances between governments and international agencies, wheat and flour industries, and consumer and civic organizations to increase the vitamin and mineral content in flour. The network of partners, including the Centers for Disease Control (CDC), is working to make flour fortification standard practice (CDC Foundation, n. d.).

Nutrients such as niacin, vitamin D, iron and folic acid have been mainstays on the backsides of cereal boxes around the globe for the better part of the 20th century. Mandated food modification has grown exponentially throughout the duration of its lifespan. However, the global initiative is now sparking a formidable amount of controversy and debate. The opposition now challenges that notion of food fortification being widely championed since its inception.

Previously, a sufficient amount of research has been geared toward iron deficiency anemia, however, not as much data has been explored concerning iron in excess. There is now concern surrounding the possibility that there may be a large amount of the present population with high levels of iron in the body (Ellervik, Marott, Tybjærg-Hansen, Schnohr & Nordestgaard, 2014). This is a notion not so farfetched concerning how explosive the Food
Should Ferritin Tests Be Added

Fortification Initiative has become, which is in large part due to the zeal of manufacturing companies to use higher and higher fortification specifications as a selling point to consumers. Can we possibly be consuming too much iron? In June of 2001, a study was published by the Center for Food Safety and Applied Nutrition of the Food and Drug Administration concerning the probability of over-fortification of iron and folic acid in breakfast cereals.

 Analyzed values of iron and folic acid in breakfast cereals were considerably higher than labeled values. For adults, the amount of cereal actually consumed was approximately 200% of the labeled serving size. When the quantity of cereal consumed is more than the labeled serving size and when the levels of iron and folate are higher than declared, the intake of both will be significantly greater than the labeled values. It will be important to continue monitoring serum ferritin and folate levels in NHANES IV, since daily consumption of breakfast cereals may contribute to excessive intakes of iron and folate. (Whittaker, Tufaro, & Rader, 2001)

With this margin of possible disproportion between the suggested amount of iron and folate ingestion versus the amount that is actually being consumed, hemochromatosis becomes a glooming threat to populations affected by food fortification. This threat can prove to be especially insidious seeing as how our iron stores are not routinely monitored. This presents a relevant issue for public health.

Too much iron consumption can lead to acute exacerbation of iron toxicity. Iron toxicity occurs when the iron in the blood, or serum iron, has exceeded levels compatible with life (Abhilash, Arul, & Bala, 2013). Symptoms suggesting acute iron toxicity would include vomiting blood, diarrhea, abdominal pain, unconsciousness, seizures, and jaundice. Severe levels can lead to liver failure, metabolic acidosis, and finally, death (O’Malley & O’Malley, n.d). Most of these symptoms experienced during acute onset make it glaringly obvious that there is a functional abnormality present in the individual experiencing such sequelae. However, the build-up of iron gradually over time would present as much more clandestine. This insidious form of toxic poisoning would be referred to as chronic iron overload, otherwise known as hemochromatosis (Duchini & Roy, 2017). With hemochromatosis, iron tends to build up and deposit within tissues throughout the body, including major organs like the heart, liver and pancreas. Hemochromatosis, presently, is not measured by the amount of serum iron detected, as in acute iron toxicity, but rather best by ferritin levels. Ferritin is a protein found in trace
amounts within the blood. The levels detected have been found to be comparable to the amount of iron being stored throughout the entire body. Therefore, hemochromatosis is currently, most accurately measured by the serum ferritin levels of the subject in question (Nall, 2015). With that said, it can be inferred that the probability of hemochromatosis being a pertinent public health issue would be directly proportionate to the strength in correlation between serum ferritin levels and inflammatory disease and early mortality.

**Problem Statement**

Blood screenings are not currently part of an individual’s annual routine medical checkup. Hemochromatosis could be discovered in such a blood screening and prevent inflammatory disease along with early mortality. The present concern is that the current healthcare system is quite possibly overlooking a simple fix to what may potentially reveal itself as a pestilence of global proportion.

**Purpose of Integrative Literature Review**

The purpose of this literature review was to explore the significance of the research that may have found a correlation between ferratin and the aggravation of disease and/or mortality. If research suggested that high ferritin levels were a reliable marker for multiple chronic disease manifestations in the body, then by default, hemochromatosis would then become a suspect to the festering of an environment supportive to these enigmatic pathologies. If individuals on their annual routine medical checkup were screened for ferritin on a regular basis, we could gather more research exploring the link between ferritin levels and the presence or advancement of certain chronic disease manifestations. We would also get a better idea of what percentage of the population may be walking the streets in hemochromatosis, having no knowledge of the existence of such a potentially formidable risk factor. Furthermore, this review examined whether an annual physician visit should include routine lab work for present ferratin levels.

**Research Questions**

1. Is there a statistically significant positive correlation between ferritin levels and inflammatory disease as well as early mortality?
2. What are the present percentages of ferritin levels in the general population?
3. Would routine blood testing of ferritin levels decrease the associated mortality rate in the general population?
4. Would this be a cost effective procedure?

Conceptual Framework

The RE-AIM Framework best suited this research objective primarily because its theoretical construct was designed to attempt to measure efficacy, or the effectiveness of a health promotion program. The framework was also developed to quantify the reach (size of the population that it has the capacity to influence), adoption (amount of people who will be expected to engage in the program), implementation (the extent to which the program accomplishes what it intends to carry out) and maintenance (the feasibility of sustaining such a program in the long term). These are all factors which helped to decide whether or not a ferritin test should be adopted in combination with your regular, yearly medical check-up (Raingruber, 2014).

Chapter 2: Methods

Research Design

The design of this study was an integrative literature review structured to assess how strong the correlation is between ferritin levels and inflammatory disease and mortality. There was a search conducted to find literature that either supported or opposed the link between these two variables. Each study was reviewed and analyzed for its reliability, validity and relativity to the subject matter. This review was to take on the form of the RE-AIM Framework, utilizing the constructs of efficacy, reach, adoption, and maintenance. These constructs assisted in investigating the viability of implementing a routine ferritin test during annual physician visits. This was accomplished by way of methodizing the data assessed within the literary search.

Literature Search Strategies

For this review, National Center for Biotechnology Information’s online search engine, PubMed, was utilized along with Depaul University’s online library database. Specific databases that were searched are MEDLINE, UpToDate, and Current Index to Nursing and Allied Health Literature (CINAHL). Key words for the initial search were “ferritin”, “chronic iron overload”, and “hemochromatosis”.

SHOULD FERRITIN TESTS BE ADDED
Literature Search Limitations and Inclusion/Exclusion Criteria

The search for this review was limited to peer reviewed articles published after the year, 2000. The search for articles using key words “ferritin”, “chronic iron overload”, and “hemochromatosis” initially produced 706 search results. These were then filtered down to articles that featured content concerning the link between hemochromatosis, inflammatory pathology and early mortality observed in patients.

Data Analysis

The studies were categorized within a table consisting of the following headings: author(s), year, purpose/problem, sample, comments, design, major findings, and significance to the issue/problem. The works shown were compared and contrasted based on the said categories, while using the RE-AIM Framework as a tool for comparison. Each of these works featured key information relative to the topic at hand. Studies were assessed for validity and reliability, in order to determine whether that data should have been taken into account for the purposes of this literature review.

Chapter 3: Results

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Purpose/Problem</th>
<th>Design</th>
<th>Sample</th>
<th>Comments</th>
<th>Major findings</th>
<th>Significance to the issue/problem</th>
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<tbody>
<tr>
<td>DePalma, R. G., Hayes, V. W., Chow, B. K., Shamayeva, G., May, P. E. &amp; Zacharski, L. R.</td>
<td>2010</td>
<td>A sub-study of a trial performed to assess whether phlebotomy would influence clinical outcomes in PAD patients</td>
<td>Long term cooperative study recording inflammatory biomarkers, and mortality through the duration of 6 years</td>
<td>100 cancer free participants from the VA SNHCS with PAD who were a mean age of 67 years (range, 45-82)</td>
<td>Only concentrates on subjects with PAD/small sample size in comparison to world population /many other complications that</td>
<td>Positive statistical correlation between ferritin levels, inflammatory cytokines, CRP, and mortality</td>
<td>Correlation between inflammation markers and mortality rates can be extrapolated to suggest probabilities of the general population without PAD</td>
</tr>
<tr>
<td>Year</td>
<td>Study Title</td>
<td>Study Details</td>
<td>Participants</td>
<td>Results</td>
<td>Conclusion</td>
<td>Further Notes</td>
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<td>2013</td>
<td>Study of the association of different markers of iron metabolism (namely ferritin, erythrocyte protoporphyrin and transferrin saturation) with prediabetes in US adults without chronic kidney disease anemia, and iron deficiency</td>
<td>Data analysis and experiment replication</td>
<td>3,876 participants of the NHANES III (1988–1994) who were free of diabetes, chronic kidney disease, iron deficiency, and anemia</td>
<td>Replication allows for analysis of results across time and across experimenters but limited information provided on the limitations of the study</td>
<td>Higher ferritin and lower TSAT are associated with higher risk of pre-DM in a general population without confounding diseases</td>
<td>Positive correlation found between ferritin and Diabetes</td>
<td></td>
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<td>2014</td>
<td>Observation of the possible association of increased ferritin concentrations with increased risk of total and cause-specific mortality in</td>
<td>Participants who had a measurement of plasma ferritin were followed prospectively from the 1981 through 2013</td>
<td>A total of 8,988 participants randomly selected on the basis of the Danish Civil Registration System Code to reflect the adult</td>
<td>Reliability of study can be questioned considering the probability of a high volume random error</td>
<td>Moderately and markedly increased ferritin concentrations represent a biological biomarker predictive of early death in</td>
<td>Directly relates to ferritin being linked to early mortality and importance of routine ferritin screenings</td>
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<tr>
<td>Year</td>
<td>Study Title</td>
<td>Design</td>
<td>Population</td>
<td>Findings</td>
<td>Table Title</td>
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<td>2012</td>
<td><strong>Holay, M. P., Choudhary, A. A. &amp; Suryawanshi, S. D.</strong></td>
<td>Study of the relationship of serum ferritin with acute myocardial infarction (AMI) in univariate and multivariate analysis and to assess the relationship of high serum ferritin with established conventional risk factors</td>
<td>General population</td>
<td>High serum ferritin is strongly and independently associated with AMI.</td>
<td>SHOULD FERRITIN TESTS BE ADDED</td>
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<td>Hospital based case-control study cases of AMI</td>
<td>75 age and equal number of age, and gender-matched controls without having AMI in the age group of 30–70 years.</td>
<td>Study provides minimal information on study design and sources not cited</td>
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<td>2012</td>
<td><strong>Alkhateeb, A. A., Leitzel, K., Ali, S. M., Campbell-Baird, C., Evans, M., et al.</strong></td>
<td>An examination of the predictive value of inflammatory biomarkers in breast cancer patients, by measuring serum ferritin and CRP prior to</td>
<td>66 breast cancer patients</td>
<td>Limited information presented within the article concerning characteristics of the patient pool and parameters of the actual experiment</td>
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<td>Pre-treatment testing coupled with analysis of the progression-free survival of dichotomous categorical groups in order to quantify responsiveness to therapy with a mean</td>
<td></td>
<td>The elevation in pre-treatment serum ferritin (&gt;250 ng/ml) or CRP (&gt;7.25 mg/l) was a significant predictor of reduced progression-free survival and ferritin and breast cancer survival over all</td>
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Research suggested that high levels of ferritin may be directly correlated with many types of chronic disease and early mortality. In 2014, the Copenhagen City Heart Study conducted a study consisting of 8,988 subjects within the Danish population, in which they were followed over an extended period of time (median follow up of 23 years). The purpose of the study was to explore whether there was a relationship between ferritin levels and total mortality. The results of the study led to the conclusion that “Moderately to markedly increased ferritin concentrations represent a biological biomarker predictive of early death in a dose-dependent linear manner in the general population” (Ellervik, Marott, Tybjærg-Hansen, Schnohr, & Nordestgaard, 2014).

Hereditary hemochromatosis is a genetic disorder associated with dysfunctional iron metabolism. Approximately 25-60% of these patients whom are usually associated with high serum ferritin levels ranging from 1000 to 10,000 ng/ml, go on to develop type 2 diabetes (Rajpathak et al., 2009). Though the link isn’t commonly made by current conventional medicine, hemochromatosis may be the very reason why diabetes is a marker for diagnosis of the disease.

Serum ferritin is elevated in patients with Hodgkin's lymphoma, hepatocellular carcinoma, neuroblastoma, glioblastoma, squamous cell carcinoma of the head and neck, renal cell carcinoma, melanoma, non-small-cell lung cancer, pancreatic cancer, and breast cancer. This increase is often associated with more progressive disease and shorter survival. (Alkhateeb & Connor, 2013)

The elevation of ferritin in patients with inflammatory conditions has now led scientists to view ferritin as a pro-inflammatory cytokine (Alkhateeb & Connor, 2013). Many of the studies reviewed conclude that ferritin is predictive of a current inflammatory condition, similar to the way CK (creatinine kinase) is used to assess inflammation of the muscles in the body during an acute event. Research is warranted to explore the concept that ferritin should be used as a marker for inflammation secondary to hemochromatosis, which may be an important precursor to the pathology in many of these cases of chronic disease.
Discussion

Reach and Adoption

Ferritin blood tests are not standard for annual check-ups. Patients would be indicated for a ferritin test under suspicion of certain conditions such as anemia and renal disease. The test would also be used to monitor patients’ responses to certain therapies, such as blood transfusions. These conditions are very specific and are geared toward the general population. With that said, ferritin levels are most likely to be checked when a patient is already combatting disease. Serum ferritin lab tests are generally not thought to be a particularly useful tool when considering preventative medicine. It is this researcher’s recommendation that his idea be explored because of the high probability that over-fortified foods are being distributed across the globe in mass.

According to the Food Fortification Initiative (n.d.), 87 countries around the world are now legislated to mandate at least one industrially milled cereal grain (Food Fortification Initiative, n.d.). This coincides with their mission to improve nutrition all over the world, especially in lesser developed countries where iron and folate deficiencies are rampant. Unfortunately, this doesn't guarantee that the methods and amounts of minerals infused are being adequately monitored. This puts the entire population within all 87 countries at risk for developing hemochromatosis. This realization makes the possible reach and adoption of a routine ferritin program affect a significant amount of the world’s population. “We estimate that 34.1% of the world's industrially milled wheat flour, 57.0% of industrially milled maize flour, and 0.1% of industrially milled rice is fortified with at least iron or folic acid through these mandatory and voluntary efforts” (Food Fortification Initiative, n.d.). The program should at least be mandated for patients over 30 years, as this is the population that would most likely have accumulated enough iron in the body to reach hemochromatosis. Both the reach and adoption for such a program could be monumental to say the least.

Maintenance and Efficacy

Hospital budgeting is a subject that needs to be coddled with attention to the many facets and layers of a business. Adding to this idea, hospital budgeting must surely morph from hospital to hospital. Implementing a mandate within health facilities across the US (not to mention the
many other countries all over the globe) is a feat that will no doubt take some time to come into fruition. A ferritin blood test today in 2018 can be had online at various independent companies such as Lifeextension, for as little as $28 per test, excluding tax. This price tag of course cannot be translated into what such a test would run a hospital for all of its patients’ annual physicians visits. The urgency of such a program may be questioned, especially concerning the need for further research on ferritin as preventative tool.

In order to evaluate the cost benefit ratio of an annual, mandatory ferritin test screening, data would need to be collected relating to the percentage of patients that are likely to benefit if this program were mandated. Quality of benefit along with monetary costs required from the hospital are also important factors that need to be considered. It is this researcher’s suggestion that a controlled study be conducted as a test run of the program with a single hospital for a finite period of time. It is recommended that a random sample size be gathered, large enough to represent the population size of at least that hospital facility. These subjects should be followed for a period of at least 5 to 10 years. Tracking the subjects’ serum ferritin levels along with the progression of disease should produce data sufficient enough to assess the feasibility of implementing this program yearly for the entire hospital patient population. This could serve as a worthy first step to assessing the future viability of a state, and possible nationwide mandate. This should help the health community begin to form a better understanding of the cost benefit ratio. It would be at this level of the program where efficacy would also be properly evaluated

Nursing Implications

The implications of this program would be overarching across the healthcare structural stratosphere. It holds the possibility to change how healthcare is handled for chronic disease throughout all practices. The most glaring implication for nurses is in the patient education sector of nursing skills and duties. It would help to build awareness, and thereby compliance, if patients were told that they should be getting these tests done routinely, or at least at a frequency they consider sufficient for self-monitoring. If hemochromatosis were found to be as big a public health issue as can be presumed, it would be imperative to implement teaching about ferritin screening as a staple of preventative care along with diet and exercise. As nurses, it would be imperative to inform patients how important it is to pay attention to the ingredients and
consumption of fortified foods. Patients should be getting tested for excess iron stores at the same times they plan to check their blood pressures and cholesterol levels.

**Conclusion**

In conclusion, the results gathered from this literature review are substantial enough to imply that serum ferritin levels in the blood hold a strong correlation with chronic disease and early mortality. In fact, the mission of this study was to explore the suggestion that much of the prevalence of chronic disease today can be attributed to a budding surge of hemochromatosis in the general public. At the very least, the results compiled give merit to the need for more research concerning the matter. Moving forward from this review, based on the research compiled, it is warranted that more studies be performed for an accurate calculation of what the cost benefit ratio would be for the mandate that a serum ferritin test be coupled with regularly scheduled annual physicals for all patients over the age of 30 with their primary care provider.
References


SHOULD FERRITIN TESTS BE ADDED


