Higher Heart Disease Risk in Post-Menopausal Women Is Due to Iron

One of the key pieces of evidence leading to the implication that iron causes heart disease is the differential incidence of heart disease between men and women. Men have far higher rates of heart disease, and they have much higher iron levels, since women lose iron via menstruation. When women cease menstruation at menopause, their risk of heart disease goes way up, and this is not due to hormones, as both of the pieces below note.

That's the topic of two letters just published in JAMA Cardiology, one by Luca Mascitelli, M.D. and Mark Goldstein, M.D., the other by Virginia Mary Hayes, M.S., Ralph George DePalma, M.D., and Leo Zacharski, M.D., all of them experts on the relation between iron and health. I know a couple of these people, and Dr. Mascitelli kindly sent me these letters, which I'm publishing here because otherwise the public won't get to see them due to a paywall.

Effect of Iron Levels on Women After Premature or Early-Onset Menopause

To the Editor Muka et al[1] found a higher risk of adverse cardiovascular outcomes in women who experience premature or early-onset menopause. This detrimental association is usually thought to be associated with the early loss of the ovarian function through menopause. However, the estrogen hypothesis is not consistent with epidemiological findings that premenopausal hysterectomy essentially cancels the protection even in patients with preserved functioning ovaries.[2] Of note, healthy premenopausal women are largely protected from coronary heart disease; remarkably, so are women with heterozygous familial hypercholesterolemia.[3] Despite a genetically determined, grossly unfavorable lipid phenotype, cardiovascular protection suggests not only that the protective factor is powerful but also that it does not operate through a lipid-related mechanism. Therefore, it has been proposed that an intact uterus has an important role in the protection of premenopausal women, and this is likely associated with the beneficial effect of iron depletion in menstruating women, ie, the iron hypothesis suggested by Sullivan[4] in 1981.

During late adolescence, men begin a steady accumulation of stored iron with age, but women fail to acquire significant iron stores because of their continual losses of iron in menstrual blood, pregnancies, and deliveries. A protective effect of iron depletion that may have multiple beneficial consequences is decreased availability of redox-active iron, which may participate in the generation of powerful oxidant species, such as hydroxyl radical, and in lipid peroxidation and in turn induce atherosclerotic plaque vulnerability.

A recent trial[5] found that phlebotomy of 1 unit of whole blood twice a year among predominantly white middle-aged and elderly men with peripheral arterial disease resulted in a significant decrease in overall mortality, myocardial infarction, and stroke over a several-year period compared with the control group not phlebotomized. Interestingly, average menstrual blood loss each year (780 mL) approximates two 500-mL units of whole blood. Therefore, higher body iron stores might be involved in determining the higher risk of adverse cardiovascular outcomes in women who experience premature or early-onset menopause.

Future studies should be conducted to find out the exact role of iron depletion in the prevention of atherosclerosis progression and plaque destabilization in women with premature menopause.

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Muka T, Oliver-Williams C, Kunutsor S, et al. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. *JAMA Cardiol*. 2016;1(7):767-776.

2. Kannel WB, Levy D. Menopause, hormones, and cardiovascular vulnerability in women. *Arch Intern Med*. 2004;164(5):479-481.

3. Hill JS, Hayden MR, Frohlich J, Pritchard PH. Genetic and environmental factors affecting the incidence of coronary artery disease in heterozygous familial hypercholesterolemia. *Arterioscler Thromb*. 1991;11(2):290-297.

4. Sullivan JL. Iron and the sex difference in heart disease risk. *Lancet*. 1981;1(8233):1293-1294.

5. Zacharski LR, Shamayeva G, Chow BK. Effect of controlled reduction of body iron stores on clinical outcomes in peripheral arterial disease. *Am Heart J*. 2011;162(5):949-957.e1.

COMMENT & RESPONSE

Effect of Iron Levels on Women After Premature or Early-Onset Menopause

To the Editor In a systematic review, Muka et al[1] found a higher risk of cardiovascular disease mortality and a higher overall mortality in women who experience premature or early-onset menopause. We suggest that the substantial increase in serum ferritin levels at menopause signals a dramatic alteration in iron metabolism possibly associated with enhanced inflammatory responses. We ask the authors to consider that the observed and significant increase in risk of cardiovascular disease in women is associated with altered iron homeostasis and the possible increase in body iron stores after menstrual blood flow cessation.[2]

The 1976 Framingham Study[3] provided groundbreaking evidence that menopause is associated with a highly significant, 2-fold increase in the incidence of heart disease. Cardiovascular protection diminished after surgical menopause, regardless of whether oophorectomy had been performed. Muka et al[1] emphasize the striking association between menopause and coronary risk without comment on the significant alteration in iron metabolism accompanying menstrual cessation.

The hypothesis that increased cardiovascular disease following menopause results from oxidative stress catalyzed by excess iron accumulation was tested in the Veterans Affairs Cooperative Study Trial 410, The Iron and Atherosclerosis Study. Phlebotomy effects on clinical outcomes were tested in patients with peripheral arterial disease with iron store reduction, estimated by serum ferritin levels, to levels approaching 25 ng/mL, which occur in healthy menstruating women.[4] Data from this prospective study demonstrated that lower ferritin levels (eg, 76-78 ng/mL) predicted improved outcomes in younger men with peripheral arterial disease (later in smokers) on removal of an amount of iron represented by approximately a liter of blood. Lower ferritin levels strongly predicted improved clinical outcomes, regardless of randomization group, with a threshold for benefit below 76-78 ng/mL.

We suggest that iron in catalytic form stimulates inflammatory responses and leukocyte activity and associates with elevation of interleukin 6 and other inflammatory biomarkers. We have reported direct associations[5] between elevated ferritin levels and inflammatory biomarkers, predominantly interleukin 6, and mortality.

Data from multiple sources support a clear need for additional studies testing the relationship between increased cardiovascular disease risk associated with changing iron homeostasis in women during and after menopause. We recommend sequential measurements of ferritin levels, along with levels of iron, hepcidin, and inflammatory biomarkers in premenopausal and postmenopausal women to assess the effects of these biomarkers as risk factors for cardiovascular mortality.[2] Provision of a biological basis for the effect of early menopause on cardiovascular disease requires further investigation of the crucial role of iron metabolism.

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1. Muka T, Oliver-Williams C, Kunutsor S, et al. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. *JAMA Cardiol*. 2016;1(7):767-776.

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Iron (ferritin) levels above the minimum serve no purpose; it's merely storage. (Admittedly, if you lost a lot of blood, didn't die from it, and had no medical care, you might return to health faster if you had more iron stores, but that's about the only example I can think of where more iron might be better.) Basically, there's no downside to keeping ferritin within a low normal range, and it could save you from a heart attack.

Premenopausal women have naturally low levels of iron, and this almost completely protects them from heart disease.

By the way, another possible explanation as to how lower iron decreases heart disease risk concerns microbes: iron allows them to grow, and they may cause heart disease.

PS: For more, read my book, Dumping Iron.

PPS: You can support this site by purchasing through my Supplements Buying Guide for Men.