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Vulnerable atherosclerotic plaque and iron homeostasis: the role of intraplaque erythrophagocytosis, ferroptosis and heme oxygenase-1 overexpression

Short title: Vulnerable plaque and iron homeostasis

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We have read with great interest the article by Dr. Oleksiak et al. [1] on the relationship between iron levels and the type and composition of coronary atherosclerotic plaques. The authors found that higher iron levels were associated with the presence of low-attenuation plaque and greater vulnerable component of coronary plaques, as assessed by computed tomography angiography.

Iron is an essential trace element involved in numerous fundamental biologic processes, including heme synthesis, iron-dependent catalytic reaction, mitochondrial respiration and DNA synthesis. To our knowledge, only one organism is known so far on Earth that does not require iron to live and relies on manganese for its metabolism. This is the Gram-negative spirochete *Borrelia burgdorferi*, which causes Lyme disease, the most common anthrozoosis in the Northern Hemisphere.

Growing evidence suggests a close relationship between atherogenesis and iron metabolism [1, 2]. The understanding of the pathomechanisms of hereditary hemochromatosis, as well as the results of many experimental and clinical studies confirm that not only iron deficiency but also iron overload have adverse health effects.

However, we would like to highlight some important issues in the paper by Oleksiak et al. [1] that may affect the clinical interpretation of the study results and conclusions. First, it seems unlikely that this study really assessed non-transferrin-bound iron (NTBI) or highly toxic free iron levels. Although the manuscript lacks detailed information regarding the methodology for iron measurements, considering the presented reference values (33–193 µg/dl), it can be assumed that serum/plasma iron levels were evaluated using a routine colorimetric method. The term NTBI refers to a group of circulating toxic forms of iron which are bound to ligands other than transferrin, ferritin, or heme (i.e., serum albumin, citrate, and other undefined negatively charged ligands) and result from iron overload or other rare conditions associated with severe dysregulation of iron metabolism [3]. Increased NTBI levels have been found in sickle cell anemia, thalassemias, hemochromatosis, cancers and in patients receiving myeloablative chemotherapy, but their measurement required other methodologies, e.g., chelation of iron with nitrilotriacetic acid [3]. Population-based studies have shown that NTBI levels in healthy individuals usually do not exceed 1 µmol/l or are undetectable by most methods.

Second, it is worth noting that in humans, as in all mammals, serum iron levels show a significant diurnal variation, with the highest levels usually occurring in the morning and after many hours (>5–6 h) of fasting, and the lowest in the evening. This may have affected the study results, particularly if blood samples were collected at different times of the day.

Third, the complex metabolism of iron was not evaluated in detail in this study. Assessment of iron levels in isolation from other parameters of iron metabolism and hemogram is very difficult to interpret and can be misleading. More attention should also have been paid to biomarkers of inflammation, which is closely related to iron homeostasis, ferritin (a positive acute phase reactant and marker of acute and chronic inflammation), transferrin (a negative acute phase reactant) and NTBI. Importantly, human tissues present an iron-restricted environment for bacterial pathogens, and during infection and inflammation, further sequestration of iron ions by the host to limit pathogenicity by invading microorganisms occurs, underlying the evolutionarily conserved defense mechanism of “nutritional immunity”, common to vertebrates but also invertebrates and even plants.

There is increasing evidence that intraplaque neovascularization and hemorrhages are a key feature of advanced/vulnerable atherosclerotic plaques [4]. The newly formed immature

intraplaque neovessels are fragile and leaky, which leads to the release of erythrocytes and their phagocytosis by macrophages (erythrophagocytosis). This is accompanied by overexpression of heme oxygenase-1 (HO-1, EC 1.14.14.18), an inducible cytoprotective enzyme, which protects cells from toxic free heme by catalyzing the first and rate-limiting step in the oxidative cleavage of heme to biliverdin, carbon monoxide (CO) and ferrous iron (Fe^{2+}) [4]. However, the iron accumulation in phagocytes, increased intracellular oxidative stress and lipid peroxidation trigger a cascade of mechanisms of non-canonical ferroptosis, a form of iron-dependent, non-apoptotic programmed cell death, that seems to contribute significantly to plaque destabilization. Interestingly, ferroptosis can be inhibited pharmacologically, e.g. by ferrostatin-1 (Fer-1) and its analogues, which is explained by their ability to scavenge free radicals, especially in lipid bilayers/biomembranes [4].

Therefore, it would be extremely valuable to continue research on the role of iron metabolism in atherogenesis and atherosclerotic plaque destabilization, also using imaging methods, such as magnetic resonance imaging and optical coherence tomography, to assess intraplaque hemorrhage [5].

In conclusion, we congratulate the authors of this very interesting and inspiring article.

Article information

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