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Should Physicians Avoid Routine Iron Supplementation in Rheumatic Musculoskeletal Diseases (RMDs)?

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Most of the RMDs invite inflammatory cascades. Free radicals are produced in inflammatory reactions. Alterations in the metabolism of trace elements frequently occur in RMD patients. This alteration occur may be partly due to inflammatory processes driven by interleukin-1 (IL-1), tumour necrosis factor-α (TNF-α), and interleukin-6 (IL-6).[1] Trace elements act as cofactor for most of the enzymes, including several antioxidant enzymes which prevent cellular damage and cell death caused by free radicals especially produced during an inflammatory reaction. Recently, different studies investigated the status of trace elements in RMDs aiming to define their roles in in the aetiology and pathogenesis of these diseases.

Iron is the most abundant transition metal in living organisms. Beside erythropoiesis, it is also involved in the transport of oxygen, electron transfer, DNA synthesis, oxidations by oxygen and hydrogen peroxide and in many other processes maintaining normal structure and function. Thus, the ability of a cell, tissue and organism to procure this metal is essential for survival.

Iron is necessary for normal immune function: deficiency has been associated with mild immunosuppression, whereas concentrations in excess can elevate oxidative stress and risks for infection. As a result, a complex mechanism of regulating iron is naturally in place. However, in RMDs this homoeostasis can be disrupted.[2] Hepcidin is the main regulator of iron release; it is secreted by the liver in response to haemoglobin, hypoxia, iron deficiency, iron overload and inflammation and binds to ferroportin to control the release of iron from body stores in macrophages, hepatocytes and enterocytes. Thus, following immune activation, the serum becomes iron-starved and erythroid precursors lack sufficient iron for proliferation and haemoglobin synthesis; mature red blood cells and precursors can be tagged by autoantibodies for degradation, contributing to the hyporegenerative anaemia; renal erythropoietin (EPO) production is reduced. In the end, a mild to moderate normocytic anaemia with evidence of iron-restricted erythropoiesis occurs.

Chronic inflammation may induce sideropenic anaemia through different mechanisms[3], but it is fundamental to distinguish inflammatory anaemia from iron-deficiency anaemia in RMDs. In inflammatory anaemia, serum iron, transferrin and transferrin saturation is low and ferritin level is normal or high. However, in iron deficiency anaemia, serum iron, transferrin saturation, ferritin are found low, while transferrin is high. It is quite recurrent in RMD patients to have low iron serum concentrations: the mechanism of iron sequestration in RMDs is likely to be the same as in infections. However, while in infections it could give some benefits, there are few data to support possible advantages in autoimmune and other non-infectious diseases.

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Patients with RA have higher concentrations of free iron, lactoferrin and other iron-binding proteins in synovial fluid.[4] It seems that lactoferrin may prevent toxic damage to the synovium from free iron which accumulates during the inflammatory response. Notably, it has been reported that iron dextran infusions for anaemia could have negative impact of on disease activity among RA patients, whereas treatment with iron-chelating agents can improve it.[5,6] In patients with SLE, ferritin levels correlate with disease activity which can further worsen with infusion of iron.[7] Moreover, by inducing hepcidin to increase iron sequestration in macrophages within atherosclerotic plaques, relative iron overload may exacerbate atherosclerosis and the cardiovascular risk in SLE patients.[8] In the case of gout, iron supplementation can trigger flares since urate crystals form complexes with iron and in turn stimulate oxidative stress, granulocyte and complement activation and lymphokine production.[9]

To conclude, it appears that altered iron homoeostasis may represent a purposeful response to inflammation that could have theoretical anti-inflammatory benefits.[10] Thus, physicians should avoid routine iron supplementation in those patients without depleted iron stores (ferritin level > 60–100 mcg/l).

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