The changing landscape of iron overload disorders at the beginning of the 21st century

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It is my pleasure and great honor to guest edit this issue of the Quarterly Medical Review (QMR) devoted to iron overload disorders. Together with Professor Loïc Guillevin, the Editor-in-chief of QMR, we have brought together the best experts in this field in order to keep you informed on the latest developments in these complex disorders.

We start with Raed Daher, Hana Manceau and Zoubida Karim from Inserm U773 at Paris Diderot University in France, who introduce us, clearly to iron metabolism and the role of iron-regulating hormones. Hepcidin-25 is now recognized as the master hormone of iron metabolism. It is synthesized in the liver and acts negatively on both intestinal iron absorption and iron release from reticulo-endothelial macrophages and liver cells by reducing the expression of ferroportin, a protein that regulates iron export out of these cells [1]. Iron itself and inflammation (via IL-6) enhance hepcidin-25 synthesis, while anemia, hypoxia, bleeding, iron deficiency, erythropoietin, and increased medullary erythropoiesis all downregulate hepcidin-25 synthesis [1]. The mechanism by which erythropoietic stimulation after blood loss downregulates hepcidin synthesis has recently been linked by Tomas Ganz's research group to a new peptide hormone called erythroferrone, which is secreted by erythroblasts and acts directly on the liver [2]. Hepcidin and erythroferrone can be seen as the iron metabolism counterparts of the glucose-regulating hormones insulin and glucagon. Deficient hepcidin-25 synthesis plays a central pathophysiological role in genetic hemochromatoses, whereas unregulated hepcidin synthesis is responsible for a newly discovered genetic (autosomal recessive) form of iron deficiency anemia called IRIDA (iron refractory iron deficiency anemia), due to mutation of the TMPRSS6 gene that encodes matriptase-2 [1,3]. IRIDA is refractory to oral iron but responds partially to IV iron [3].

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Yves Gandon et al. at the Division of Radiology of Rennes University in France superbly describe the progress made in magnetic resonance imaging (MRI) for the measurement of liver iron content and for the diagnosis and follow-up of iron overload disorders. The liver is the main iron storage site, and the liver iron concentration (LIC) gives a very accurate picture of total body iron stores in patients with secondary hemosideroses, such as thalassemia major, sickle cell disease and genetic hemochromatosis [4]. Non-invasive radiological techniques for estimating LIC have been developed in the past two decades in order to avoid liver biopsy. They include superconducting quantum
interference devices (SQUID), quantitative computed tomography, and MRI [5]. MRI is now the preferred technique, because of its reproducibility, sensitivity, availability and ability to scan multiple organs in the same session [5-7]. Quantitative MRI is based on the paramagnetic properties of iron: the magnetic resonance signal falls as the liver iron concentration rises [5]. There are three MRI modalities for liver iron assay: the signal-intensity ratio with the Rennes algorithm, R2 relaxometry, and R2* relaxometry, all published in the years 2004-2005 and validated in cohorts of patients with secondary hemosiderosis, genetic hemochromatosis and hepatic disorders requiring liver biopsy for biochemical iron assay [8-10]. These authors discuss the practical use of the main MRI techniques and their technical requirements, together with the present and future perspectives of T2* relaxometry. As advocated by Yves Gandon et al.’s in their article, there is now great interest in combining the signal-intensity ratio method with R2* relaxometry in the same exam for precise liver iron quantification. This latter approach not only quantifies liver iron but can also detect iron overload in the heart, spleen and pancreas during the same session.

The review of genetic hemochromatosis by Pierre Brissot et al. from the Hepatology Department of Rennes University in France elegantly reveals how genetic research and new radiological tools have deeply modified this field in the past decade, especially with the use of non-invasive procedures that greatly benefit the patients concerned. Moreover, these authors show how the field of genetic hemochromatosis has recently evolved into a complex world of plural, well-characterized hemochromatoses. Finally, the authors postulate that, while phlebotomy remains the pivotal treatment for HFE 282Y homozygous patients, hepcidin itself or agonists may become the future pathophysiological treatment of choice for these genetically deficient patients.

Eitan Fibach from Hadassah-Hebrew University Medical Center in Jerusalem, and Eleizer Rachmilewitz from the Edith Wolfson Medical Center at Holon, Israel, provide a panorama of the numerous genetic and acquired red blood cell disorders leading to secondary hemosiderosis, together with their pathophysiological pathways. They list the huge benefits, in terms of morbidity and mortality, in thalassemia and other hematological diseases achieved in the last decade through early detection of cardiac ferric cardiomyopathy by T2* MRI and chelation therapy (often combined). Eitan Fibach and Eleizer Rachmilewitz stylishly demonstrate the toxic role of labile iron and oxidative stress at the cellular level, and describe new tools for diagnosing and monitoring this toxicity.

Yves Deugnier, Edouard Bardou-Jacquet and Fabrice Lainé from the Pathology and Hepatology Departments of Rennes University in France provide an outstanding review of the dysmetabolic iron overload syndrome. This syndrome, first described in the Lancet in 1997 by the Rennes hepatology group [11], has become epidemic in Europe and the USA (alongside diabetes and overweight) and has emerged as one of the most frequent causes of hyperferritinemia. Cross-talk between visceral fat and the liver is thought to be pivotal. No beneficial role of phlebotomy has been demonstrated in this setting. The dysmetabolic iron overload syndrome is an area of active research into its pathophysiological mechanisms and potential therapeutics.

In a "transatlantic" article, Guy Rostoker (Claude-Galien Hospital, Quincy, France), and Nosratola Vaziri (University of California, Irvine, USA) summarize recent studies of LIC in hemodialysis patients, as measured by quantitative MRI (and also a forgotten SQUID study performed 13 years ago), which demonstrate a strong relationship between the risk of iron overload and the use of intravenous (IV) iron products prescribed at doses advocated in current anemia management guidelines for dialysis patients [12-15]. Three long-term epidemiological studies (including the DOPPS study of 32,435 hemodialysis patients followed for a median of 1.7 years in 12 industrialized countries) have also recently shown that excessive IV iron doses are associated with an increased risk of cardiovascular events and death among hemodialysis patients [16]. Moreover, high hepcidin-25 levels were recently linked to fatal and nonfatal cardiovascular events in dialysis patients, suggesting that the main pathophysiological pathway leading to these adverse effects of iron therapy and iatrogenic iron overload may involve the pleiotropic master hormone hepcidin [17]. These latter data on potential harms to the cardiovascular system due to excessive hepcidin levels in dialysis patients may be particularly relevant to the potential future therapeutic use of hepcidin and its analogs in deficiency states.

Clinicians and young physicians often struggle with patients seeking advice on hyperferritinemia, owing the complexity of the situation, the need for specific expertise, and the lack of specific reviews devoted to positive and differential diagnosis of hyperferritinemia in routine clinical practice. Bernard Lorcère et al. from the Internal Medicine Department of Dijon University hospital in France have undertaken the huge task of synthesizing the medical literature focusing on the main clinical features of the various disorders associated with elevated ferritin levels, together with new diagnostic tools and diagnostic approaches to the main disorders. Their outstanding review and proposed diagnostic pathways will be very helpful for clinicians, young physicians, and teaching departments.

I warmly thank the authors of these different articles for their comprehensive reviews and wish readers pleasant and instructive perusal. On closing this issue of Quarterly Medical Review, I hope you will be convinced that the landscape of iron overload disorders has progressed markedly the past decade, for patients, researchers and physicians alike.

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