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COMMENTARY

Obesity, liver steatosis and metabolic syndrome: The hidden enemies in transfusion-dependent thalassaemia

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In their paper, the authors quantified liver iron concentration (LIC) and hepatic steatosis (HS) using MRI-T2* technology in transfusion-dependent thalassaemia (TDT) patients and healthy controls and found that the prevalence of HS among patients with TDT was 36.4%. In comparison with healthy controls, the hepatic fat fraction (FF) was significantly higher in the TDT population ($p = 0.013$). Active hepatitis C virus infection, body mass index (BMI) and LIC were independent predictors of HS. An inverse correlation between hepatic FF and high-density lipoprotein cholesterol ($p = 0.042$) and a significant association of high glycaemia level ($p = 0.037$) with higher hepatic FF and a significant relationship ($p = 0.026$) between HS and higher BMI (though in a 'lean' group of patients) in TDT patients indicated that 'metabolic syndrome' was present in this subset with TDT. The impact of metabolic syndrome on TDT, including cardiac disease unrelated to iron overload, needs further study.

Commentary on: Ricchi et al. Liver steatosis in patients with transfusion-dependent thalassaemia. Br J Haematol 2024;204:2458–2467.

KEYWORDS
liver steatosis, NAFLD, metabolic syndrome, transfusion-dependent thalassaemia

Chronic liver disease is an important complication in patients with transfusion-dependent thalassaemia (TDT), mainly due to iron overload, and in some communities due to transfusion-transmitted infections, mainly hepatitis C virus (HCV). Globally, non-alcoholic fatty liver disease (NAFLD) is on the rise, and it has been estimated that 32% of the world population is affected by NAFLD.[1,2] Metabolic syndrome, too, is ubiquitous in non-thalassaemia people globally, and it is well known to increase the cardiovascular risk of those affected.[2,3] In patients with thalassaemia, the role that metabolic syndrome might play has rarely been studied. With the increasing age of thalassaemia patients in many countries, it would be no surprise that conditions other than anaemia and iron overload would come into play in the pathogenies of the disease and affect life expectancy.

In their paper, the authors, the first-ever case-controlled study, assessed the prevalence of liver steatosis (LS) and its associations and went on to show that patients with TDT have a higher degree of fat fraction (FF) compared with healthy controls ($p = 0.013$). After investigating 247 patients with TDT in 66 thalassaemia centres, the authors found that the prevalence of LS among this cohort was 36.4%. They also showed that iron overload (liver iron concentration [LIC], but not ferritin), active HCV infection and body mass index (even though found in a group of 'lean NAFLD' individuals) were independent predictors of LS in this cohort. Further, the authors showed an inverse correlation between hepatic FF and high-density lipoprotein cholesterol (Spearman's rho = −0.190; $p = 0.042$) and a significantly high glycaemia level ($p = 0.037$) in TDT patients with higher hepatic FF.[4]

The first reference to the effects of LS increasing fibrosis in patients with TDT was the publication by Padeniya et al., which showed the effect was found even in lean patients with very high iron levels (ferritin >2000 ng/dL; LIC >7 mg/g dw).[5] Curiously, in this group, there was no demonstrable direct effect of iron levels on the degree of steatosis, unlike that shown by Ricchi et al. The study designs of the two papers were quite different—Ricchi et al. excluded those with

very high LIC (hepatic T2* value >3 ms). This is due to the confounding effects of LIC on LS measurements by MRI.[6,7] Padeniya et al. studied only those with high ferritin levels and LIC levels since their fat estimation was carried out by transient elastography. Nevertheless, both studies agree on the presence of steatosis in TDT patients.

Though steatosis may be reflecting liver injury from iron overload, Ricchi et al.'s study highlights the likelihood that 'metabolic syndrome' would be playing a role in the pathogenesis of liver injury and perhaps in cardiac disease unrelated to iron overload in TDT. It has been clearly documented that NAFLD is the hepatic manifestation of metabolic syndrome and has a strong relationship with insulin resistance. With insulin resistance, there will be an excess of fatty acids in the circulation, which promotes simple hepatic steatosis. Accumulation of lipids in hepatocytes promotes lipid peroxidation and mitochondrial dysfunction due to oxidative stress resulting from various insults, including cytokine injury, hyperinsulinaemia, hepatic iron and immune mechanisms causing cellular injury.[8] Thus, it is well proven that hepatic steatosis is the driver of liver damage and subsequent fibrosis.[2]

Ricchi et al.'s study highlights the need to pay attention to steatosis not merely as a feature of iron overload but as an issue related to body weight, even in this relatively lean group of patients, an area that has largely been neglected in the current guidelines for TDT management.

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