COMMENTS AND RESPONSES

Bloodletting Ameliorates Insulin Sensitivity and Secretion in Parallel to Reducing Liver Iron in Carriers of *HFE* Gene Mutations

Response to Equitani et al.

Equitani et al. (1) reported on the effect of iron depletion by phlebotomy on insulin resistance and release in 17 carriers of mutations of hereditary hemochromatosis *HFE* gene with nonalcoholic fatty liver disease (NAFLD). They found that iron depletion ameliorated insulin sensitivity and secretion and reduced hepatic iron stores and nonalcoholic steatohepatitis activity score, and they concluded that results justify glucose tolerance testing and preventive iron depletion in asymptomatic carriers of *HFE* mutations. The study adds new valuable information to the field, but we suggest that the conclusions be tempered for a number of reasons.

First, the large majority of subjects included in the study by Equitani et al. carried *HFE* genotypes conferring predisposition to develop iron overload (C282Y/C282Y, C282Y/H63D, H63D/H63D, C282Y/wt: 16 of 17 [94%]) (2). The large majority of *HFE* mutations carriers in the general population are heterozygous for the H63D mutation (prevalence 23 vs. 6% of the aforementioned genotypes in Italy), which, in the absence of cofactors, has never been associated with increased iron stores (2).

Second, all of the subjects included in the study had histologically confirmed NAFLD, which per se is associated with hepatic insulin resistance, increased risk of diabetes, and mild iron overload (3).

Last, the study was not controlled; therefore, the effect of lifestyle modifications and weight loss (which appeared to be significant after 2 years) on insulin release and resistance could not be fully ascertained.

Nevertheless, iron depletion has recently been reported to improve insulin resistance (as evaluated by the homeostasis model assessment of insulin resistance index) more than lifestyle modifications alone in a case-control study including 128 patients with NAFLD without diabetes and hereditary hemochromatosis followed for 1 year (4). However, serum lipids and alanine aminotransferase levels did not further improve compared with those in standard treatment. The effect of iron depletion on insulin sensitivity was more marked in patients positive for *HFE* mutations, whereas an increase in insulin release was not observed. A controlled trial evaluating liver damage and glucose tolerance as end points is required to support iron depletion in *HFE* mutation carriers with NAFLD.

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