COMMENTS AND RESPONSES

The Role of Iron in Diabetes and Its Complications

Reponse to Swaminathan et al.

Markers of fatty liver such as γ-glutamyltransferase (GGT) are independently associated with an increased risk of type 2 diabetes (1). Some recent studies have shown that hyperferritinemia may also predict new-onset type 2 diabetes (2).

We assessed the cross-sectional relationships between ferritin, GGT, and glucose intolerance status in a large cohort of adults. We performed a retrospective analysis on the database of our clinical chemistry laboratory to retrieve results of serum ferritin, GGT, lipids, glucose (fasting plasma glucose [FPG]), and C-reactive protein (high-sensitivity C-reactive protein [hs-CRP]) tests, which were performed on the whole cohort of outpatient adults (aged ≥35 years) consecutively referred by general practitioners for routine blood testing over the past 2 years. Fasting GGT, FPG, and lipids were measured by standard enzymatic procedures (Roche Diagnostics), ferritin by a chemiluminescence assay (DiaSorin-Liaison), and hs-CRP by a nephelometric assay (Dade-Behring).

We used separate multivariable logistic regression analyses to examine the interaction relationships with impaired fasting glycemia (impaired fasting glucose [IFG] as defined by an FPG value ≥5.6 mmol/l) or diabetes (FPG value ≥7.1 mmol/l) as the dependent variables predicted from ferritin quartiles (<42, 42–80, 80–156, and ≥156 μg/l) within the quartiles of GGT (<16, 16–25, 26–35, and ≥36 units/l). Adjusting variables were sex, age, lipids, and hs-CRP.

Cumulative results of FPG and ferritin were retrieved for 2,637 individuals. After excluding subjects with C-reactive protein >10 mg/l (because inflammation may increase ferritin) and those with very low ferritin, which might be due to anemia (<15 μg/l), and very high ferritin, which might be due to hemochromatosis (>400 μg/l in men and >300 μg/l in women), the final study population consisted of 2,449 subjects (63% female) with a mean ± SD (range) age of 61.8 ± 15 years (35–107). Overall, 161 (6.6%) subjects had a FPG value ≥7.1 mmol/l, and 559 (22.8%) subjects had IFG. Mean GGT and ferritin concentrations were 33 ± 46 units/l and 108 ± 84 μg/l, respectively.

Although the prevalence rates of ferritin quartiles increased steadily across IFG/diabetes categories (ranging from 17 to 27% for IFG and from 4 to 8% for diabetes; $P < 0.0001$), these prevalences remarkably varied by GGT quartiles. As GGT increased, the prevalence rates of ferritin quartiles across IFG/diabetes categories strengthened ($P < 0.001$ for interaction). For example, within the lowest GGT quartile, ferritin quartiles were not associated with IFG (ranging from 12.7 to 14.5%) or diabetes (from 1.2 to 1.5%), in contrast to the highest GGT quartile, wherein the prevalence rates ranged from 19.2 to 28.3% for IFG and from 9.4 to 13.5% for diabetes ($P < 0.01$). These results remained significant even after adjustment for sex, age, lipids, and hs-CRP.

Our findings, although only correlative in nature, indicate that ferritin is associated with a greater frequency of IFG or diabetes only among those with high-normal GGT (≥36 units/l), not in those with low-normal GGT, and suggest that ferritin itself might not be a sufficient risk factor for developing IFG/diabetes. The association between increased GGT and glucose intolerance might be explained by some underlying, biological, mechanisms such as enhanced oxidative stress, insulin resistance, and fatty liver (3).

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