Homeostasis model assessment of insulin resistance and lobular inflammation in patients with nonalcoholic fatty liver disease: methodological considerations and perspectives

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Dear Editor

Ye *et al.* recently showed that the homeostasis model assessment of insulin resistance (HOMA-IR) is strongly and independently associated with lobular inflammation (LI) in patients with nonalcoholic fatty liver disease (NAFLD) and without diabetes, prediabetes, or metabolic syndrome [1]. HOMA-IR reflected more LI than steatosis, which was unexpected since insulin and glucose are biomarkers of metabolism rather than inflammation. Indeed, HOMA-IR has been shown to be strongly associated with liver fat content, and it was suggested as useful for the identification of subjects with "metabolic NAFLD" [2]. Comparing frequencies of liver histological stages between HOMA-IR quartiles, Ye *et al.* found a significant difference for LI only (P <0.001), which they later tested in their multivariate regression analysis, discarding steatosis (P <0.052), fibrosis, and ballooning. However, age (P =0.009) and BMI (P =0.004) were significantly different between HOMA-IR quartiles, and were therefore probable confounding variables. Statistical analyses should be reassessed using age- and BMI-adjusted HOMA-IR, after log-transformation as appropriate, as done elsewhere [2]. Furthermore, the authors determined a HOMA-IR cutoff value of 2.995 for advanced LI, with good sensitivity (0.94) but poor specificity (0.57), encouraging its use in clinical practice for the identification of advanced LI in patients with NAFLD and with uncertainty around progression to nonalcoholic steatohepatitis. This suggestion should be tempered, since HOMA-IR suffers from high inter-assay variation in insulin measurement. Indeed, serum insulin measurements with different assays have shown differences of up to 1.8-fold [3], and inter-assay variations in insulin may result in an inter-laboratory CV% of HOMA-IR of approximately 25% [2]. Unfortunately, Ye *et al.* did not provide any information regarding assay methods nor analyzers. A relevant alternative would be the triglyceride glucose index (TyG) [4-7], whose capacity to discriminate advanced LI in NAFLD could be compared to that of HOMA-IR in the Ye *et al*. cohort.

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