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

Denis Monneret1\*, PharmD, PhD; Dominique Bonnefont-Rousselot, PharmD, PhD2,3.

1 Laboratory of Biochemistry and Molecular Biology, Multisite Laboratory of Medical Biology (LBMMS), Hospices Civils de Lyon (HCL), F-69000 Lyon, France.

2 Department of Metabolic Biochemistry, La Pitié Salpêtrière-Charles Foix University Hospital (AP-HP), F-75013 Paris, France.

3 University of Paris, UTCBS, CNRS, INSERM, F-75006 Paris, France.

**\* Corresponding author**: Dr Denis Monneret

Former address: Department of Metabolic Biochemistry, La Pitié Salpêtrière-Charles Foix University Hospital (AP-HP), F-75013 Paris, France.

E-mail: dmonneret2@gmail.com. Phone: (+33) 6 66 10 77 06

**Author contributions:** The authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
**Research funding:** None declared.
**Employment or leadership:** None declared.
**Honorarium:** None declared.
**Competing interests:** None declared.

**Description**: ±300 words, 7 references.

**Keywords:** homeostasis model assessment of insulin resistance; nonalcoholic fatty liver disease; lobular inflammation; insulin.

*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.

1. Ye FZ, Liu WY, Zheng KI, Pan XY, Ma HL, Wang XD, *et al*. Homeostatic model assessment of insulin resistance closely related to lobular inflammation in nonalcoholic fatty liver disease. *Eur J Gastroenterol Hepatol* 2019. [Epub ahead of print]

2. Isokuortti E, Zhou Y, Peltonen M, Bugianesi E, Clement K, Bonnefont-Rousselot D, *et al*. Use of HOMA-IR to diagnose non-alcoholic fatty liver disease: a population-based and inter-laboratory study. *Diabetologia* 2017; 60:1873-1882.

3. Tohidi M, Arbab P, Ghasemi A. Assay-dependent variability of serum insulin concentrations: a comparaison of eight assays. *Scand J Clin Lab Invest* 2017; 77:122-129.

4. Guerrero-Romero F, Simental-Mendía LE, González-Ortiz M, Martínez-Abundis E, Ramos-Zavala MG, Hernández-González SO, *et al*. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. *J Clin Endocrinol Metab* 2010; 95:3347-3351.

5. Lee SB, Kim MK, Kang S, Park K, Kim JH, Baik SJ, *et al*. Triglyceride Glucose Index Is Superior to the Homeostasis Model Assessment of Insulin Resistance for Predicting Nonalcoholic Fatty Liver Disease in Korean Adults. *Endocrinol Metab (Seoul)* 2019; 34:179-186.

6. Zhang S, Du T, Zhang J, Lu H, Lin X, Xie J, *et al*. The triglyceride and glucose index (TyG) is an effective biomarker to identify nonalcoholic fatty liver disease. *Lipids Health Dis* 2017; 16:15.

7. Simental-Mendía LE, Simental-Mendía E, Rodríguez-Hernández H, Rodríguez-Morán M, Guerrero-Romero F. The product of triglycerides and glucose as biomarker for screening simple steatosis and NASH in asymptomatic women. *Ann Hepatol* 2016; 15:715-720.

**Acknowledgements:** The authors are grateful to Vincent Fitzpatrick for his English rereading.