



## Letter to the Editor

# Lean non-alcoholic fatty liver disease: Is there a place for novel antidiabetics in the therapeutic management of this underappreciated “enemy”?

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Dear Editor,

We have read with profound interest the very informative review article authored by Kim and Lee<sup>1</sup> regarding the effects of antidiabetic drug classes in patients with concomitant non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus. Therefore, we would like to point out some aspects regarding the phenotype of lean NAFLD, with potential insights into clinical practice.

According to the most recent high level evidence, prevalence of lean NAFLD is 19.2% within the NAFLD population and 5.1% within the general population, while it correlates with significant liver and non-liver morbidity and mortality.<sup>2</sup> Interestingly, besides blood pressure and Homeostatic Model Assessment of Insulin Resistance, lean and obese NAFLD subjects do not differ substantially in terms of physical and metabolic parameters.<sup>2</sup>

Recent real-world data suggest that lean NAFLD subjects might feature greater 15-year cumulative all-cause mortality and similar cardiovascular and cancer-related mortality, compared to obese

NAFLD patients,<sup>3</sup> while others have demonstrated that lean NAFLD subjects have lower prevalence of cirrhosis, diabetes, hypertension, dyslipidemia and cardiovascular disease, compared to non-lean subjects with NAFLD.<sup>4</sup> A sub-analysis of data retrieved from the National Health and Nutrition Survey (NHANES) III database revealed that lean NAFLD patients experience significantly greater all-cause and cardiovascular mortality, compared to lean non-NAFLD subjects.<sup>5</sup> Despite the high heterogeneity of available data, it is undoubted that lean NAFLD subjects require a thorough initial evaluation and a close monitoring for the development or manifestation of metabolic complications. Of note, another sub-analysis of data from the NHANES III database demonstrated that presence of visceral obesity, especially among lean NAFLD patients, has significant prognostic implications regarding all-cause mortality and can be a determinant of selected therapeutic intervention.<sup>6</sup>

Novel antidiabetics, namely glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter-2 (SGLT-2) inhibitors have attracted scientific interest during the last decade

### Abbreviations:

GLP-1RAs, glucagon-like peptide-1 receptor agonists; NAFLD, non-alcoholic fatty liver disease; NHANES, the National Health and Nutrition Survey; SGLT-2, sodium-glucose co-transporter-2

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due to their multiple pleiotropic effects, extending far beyond their hypoglycemic effect. Since lean NAFLD patients feature a metabolic profile that does not differ significantly from that observed among obese patients, it seems reasonable that GLP-1RAs and SGLT-2 inhibitors might also have a role in the therapeutic management of these patients, especially when considering their increased cardiovascular risk and the established cardiovascular benefits observed with these drug classes.<sup>7</sup> Mechanisms of their action are thoroughly discussed by Kim and Lee.<sup>1</sup>

However, there is an outstanding gap in literature regarding the efficacy and safety of pharmacologic agents, in general, and of novel antidiabetics, in specific, for the management of lean NAFLD, except for some sparse experimental data.<sup>8</sup> Thus, based on the aforementioned epidemiologic data, there is an urgent need for well-designed prospective studies enrolling lean NAFLD subjects to investigate the efficacy and safety of the promising novel antidiabetics.

### Authors' contribution

Dimitrios Patoulas and Michael Doulas: manuscript writing and critical revision.

### Conflicts of Interest

The authors have no conflict to disclose.

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