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Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 39006-minireview.doc).

Title: Mediterranean diet and nonalcoholic fatty liver disease

Author: Caterina Anania, Francesco Massimo Perla, Francesca Olivero, Lucia Pacifico, Claudio Chiesa

Name of Journal: *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of reviewer:

- We have replaced the hypercaloric term by hyperenergetic, and caloric by energy;
- We have discussed NAFLD in lean subjects:

  "Obesity is considered a key player in the development of NAFLD, and the majority of patients with NAFLD are either obese or overweight. However, NAFLD has been reported also in lean subjects. "Lean" NAFLD represents subpopulation of patients with fatty liver and normal BMI. These patients are usually insulin resistant and have low HDL-C and higher triglyceride concentrations when compared to lean healthy controls [Kumar P, 2018]. Visceral obesity (as opposed to general obesity), insulin resistance, high fructose and high cholesterol intake are the most prevalent risk factors for lean NAFLD, although genetic factors (e.g. Palatin-like phospholipase domain -containing 3 and Transmembrane 6 superfamily member 2 gene variants) may have an important role";
- We have described the diagnostic methods of NAFLD:

  NAFLD diagnosis requires proof of steatosis, which relies on imaging techniques in clinical practive. Liver biopsy remains the gold standard to address such diagnosis and is the only valid method for differentiating NASH from simple steatosis, however it is neither feasible nor ethical to perform liver biopsy as a tool in all putative patients. Noninvasive imaging

techniques, such as ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and proton magnetic resonance spectroscopy (MRS), can also identify fatty infiltration of the liver. US is perhaps the most practical way to assess hepatic steatosis, due to its relatively low cost, availability, and safety. A major limitation of this operator-dependent technique is its limited sensitvitiy and specificity for diagnosing and quantifying hepatic steatosis. MRS is considered the non-invasive reference standard in the assessment of liver steatosis, because it is able to measure the real concentration of triglycerides within the hepatocytes. However, MRS is too time consuming for routine clinical practice, and requires a skilled operator to correctly perform the examination, process the data, and interpret the results. MRI has shown greater promise for the quantitative assessment of hepatic steatosis in adults and children. Until recently, the most widely used method was based on the modified Dixon technique. This imaging method is reliable in the absence of magnetic field non-homogeneity and iron deposition. Recent improvement in MRI have provided measurement of the proton density fat-fraction [(PDFF): the fraction of the liver proton density attributable to liver fat],which is a inherent property of tissue and a direct measure of liver fat content. MRI-PDFF is accurate,precise,and reliable for quantifying liver steatosis having been validated against liver biopsy in both adults and children;

- Trans fatty acids and saturated fatty acids are now mentioned together;
- We rewrote the sentence "… and micronutrients with antioxidant and anti-inflammatory capacity such as fiber, monounsaturated and omega-3 fatty acids and phytosterols" to read "…. and phytochemicals with antioxidant and anti-inflammatory capacity such as fiber, monounsaturated and omega-3 fatty acids and phytosterols";
- We have discussed the mechanisms through which MD improves fatty liver: "NAFLD is associated with visceral obesity, insulin resistance, dyslipidemia, and chronic inflammation all of which are features of Mets. MD may improve NAFLD by modulating the presence of these conditions. In particular, the antioxidant and anti-inflammatory effects as well as the lipid-lowering effects and gut-microbiota-mediated production of metabolites are the principal mechanisms by which MD can influence metabolic health as well as NAFLD";
- We have incorporated into the revised manuscript how clinical studies were selected, and the language, the keywords, and the data base used to select them:

"To identify relevant studies, a systematic literature search on MEDLINE and EMBASE databases was conducted using the following keywords: "Mediterranean diet", "nonalcoholic fatty liver disease", "hepatic steatosis", "steatohepatitis". All searches were limited to studies published in English language";

- We clarified the mechanisms through which omega-3 PUFA can act positively in NAFLD: "PUFA regulate three major transcriptional factors controlling multiple pathways involved in hepatic carbohydrate and lipid metabolism. PUFA activation of hepatic peroxisome proliferator-activated alpha (PPARα) enhances fatty acid oxidation, while PUFA suppression of sterol regulatory element binding protein-1 (SREBP-1) and of carbohydrate regulatory element binding protein (ChREBP)/Max-like factor X (MLX) results in the inhibition of glycolysis and of de-novo lipogenesis. As such, PUFA promote a shift in metabolism toward fatty acid oxidation and away from fatty acid synthesis and storage, and may positively affect NAFLD. In addition to improvement in steatosis, PUFA may induce an independent, anti-inflammatory effect via suppression of tumor necrosis factor and interleukin-6, responsible for the inflammation occurring in NASH";
- We have added C-reactive protein before the abbreviation CRP;
- We have incorporated in the revised manuscript a table containing the food sources of the MD components;
- The available literature on the efficacy of MD in NAFLD is scanty; anyway, we have included all the most recently available references on the topic.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Claudio Chiesa, MD
Corresponding Author
Institute of Translational Pharmacology,
National Research Council,
Via Fosso del Cavaliere 100, 00133-Rome, Italy
E-mail: claudio.chiesa@ift.cnr.it