Orlistat for Overweight Subjects with Nonalcoholic Steatohepatitis

To the Editor:

We read with great interest the article by Harrison et al. reporting the effect of Orlistat, an inhibitor of fat absorption, on the metabolic abnormalities, histopathologic findings, and cytokine levels in subjects with nonalcoholic steatohepatitis (NASH).[1] They showed that when compared to controls, Orlistat did not enhance weight loss or improve liver enzymes, measures of insulin resistance, and histopathology. Certainly, this study is important because it provides scientific information on this clinically relevant condition. However, we think that some points should be discussed.

First, nonalcoholic fatty liver disease (NAFLD) is the most common liver abnormality in the Western world and is strongly associated with the features of the metabolic syndrome (MetS) and insulin resistance.[2] The pathogenesis of NAFLD is a multiple-hit process resulting from hepatic fat deposition that is related to several conditions, including insulin resistance and central obesity. Additional hits, such as oxidative stress or adipocytokines (leptin, adiponectin, tumor necrosis factor-alpha, interleukin-6, etc.), can further enhance liver damage leading to NASH or fibrosis.[3] In addition, a clear relationship was demonstrated between the components of the MetS and histopathologic findings of NASH.[4-6] In light of these data, we think that the description of the components of the MetS should be an essential part of the present study that investigates the relationship of adipocytokines, inflammation, and fibrosis in NASH.

Second, as shown in Table 1 of the article, most of the study participants are obese and some of them are even morbidly obese. Obesity is a strong risk factor for diabetes mellitus (DM), prediabetes, hypertension, and also dyslipidemia. Although it was stated in the article that only four subjects were diabetic at baseline, there is no information regarding the blood pressure, high density lipoprotein cholesterol and triglyceride levels, and also the glucose tolerance status of the subjects. It is well known that all components that constitute the MetS are also risk factors for DM and also prediabetes, namely, impaired fasting glucose and/or impaired glucose intolerance. We think that some of the study participants may still have overt glucose dysregulation or DM without implementation of the glucose tolerance test. In addition, matching the groups for glucose and body mass index may not be enough to make clear comparisons at this point, because DM and even glucose intolerance is itself a predictor of presence of insulin resistance. Moreover, plasma insulin and adipocytokine levels differ according to the degree of glucose dysregulation.[7,8] The same subject is also true for hypertension and dyslipidemia.[9,10]

We think all these points make the resultant comparisons and correlations questionable. Therefore, we would like to ask the authors whether they can present some new results by categorizing the subjects with NASH according to metabolic confounders such as impaired glucose tolerance, dyslipidemia, and blood pressure. This may provide the readers clearer information about the effect of Orlistat on the inflammatory mechanism in NAFLD.

TEOMAN DOGRU[1]
CEMAL NURI ERCIN[1]
ILKER TASCI[2]
SERKAN TAPAN[3]
ZEKI YESILOVA[1]
AHMET UYGUN[1]
[1] *Department of Gastroenterology*
[2] *Department of Internal Medicine and*
[3] *Department of Biochemistry*
Gulhane Medical School
Ankara, Turkey

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Potential conflict of interest: Nothing to report.

Reply:

We thank Dogru et al. for their thoughtful comments on our article describing the results of a pilot study using orlistat as a potential adjunct to achieve weight loss in calorically restricted patients with nonalcoholic steatohepatitis (NASH). We agree that the histopathological changes identified as NASH are the result of complex and poorly understood relationships among lipotoxicity, insulin resistance, and dysregulated adipokines and cytokines. As summarized in their letter, a number of much larger studies have already examined these relationships. We feel that analyzing subgroups of a small cohort such as the one we enrolled in this trial would not contribute to what has already been described. We agree that some of our patients may have had previously unrecognized diabetes, and this seems to be a frequent finding when patients with NASH are studied closely during study enrollment. However, we are not aware of any data to suggest that patients with diabetes respond differently to weight reduction than those without diabetes