RESPONSE TO COMMENT ON TANG ET AL.

Effects of Insulin Glargine and Liraglutide Therapy on Liver Fat as Measured by Magnetic Resonance in Patients With Type 2 Diabetes: A Randomized Trial. Diabetes Care 2015;38:1339–1346

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Shan et al. (1) raise important points regarding treatment duration, sample size, mean values of magnetic resonance (MR)-based biomarkers, and severity of liver steatosis in our study (2).

The 12-week duration of our study was justified by the exploratory aim to compare two second-line injectable treatment alternatives on liver steatosis as measured by MR-based techniques. To acknowledge that the study duration was too short to address the long-term effects on liver steatosis, we preemptively stated in our discussion that "a longer study would have favored GLP-1 agonist therapy in terms of body weight loss and, possibly, a concomitant reduction in the liver fat fraction" (2).

Anticipating liver steatosis changes based on body weight projections alone may not be sufficient, as suggested by the weak correlation ($r = 0.342$) between changes in body weight and mean liver fat fraction. To highlight potential discrepancies between fat depots, we observed that insulin glargine was associated with a decrease in liver fat fraction despite stable body weight. Our results are consistent with prior studies that have shown liver fat fraction reduction with insulin therapy even in the presence of body weight gain. Lingvay et al. (3) reported a 45% relative liver fat fraction decrease despite weight gain of 2.2 kg during a 12-week study. Even in a 7-month study, Juurinen et al. (4) reported a 3% absolute liver fat fraction decrease despite a 3-kg weight gain in their cohort.

In our study, sample size calculated a priori was small but sufficient to detect a 5% absolute difference in fat fraction with a 5% deviation estimate (two-tailed $\alpha = 0.05$, $\beta = 0.20$). These estimates were based on similar publications that used MR spectroscopy, as cited in our article. Postexperiment calculations would expectedly reveal insufficient power if smaller differences or larger deviations were observed. This should be taken into account in future studies.

The difference in mean values of some baseline characteristics between the two tables in our article (2) is attributed to rounding differences, whereas the difference in baseline MR spectroscopy and waist measurement obtained by arithmetic mean (Table 1) and linear mixed model (Table 2) is attributed to imbalance between subjects available before and after therapy.

In this study, patients were included based on inadequate control under metformin monotherapy or combined with another oral antidiabetes medication. Patients were not included or excluded on the basis of liver steatosis severity. In future studies, reliance on MR-based techniques (5), which provide the advantage of quantification along a continuous measure (as opposed to grading along an ordinal scale with histopathology), could help address the hypothesis of Shan et al. (1) that decrease in liver fat fraction may be more important with higher baseline levels of steatosis.

The take-home messages from this correspondence would be to consider a longer observation period for assessing effect on liver fat fraction, to increase sample size and anticipate higher drop-out rate in patients receiving liraglutide, to monitor liver fat fraction independently from total body weight, and to consider measuring

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MR-based biomarkers for continuous measure of liver fat fraction.

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