



## Reply to “Crashing NASH in Patients Listed for Bariatric Surgery”

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We thank [G. Koek et al.] for their letter in response to our paper. They have brought up a valid discussion point regarding the use of pre-operative very low calorie diet (VLCD), and whether short-term pre-operative weight loss significantly alters the degree of liver inflammation or nonalcoholic steatohepatitis (NASH) observed on peri-operative biopsy specimens.

In our study, pre-operative weight loss did not appear to significantly influence nonalcoholic fatty liver disease (NAFLD) status. We did not report these results, due to the focus of our study, the heterogeneity of VLCD prescription and patient compliance, as well as the non-significance of our findings. Our cohort had a varied amount of pre-operative weight loss, measured as weight change between pre-anesthesia clinic and surgery. There were no significant differences between those with normal liver biopsies, non-NASH NAFLD and NASH/steatofibrosis (percentage weight loss:  $2.9 \pm 5.2\%$  vs  $4.0 \pm 3.6\%$  vs  $3.4 \pm 4.5\%$  respectively,  $p = 0.536$ ).

Other studies have shown amelioration of nonalcoholic fatty liver disease (NAFLD) and NASH with weight loss. Serial imaging studies using magnetic resonance imaging and spectroscopy showed that short-term use of VLCD-reduced liver volume and intrahepatic fat content [1, 2]. It is important to note that these diagnostic tests reflect the effects on steatosis only, and do not measure inflammation (and therefore NASH). Biopsy is the only current reliable diagnostic method for determining degree of inflammation, ballooning and fibrosis [3]. Longer-term weight loss studies, such as

those by Lassailly et al [4] and Vilar-Gomez et al [5], have utilized repeat liver biopsies and reported improvements in NASH prevalence and severity. Again, these changes occurred after progressive, substantial, and sustained weight loss over a 1-year duration.

The effects of very short-term (i.e., 2 weeks) VLCD on NASH have not been well studied, as this requires pre- and post-treatment liver biopsies to accurately diagnose NASH. The risks of liver biopsy are not insignificant [6]. Performing serial biopsies in such close temporal proximity to assess short-term benefits of rapid weight loss is questionable, particularly given the dubious longevity of short-term weight loss and its benefits [7]. Despite significant research into refining diagnostic tools for NASH, current non-invasive tests are inadequate, particularly in obese populations [8, 9]. Accurate non-invasive tools are greatly anticipated, and would be instrumental in research aimed at answering questions such as this.

Another consideration is the difficulty in discerning the influence of pre-operative weight loss on NAFLD prevalence, in the face of a multitude of other factors. Differing anthropometric, metabolic, and baseline patient characteristics, as well as sampling and histological inter-observer variability [10], likely account for variation in reported NAFLD severity. In our study [11], major and significant contributing factors to disease prevalence were body mass index (BMI) as well as metabolic disease. Those with NASH or steatofibrosis had a significantly higher BMI ( $50.5 \text{ kg/m}^2$  vs  $43.6\text{--}45.5 \text{ kg/m}^2$ ,  $p = 0.001$ ), with substantially more metabolic abnormalities. In fact, the baseline characteristics of the patient cohort reported by [Authors] are very similar to our subgroup with normal liver biopsies and simple steatosis.

Overall, we cannot comment on the effects of pre-operative weight loss on NASH, as we have not conducted pre- and post-weight loss liver biopsies and certainly, this was not the focus of our study. We concur however that pre-operative weight loss is vital for peri-operative safety and surgical access. We agree that pre-operative intervention(s) should be identified and considered when conducting NAFLD research in bariatric populations.

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## Compliance with Ethical Standards

**Disclosures** Geraldine Ooi, Paul Burton, and Wendy Brown report being affiliated with The Centre for Obesity Research and Education. The center has received funding for research purposes from Allergan and Apollo Endosurgery, the manufacturers of the LapBand™. The grant is not tied to any specific research project, and neither Allergan nor Apollo Endosurgery have control of the protocol, analysis, and reporting of any studies. The center also receives a grant from Applied Medical towards educational programs.

Wendy Brown reports financial support for a bariatric surgery registry from the Commonwealth of Australia, Apollo Endosurgery, Covidien, Johnson and Johnson, Gore and Applied Medical. Since initial submission of this paper, she has also received a speaker's honorarium from Merck Sharpe and Dohme and a speaker's honorarium and fees from participation in a scientific advisory board from Novo Nordisk. The bariatric registry and the honorariums are outside of the submitted work.

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