retrospective (46%) and prospective (28%) cohorts. We think the lower frequency of serum for antinuclear antibody positivity we found compared with the data from Volta et al is much less relevant among our findings. We studied only a small group of celiac disease patients as a control group, and our study was not designed to evaluate this aspect of celiac disease.

Regarding the frequency of autoimmune disorders associated with NCWS, we underline that ours is the first single-center study designed to provide data on this point. The discrepancy between the frequency we observed (24% vs 29%) and that reported in the Italian multicenter study (14%)\(^2\) could be owing to the heterogeneity of the patients included in that study. In a brilliant editorial Lebwohl and Lefler have written, “in critical moments, men sometimes see exactly what they wish to see,”\(^3\) and it is evident that at the moment there is no agreement in the scientific community not only about NCWS pathogenesis, but even on its real existence. Although relevant in many ways, the Italian multicenter study probably suffered from the “negative preconception” of those centers skeptical about NCWS, a preconception that was amplified by the confuse diagnostic criteria and the lack of a double-blind challenge as diagnostic method.

In contrast, it is certain that NCWS should be considered a heterogeneous condition as we first suggested some years ago,\(^4\) in which different kinds of patients with different pathogenesis of their wheat-related symptoms are still lumped together. Since the beginning of our interest in NCWS, we have focused on the patients who had an “immunologic characteristic”: food allergy in infancy, associated atopic disease, eosinophil or lymphocyte infiltration in the intestinal mucosa, and so on.\(^5\) Consequently, in the Rorschach test of sorts\(^6\) we view a strong immunologic basis for NCWS pathogenesis, but in the discussion section we warned readers about this possible bias of a highly selected study population.

In conclusion, we feel that the “NCWS field” still remains a “fertile crescent” for research\(^6\) and in this respect, understanding the immunological path is the most promising, as suggested by our recent data,\(^3\) especially considering the possible role of amylase/trypsin inhibitors as activators of innate immunity.\(^7,8\)

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References

High False-Negative Rate for Nonalcoholic Steatohepatitis in Extreme Obesity

Dear Editor:
The article by Lassailly et al\(^1\) reported on 1540 patients who had undergone a bariatric surgery procedure that included 1489 cases in whom intraoperative liver biopsies were obtained. Surprisingly, histologic nonalcoholic steatohepatitis (NASH) was diagnosed in only 115 of the 1489 cases (7.7%). In the Discussion, this unusually low rate of disease is given only sparse attention. In addressing limitations of the study the authors state that, “the prevalence of NASH was lower than in other studies, but this could be explained by the absence of any selection of enrolled patients among surgical candidates.” This is not an adequate explanation for results that are significantly discrepant from other published studies of liver biopsy data from patients with extreme obesity undergoing bariatric surgery procedures. A review\(^2\) of such studies found the prevalence of nonalcoholic fatty liver disease (NAFLD) and NASH averaged 90% and 37%, respectively, consistent with our own recent data.\(^3\) Rather than an absence of selection criteria as an underlying cause, the results presented are more likely highly biased owing to a lack of representative sampling from an extremely high false-negative detection rate, that is, many individuals from a cohort with extreme obesity expected to manifest NASH were excluded. We believe that sampling error from the use of needle biopsies versus the much larger size of wedge biopsies commonly used in other studies contributes to the disparity in the NASH prevalence reported. Wedge biopsies have consistently been shown to be superior to needle biopsies for assessment of liver histology primarily because substantially more tissue is obtained for evaluation.\(^4,5\)

In addition, the lack of correction for multiple comparisons is highly problematic and further weakens the
analysis. These factors render the conclusions drawn from the data uncertain and in need of replication.

**References**


**Conflicts of interest**

The authors disclose no conflicts.

**Reply.** We thank Drs Gerhard, Still, and DiStefano for their interest in our paper. These authors mainly draw attention to the prevalence of nonalcoholic steatohepatitis (NASH) in our prospective cohort of bariatric surgery patients (7.7% of NASH in 1540 obese patients), which was lower than in their own experience.

In their study, Gerhard et al2 based the diagnosis of NASH on the concomitant presence of steatosis and lobular inflammation. This is a misuse of the Brunt classification which does not follow the expert recommendation.3–5 The Brunt score can be applied only after the pathologist has established the diagnosis of NASH, based on a large spectrum of histologic features associated with nonalcoholic fatty liver disease (NAFLD).5 Among these histologic lesions, hepatocellular ballooning is the most challenging and important feature for the diagnosis of NASH.3 Not following this step-by-step procedure, authors may overestimate the prevalence of NASH. To support this explanation and confirm that the NAFLD activity score (NAS) has been misused, we have detail the proportion of patients with a NAS of ≥3 (probable NASH), a NAS of ≥5 (definite NASH), or a formal histologic diagnosis of NASH in our cohort (Table 1). As previously reported and like in most studies that have used NAS as a diagnosis tool for the diagnosis of NASH in bariatric patients, the proportion of patients with NAS ≥3 was around 30%.6

Furthermore, differences in the design of published studies on hepatic histology during bariatric surgery likely contribute to the great heterogeneity in the prevalence of NASH (25%–98%) reported in the literature.7 The prospective design of our study, based on the systematic histologic evaluation of the liver at time of surgery, is the best approach to accurately explore prevalence of NASH by avoiding the potential bias of overestimation.

We also disagree with Gerhard et al about the alleged superiority of wedge liver biopsy on needle biopsy. The authors based this assumption on 1 study with a sample size of only 10 patients.8 Furthermore, this statement contradicts the experts’ recommendations for the quality of liver biopsy in the context of NASH. Guidelines for clinical trial design in NASH were published in 2011,9 and clearly state that the quality of the histologic data is affected by several factors, including the sampling technique (“intraoperative techniques may induce inflammation”), and recommend the use of “needle biopsy of at least 16-gauge diameter.”9 The timing of the liver biopsy during the operative procedure also could impact the rate of NASH observed in some series. In our study, liver biopsy was performed in the first 10 minutes of the operative procedure to avoid the artifact related to a prolonged exposure of the liver to get away from an artificial increase of liver inflammation (see for more details the Methods section of our work).

Finally, the rigorous and conservative methodologic approach of our study makes us confident in the fact that bariatric surgery led to disappearance of NASH in 85% of cases as observed by previous studies.10,11

**Table 1.** Distribution of Patients in the Lille Bariatric Cohort According to Nonalcoholic Fatty Liver Disease Activity Score (NAS) and Nonalcoholic Steatohepatitis (NASH) Diagnosis

<table>
<thead>
<tr>
<th>Score</th>
<th>Overall Cohort (%)</th>
<th>Biopsy-Proven NASH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAS ≥ 3</td>
<td>29.9</td>
<td>30.5</td>
</tr>
<tr>
<td>NAS ≥ 5</td>
<td>6.7</td>
<td>87.5</td>
</tr>
<tr>
<td>NASH</td>
<td>7.7</td>
<td>—</td>
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</tbody>
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