Improvements in hepatic steatosis, obesity, and insulin resistance in adults with nonalcoholic fatty liver disease after the primary obesity surgery endoluminal 2.0 procedure

ABSTRACT

Background The primary obesity surgery endoluminal 2.0 (POSE 2.0) procedure involves full-thickness gastric body plications to narrow the stomach using durable suture anchor pairs. We evaluated POSE 2.0 as a treatment strategy...
for nonalcoholic fatty liver disease (NAFLD) in patients with obesity.

Methods Adults with obesity and NAFLD were prospectively allocated based on their preference to undergo POSE 2.0 with lifestyle modification or lifestyle modification alone (control). Primary end points were improvement in controlled attenuation parameter (CAP) and resolution of hepatic steatosis at 12 months. Secondary end points included %total body weight loss (%TBWL), change in serum measures of hepatic steatosis and insulin resistance, and procedure safety.

Results 42 adult patients were included (20 in the POSE 2.0 arm and 22 in the control arm). At 12 months, POSE 2.0 significantly improved CAP, whereas lifestyle modification alone did not ($P<0.001$ for POSE 2.0; $P=0.24$ for control). Similarly, both resolution of steatosis and %TBWL were significantly higher with POSE 2.0 than with control at 12 months. Compared with controls, POSE 2.0 significantly improved liver enzymes, hepatic steatosis index, and aspartate aminotransferase to platelet ratio at 12 months. There were no serious adverse events.

Conclusion POSE 2.0 was effective for NAFLD in patients with obesity, with good durability and safety profile.
Recruitment of adults with NAFLD and obesity

- POSE 2.0 + Lifestyle n = 20
- 1 loss to follow-up
- Lifestyle n = 22
- CAP, liver elastography, labs, weight, and questionnaires

- POSE 2.0 + Lifestyle n = 19
- 1 loss to follow-up
- Lifestyle n = 22
- CAP, liver elastography, labs, weight, and questionnaires

- POSE 2.0 + Lifestyle n = 19
- 1 loss to follow-up
- Lifestyle n = 21
- CAP, liver elastography, labs, weight, and questionnaires

Baseline 6 months 12 months

Fig. 1 Study schematic and flow chart. NAFLD, nonalcoholic fatty liver disease; CAP, controlled attenuation parameter.

were applied accordingly. Continuous variables were compared using Student’s t test or the Wilcoxon signed-rank test, either for dependent or independent samples, as appropriate. Categorical variables were compared using Fisher’s exact test. We employed the repeated-measures analysis of variance or the Kruskal–Wallis test for within-group comparisons of more than two means. If we found statistically significant differences, we ran post hoc analyses using the general linear model for adjusted pairwise comparisons. We employed IBM SPSS Statistics for Windows (IBM Corp., Armonk, New York, USA) and considered \( P < 0.05 \) as statistically significant.

Results

A total of 20 adults with median age of 30.5 years (IQR 26.5–38.2) and median BMI of 38.0 kg/m² (IQR 36.8–39.0) elected to undergo POSE 2.0, and 22 adults were included in the control arm and followed lifestyle modification alone (median age 41.0 years [IQR 30.0–49.0]; BMI 38.0 kg/m² [IQR 36.2–40.0]) (Fig. 1). There were no significant demographic differences between groups (see Table 1 in the online-only Supplementary material). The mean procedure duration was 38.9 minutes (SD 4.9), and there were no serious adverse events.

Measures of hepatic steatosis

In the POSE 2.0 arm, mean CAP improved from 322.7 dB/m (95% CI 322.7 to 336.8) at baseline, 6, and 12 months, respectively (\( P < 0.001 \)). In contrast, the control arm presented CAP of 338.6 dB/m (95% CI 322.3 to 354.9), 326.8 dB/m (95% CI 312.4 to 341.3), and 320.9 dB/m (95% CI 304.9 to 336.8) at baseline, 6, and 12 months, respectively (\( P = 0.24 \)). The mean change in CAP was \(-88.8\) dB/m (95% CI \(-110.2\) to \(-67.3\)) in the POSE 2.0 arm vs. \(-17.6\) dB/m (95% CI \(-35.7\) to \(-0.5\)) in the control arm (\( P < 0.001 \)). There were no significant changes in liver stiffness (Table 1).

Among patients undergoing POSE 2.0, 6/19 (31.6%) achieved S0 steatosis at 6 months, and 10/19 (52.6%) achieved S0 steatosis at 12 months. None of the patients undergoing POSE 2.0 experienced progression in steatosis during the study period. In contrast, none of the control patients achieved S0 steatosis at 6 or 12 months. Resolution of steatosis occurred more frequently with POSE 2.0 than with lifestyle modification alone at both 6 (\( P = 0.02 \)) and 12 months (\( P < 0.001 \)) (Fig. 2). All patients experienced stable or improved fibrosis stages in both arms at 6 and 12 months, except for one patient in the POSE 2.0 arm who achieved stable or improved fibrosis stages in both arms at 6 and 12 months.
arm who experienced worsening of fibrosis from 4.8 kPa (F0–F1) to 8.3 kPa (F3) at 12 months (▶ Table 1).

Throughout follow-up, POSE 2.0 patients presented significant improvements in liver biochemical parameters of NAFLD, including aspartate aminotransferase, alanine aminotransferase, and HSI and APRI scores (▶ Table 2). In contrast, only the HSI score improved in the control arm. Nevertheless, this change was more significant in the POSE 2.0 arm than in the control arm (P=0.002) (▶ Table 2). Neither group had any significant changes in lipid profile or thyroid function (Table 2s).

Measures of obesity, insulin resistance, and patient-reported outcomes

In the POSE 2.0 arm, mean BMI improved from 37.9 kg/m² (95% CI 36.7 to 39.1) at baseline to 31.6 kg/m² (95% CI 29.1 to 33.5) at 12 months (P<0.001) (Table 3s). Mean BMI also improved in the control arm, from 38.4 kg/m² (95% CI 37.1 to 39.7) at baseline to 36.8 kg/m² (95% CI 35.1 to 38.3) at 12 months (P=0.01). At 12 months, the mean BMI was statistically lower in the POSE group (P<0.001). The mean %TBWL was 18.0 (95% CI 15.1 to 20.9) at 6 months and 17.5 (95% CI 12.2 to 23.0) at 12 months in the POSE 2.0 arm compared with 4.5 (95% CI...
### Table 2  Laboratory outcomes of primary obesity surgery endoluminal 2.0 (POSE 2.0) versus control.

<table>
<thead>
<tr>
<th>Variable</th>
<th>POSE 2.0: Comparison of variables between baseline, 6 months, and 12 months (mean, 95%CI)</th>
<th>Control: Comparison of variables between baseline, 6 months, and 12 months (mean, 95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (n=20)</td>
<td>6 months (n=19)</td>
</tr>
<tr>
<td></td>
<td>Within group P value</td>
<td>Change at 12 months</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>28.75 (24.81 to 32.69)</td>
<td>18.18 (15.95 to 20.41)</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>40.90 (29.23 to 52.57)</td>
<td>21.53 (16.53 to 26.52)</td>
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<tr>
<td>ALP, U/L</td>
<td>62.73 (56.71 to 68.76)</td>
<td>62.80 (55.41 to 67.96)</td>
</tr>
<tr>
<td>Platelets, ×10&lt;sup&gt;3&lt;/sup&gt;/µL</td>
<td>261.45 (227.45 to 295.45)</td>
<td>268.37 (236.41 to 299.85)</td>
</tr>
<tr>
<td>HSI score</td>
<td>49.96 (47.55 to 52.37)</td>
<td>41.23 (37.65 to 44.81)</td>
</tr>
<tr>
<td>APRI score</td>
<td>0.29 (0.16 to 0.24)</td>
<td>0.20 (0.16 to 0.24)</td>
</tr>
<tr>
<td>FIB-4 score</td>
<td>0.63 (0.48 to 0.78)</td>
<td>0.57 (0.44 to 0.70)</td>
</tr>
<tr>
<td>HOMA-IR score</td>
<td>4.02 (2.42 to 5.62)</td>
<td>3.07 (2.41 to 5.74)</td>
</tr>
</tbody>
</table>

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; HSI, hepatic steatosis index; APRI, AST to platelet ratio; FIB-4, fibrosis-4; HOMA-IR, homeostatic model assessment for insulin resistance.

1 Repeated-measures analysis of variance.
2 General linear model: P <0.01 for baseline vs. 6 months and P < 0.05 for baseline vs. 12 months.
3 Independent sample t test.
4 Paired samples Student’s t test.
5 Wilcoxon signed-rank test for paired samples.
2.0 to 7.0) and 4.0 (95%CI 2.0 to 7.0) at 6 and 12 months, respectively, in the control arm. At 6 and 12 months, the %TBWL was significantly higher in the intervention group than in the control group (P<0.001). In the POSE 2.0 arm, 100% and 73.7% achieved ≥10%TBWL at 6 and 12 months, respectively, compared with 18.2% and 23.8% in the control arm. In the POSE 2.0 arm, 68.4% and 57.9% achieved ≥15%TBWL at 6 and 12 months, respectively, compared with 0% and 4.8% in the control arm.

POSE 2.0 patients experienced improvements in glycated hemoglobin, insulin, and 2-hour postprandial glucose level, and a trend toward improvement in the homeostatic model assessment for insulin resistance score (P=0.07). No changes in insulin resistance and glucose homeostasis were observed in the control arm (Table 4s).

Patients in the POSE 2.0 arm presented an overall improvement in their Three-Factor Eating Questionnaire 18 scores, driven by an improvement in the uncontrolled eating subscore (Table 5s); we observed no improvements in the questionnaire scores of patients following lifestyle modification alone. Patients in the POSE 2.0 arm showed improvement in the bloating subscores of the Gastroparesis Cardinal Symptom Index questionnaire, but no other significant changes were documented (Table 6s).

Discussion

This prospective, single-center, pragmatic study represents the first prospective assessment of the POSE 2.0 procedure in the management of NAFLD and obesity. Patients undergoing POSE 2.0 achieved notable and superior improvements in sonographic and biochemical measures of hepatic steatosis, obesity, and insulin resistance compared with a similar cohort of adults motivated to lose weight through high-intensity lifestyle modification alone.

Endoscopic sleeve gastroplasty, a similar gastric remodeling procedure, has shown promising results in NAFLD management [5, 6, 11, 12], mirroring the results from our study [5]. Intragastric balloons have similarly demonstrated improvements in patients with NAFLD by multiple measures, including histologic activity [13, 14], transaminases [13–15], imaging-based hepatic steatosis [15], and serum glucose and insulin [13, 15]. The current study adds prospective controlled evidence to support the use of endoscopic bariatric and metabolic therapies such as POSE 2.0 for NAFLD management, as the majority of our interventional patients reached the critical threshold of ≥10%TBWL associated with histologic steatohepatitis resolution and regression of fibrosis [3, 16]. Of note, one POSE 2.0 patients had worsened fibrosis from F0–F1 to F3 at 1 year, which indicates that liver surveillance is warranted.

Mechanisms of NAFLD improvement are understood to involve weight-dependent and weight-independent pathways, with the latter pathway likely to involve insulin resistance, inflammation, and incretin imbalances, among others [4]. The POSE 2.0 procedure is a restrictive gastric remodeling technique that affects appetite and results in metabolic improvements through weight-loss-dependent pathways [7]. Thus, future management can combine this procedure with small-intestinal endoscopic bariatric and metabolic therapies and or metabolically active pharmacotherapies, such as glucagon-like peptide 1 receptor agonists in tandem or in sequence as a chronic disease management paradigm for NAFLD [17].

One strength of this study is its pragmatic real-world design. A frequent limitation of randomized clinical trials assessing weight loss interventions is that patients are randomly allocated to a particular intervention that may not be their preference, limiting generalizability and affecting compliance. Our pragmatic design permitted patients who were highly motivated to lose weight through lifestyle means to self-allocate to the control arm, further validating the robust differences in outcomes favoring POSE 2.0 over lifestyle modification alone [8].

One major limitation of this study is the lack of histologic assessment. Although NAFLD is a prevalent diagnosis, the subset of patients with NASH and liver fibrosis is an elevated risk for progression and overall mortality [18]. As NASH is a histologic diagnosis, recognizing this at-risk subset can only be achieved with liver biopsy. Nevertheless, liver biopsies have the limitations of sampling errors and invasiveness. In NAFLD, liver biopsies are not commonly used clinically, as reflected in published endoscopic and surgical articles using an approach similar to ours [5]. Moreover, we could further mimic real-world scenarios, reduce invasiveness, and increase patient compliance by not using liver biopsies for research purposes only. Our primary outcome, CAP, is a widely used, reproducible, practical biomarker for identifying and stratifying steatosis, with an area under the curve of 0.87 for ≥S1, 0.77 for ≥S2, and 0.70 for ≥S3 [19]. HSI has high sensitivity (93%) and specificity (92%) for NAFLD, and the relevance of APRI in NAFLD is shown by its correlation with mortality [20]. Furthermore, nearly 75% of patients in the POSE 2.0 arm achieved ≥10%TBWL, the threshold of weight loss linked to NASH resolution [3], suggesting that POSE 2.0 is likely to benefit patients with NASH and simple steatosis in the context of metabolic disease. Finally, the degree of engagement and commitment could not be measured, which limits to some extent the generalizability of our results.

A separate limitation of this study is that most patients did not have elevated liver stiffness at baseline. While the goal of such interventions would be to address NAFLD before it reaches advanced stages, those with advanced fibrosis represent a population at high risk for progression to cirrhosis and thus warrant further attention. Finally, given that most improvements in NAFLD were correlated with amelioration in obesity-related outcomes, it is unclear whether POSE 2.0 would be helpful for nonobese NAFLD patients.

In conclusion, our data show that the POSE 2.0 procedure was safe and effective in treating patients with NAFLD and obesity. Further studies are required to elucidate its role in subsets of patients with NASH, the physiologic mechanisms of NAFLD improvement, and the efficacy and safety for individuals with advanced fibrosis.
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Competing Interests

B.K. Abu Dayyeh reports consultant roles with Endogencx, Endo-TAGSS, Metamodix, and BFkW; consultant and grant/research support from USGI, Apollo Endosurgery, Spatz Medical, Cairn Diagnostics, Aspire Bariatrics, Boston Scientific; Speaker roles with Olympus, Johnson and Johnson; and speaker and grant/research support from Medtronic, Endogastric solutions. A.C. Storm reports institutional research grants from Boston Scientific, Entersense, Endogencx; consulting fees from Olympus; consulting fees and research grants from Endo-TAGSS, and Apollo Endosurgery; and participation in Data Safety Monitoring Board with GI Dynamics, and ERBE. M. Alkhattery, B. Rappaka, D.B. Maselli, D.M. Abboud, V.O. Brunaldi, T. Mahmoud, R. Cházi, F. Abdul Razzak, K. Gala, J. Joudah, F. Housen, S. Al Qadi, and E.J. Vargas declare that they have no conflict of interest.

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Clinical trial

 Trial Registration: ClinicalTrials.gov | Registration number (trial ID): NCT05611567 | Type of study: Prospective, open-label, single center

References