Endoscopic duodenal-jejunal bypass liner rapidly improves plasma parameters of nonalcoholic fatty liver disease

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BRIEF COMMUNICATION

Endoscopic Duodenal–Jejunal Bypass Liner Rapidly Improves Plasma Parameters of Nonalcoholic Fatty Liver Disease

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Bariatric surgery reduces nonalcoholic fatty liver disease (NAFLD). We investigated the effects of duodenal–jejunal bypass liner (DJBL), nonsurgical bariatric device, on plasma parameters of NAFLD. Seventeen obese subjects with type 2 diabetes received the DJBL for 24 weeks. Before, during, and after DJBL implantation, we determined plasma levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyltransferase (γ -GT), albumin, caspase-cleaved cytokeratin-18 (CK-18), and liver fatty acid-binding protein (L-FABP). At baseline, subjects had increased levels of AST (35 ± 4 IU/L), ALT (54 ± 5 IU/L), and γ -GT (66 ± 14 IU/L), compared with healthy individuals; subjects' mean concentrations of caspase-cleaved CK-18 and L-FABP were 214.4 ± 35.6 U/L and 29.3 ± 2.6 ng/mL, respectively. Three months after implantation of DJBL, all NAFLD-related parameters had decreased from baseline (AST, 28 ± 3 IU/L; ALT, 32 ± 2 IU/L; γ -GT, 44 ± 7 IU/L; caspase-cleaved CK-18, 140.6 ± 16.3 U/L; and L-FABP, 18.2 ± 1.5 ng/mL; all $P < .05$). After 6 months, levels of ALT and γ -GT had further decreased (ALT, 28 ± 2 IU/L and γ -GT, 35 ± 5 IU/L), whereas levels of AST, caspase-cleaved CK-18, and L-FABP had stabilized ($P =$ not significant). Six months after DJBLs were removed, levels of ALT (37 ± 3 IU/L), γ -GT (42 ± 5 IU/L), and caspase-cleaved CK-18 (124.5 ± 12.5 U/L) were still reduced ($P < .05$), whereas AST and L-FABP had returned to near baseline levels ($P =$ not significant). Therefore, in obese subjects, DJBL reduces plasma parameters of NAFLD. **ClinicalTrials.gov, Number: NCT00985114.**

Keywords: Insulin Resistance; Intestine; Stomach; Steatosis.

Recently, a nonsurgical bariatric technique, the duodenal–jejunal bypass liner (DJBL) (GI Dynamics, Lexington, MA), was developed. The initial purpose of the DJBL was to treat obesity.¹ Remarkably, this device turned out to not only lead to significant weight loss but also to rapid improvement of type 2 diabetes.^{2,3} Because both conditions are important risk factors for nonalcoholic fatty liver disease (NAFLD)^{4,5} and previous research with surgical bariatric techniques has revealed beneficial effects on NAFLD,^{6–9} we hypothesized that DJBL treatment would also have a favorable impact on NAFLD. We therefore investigated the effect of DJBL treatment on plasma parameters that have been linked to NAFLD. Changes in aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyltransferase (γ -GT), liver fatty acid-binding

protein (L-FABP), caspase-cleaved cytokeratin-18 (CK-18), and albumin in obese subjects with type 2 diabetes before, during, and after DJBL treatment are reported.

Methods

Subjects

Seventeen subjects with obesity and type 2 diabetes were included in the study by the Maastricht University Medical Center, Maastricht, and the Atrium Medical Center Parkstad, Heerlen, the Netherlands. Inclusion criteria were age 18–65 years, body mass index (BMI) 30–50 kg/m², duration of type 2 diabetes <10 years, and glycosylated hemoglobin 7.5%–10.0%. Main exclusion criteria were alcohol consumption >1 unit/day for women or >2 units/day for men, weight loss >4.5 kg within 12 weeks before screening, use of weight loss medication or anti-inflammatory drugs, history of inflammatory diseases or other known liver diseases than NAFLD, and exclusion criteria regarding DJBL compatibility. The study was approved by the Medical Ethics Committee of each center and conducted according to the revised version of the Declaration of Helsinki (October 2008, Seoul). Written informed consent was obtained before study participation.

Duodenal–Jejunal Bypass Liner Treatment

Subjects were treated with the DJBL for 24 weeks. The DJBL was delivered and retrieved endoscopically as described previously.¹ Subjects were provided a standard of care nutritional counseling program, which suggested a regular diet with a maximum of 1200 kcal for women and 1500 kcal for men that was liquid for the first week after DJBL placement. Dietary adaptations were made during follow-up if necessary.

Study Design

Subjects were studied on 4 occasions: within 1 month before the start of the study (D0), 3 and 6 months after

Abbreviations used in this paper: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CK-18, cytokeratin-18; DJBL, duodenal–jejunal bypass liner; γ -GT, gamma-glutamyltransferase; L-FABP, liver fatty acid-binding protein; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

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Table 1. Baseline Characteristics of the Study Population

	D0, baseline	M3, treatment	M6, treatment	M12, after treatment	Reference limit
Weight (kg)	116.0 ± 5.8	105.3 ± 5.5	103.3 ± 5.5	106.7 ± 6.1	
BMI (kg/m ²)	37.0 ± 1.3	33.6 ± 1.2	32.9 ± 1.2	34.3 ± 1.5	
AST (IU/L)	35 ± 4	28 ± 3	23 ± 2	34 ± 3	Male <35; female <30
ALT (IU/L)	54 ± 5	32 ± 2	28 ± 2	37 ± 3	Male <45; female <35
γ-GT (IU/L)	66 ± 14	44 ± 7	35 ± 5	42 ± 5	Male <55; female <40
L-FABP (ng/mL)	29.3 ± 2.6	18.2 ± 1.5	20.2 ± 1.6	29.5 ± 3.1	
CK-18 (U/L)	214.4 ± 35.6	140.6 ± 16.3	149.2 ± 23.1	124.5 ± 12.5	

NOTE. Data are shown as mean ± standard error of the mean.

implantation of the DJBL (M3 and M6, respectively), and again 6 months after explantation of the DJBL (M12). The baseline visit included physical examination and history taking. At all study visits, body weight was determined, and fasting venous blood samples were collected (BD Vacutainer EDTA tube; BD Diagnostics, Erembodegem-Aalst, Belgium). Samples were immediately cooled, centrifuged, and stored at -80°C until further analysis.

Plasma Parameters

Plasma levels of AST, ALT, γ-GT, albumin, and glycosylated hemoglobin were determined routinely at the Department of Clinical Chemistry at the Maastricht University Medical Center. Reference limits can be found in Table 1.

Recent reports indicate that plasma levels of caspase-cleaved CK-18 reflect hepatocyte apoptosis and are closely related to NAFLD severity.¹⁰⁻¹³ We therefore determined this parameter by using an enzyme-linked immunosorbent assay (caspase-cleaved CK-18: M30 Apoptosense ELISA; Peviva AB, Bromma, Sweden). In addition, an enzyme-linked immunosorbent assay was used to determine plasma L-FABP concentrations (L-FABP ELISA, provided by Hycult Biotechnology, Uden, the Netherlands).

Statistical Analyses

Statistical analyses were performed by using GraphPad Prism 5.0 (La Jolla, CA). Longitudinal changes were tested by using Wilcoxon signed rank test. A *P* value <.05 was considered statistically significant. Data are presented as mean and standard error of the mean.

All co-authors had access to the study data and reviewed and approved the final manuscript.

Results

Duodenal–Jejunal Bypass Liner Treatment Results in Significant Weight Loss

At baseline, subjects were aged 51 ± 2 years, and the majority of subjects were male (14 of 17). Additional baseline characteristics of the study subjects and subsequent changes are shown in Table 1.

Three months after DJBL implantation, body weight had decreased from 116.0 ± 5.8 to 105.3 ± 5.5 kg, corresponding with an excess weight loss of 25.2% ± 3.1% and a BMI reduction of 3.4 ± 0.4 kg/m² (*P* < .01). After 24 weeks at the time of device explantation, weight had further decreased to 103.3 ± 5.5 kg, resulting in a total weight loss of 12.7 ± 1.3 kg, corresponding to an excess weight loss of 29.8% ± 3.5%

and a BMI reduction of 4.1 ± 0.4 kg/m² (*P* < .01). Six months after explantation of the device (M12), body weight had increased slightly to 106.7 ± 6.1 kg but was still significantly decreased when compared with baseline (*P* < .01). BMI and excess weight loss were 34.3 ± 1.5 kg/m² and 19.9% ± 3.9%, respectively.

Established Clinical Plasma Liver Parameters Decrease After Duodenal–Jejunal Bypass Liner Implantation

To gain insight into the potential effects of DJBL treatment on NAFLD, several established clinical plasma parameters that have been linked to NAFLD^{14,15} were evaluated. At baseline, mean plasma AST level was 35 ± 4 IU/L (Figure 1A). In addition, plasma ALT and γ-GT were above the upper reference limits (54 ± 5 IU/L and 66 ± 14 IU/L, respectively; Figure 1B and C).

Three months after DJBL implantation, plasma AST had decreased from 35 ± 4 to 28 ± 3 IU/L (*P* < .05). AST levels continued to decrease, and 6 months after implantation the mean AST level was 23 ± 2 IU/L (*P* < .01). Furthermore, a significant reduction in ALT levels was observed from 54 ± 5 at baseline to 32 ± 2 IU/L after 3 months and to 28 ± 2 IU/L after 6 months (both *P* < .01). The γ-GT levels also decreased from 66 ± 14 IU/L at baseline to 44 ± 7 and 35 ± 5 IU/L at 3 and 6 months after DJBL implantation, respectively (both *P* < .01).

Six months after explantation of the device at month 12, AST had increased and returned to baseline levels (34 ± 3 IU/L, *P* = .63). In contrast, ALT and γ-GT levels were still diminished (ALT: 37 ± 3 IU/L, γ-GT: 42 ± 5 IU/L; both *P* < .01). Albumin levels of all subjects, data not shown, stayed within the reference range at all times.

Duodenal–Jejunal Bypass Liner Treatment Rapidly Reduces Plasma Markers of Liver Damage and Liver Apoptosis

The effect of DJBL treatment on NAFLD-related liver damage, reflected by a marker of hepatocyte injury, L-FABP,¹⁶ is shown in Figure 1D. Plasma L-FABP levels decreased from 29.3 ± 2.6 ng/mL at baseline to 18.2 ± 1.5 ng/mL after 3 months of treatment (*P* < .01). Until month 6, plasma L-FABP levels stayed at a lower level (20.2 ± 1.6 ng/mL, *P* < .05). At month 12, six months after device removal, L-FABP levels had returned to baseline level (29.5 ± 3.1 ng/mL, *P* = .85).

We next determined the effect of DJBL treatment on hepatocyte apoptosis, as indicated by plasma caspase-cleaved CK-18 concentrations. Changes in caspase-cleaved CK-18

Figure 1. Effects of DJBL treatment on AST, ALT, γ -GT, L-FABP, and caspase-cleaved CK-18. (A) Plasma AST levels at baseline (D0) and 3 (M3) and 6 (M6) months after implantation of DJBL and 6 months after removal of DJBL (M12). (B) Plasma levels of ALT at these time points, whereas (C) shows plasma concentrations of γ -GT. (D) Plasma L-FABP levels at these time points. (E) Plasma levels of caspase-cleaved CK-18 at these time points. * $P < .05$; ** $P < .01$.

showed a similar pattern as the changes in L-FABP concentration (Fig. 1E). At baseline, caspase-cleaved CK-18 levels were 214.4 ± 35.6 U/L. After 3 months, the levels had decreased to 140.6 ± 16.3 U/L ($P < .05$). During the remainder of the study, the decrease in caspase-cleaved CK-18 concentrations stabilized (149.2 ± 23.1 U/L at month 6 and 124.5 ± 12.5 U/L 6 months after DJBL removal; $P = .12$ and $P < .01$, respectively).

Discussion

Bariatric surgery effectively treats obesity and also leads to improvement of NAFLD.⁶⁻⁹ However, bariatric surgery is invasive and associated with complications, causing a hesitant

attitude in patients toward this type of surgery.¹⁷ Therefore, there is need for less invasive devices like the DJBL. The DJBL has been shown to be safe and effective in treating obesity and different aspects of metabolic syndrome, including type 2 diabetes.¹⁻³ The effect of DJBL treatment on plasma parameters that are associated with NAFLD was investigated in the current study. We report that plasma liver parameters improve after duodenal-jejunal exclusion by DJBL.

In the current study with a minimally invasive bariatric technique, we chose not to expose our subjects to repeated invasive liver biopsies, but instead, plasma parameters reflecting NAFLD were used. Our data show that clinical plasma liver parameters decreased after DJBL implantation. Normalization of AST, ALT, and γ -GT levels occurred in almost all subjects.

Dixon et al¹⁸ have shown that a decrease in γ -GT and AST levels is associated with improvement of liver histology in NAFLD patients after weight loss by bariatric surgery. This advocates for improvement of NAFLD by DJBL treatment in our subjects. In addition, DJBL treatment resulted in diminished plasma levels of L-FABP, a small intracellular protein that rapidly leaks out of damaged hepatocytes into the circulation.¹⁶ A similar response pattern was observed for caspase-cleaved CK-18. Caspase-cleaved CK-18 is a protein generated during hepatocyte apoptosis, a prominent pathologic feature of nonalcoholic steatohepatitis (NASH),¹⁹ the more severe form of NAFLD. Plasma levels of caspase-cleaved CK-18 positively correlate with NAFLD severity, independently predicting the presence of NASH.¹⁰⁻¹³ In our subjects, a decrease in caspase-cleaved CK-18 was observed after initiation of the DJBL treatment, potentially indicating NASH regression. Taken together, all plasma parameters associated with NAFLD improved after DJBL implantation. Interestingly, 6 months after DJBL removal, ALT, γ -GT, and caspase-cleaved CK-18 were still diminished when compared with baseline, suggesting a sustained effect of the DJBL treatment.

Notably, NAFLD severity was probably limited in our study population, which was characterized by modest elevation of plasma liver parameters.^{10,13} The subjects are therefore probably in an early, still reversible stage of NAFLD, when cure through intervention is still possible.²⁰

In conclusion, a rapid improvement of all NAFLD parameters after initiation of DJBL treatment was observed. It appears that the DJBL reverses liver parameters associated with NAFLD at least temporarily. Further research evaluating longer-term follow-up and/or histologic changes of the liver is needed to fully elaborate the potential positive effect of DJBL treatment on NAFLD.

References

- Schouten R, Rijs CS, Bouvy ND, et al. A multicenter, randomized efficacy study of the EndoBarrier Gastrointestinal Liner for presurgical weight loss prior to bariatric surgery. *Ann Surg* 2010; 251:236-243.
- Escalona A, Pimentel F, Sharp A, et al. Weight loss and metabolic improvement in morbidly obese subjects implanted for 1 year with an endoscopic duodenal-jejunal bypass liner. *Ann Surg* 2012; 255:1080-1085.
- de Jonge C, Rensen SS, Verdam FJ, et al. Endoscopic duodenal-jejunal bypass liner rapidly improves type 2 diabetes. *Obes Surg* 2013; 23:1354-1360.
- Angulo P. Obesity and nonalcoholic fatty liver disease. *Nutrition Reviews* 2007;65:63.
- Lazo M, Clark JM. The epidemiology of nonalcoholic fatty liver disease: a global perspective. *Semin Liver Dis* 2008;28:339-350.
- Blackburn GL, Mun EC. Effects of weight loss surgeries on liver disease. *Semin Liver Dis* 2004;24:371-379.
- Mattar SG, Velcu LM, Rabinovitz M, et al. Surgically-induced weight loss significantly improves nonalcoholic fatty liver disease and the metabolic syndrome. *Ann Surg* 2005;242:610-620.
- Mathurin P, Hollebecque A, Arnalsteen L, et al. Prospective study of the long-term effects of bariatric surgery on liver injury in patients without advanced disease. *Gastroenterology* 2009;137:532-540.

- Rabl C, Campos GM. The impact of bariatric surgery on nonalcoholic steatohepatitis. *Semin Liver Dis* 2012;32:80-91.
- Wieckowska A, Zein NN, Yerian LM, et al. In vivo assessment of liver cell apoptosis as a novel biomarker of disease severity in nonalcoholic fatty liver disease. *Hepatology* 2006;44:27-33.
- Diab DL, Yerian L, Schauer P, et al. Cytokeratin 18 fragment levels as a noninvasive biomarker for nonalcoholic steatohepatitis in bariatric surgery patients. *Clin Gastroenterol Hepatol* 2008;6:1249-1254.
- Feldstein A, Wieckowska A, Lopez A, et al. Cytokeratin-18 fragment levels as noninvasive biomarkers for nonalcoholic steatohepatitis: a multicenter validation study. *Hepatology* 2009;50:1072-1078.
- Shen J, Chan HL, Wong GL, et al. Non-invasive diagnosis of nonalcoholic steatohepatitis by combined serum biomarkers. *J Hepatol* 2012;56:1363-1370.
- Wieckowska A, McCullough AJ, Feldstein AE. Noninvasive diagnosis and monitoring of nonalcoholic steatohepatitis: present and future. *Hepatology* 2007;46:582-589.
- Neuschwander-Tetri BA, Clark JM, Bass NM, et al. Clinical, laboratory and histological associations in adults with nonalcoholic fatty liver disease. *Hepatology* 2010;52:913-924.
- Pelsters MM, Morovat A, Alexander GJ, et al. Liver fatty acid-binding protein as a sensitive serum marker of acute hepatocellular damage in liver transplant recipients. *Clin Chem* 2002; 48:2055-2057.
- Afonso BB, Rosenthal R, Li KM, et al. Perceived barriers to bariatric surgery among morbidly obese patients. *Surg Obes Relat Dis* 2010; 6:16-21.
- Dixon JB, Bhathal PS, O'Brien PE. Weight loss and non-alcoholic fatty liver disease: falls in gamma-glutamyl transferase concentrations are associated with histologic improvement. *Obes Surg* 2006; 16:1278-1286.
- Feldstein AE, Canbay A, Angulo P, et al. Hepatocyte apoptosis and fas expression are prominent features of human nonalcoholic steatohepatitis. *Gastroenterology* 2003;125:437-443.
- Smith BW, Adams LA. Non-alcoholic fatty liver disease. *Crit Rev Clin Lab Sci* 2011;48:97-113.

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Conflicts of interest

These authors disclose the following: Dr Bouvy received an open research grant from GI dynamics. Dr Greve received an open research grant from and is a consultant for GI Dynamics, and received support for travel to meetings for the study or other purposes from GI dynamics. The remaining authors disclose no conflicts.

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