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Duodenal Switch Has No Detrimental Effects on Hepatic Function and Improves Hepatic Steatohepatitis after 6 Months

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Background: Nonalcoholic steatohepatitis (NASH) is a common histological finding on liver biopsy in morbidly obese patients. The condition, although benign, can progress to cirrhosis and liver failure. We investigated the effect of the duodenal switch (DS) operation on hepatic function and architecture, specifically hepatic steatosis and NASH.

Methods: Between November 1999 and June 2004, 697 DS operations were performed for the treatment of morbid obesity. A Tru-Cut needle liver biopsy was routinely performed during the DS operation. Liver function tests were drawn preoperatively for AST and ALT, and again postoperatively at 6, 12 and 18 months and yearly thereafter. Repeat Tru-Cut liver biopsy was performed on all patients (n = 78) who underwent a second intra-abdominal operation for any indication ≥6 months postoperatively. The pathologist evaluated the 2 sets of liver biopsies in a blinded fashion. The hepatic adipose tissue content and the degree of hepatitis were compared in these patients.

Results: A transient worsening of the AST (13% of the baseline value, *P*<.02) and ALT (130-160% of the baseline value, *P*<.0001) levels was found at 6 months after the DS operation. Normal levels were achieved by 12 months postoperatively. A progressive improvement of about 3 grades in severity of NASH and a 60% improvement in hepatic steatosis, were seen by 3 years after the DS operation.

Conclusion: DS improves both hepatic steatosis and its resulting inflammation. No detrimental effects on hepatic function were noted after 6 months.

Key words: Morbid obesity, biliopancreatic diversion and duodenal switch, nonalcoholic hepatic steatosis, hepatic function

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Introduction

Hepatic steatosis is prevalent in morbidly obese patients. The resulting inflammation, also referred to as *nonalcoholic steatohepatitis* (NASH), is a common histological finding on liver biopsy in morbidly obese patients.[1-5]

The duodenal switch (DS) operation for the treatment of morbid obesity results in resolution of hepatic steatosis.[6] For analysis, routine liver biopsy during bariatric operations has been advocated.[2,4,7] In general, DS is considered a safe operation that provides optimal long-term weight loss.[8,9] DS has also been found to be a safe choice for patients who have failed to lose weight with other bariatric procedures.[10]

Papadia et al,[11] performing the Scopinaro biliopancreatic diversion (BPD), found mild elevation of liver function tests peaking at 2 months postoperatively, decreasing afterwards, and remaining normal after 1 year. Recently, Baltasar et al,[12] performing the DS operation (a variant of the BPD), reported 10 patients (out of a total of 470) who showed clinical hepatic impairment <2 months postoperatively, which resolved in 9 of these patients by the 4th postoperative month. We studied the course of liver function tests (LFTs), hepatic steatosis and NASH after DS.

Methods

Study Method

We conducted a retrospective analysis of the charts of 697 patients who underwent DS from 1999-2004 at Delano Regional Medical Center. A Tru-Cut nee-

dle liver biopsy was performed routinely during the DS surgery. In addition, a repeat Tru-Cut biopsy was performed in all patients who underwent a second intra-abdominal operation for any indication. Liver biopsies were stained with hematoxylin & eosin and Masson's trichrome stains. Also, LFTs – plasma aspartate aminotransferase (AST) and alanine aminotransferase (ALT) – were assayed on all patients before DS and at 6, 12 and 18 months after the DS and then yearly thereafter.

The technique for DS is well described.[6,9,13] We have also described our technique for the stapled Roux-en-Y anastomosis.[14] The length of the common channel varied at 50-100 cm, depending on the BMI, sex, age, co-morbidities, and activity level of the patient.

In the 78 patients who had a second intra-abdominal operation ≥6 months after their DS operation, Tru-Cut needle liver biopsy was performed, and the pathology slides were reviewed in a blinded fashion by one expert pathologist.

Histological Review

NASH severity was graded from I to V, based on the subjective assessment of extent and pattern of the inflammation present (Table 1). The pre- and the postoperative pathology slides, stained with H & E, were reviewed. Each slide was assigned a case study number, and all information regarding patient identification and the time-frame was blinded to the pathologist, who was an expert in GI and hepatic histopathology. The amount of steatosis was reported as the percentage of hepatic cells replaced by fat per high power field. Change at each time interval was analyzed for statistical significance compared to the preoperative baseline, using paired Student's *t*-test.

Three patients with conditions affecting the LFTs independent of obesity were excluded from the study from the very beginning of the data analysis.

Table 1. Grading system used for degree of NASH

Grade I	-	None
Grade II	-	Mild
Grade III	-	Moderate
Grade IV	-	Severe: Zonal Distribution
Grade V	-	Severe: Diffuse Distribution

Results

A total of 697 patients underwent DS at our institution from 1999 to 2004. Of these, 128 were males and 569 were females. BMI ranged from 35.0 to 100.9, with an average BMI of 50.5. Age ranged from 16 to 69 years, with an average of 43.5 (Table 2).

Three patients were excluded from the study because of conditions affecting the LFTs. Two were on methotrexate therapy for severe rheumatoid arthritis, and one patient had pre-existing cirrhosis from viral hepatitis and distant alcohol intake.

A subset of the above population consisting of 78 patients underwent a second intra-abdominal operation for various indications (Table 3). The most common indication for the second operation was ventral hernia repair. One patient was found to have a pancreatic mass, which was found to be pancreatic cancer on

Table 2. Demographics

Study Material	No. of Patients
Total DS operations	697
Patients undergoing a later operation*	78
Age	
• Average	43.5
• Range	16-69
Sex	
• Males: Females	128:569
BMI	
• Average	50.51
• Range	30.5-100.9

*≥6 months after DS

Table 3. Indications for a second surgery after the DS operation

Indications	No. of Patients
Ventral hernia repair	69
Small bowel obstruction	2
Pancreatic mass	1
Revision of the common channel	
• Shortened	1
• Lengthened	4
Feeding tube placement	1
Total no. of patients undergoing a later abdominal operation (6 months – 3 years after DS)	**78**

biopsy, and that patient underwent a pylorus-preserving Whipple procedure. A feeding jejunostomy tube was placed in one patient for poor oral intake.

The time interval between the DS surgery and the second surgery ranged from 6 months to 3 years (Table 4).

Effect on Liver Function

The serum AST and ALT levels in all patients, measured at the preoperative visit, and postoperatively at 6, 12, 18, 24 and 36 months and yearly thereafter, were plotted against time after the DS along with the BMI (Figure 1). The minimum and maximum values, as well as the mean, median and standard deviation (SD) for the AST and ALT levels are shown in Tables 5 and 6 respectively. Statistical significance was assessed using paired Student *t*-test for the values at each time period against the baseline values. The largest rise from the baseline was seen at 6 months, and a return to baseline value was evident by 12 months. The increase at 6 months in AST was 130% of the baseline value ($P<.02$) and in ALT was 160% of the baseline value ($P<.0001$). Also, the trend in AST levels corresponded well with the ALT levels. Changes at 1 year and afterwards were not significant and remained within the normal range. Importantly, no patient had any sign or symptom during this entire time period that could be attributed to the transient elevation in LFTs.

Effect on Liver Architecture

The average change in the percentage of steatosis and in the grade of NASH (defined in Table 1) in the postoperative "second operation" biopsy sample is shown in Figures 2 and 3. The data are also given in Table 7. An example of the reduction in the hepatic steatosis and reduction in NASH on the histology slides is shown in Figures 4 and 5.

Table 4. Number of months after DS operation that a second abdominal operation was performed

Duration between DS and second operation	No. of Patients
6 months	9
12 months	24
18 months	24
24 months	15
36 months	6

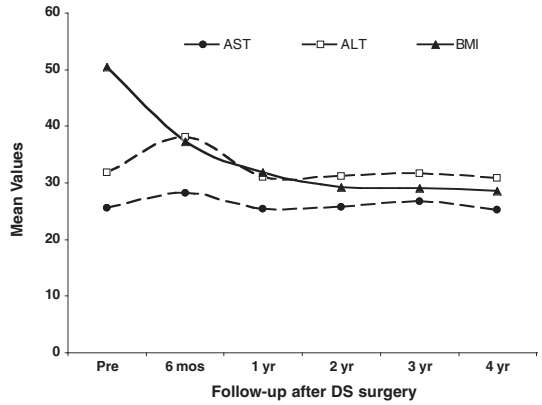

Figure 1. Changes in AST, ALT and BMI after the DS operation. LFTs had a slight increase at 6 months, but were normal at and beyong 12 months. Variations at 12 months and beyond were not statistically different from the baseline level.

Most patients had a NASH grade between moderate to severe at the time of DS operation, whereas by the 2nd year postoperatively, most patients had dropped their NASH grade to mild to moderate levels. By the 3rd year, some patients had complete resolution of the NASH. Similarly, most patients had hepatic steatosis of 50-70% before DS surgery, which improved to 20-30% by 2 years. Analysis of both data shows that the percentage of steatosis and of inflammation in the liver architecture improved progressively after the DS operation. This progressive improvement was found to be statistically significant for both hepatic steatosis and NASH.

Interestingly, there was a slight worsening of the hepatic inflammation at the 6-month interval after DS, which corresponded to the elevation in the LFTs at that time. No such increase was seen in the hepatic steatosis. Both results were statistically significant when analyzed by paired *t*-test.

Discussion

Morbidly obese patients show a high prevalence of hepatic steatosis and steatohepatitis.[1,2] Elevation in common LFTs (AST and ALT) has been found to correspond to mild worsening in hepatic pathology in the early months following BPD and DS. The tran-

Table 5. Analysis of pre- and postoperative AST levels

	Pre	6 mos	1 yr	2 yr	3 yr	4 yr
Mean	25.6	28.2	25.4	25.7	26.7	25.2
Median	22	24	21	22	22	20.5
SD	13.4	21	24.6	16.6	16.8	12.9
Minimum	5	11	8	11	10	14
Maximum	102	305	446	174	142	70
Corresponding BMI	50.5	37.2	31.8	29.2	29	28.5
P-value	-	**0.02**	0.4	0.1	0.3	0.4

Table 6. Analysis of pre- and postoperative ALT levels

	Pre	6 mos	1 yr	2 yr	3 yr	4 yr
Mean	31.8	38	31	31.1	31.6	30.9
Median	26	32	26	27	26	25
SD	19.5	26.7	22.1	19.2	18.9	19.5
Minimum	3	10	6	8	10	14
Maximum	150	288	259	169	150	112
Corresponding BMI	50.5	37.2	31.8	29.2	29	28.5
P-value	-	**0.0001**	0.1	0.3	0.5	0.3

sient elevation of LFTs in the first 6 months after DS was minimal and not harmful. A return to the normal range was evident by 1 year after DS, and continued as relatively constant weight was attained.[11,12]

We also found that DS improves liver architecture. Progressive improvement was seen in the hepatic steatosis as the postoperative period increased after the DS operation. A mild worsening in the severity of NASH was found at 6 months after the DS, which corresponded to the worsening in the LFTs. Once again, this deterioration was mild, transient and clinically non-harmful to the patient. Rapid and progressive improvement was observed at and after 12 months after the DS operation, and continued beyond 3 years.

The transient postoperative hepatic dysfunction may be related to early rapid weight loss, a degree of protein malnutrition and lack of hepatotrophic factors, and the effect of high levels of mobilized circulating free fatty acids.[11] We stress to our patients a high-protein nutritional diet, with supplements including iron, calcium, and fat-soluble vitamins after the DS.[15]

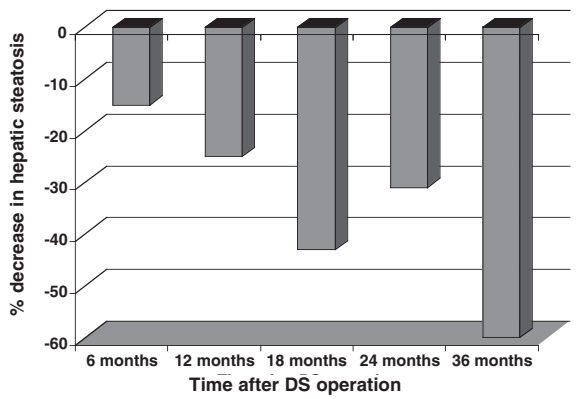

Figure 2. Reduction in percentage of hepatic steatosis with time after DS operation (*P*<0.0001 at 12, 18, 24 and 36 months compared to baseline).

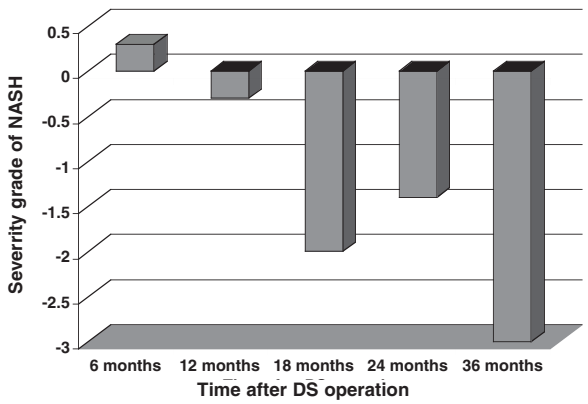

Figure 3. Reduction in NASH grade after the DS operation (*P*<0.001 at 18, 24 and 36 months) compared to the preoperative grade. Slight increase in NASH grade in 6-month period corresponds to slight worsening of LFTS at that time.

Table 7. Reduction in percentage of steatosis and in grade of NASH

Time Period after DS	Steatosis reduction		NASH grade reduction	
	Mean	SD	Mean	SD
6 months	-15	15	0.3	1.5
12 months	-25	19	-0.3	1.6
18 months	-43	14	-2	1
24 months	-31	7.4	-1.4	0.5
36 months	-60	7	-3	0.5

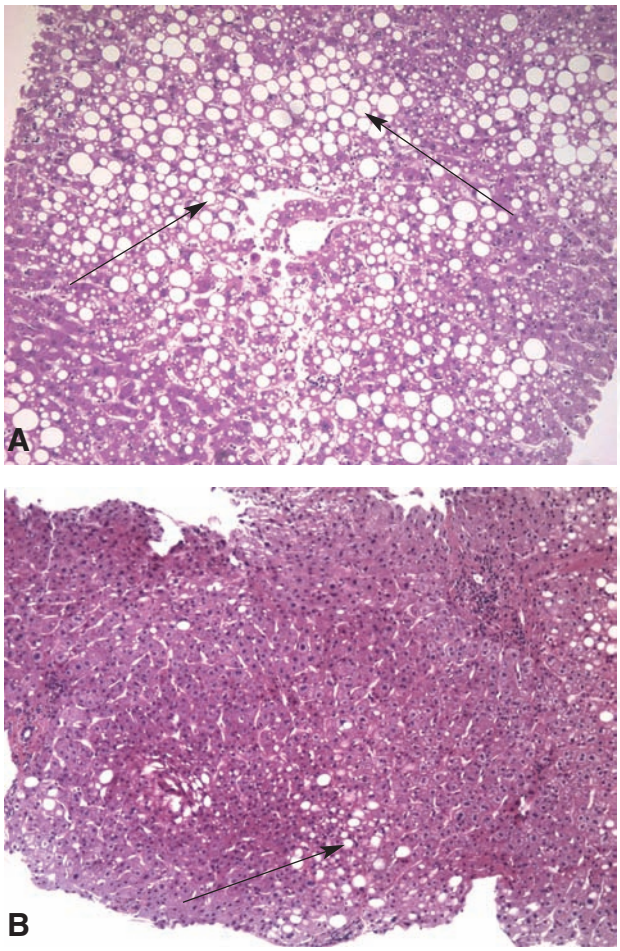

Figure 4. Photomicrographs of liver biopsies. **A.** Hepatic steatosis at time of DS surgery. **B.** Biopsy in same patient 2 years after DS surgery; note significant reduction in percentage of fat content (arrows). (H & E).

Because NASH has the potential to progress to cirrhosis and liver failure, and because BPD and DS have resulted in the resolution of NASH,[3,5,13] DS should have long-term benefit in reducing the occurrence of cirrhosis and liver failure in obese patients. We continue long-term follow-up.

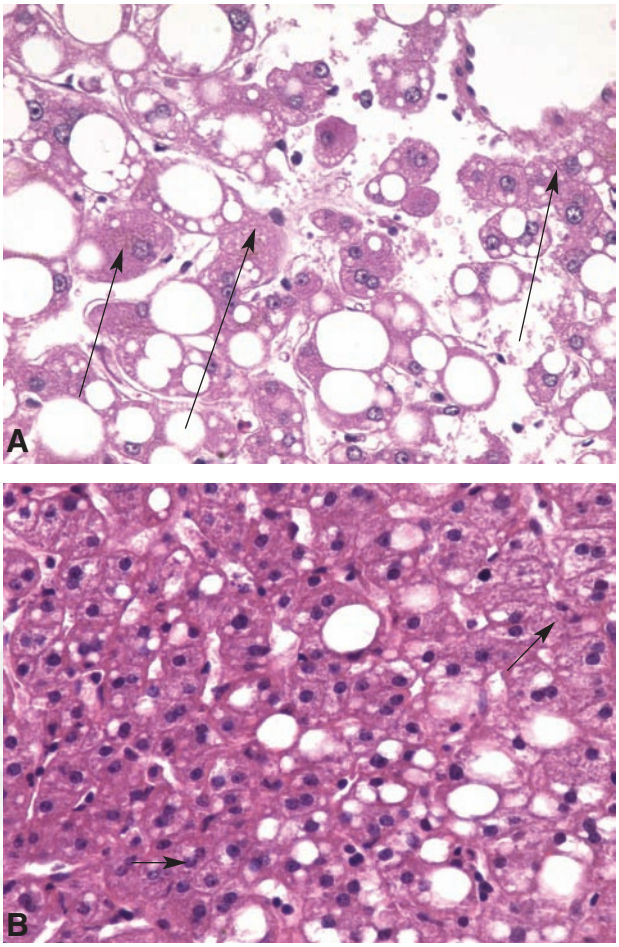

Figure 5. Photomicrographs of liver biopsies. **A.** NASH at time of DS surgery. **B.** Biopsy in same patient 2 years after DS surgery; note significant improvement in inflammation in the liver parenchyma. Arrows point to inflammatory cells (neutrophils and lymphocytes). (H&E).

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