



ORIGINAL ARTICLE

HSCRp as surrogate marker in predicting long term effect of bariatric surgery on resolution of non-alcoholic steatohepatitis



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Summary *Background:* Nonalcoholic steatohepatitis (NASH) is closely associated with obesity and is one of the important etiologies of hepatocellular carcinoma (HCC and liver failure). Bariatric surgery is proven to be effective in causing weight loss and improvement of NASH) but there is limited long term data.

Objectives: To identify the predictors of NASH in morbidly obese patients and evaluate long term data of bariatric surgery effects on NASH.

Methods: 308 bariatric patients (mean age 30.2 years old, body mass index (BMI) 45.0 kg/m²) with concurrent liver biopsy from 2003 to 2008 were included. We compared the clinical data between the NASH and non-NASH group and identify predictors of NASH in this cohort of patients. Remission of NASH was evaluated using the predictor of NASH.

Results: Prevalence of NASH was 43.8%. At baseline, the NASH and non-NASH groups both had similar age, BMI and sex ratio but the NASH group had significantly worse glycemic control, liver enzymes, triglycerides and uric acid. Highly sensitive-C Reactive Protein (HSCRp) level was identified as the only independent predictor of NASH. Ten years follow up (60.4% loss to follow up) showed good weight loss, resolution of co-morbidities and reduction of HSCRp. Patients with bypass surgery had better weight loss and lower levels of HSCRp. (HSCRp 0.2 ± 0.1 mg/dL vs. 0.8 ± 0.7 mg/dL, p = 0.009). than non-bypass group.

Conclusion: NASH is common in bariatric patients. HSCRp is the only independent predictor of NASH and can be used as a surrogate marker in predicting long term effect of Bariatric Surgery on resolution of non-alcoholic steatohepatitis Bypass procedure was better in resolution of NASH than non-bypass procedure.

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1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is characterized by abnormal fat accumulation in liver cells and is a major health concern worldwide.^{1,2} It is closely associated with obesity and is one of the important etiologies of hepatocellular carcinoma (HCC) and liver failure.³ The development process of NAFLD can start from simple steatosis (NAFLD) to non-alcoholic steatohepatitis (NASH) and finally leads to cirrhosis and HCC in the absence of excessive alcohol intake.^{3,4} NASH has a high prevalence of up to 30% in obese patients.^{5,6} Therefore, NASH is becoming an important co-morbidity of obese patients. Several studies have shown the improvement of NASH after bariatric surgery at short term.^{7–12} However there is limited long term data on effects of bariatric surgery on NASH. The aim of this study is to identify any independent pre-operative predictors for NASH and evaluate long term outcome of bariatric surgery in the treatment of NASH. We also would like to identify if there was any bariatric procedure that was better in resolving NASH compared to the other bariatric procedures.

2. Materials and methods

This study was performed with approval of Ethics Committee of the Min-Sheng General Hospital in Taiwan. There were 308 patients who underwent bariatric surgery and intra-operative liver biopsy from 2003 to 2008 for the study of prevalence and predictors of NASH in our previous studies.^{13,14} The degree of NAFLD in each biopsy was scored using the National Institute of Health – sponsored NASH Clinical Research Network NAFLD Activity Score (NAS)¹⁵ NAS score of ≥ 5 correlated with a diagnosis of NASH and biopsies with scores of < 3 were diagnosed as non-NASH.¹⁶ Each liver biopsy specimen had grades of steatosis, ballooning, mallory body, lobular and portal inflammation scored by a single pathologist. Liver fibrosis stage was assessed on a five stage score. Definition of NASH was not only defined on histology, but also with clinical history of non-alcoholic consumption and exclusion of viral hepatitis. We evaluated the basic demographic details, anthropometric measurements, laboratory results of the above 2 groups and identify predictors of NASH in this cohort of patients. Predictors of NASH from previous clinical studies were analyzed using logistic regression model. Long term clinical outcome data were prospectively obtained from patient records and followed up for 10 years. Laboratory tests included liver function test, fasting lipid profiles, fasting glucose profile, fasting insulin, C-peptide, and HbA1c. Annual follow up details recorded similar anthropometric measurements and laboratory test. Patients with NASH were then categorized according to the type of procedure they underwent and evaluated for any differences at baseline and long term outcome.

2.1. Statistical analysis

Data were expressed as mean \pm SD and percentages. Statistical analyses were performed using Chi-square test, Mann Whitney U tests and Student's *t*-test. Logistic regression was used to assess the significance of associations between ordinal or continuous predictors' variables. A *P*-value < 0.05 was considered statistically significant. SPSS statistical software (SPSS, Inc., Chicago, IL) was used for statistical analysis.

3. Results

3.1. NASH versus non-NASH

There were 308 patients with a male: female ratio of 1: 1.39. The mean age was 30.2 ± 8.8 years old; mean weight and BMI were 127.9 ± 21.7 kg and 45.4 ± 5.7 kg/m² respectively. There were 135 (43.8%) patients who had NASH (NAS score > 5) while 96 (31.1%) patients did not have NASH. (NAS score < 3). There was no statistical difference between the 2 groups at baseline in terms of age, weight, BMI and male: female ratio (Table 1). However, significant differences were found between the 2 groups in terms of pathological features of NAS score including steatosis, ballooning, lobular inflammation, portal inflammation, mallory body. The NASH group had a higher fibrosis stage than the non-NASH group (1.92 ± 0.88 vs. 1.52 ± 0.78 , $p = 0.002$). Comparing the laboratory values the NASH group had significantly worse fasting glucose control (117.5 ± 53.3 mg/dL vs. 97.6 ± 26.1 mg/dL, $p < 0.001$), triglycerides (194.7 ± 183.6 mg/dL vs. 135.9 ± 80.9 mg/dL, $p = 0.004$), uric acid (7.8 ± 2.0 mg/dL vs. 7.1 ± 1.7 mg/dL, $p = 0.007$), GOT (49.7 ± 33.1 U/L vs. 22.4 ± 15.7 U/L, $p < 0.001$), GPT (80.3 ± 59.3 U/L vs. 30.8 ± 22.2 U/L, $p < 0.001$), GGT (62.5 ± 42.8 U/L vs. 33.7 ± 23.8 U/L, $p < 0.001$) and HbA1c ($6.5 \pm 1.7\%$ vs. $5.9 \pm 1.0\%$, $p < 0.001$) than non-NASH group (Table 1).

3.2. Predictors

Using multivariate logistic regression analysis of clinical factors, HSCRp was the only independent clinical predictor of NASH. (HSCRp Odds Ratio 4.9, 95% CI: 1.4–17.4, $p = 0.013$). Evaluation of other factors such as age, BMI, GOT and GPT levels did not show any significant difference (Table 2).

3.3. Follow up

Mean BMI dropped from 45.4 kg/m² to 30.3 kg/m², 28.9 kg/m², 30.6 kg/m², 33.2 kg/m² at 1, 3, 5, 10 years after bariatric surgery. 122 patients (39.6%) were available for follow up at

Table 1 Comparison baseline patient characteristics prior to bariatric surgery.

	Non NASH(n = 96)	NASH(n = 135)	p value
Male: Female Ratio	1:1.53	1: 1.38	0.607
Age (years old)	29.1 ± 8.6	30.7 ± 8.9	0.171
BMI (kg/m ²)	45.8 ± 6.4	45.0 ± 5.7	0.275
Waist (cm)	127.0 ± 16.2	127.0 ± 13.0	0.995
Hip (cm)	137.7 ± 12.4	134.9 ± 11.3	0.081
W/H Ratio	0.92 ± 0.09	0.94 ± 0.08	0.063
Pathological Features			
- Steatosis	0.69 ± 0.57	2.35 ± 0.66	<0.001*
- Ballooning	0.96 ± 0.48	1.55 ± 0.54	<0.001*
- Lobular inflammation	0.94 ± 0.32	2.07 ± 0.71	<0.001*
- Portal Inflammation	0.64 ± 0.81	0.97 ± 0.85	0.008*
- Mallory Body	0.95 ± 0.52	1.25 ± 0.56	0.002*
Fibrosis Stage	1.52 ± 0.78	1.92 ± 0.88	0.002*
SBP (mmHg)	132.2 ± 16.6	134.9 ± 15.4	0.212
DBP (mmHg)	78.7 ± 12.1	82.0 ± 12.0	0.041*
Fasting Glucose (mg/dL)	97.6 ± 26.1	117.5 ± 53.3	<0.001*
T Cholesterol (mg/dL)	189.7 ± 35.2	195.3 ± 38.5	0.261
TG (mg/dL)	135.9 ± 80.9	194.7 ± 183.6	0.004*
UA (mg/dL)	7.1 ± 1.7	7.8 ± 2.0	0.007*
GOT (U/L)	22.4 ± 15.7	49.7 ± 33.1	<0.001*
GPT (U/L)	30.8 ± 22.2	80.3 ± 59.3	<0.001*
Albumin (g/dL)	4.3 ± 0.4	4.3 ± 0.3	0.036*
ALP (U/L)	68.8 ± 25.7	72.2 ± 20.0	0.373
WBC (/uL)	8.9 ± 2.7	8.9 ± 2.2	0.880
Hb (g/dL)	14.1 ± 1.7	14.3 ± 1.6	0.356
MCV (fL)	85.6 ± 8.2	85.4 ± 6.0	0.814
Insulin (uIU/ml)	22.0 ± 25.6	27.6 ± 23.1	0.089
HSCRP (mg/dL)	0.8 ± 0.7	0.9 ± 0.8	0.123
T Protein (g/dL)	7.4 ± 0.4	7.6 ± 0.5	0.027*
HDL-c (mg/dL)	47.0 ± 11.2	45.2 ± 18.4	0.387
HbA1c (%)	5.9 ± 1.0	6.5 ± 1.7	<0.001*
C Peptide (ng/ml)	5.3 ± 9.1	5.0 ± 2.9	0.781
GGT (U/L)	33.7 ± 23.8	62.5 ± 42.8	<0.001*

Data are presented as the Mean ± Standard Deviation; BMI: body mass index; W/H ratio: waist hip ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; T cholesterol: total cholesterol; TG: triglycerides; UA: uric acid; GOT: also known as Aspartate Aminotransferase (AST); GPT: also known as Alanine Aminotransferase (ALT); ALP: alkaline phosphatase; WBC: white blood cells; Hb: hemoglobin; MCV mean corpuscle volume; HSCRP: highly sensitive C-reactive protein (CRP); T Protein: total protein; HDL-c: high density lipoprotein, HbA1c: glycated hemoglobin; GGT: gamma-glutamyl transferase, P < 0.05.

10 years. There were no significant differences between NASH and non-NASH group in weight loss, BMI, EWL and % EWL at 10 years follow up (Table 3). Laboratory data at 10 years follow up showed that fasting glucose level, triglycerides, GOT, GPT, GGT and HbA1c have now become not significant between the 2 study groups (Table 3). The independent predictor of NASH, HSCRP remained low after surgery and remained so up to 10 years. Fig. 1 depicts the NASH and non-NASH groups change of HSCRP over 10 years.

3.4. Bypass versus non-bypass

Of the 135 patients who had NASH, 113 (83.7%) underwent single anastomosis (mini)gastric bypass procedure while 22 patients (16.3%) underwent non bypass procedures, of which 19 patients (14.1%) underwent laparoscopic adjustable bands and 3 patients (2.2%) underwent sleeve gastrectomy. There was no difference in basic characteristics

between the 2 groups; however there was better weight loss in the bypass group compared to the non-bypass group at 10 years follow up (46.2 ± 19. kg vs.17.1 ± 18. kg,

Table 2 Identifying the independent predictor of NASH prior to surgery.

Variable	Odds Ratio	95% CI	P value
HSCRP (mg/dL)	4.90	1.4–17.4	0.013*
Age (years old)	1.01	0.93–1.1	0.79
BMI(kg/m ²)	0.39	0.14–1.08	0.07
GOT (U/L)	1.05	0.98–1.13	0.218
GPT (U/L)	1.03	0.99–1.07	0.147

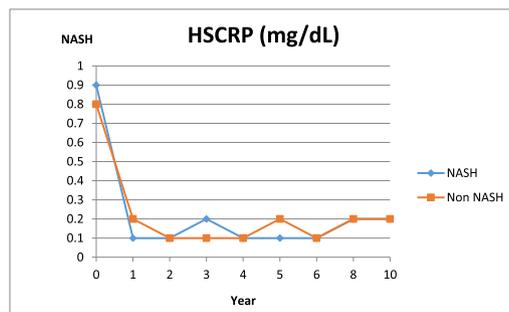
HSCRP: highly sensitive C-reactive protein (CRP); BMI: body mass index; GOT: also known as Aspartate Aminotransferase (AST); GPT: also known as Alanine Aminotransferase (ALT), *P < 0.05.

Table 3 Follow up of patients at 10 years.

	Non NASH(n = 41)	NASH(n = 81)	p value
10 years follow up			
Weight (kilogram)	87.8 ± 16.9	93.7 ± 25.0	0.877
BMI (kg/m ²)	32.7 ± 6.3	33.3 ± 8.8	0.938
Weight loss (kilogram)	37.8 ± 29.1	35.4 ± 19.3	1.000
%EWL (%)	53.0 ± 32.9	60.8 ± 21.6	0.837
%Weight Loss (%)	28.3 ± 19.4	29.9 ± 10.7	0.967
10 years follow up			
Fasting Glucose (mg/dL)	95.6 ± 22.6	98.1 ± 22.7	0.694
T Cholesterol (mg/dL)	205.4 ± 32.2	154.6 ± 24.1	0.004*
TG (mg/dL)	101.1 ± 69.2	56.4 ± 27.7	0.318
UA (mg/dL)	5.9 ± 1.0	5.5 ± 1.9	0.209
GOT (U/L)	21.4 ± 5.9	23.9 ± 9.8	0.902
GPT (U/L)	23.0 ± 8.4	23.9 ± 14.1	0.805
Albumin (g/dL)	4.4 ± 0.1	4.2 ± 0.3	0.318
ALP (U/L)	75.7 ± 27.0	65.7 ± 17.4	0.620
Insulin (uIU/ml)	7.5 ± 5.8	6.2 ± 3.5	1.000
HSCRP (mg/dL)	0.3 ± 0.2	0.2 ± 0.2	0.707
T Protein (g/dL)	7.1 ± 0.3	7.2 ± 0.5	1.000
HDL-c (mg/dL)	59.6 ± 13.9	50.3 ± 10.4	0.259
HbA1c (%)	5.9 ± 1.5	5.7 ± 0.7	0.536
C Peptide (ng/ml)	1.8 ± 1.0	1.7 ± 0.9	0.945
GGT (U/L)	20.1 ± 15.9	17.6 ± 10.1	0.902

Data are presented as the Mean ± Standard Deviation; BMI: body mass index; EWL: excess weight loss;; T cholesterol: total cholesterol; TG: triglycerides; UA: uric acid; GOT: also known as Aspartate Aminotransferase (AST); GPT: also known as Alanine Aminotransferase (ALT); ALP: alkaline phosphatase; HSCRP: highly sensitive C-reactive protein (CRP); T Protein: total protein; HDL-c: high density lipoprotein, HbA1c: glycated hemoglobin; GGT: gamma-glutamyl transferase, *P < 0.05.

$p < 0.001$) although they started from similar body weight. Both groups had similar clinical laboratory data at baseline. At 10 years, bypass group had significantly better total cholesterol (157.8 ± 32.5 mg/dL vs. 197.5 ± 22.9 mg/dL, $p = 0.006$), triglycerides (71.9 ± 42.5 mg/dL vs. 120.7 ± 28.5 mg/dL, $p = 0.001$), HSCRP (0.2 ± 0.1 mg/dL vs. 0.8 ± 0.7 mg/dL, $p = 0.006$), HbA1c ($5.5 \pm 1.1\%$ vs. $6.1 \pm 0.4\%$, $p = 0.006$) and GGT levels (14.4 ± 8.5 U/L vs. 33.0 ± 16.5 U/L, $p = 0.014$) than non-bypass group (Table 4).



Years (no. of patients)	0 (308)	1 (150)	2 (93)	3 (61)	4 (34)	5 (35)	6 (26)	7 (26)	8 (12)	9 (10)	10 (122)
NASH	0.9	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.2	0.1	0.2
Non NASH	0.8	0.2	0.1	0.1	0.1	0.2	0.1	0.1	0.2	0.2	0.2

Figure 1 Change of HSCRP over 10 years comparing NASH and Non-NASH groups.

4. Discussion

This study proves the long term efficiency of bariatric surgery in the resolution of NASH using HSCRP as a surrogate predictive marker. Several reports had shown a good resolution of NASH after bariatric surgery but most of them were short term studies.^{9,17,18} Raj et al⁹ repeated biopsies in 30 patients 6 months later and showed steatosis resolution in 19 patients and improvement in the remaining 11 patients. Taitano et al¹⁸ repeated liver biopsy at mean of 31 months after surgery and showed a 90% resolution of steatohepatitis and 53% fibrosis grade resolution. Mummadi et al¹⁷ reported 91.6% resolution rates of steatosis in 15 studies and 766 paired liver biopsies from a range of 2–111 months after bariatric surgery. Our study is the first study to investigate the long term remission of NASH in a large patient cohort using a surrogate marker.

Although liver biopsy is the only definite diagnosis of NASH, repeated liver biopsy after bariatric surgery is very difficult, especially in a large cohort. Therefore, clinical predictor of NASH is important for us to investigate the resolution of NASH in clinical practice. AST, ALT and BMI are commonly reported predictors of NASH in previous studies.^{18–20} Other important predictors include GGT, C-peptide, insulin, HOMA-IR, adiponectin, hypertension, Type 2 diabetes, age, waist/hip ratio, triglycerides.^{18,19} In this study HSCRP was the only predictor of NASH. Yoneda et al,²⁰ previously reported that HSCRP was a clinical predictor of NASH, similar to our study. He also found that HSCRP was associated with the severity of hepatic fibrosis.

Table 4 Clinical outcome in relation to type of surgery performed.

	NASH (n = 135)		P Value
	Bypass (n = 113)	Non bypass (n = 22)	
Baseline			
Weight (kilogram)	126.7 ± 22.3	131.0 ± 19.9	0.238
BMI (kg/m ²)	44.8 ± 5.6	45.8 ± 6.0	0.480
Fasting Glucose (mg/dL)	120.0 ± 55.0	105.0 ± 42.7	0.010
T Cholesterol (mg/dL)	193.4 ± 36.9	205.0 ± 45.7	0.249
TG (mg/dL)	197.1 ± 95.5	182.5 ± 104.5	0.948
UA (mg/dL)	7.8 ± 2.0	7.8 ± 1.7	0.661
GOT (U/L)	51.9 ± 34.8	38.3 ± 19.3	0.054
GPT (U/L)	83.1 ± 60.4	65.7 ± 52.1	0.059
Albumin (g/dL)	4.4 ± 0.3	4.3 ± 0.3	0.197
HSCRP (mg/dL)	0.9 ± 0.8	0.9 ± 0.7	0.734
HbA1c (%)	6.5 ± 1.7	6.3 ± 1.6	0.232
GGT (U/L)	64.6 ± 44.4	53.2 ± 34.2	0.242
10 Year follow up			
	n = 45	n = 9	
Weight (kilogram)	85.6 ± 15.2	113.0 ± 23.4	<0.001*
Weight loss (kilogram)	46.2 ± 19.9	17.1 ± 8.9	<0.001*
BMI (kg/m ²)	29.6 ± 4.1	42.2 ± 6.4	<0.001*
Fasting Glucose (mg/dL)	94.1 ± 33.2	92.3 ± 6.6	0.324
T Cholesterol (mg/dL)	157.8 ± 32.5	197.5 ± 22.9	0.006*
TG (mg/dL)	71.9 ± 42.5	120.7 ± 28.5	0.001*
UA (mg/dL)	5.2 ± 1.3	6.1 ± 1.9	0.346
GOT (U/L)	26.5 ± 12.9	28.2 ± 9.7	0.569
GPT (U/L)	27.7 ± 20.1	41.5 ± 32.3	0.456
Albumin (g/dL)	4.3 ± 0.4	4.1 ± 0.3	0.153
HSCRP (mg/dL)	0.2 ± 0.1	0.8 ± 0.7	0.009*
HbA1c (%)	5.5 ± 1.1	6.1 ± 0.4	0.006*
GGT (U/L)	14.4 ± 8.5	33.0 ± 16.5	0.014*

Data are presented as the Mean ± Standard Deviation; BMI: body mass index; EWL: excess weight loss;; T cholesterol: total cholesterol; TG: triglycerides; UA: uric acid; GOT: also known as Aspartate Aminotransferase (AST); GPT: also known as Alanine Aminotransferase (ALT); ALP: alkaline phosphatase; HSCRP: highly sensitive C-reactive protein (CRP); T Protein: total protein; HDL-c: high density lipoprotein, HbA1c: glycated hemoglobin; GGT: gamma-glutamyl transferase, *P < 0.05.

Yeniova et al²¹ also reported HSCRP as a strong predictor of NAFLD. Using HSCRP as the surrogate of NASH in this study, we have shown the improvement of NASH 10 years after bariatric surgery.

There are no differences in baseline characteristics between NASH and non-NASH group which implicate a genetic vulnerability in morbidly obese patients associated with NASH. Liver, glucose and cholesterol profiles were significantly worse in the NASH group compared to the non-NASH group before surgery. After surgery there was improvement in liver, glucose and cholesterol laboratory profiles in the NASH group, another indirect indicator of resolution of NASH. Of note there were no differences in both groups' baseline characteristics. These findings are similar to majority of studies investigating the effect of bariatric surgery and confirm a similar favorable outcome of resolution of NASH.^{11,12,22–28}

Another important finding in this study is that bypass surgery may provide a better resolution of NASH than non-bypass surgery in the long term. Although there are concerns with malabsorption procedures having high incidence of liver injury, our own data confirmed that bypass surgery had a better result in NASH resolution than non-bypass surgery. The reason for a better resolution of NASH may be due to a better weight loss profile in patients who underwent bypass procedure compared to a non-bypass

procedure. Although the bypass and non-bypass groups had similar background at baseline, after 10 years follow, the bypass group had significantly better weight loss, total cholesterol, triglycerides, HSCRP, HbA1c and GGT levels. There were similar findings in a recently published paper which showed superiority of bypass compared to adjustable band in the improvement of NAFLD.²⁹

Our study has several limitations related to the retrospective nature of the study and subsequent liver biopsies were not performed. It would be ideal if histological specimen could be obtained for all the patients post bariatric surgery to compare pre and post bariatric operation liver biopsies. However this would need Ethics board approval, in our opinion, will be very difficult because of the unnecessary risk of liver biopsies at multiple time intervals. Another limitation is that we do not know if these patients that we followed up were also receiving medications or other therapies that may have caused changes in their liver profile. However, we use HSCRP as the follow up indicator, which is not influenced by medications. HSCRP is highly correlated with obesity and metabolic syndrome; this could be a confounder in our study. Choice of bypass versus non bypass operation could also be due to patient/surgeon preference, comorbidities and hence leading to some selection bias in the paper.

5. Conclusion

NASH is a common co-morbidity in bariatric patients. HSCRCP is the independent pre-operative predictor of NASH and may be used as an assessment tool for the resolution of NASH without liver biopsy. HSCRCP can be used as a surrogate predictive marker of remission of NASH after bariatric surgery. Bypass operation is better in achieving long term resolution of NASH than non-bypass operation.

Conflict of interest statement

Study team does not have financial or other relationship to declare that could inappropriately bias the work, leading to a conflict of interest. All authors contributed to the manuscript. The manuscript has been read and approved by all authors.

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