Non-alcoholic steatohepatitis (NASH) and metabolic surgery in Asia

Palanivelu Praveen Raj[1], Siddhartha Bhattacharya[1], S. Saravana Kumar[1], Sandeep C. Sabnis[2], Ramakrishnan Parthasarathi[2], Parimala Devi Kumara Swamy[1], Chinnusamy Palanivelu[2]

[1]Department of Bariatric Surgery, [2]Department of Surgical Gastroenterology, GEM Hospital & Research Center, Coimbatore, India

Contributions: (I) Conception and design: P Praveen Raj, S Bhattacharya, C Palanivelu, R Parthasarathi, SC Sabnis; (II) Administrative support: C Palanivelu, R Parthasarathi, P Praveen Raj, S Bhattacharya; (III) Provision of study materials or patients: P Praveen Raj, S Bhattacharya, SS Kumar, PD Kumara Swamy, R Parthasarathi, C Palanivelu; (IV) Collection and assembly of data: S Bhattacharya, SC Sabnis, PD Kumara Swamy; (V) Data analysis and interpretation: S Bhattacharya, P Praveen Raj, SC Sabnis; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Palanivelu Praveen Raj. Department of Bariatric surgery, GEM Hospital & Research Center, Coimbatore, India. Email: drraj@geminstitute.in.

Abstract: Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide, as well as, in Asia. The incidence of NAFLD has been reported to range from 65% to 95% in patients undergoing bariatric surgery. Spectrum of NAFLD ranges from simple steatosis to non-alcoholic steatohepatitis (NASH) to fibrosis and cirrhosis. Liver biopsy is the gold standard for diagnosis of NAFLD. Other investigations including imaging of abdomen and liver function tests (LFTs) are not diagnostic *per se* but play a role in management. Treatment strategies include lifestyle modifications, pharmacotherapy and bariatric surgery. Bariatric surgery has shown promising results worldwide as well as in Asian patients. Asian literature shows that there is significant improvement in NAFLD after both restrictive and mal-absorptive procedures. Reversal of all features of NAFLD, NASH and fibrosis are reported after bariatric surgery. In conclusion, improvement of obesity associated NAFLD after bariatric surgery is well documented. Both restrictive as well as malabsorptive procedures are effective but NAFLD *per se* is not an indication for surgery.

Keywords: Non-alcoholic steatohepatitis (NASH); non-alcoholic fatty liver disease (NAFLD); bariatric surgery; metabolic surgery; Asia

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Epidemiology

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide, as well as, in Asia (1-3). The prevalence of NAFLD in the Western population ranges from 20% to 30% (4-6) The reported prevalence of NAFLD in Asian countries such as China, Japan, South Korea and India are 15% (7), 29% (5,8), 18.7% (9) and 19% (10), respectively. The prevalence of non-alcoholic steatohepatitis (NASH) ranges from 2% to 3%. NAFLD is strongly associated with metabolic syndrome; a syndrome which includes obesity, type 2 diabetes mellitus and dyslipidemia. The incidence of NAFLD has been reported to range from 65% to 95% in multiple bariatric surgery series (11-14) We performed a prevalence study on 134 patients who underwent bariatric surgery, out of whom 70.8% patients underwent laparoscopic sleeve gastrectomy (LSG) and 29.2 % patients underwent laparoscopic gastric bypass (LGB). A total of 65.7% patients had NAFLD including patients with NASH and advanced fibrosis (11).

The spectrum of pathological features of NAFLD rages from steatosis to steatohepatitis to fibrosis and eventually cirrhosis. 30% to 40% incidence of NASH has been reported in various bariatric surgery series (11-14). NAFLD has a benign course in majority of the patients but some progress to cirrhosis. Histologically, NAFLD is characterised by steatosis, ballooning, lobular inflammation and peri-sinusoidal fibrosis with zone 3 predominance (15).

Pathogenesis

The pathogenesis of NAFLD is closely associated with

insulin resistance (16). Insulin resistance in obese patients is considered to be induced by numerous substances secreted by adipose tissue. In this respect, the contribution of visceral fat has been suggested to be more important than total adipose mass (17,18). Body fat distribution in Asians tends to be more central and visceral for a given body mass index (BMI) as compared to Western population, which results in higher degrees of insulin resistance, consequently, leading to higher risk of NAFLD (19). Multiple hit hypothesis has been proposed for pathogenesis of NAFLD in the morbidly obese. Different pathogenic factors lead to hepatic steatosis which is considered "the first hit" and then to hepatic damage, considered to be "the second hit" (20). Insulin resistance leads to increased fatty acid influx, *de novo* triglyceride synthesis and decreased fatty acid oxidation within the liver thereby promoting triglyceride accumulation in the hepatocytes. What causes "the second hit" which leads to the development of liver damage and fibrogenesis still remains unknown, although several factors have been implicated including oxidative stress, mitochondrial abnormalities, tumour necrosis factor and hormones leptin and adiponectin (16). Zero percent to 4% patients with simple steatosis develop cirrhosis over one to two decades. In contrast, patients with NASH have 5–8% risk of developing cirrhosis over approximately 5 years (21).

Diagnosis

Most patients of NAFLD are asymptomatic and diagnosis is usually incidental, either by an abdominal ultrasound or by abnormal liver biochemistry, done for another reason or as a preoperative work-up. Some patients may have clinical features like fatigue, right upper quadrant abdominal pain and hepatomegaly. Some patients present with features of cirrhosis as NAFLD is now recognised as the most common cause of cryptogenic cirrhosis.

Liver biopsy, considered to be the gold standard for diagnosis as well as staging of NAFLD (22), is the only established means to differentiate necro-inflammatory lesions and fibrosis of NASH from simple steatosis and steatosis with inflammation (15). NIH-sponsored NASH Clinical Research Network NAFLD Activity Score (NAS) is a scoring system used to differentiate between NASH and non-NASH fatty liver with high degree certainty and inter-observer reproducibility. NAS scores of more than 5 co-relate with NASH and less than 3 co-relates with non-NASH fatty liver (15). The most common modality for obtaining liver biopsy is by percutaneous technique under image guidance. However, the possible risks of complications and high cost make it impractical for use in general population. Patients undergoing bariatric surgery offer a unique opportunity to perform a liver biopsy under vision ensuring haemostasis. In the NASHOST trial, we performed intraoperative tru-cut liver biopsy in all the patients undergoing bariatric surgery at our centre and found the prevalence of NAFLD in them to be 65.7%. A total of 33.6% patients had NASH and 31.3% patients had fibrosis both not mutually exclusive (11).

Fatty liver can be diagnosed on imaging modalities including ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) scans. In the general population, ultrasound has a sensitivity of 89% and specificity 93% for the identification of fatty liver but this sensitivity and specificity drops down to 49% and 75% respectively in the morbidly obese (23,24). However, due to its inability to distinguish various stages of NAFLD, ultrasound has no role in its staging (25). Presence of at least two out of three abnormal finding on abdominal ultrasound is used to diagnose steatosis: diffusely increased echogenicity of liver which is greater than kidney or spleen, vascular blurring and deep attenuation of ultrasound signal (26). The Chinese Liver Disease Association criteria defines steatosis which include alcoholic fatty liver disease (alcohol consumption of more than 40 g per day for more than 5 years), NAFLD (non-drinkers, or alcohol consumption of less than 40 g per week for the past 12 months, and life-time cumulative consumption less than 100 kg), and steatosis related to other aetiologies, such as chronic hepatitis C (CHC) (27).

No single biochemical parameter can differentiate between NAFLD and alcoholic fatty liver, however, obese diabetic patients with dyslipidemia along with abnormal liver function tests (LFTs) (low HDL-cholesterol and/or high triglycerides) are the most likely to have NAFLD. An aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio of more than 1 suggests alcoholic fatty liver rather than NAFLD (22). In patients with NAFLD, a rising trend of AST or a reversal of ALT/AST ratio suggests poor prognosis as it is seen in patients who develop cirrhosis (28).

Treatment of NAFLD

Treatment strategies for NAFLD have been focussed at different steps of its pathogenesis. As the pathogenesis of NAFLD is associated with obesity induced insulin resistance, the only measure that acts at the source of the pathogenesis

and offers cure is weight loss. Weight loss can be achieved by lifestyle modification, pharmacotherapy and bariatric surgery. Although bariatric surgery is the only option which offers durable weight loss in majority of patients, but NAFLD *per se* is not an indication for bariatric surgery (29).

Lifestyle modifications in the form of modest calorie restriction (500–1,000 Kcal per day), a low carbohydrate, low fat and high fibre diet and moderate exercise have shown beneficial effects of NAFLD. All the above measures contribute to a modest weight reduction in addition to other metabolic effects, eventually, improving features of NAFLD (30-35).

Various pharmacological therapies have been used to treat NAFLD which include weight loss drugs, oral hypoglycemic agents, anti-lipemic agents, anti-oxidants and cytoprotectants. Lipase inhibitors like orlistat and serotonin and noradrenaline reuptake inhibitor like sibutramine have both shown improvements in LFTs, ultrasound findings as well as liver histology (36-38). Glitazones including rosiglitazone and pioglitazone have shown improvement in ALT levels but this improvement was reversed on cessation of therapy (39,40). Other drugs which have shown benefit in the treatment of NAFLD include statins, vitamin E, fibrates and ursodeoxycholic acid (41-43).

Mechanism of bariatric surgery

Mechanisms of improvement of NAFLD after bariatric surgery are not fully understood and still under investigation. Post bariatric surgery weight loss leads to improvement in insulin sensitivity, thus, targeting the most recognized cause of NAFLD. It also causes improvement/resolution of other contributing metabolic abnormalities including hyperglycemia, dyslipidemia and hypertension. The chronic obesity related low grade inflammation resulting from excess production tumour necrosis factor-α, interleukin-1, interleukin-8, interleukin-18, monocyte chemo-attractant protein-1, C-reactive protein etc. is also reduced. It is also hypothesized that there are other mechanism mediated by complex changes in hormones like ghrelin, glucagon-like peptide-1, peptide YY, oxyntomodulin, adiponectin, etc. induced by bariatric surgery which play a role in improving NAFLD (44).

Although most studies have reported improvement of liver histology following bariatric surgery, some studies have also reported worsening of features of NAFLD. The suggested probable mechanisms include (I) rapid weight loss causing increased free fatty acid levels causing liver injury; (II) exposure to toxins from bacterial overgrowth after bypass procedures; (III) nutritional deficiencies; and (IV) protein malnutrition (45). Another possibility is a dramatic reduction in steatosis post surgery can lead to a "misdiagnosis" of worsening of liver histology as it can cause an over-reporting of necro-inflammatory activity by the pathologist (45).

Results of bariatric surgery

Several studies have reported histological improvement of NAFLD after bariatric surgery which included both restrictive and mal-absorptive procedures. Multiple studies which have reported improvement after gastric bypass (46-51). Studies have also shown improvement after restrictive procedures like vertical banded gastroplasty (VBG) and adjustable gastric banding (AGB) (45,52-55). We, in India, conducted the NASHOST trial in which 30 patients with NAFLD underwent paired liver biopsy, once at the time of bariatric surgery (20 patients underwent LSG; 10 patients underwent LGB) and once at 6 months follow-up. At the second biopsy, there was significant improvement in liver histology (*Table 1*). None had worsening of liver histology. The overall NAFLD score was significantly lower at the time of re-biopsy as compared to the time of surgery (P=0.001) (12). Tai *et al.* also showed similar improvement in liver histology in Chinese obese patients with NAFLD who underwent gastric bypass (56) (*Table 1*). The variation in the effect of each bariatric procedure on NAFLD is debatable. Caiazzo *et al.* have reported that the results gastric bypass with respect to improvement in NAFLD were superior to gastric banding. They have suggested that this is due to better weight loss and greater improvement of insulin sensitivity after gastric bypass (57). In our study, on Indian patients, there was no statistically significant difference in improvement of NAFLD when results of sleeve gastrectomy were compared to gastric bypass (12).

Role of bariatric surgery in cirrhosis

On literature search, we found a few series where bariatric surgery was performed safely in cirrhotics. These series suggest that patients with Child's A cirrhosis with normal hepatic synthetic function can safely undergo sleeve gastrectomy or gastric bypass. However, these patients do tend to have higher incidence of transient renal dysfunction and increased risk of haemorrhage (58-60). There are

Table 1 Studies confirming improvement of NAFLD after bariatric surgery in Asia

Author	Features	At surgery	At rebiopsy	P value
Praveen Raj *et al.* (n=30)	Steatosis	29	11	<0.001*
	Lobular inflammation	14	2	<0.001*
	Ballooning	10	0	0.007*
	Steatohepatitis	13	1	<0.001*
	Portal inflammation	24	24	0.4
	Cirrhosis	3	2	0.01*
Tai *et al.* (n=21)	Steatosis	19	1	<0.01*
	Lobular inflammation	15	6	0.02*
	Ballooning	18	9	<0.01*
	Fibrosis	6	0	<0.01*

*, statistically significant. NAFLD, non-alcoholic fatty liver disease.

certain special considerations in cirrhotics, which need to be taken into consideration in everyday practice like, although, we have reported that gastric bypass is safe in cirrhosis from a metabolic point of view but the inability to access the remnant stomach should variceal bleeding develop is a major cause for concern (12). Thus, a quick restrictive procedure, like a sleeve gastrectomy or gastric banding, is a much safer option for such patients. Clinically, another scenario may present to the surgeon when he detects unexpected cirrhosis intra-operatively. In such a scenario, as mentioned above a planned bypass procedure can be deferred and a sleeve gastrectomy can be performed if there are no contraindications. If the consent of the patient for an alternative procedure has not been taken, procedure can be deferred and a liver biopsy can be performed. Patients who present with decompensated liver disease or severe portal hypertension should be considered for bariatric surgery in combination with liver transplant.

Summary

NAFLD is an important co-morbidity associated with obesity and insulin resistance. Bariatric surgery induced weight loss improves NAFLD in morbidly obese patients. Both restrictive as well as malabsorptive procedures are effective in improving NAFLD in all stages. Choice of procedure has to be tailored to each patient's profile. Bariatric surgery can be done safely in patients with Child A cirrhosis without portal hypertension by an experienced multi-disciplinary team.

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Footnote

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