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**Non-alcoholic Fatty Liver disease: Is surgery the best current option and can novel endoscopy play a role in the future?**

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**Abstract**

Over the last decade, Non-Alcoholic Fatty Liver Disease (NAFLD) has overtaken alcohol as the leading cause for cirrhosis in the Western world. There remains to be a licensed pharmacological treatment for NAFLD. Weight loss is advised for all patients with hepatic steatosis. However, many patients struggle to lose the recommended weight with lifestyle modification alone. Many drugs have either failed to show significant improvement of steatosis or are poorly tolerated. Bariatric surgery has been shown to reduce liver steatosis and regress liver fibrosis. The pathophysiology is not fully understood, but recent evidence has pointed towards changes to the gut microbiome following surgery. Novel endoscopic treatment options provide a minimally invasive option for weight loss. Randomised controlled trials are required for further clarification.

**INTRODUCTION**

NAFLD (Non-Alcoholic Fatty Liver Disease) is an umbrella term used to describe a range of conditions characterised by accumulation of fat in the liver [1]. It ranges from steatosis through non-alcoholic steatohepatitis (NASH), fibrosis, to cirrhosis and hepatocellular cancer (HCC). [1]. Fibrosis is sub-classified from F0-F4: (F0-F1) representing no or mild fibrosis respectively, (F2) – as moderate fibrosis, F3 –severe fibrosis and F4 as cirrhosis [1]. Steatosis is defined by the presence of >5% of Hepatic Fat

(HS), whereas NASH is defined by the presence of >5% of HS with hepatic inflammation and hepatocyte injury [2]. Patients with NASH have a significantly increased risk for disease progression to fibrosis and cirrhosis, which may ultimately lead to hepatocellular carcinoma.

There is an increasing evidence-base showing the parallel association between NAFLD and the metabolic syndrome. Insulin resistance (IR), often defined as the failure of insulin to stimulate glucose transport into its target cells, is a key factor linking NAFLD and metabolic syndrome [3]. However, the exact pathophysiological factors connecting these conditions are unclear, which is a problem as they embody a growing healthcare problem [4]. Metabolic syndrome is often defined as a collection of metabolic risk factors including hypertriglyceridemia, impaired glucose tolerance, abdominal obesity, decreased HDL cholesterol and hypertension. Each component of the metabolic syndrome has the potential to raise the severity of cardiovascular disease including microvascular and cardiac dysfunction, coronary atherosclerotic plaques, myocardial infarction, and heart failure [5].

In recent literature, a group of experts have questioned the acronym NAFLD and decided to integrate the current understanding of the condition to suggest a different term which they felt more accurately describes the underlying pathogenesis [6-10]. It has been investigated that NASH is closely associated with metabolic syndrome [6]. Due to lack of clarity of the association between NAFLD with metabolic syndrome, the acronym 'MAFLD' (Metabolic Associated Fatty Liver Disease) was suggested as a more appropriate description [7]. MAFLD is a concept which proposes to be a more practical acronym for the identification of patients with hepatic steatosis with a high risk of disease progression [8]. This term however remains controversial and has not been universally adopted.

## **EPIDEMIOLOGY**

The prevalence and overall global incidence of NAFLD is increasing exponentially, and is now the leading cause of chronic liver disease in the West, as well as being more

recognised in all parts of the world <sup>[11]</sup>. The global prevalence of NAFLD was estimated to be over 1 billion in 2013 <sup>[11]</sup>, about 25% of the global population. NAFLD is recognised in Western countries to be the most common liver disorder <sup>[1,12]</sup>, affecting 17-46% of adults. The differences in percentages are according to several factors, including ethnicity, age and gender <sup>[1]</sup>. A recent study in 2020 has shown that the overall prevalence of NAFLD in Asia may have surpassed the Western populations, with an estimated prevalence to be 29.6% <sup>[13]</sup>. The prevalence of NAFLD in Middle Eastern and European populations range from 20% to 30% <sup>[14-15]</sup>. Studies conducted in the past decade have shown the prevalence of NAFLD in Asia, measured in countries such as Japan and China, are similar to countries in Europe (20-30% in Japan and 15-30% in China) <sup>[16-17]</sup>. NAFLD is associated with the similar spectrum of metabolic syndrome, which has the progressive tendency to increase the risk of more advanced disease, across the range of age groups from children to adults <sup>[1]</sup>.

### NAFLD AND OBESITY

Obesity is defined by the WHO <sup>7</sup> as 'abnormal or excessive fat accumulation that may impair health'. The most commonly used index to measure weight is the body mass index (BMI) which is defined as the person's weight in kilograms divided by the square <sup>34</sup> of their height in meters. A BMI  $\geq 25$  is considered as being overweight, and  $>30$  is defined as obese. BMI should not be used as an independent marker of obesity as a person's muscle mass can also affect the weight and may be ethnically affected. Waist circumference has been shown to be another reliable marker of obesity.

Estes *et al* (2018) built a dynamic Markov model for eight countries, including China, France, Germany, Italy, Japan, Spain, UK and the US <sup>5</sup> <sup>[18]</sup>. The results of this study suggested that if obesity and diabetes continue to increase at the current rate, in parallel, both NAFLD and NASH prevalence are also expected to increase <sup>5</sup> <sup>[18]</sup>. Conclusively, they have shown that efforts used to mitigate disease burden should be linked to strategies that slow the growth of the current obesity pandemic <sup>[18]</sup>.

## PATHOPHYSIOLOGY OF NAFLD

The pathophysiology of NAFLD has evolved over the last few years; however, it is still not clearly understood. Previously, the 'two-hit hypothesis' proposed that hepatic triacylglycerol (TG) accumulation sensitized the liver to secondary insults such as oxidative stress, which resulted in the development of NASH [19]. Additionally, more recently our understanding has moved beyond this hypothesis and we now know that the natural history of the disease is much more complex. NAFLD should be viewed as part of a metabolic disorder and management should take this into account.

One of the main events in the pathogenesis of NAFLD is a dysregulation between adipose tissue and hepatocytes [20]. Expansion of the adipose tissue results in reduced response to insulin which leads to increased lipolysis and free fatty acids (FFA) production [66]. This increasing adiposity results in chronic low-grade systemic inflammation, and essence obesity may lead to the development of NASH [20].

The “Western diet” which consists of high calories including high fructose content is thought to have contributed significantly to the increasing prevalence of NAFLD. Previous studies in animal models looking at high fructose diets in animals were found to stimulate hepatic de novo lipogenesis and lead to hepatic steatosis [21].

It has now also become more apparent that genetic factors play a key role in the development of NAFLD. Liu *et al* (2014) demonstrated <sup>19</sup> that carriage of the TM6SF2 rs58542926 variant is strongly associated with the presence of NAFLD [22]. Furthermore, carriage of this variant was associated with a significantly greater risk of developing advanced hepatic fibrosis/cirrhosis [22]. Moreover, carriage of the 1148M PNPLA3 variant has been found to be the major common genetic determinant of NAFLD.

The gut-liver axis (GLA) has long been known to play a key role in the development of NASH. Intestinal derived products which can reach the liver are thought to lead to multiple effects on liver physiology [23]. The role of the gut microbiota in patients with

NAFLD is still not clearly understood however many hypotheses have been postulated. Patients with NASH have been found to have increased levels of microbial products, ethanol and altered bile acid profiles [23].

### **HISTOPATHOLOGICAL FEATURES OF NAFLD**

Liver biopsy is currently the only method to reliably grade NAFLD. It is also beneficial in excluding other causes for abnormal liver enzymes and liver disease.

Hepatic steatosis without inflammation often carries a benign course where as NASH can progress to significant fibrosis and cirrhosis [12]. In most cases, hepatic steatosis is diagnosed on imaging such as ultrasound, CT or MRI. Magnetic Resonance Elastography (MRE) can detect hepatic fat fraction, however it cannot differentiate between steatosis and steatohepatitis [24].

A "fatty liver" is defined by >5% macrovesicular steatosis [25]. However, <sup>1</sup>NAFLD is defined as predominantly macrovesicular steatosis with the presence of visible steatosis in >5% of hepatocytes [26]. For the diagnosis of NASH, there is >5% macrovesicular steatosis, inflammation and hepatocellular ballooning which is predominantly centrilobular distribution should be seen on biopsy [24-28]. Patients found to have zone 3 accentuation of macrovesicular steatosis and the features of ballooning and lobular inflammation are defined as having definite steatohepatitis [25]. Apoptotic bodies may also be seen which may also be associated with Mallory-denk bodies [25].

Kleiner *et al* (2005) devised the NAFLD activity score. (NAS) which is a sensitive and reproducible scoring system for the histological diagnosis of steatohepatitis [26].

This scoring system comprises histologically of 4 main groups, each score as shown <sup>18</sup> Steatosis (0-3), lobular inflammation (0-2), hepatocellular ballooning (0-2) and fibrosis (0-4) (26) (Table 1). A score greater than or equal to 5 is defined as correlating with a diagnosis of NASH [26,66].



## **DIAGNOSIS AND CURRENT GUIDELINES**

Commonly, the diagnosis of NAFLD is usually suspected following the findings of abnormal liver function on routine laboratory tests or incidental findings on radiological imaging. Although imaging may be used to investigate NAFLD, the gold standard for diagnosis and assessment of NAFLD is a liver biopsy. However, the accuracy of the biopsy result is dependent on many factors including the size of the biopsy and remains observer dependent. Given that this is an invasive procedure with risks of complications, including bleeding, other modalities have been developed for the assessment of hepatic fibrosis.

Diagnostic tools using direct and indirect markers (Albumin, Bilirubin, AST, ALT, ALP, PT) such as FIB-4, ALT/AST ratio serum markers and the NAFLD fibrosis score have been developed and utilised to provide non-invasive markers of hepatic fibrosis. The NAFLD fibrosis score is a non-invasive scoring system that is calculated by the measurement of six variables; age, BMI, platelet count, blood glucose, albumin and AST: ALT ratio. Direct serum marker of liver fibrosis such as type IV collagen and glycoproteins such as hyaluronic acid, laminin, YKL-40 have been also shown to be useful non-invasive modalities for the assessment of hepatic fibrosis [29].

A previous study <sup>17</sup> in 79 patients with histologically confirmed NAFLD, had serum hyaluronic acid measured at the same time of liver biopsy [30]. The positive and negative predictive values were found to be 51% and 96% respectively and concluded that measurement of serum hyaluronic acid was a useful serum marker to identify significant fibrosis in patients with NAFLD [30]. More recently there has been a development of transient elastography (Fibroscan®), which is used to assess liver fibrosis by measuring the liver stiffness using low frequency amplitudes.

The Fibroscan allows rapid assessment of liver fibrosis which can be made safely and accurately at the bedside. Unfortunately, as many patients with NAFLD are also obese, interpretation of transient elastography may not be a reliable tool for patients

undergoing bariatric surgery. A study performed by Sandrin *et al* (2003) concluded that in patients with obesity, measurements “can be difficult or even impossible” as there is attenuation of the ultrasound waves by the fatty tissue [31].

Ultrasonography has been shown to be a reliable and cost-effective form of imaging with a sensitivity and specificity of 84.8% and 93.6% respectively [32]. Given that it is a cheaper and an easily accessible diagnostic tool, ultrasonography is the preferred initial screening modality for most centres. However, a limitation is that given it is user dependent, the findings may be subjective.

A previous study looking at radiologic evaluation of NAFLD concluded that computerised tomography (CT) has a poor sensitivity for detecting mild steatosis. However, it was found to be reasonably accurate in detecting moderate to severe hepatic steatosis [33]. Given that it is more expensive than ultrasonography, with the added concern of radiation, guidelines do not recommend the use of CT for screening or evaluation of hepatic steatosis. Lee *et al* (2010) performed a prospective comparison of four imaging examinations; including ultrasonography (USS), computed tomography (CT), dual gradient echo magnetic resonance imaging (DGE-MRI) and proton magnetic resonance spectroscopy (1H-MRS) [34]. They came to the conclusion that dual gradient echo magnetic resonance imaging (DGE-MRI) was the most accurate form of imaging, with a sensitivity and specificity greater than 90%. To add to DGE-MRIs clinical superiority in this study, it was also found to have had 76.7% sensitivity and 87.1% specificity in detecting all degrees of hepatic steatosis [34].

The Liver multiscan can be considered as an alternative option for patients who do not want or are unable to tolerate liver biopsy. Using patented technology, the liver multiscan is a software used to process MRI Liver data for quantitative characterisation of liver fibrosis and inflammation.



## EASL (EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER) RECOMMENDATIONS AND CURRENT MANAGEMENT

EASL currently recommends that the incidental finding of steatosis should “prompt a full assessment and evaluation, including metabolic work-up” [1]. They also advise that the presence of obesity, T2DM or incidental abnormal liver function tests <sup>13</sup> in patients with metabolic risk factors should undergo non-invasive screening to predict steatosis, NASH and fibrosis [1]. All patients found to have steatosis should undergo surrogate markers of fibrosis in order to exclude significant fibrosis which is defined as >F2 [1]. Patients found to have significant fibrosis on non-invasive screening should be referred to a specialist clinic and have the diagnosis confirmed on liver biopsy [1]. In terms of obesity, the current recommendation is that these patients should be referred for a structured weight loss program or an obesity specialist [1].

Current treatment regimens recommended by EASL are limited. For patients without NASH or significant fibrosis, lifestyle modification is strongly recommended with a view to achieving a 7-10% weight loss target. This target weight loss range has been proven to be associated with improvement of liver enzymes and histology [1]. This is supported with a study from Petersen *et al* (2005) that showed moderate weight loss of 8kg or 8% of body weight was associated with normalization of fasting plasma glucose concentration and a 10% decrease in plasma cholesterol [35]. Petersen *et al* (2005) also found a significant <sup>24</sup> improvement in hepatic insulin sensitivity which was associated with an 80% reduction in hepatic triglyceride content [35].

Pharmacotherapy is currently only advised for patients with NASH or significant fibrosis (>F2) [1]. EASL does state however that patients without significant disease but whom are high risk for disease progression with other components of the metabolic syndrome or persistently elevated ALT “could also be candidates to prevent disease progression” [1]. Currently only two drugs have been approved for the treatment of NASH by regulatory agencies therefore EASL do not recommend any specific drug for

the treatment of NAFLD <sup>[1]</sup>. The use of all treatments discussed would be off-label and many of the previous medications trialled have been poorly tolerated. Insulin sensitizers such as metformin and Thiazolidinediones such as pioglitazone peroxisome proliferator-activated receptor (PPAR $\gamma$ ) agonists have been used. However, the effect of metformin was found to be weak and the side-effect profile of glitazones were of a particular concern.

Moreover, treatment with Vitamin E has been shown to induce show histological improvement in patients with NASH. However, these results were not reciprocated in the paediatric and adolescent population <sup>[36, 37]</sup>. A further randomized controlled trial published in the NEJM in 2010 compared vitamin E, Pioglitazone or placebo for NASH <sup>[38]</sup>. The primary outcome was improvement in histological features of NASH. The study showed <sup>33</sup> that Vitamin E was superior to a placebo for the treatment of NASH in patients without diabetes <sup>[38]</sup>. When comparing pioglitazone over placebo, no benefit was observed for the primary outcome. However, unfortunately the trial showed that pioglitazone use was associated with weight gain which continued throughout the trial.

### **EASL AND BARIATRIC SURGERY**

Many studies have shown that weight reduction and improvement in metabolic risk factors leads to a marked improvement of hepatic steatosis. Consequently, EASL currently recommend that in patients who do not respond to lifestyle changes or pharmacotherapy, bariatric surgery can be considered. Therefore, it is imperative to outline the most efficacious lifestyle interventions and medical regimens to increase the chances of successful reduction in hepatic steatosis.

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### **AASLD (AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES)** **DIAGNOSIS & MANAGEMENT**

Similarly to EASL, AASLD currently recommend that patients with hepatic steatosis detected on imaging should have a follow-up if they present with abnormal liver biochemistry or have metabolic risk factors [39]. AASLD also advocates for routine screening for patients in the primary care whom are deemed to be high risk for NAFLD, such as patients who are diabetic or patients with obesity [39]. Although some studies have previously suggested “familial clustering” of NAFLD, AASLD do not currently recommend screening of family members for NAFLD [39].

All patients with suspected NAFLD should be screened for other causes of chronic liver disease, including genetic disease such as genetic haemochromatosis and autoimmune liver disease [39]. Parallel to previous studies with EASL, non-invasive markers of fibrosis such as diagnostic tools using serum markers and transient elastography (Fibroscan ®) are advocated for identifying patients with significant fibrosis and cirrhosis [39]. Unlike EASL, AASLD also considers magnetic resonance elastography (MRE) to be a clinically useful tool for identifying advanced fibrosis in patients with NAFLD [39].

In terms of liver biopsy, current guidance is that this should be considered in patients with NAFLD who “are at increased risk of having steatohepatitis and/or advanced fibrosis” [39]. AASLD also recommend liver biopsy for patients whom other underlying aetiology contributing to hepatosteatosis cannot be excluded [39]. Similar to EASL, lifestyle modification including a hypocaloric diet and increased activity is recommended for patients with NAFLD [39]. Pharmacological treatment is currently

only advised for patients with biopsy proven NASH and fibrosis [39]. Metformin is currently not recommended for treating NASH by AASLD [39]. With Pioglitazone, given that there is evidence that shows histological improvement in patients with and without type 2 diabetes with biopsy proven NASH, AASLD currently only advocate its use in patients with biopsy proven NASH [39]. However, given the complication risk of biopsy, both the risks and benefits should be taken into consideration and discussed with all patients so that they are able to make an informed decision [39].

Other pharmacotherapies include the glucagon-like peptide-1 agonist Liraglutide (GLP-1 agonist) which work by stimulating insulin secretion and inhibiting glucagon secretion from pancreatic islet cells. GLP-1 agonists are not currently recommended by AASLD for the treatment of patients with NAFLD or NASH [39]. In addition, vitamin E is also not currently recommended for the treatment of NASH in patients with diabetes, NASH or cryptogenic cirrhosis or without biopsy proven NASH [39].

#### **AASLD AND BARIATRIC SURGERY**

Given the strong evidence base showing improved liver histology in patients with NASH who underwent bariatric surgery, AASLD state that bariatric surgery can be considered in patients with obesity and NAFLD or NASH who are eligible for surgery [39]. There is currently no published literature on Randomised Controlled Trials (RCT) of the effects of bariatric surgery on patients with NASH. Although bariatric surgery can be considered, AASLD do not recommend bariatric surgery as an established option to specifically treat NASH [39]. Interestingly, AASLD do not consider cirrhosis as an absolute contraindication for bariatric surgery and state <sup>10</sup> in patients with compensated NASH or cryptogenic cirrhosis “bariatric surgery may be considered on a case-by-case basis” [39].

#### **BARIATRIC SURGERY AND NAFLD**

In essence, bariatric surgery aims to achieve weight loss by one of three means. Either “restrictive surgery” such as a laparoscopic sleeve gastrectomy (LSG) which aims to reduce the amount the patient is able to eat by gastric volume reduction or “malabsorptive surgery” such as biliopancreatic diversion (BPD) which leads to weight loss by inducing malabsorption. However, this procedure is now less commonly performed due to the risk of significant nutritional deficiencies. Lastly, Roux-en-Y gastric bypass (RYGB) is a form of “combined surgery” which aims to achieve weight loss by both volume reduction and malabsorption.

### IFSO position statement & recommendations

A position statement from IFSO in 2016 concluded that <sup>2</sup> 'comprehensive, sustainable, and proactive strategy to deal with the challenges posed by the obesity epidemic is urgently needed' [40]. Weight loss induced by surgery has proven to be highly efficacious in treating obesity and its comorbidities [40]. With regards to non-alcoholic fatty liver disease (NAFLD) the consensus was that this may be improved after surgery for obesity <sup>2</sup> [40]. Weight loss after surgery for obesity and weight-related diseases provide improvement or resolution of NAFLD and NASH [40].

Given the current lack of medical therapies available to manage NAFLD, bariatric surgery at present remains the only proven effective treatment. However, it is imperative for further studies, including RCTs, to assess the long-term benefit.

### Systematic reviews and post-surgical improvements in NAFLD

Bariatric surgery has been shown to be <sup>2</sup> associated with a significant improvement in both histological and biochemical markers of NAFLD [41]. There have been several previous systematic reviews which have studied the improvement of NAFLD with different types of bariatric surgery [41-44]. Lee *et al* (2019) conducted a systematic review which has analysed data from 32 cohort studies comprising of 3093 biopsy specimens, observed a significant improvement in steatosis, inflammation, balloon degeneration and fibrosis in patients with NAFLD <sup>3</sup> [42]. Patients' mean NAFLD activity score was



reduced significantly after bariatric surgery (mean difference, 2.39; 95%CI, 1.58–3.20;  $P < .001$ ). However, 12% of patients (95%CI, 5%–20%) had worsening features of NAFLD, such as fibrosis. There are a variety of different types of bariatric surgery and Baldwin *et al* (2019) conducted a systematic review and meta-analysis of RYGB compared with LSG for improving liver function in patients with NAFLD [43]. They compared the efficacy of both surgical interventions using four criteria; liver enzymes (AST and ALT) NAFLD fibrosis score, and NAS. Although, both RYGB and LSG significantly improved the 4 criteria, the comparisons of both surgical interventions proved equal efficacy.

Moreover, there have been several studies analysing the post-surgical improvements in other types of bariatric surgery such as gastric bypass, gastric banding, biliopancreatic diversion and jejunal bypass. Bariatric surgery has the potential to cause substantial and sustained weight loss and weight loss is the primary factor which initiates the treatment of NAFLD. One study reflected on the effect of gastric bypass and sleeve gastrectomy on liver function [45]. Liver enzymes, including ALT, AST and ALP, were the main determinants of liver function. Patients which had undergone gastric bypass surgery had raised ALT at 6 mo and raised AST and ALP at 6 and 12 mo. Patients which had undergone LSG showed significantly lower ALT at 12 mo and AST and ALP levels at 6 and 12 mo. Although both cohorts were comparable 24 mo post-operatively, conclusively sleeve gastrectomy showed more favourable liver biochemistries within the first 12 mo post-surgery.

Keshishian *et al* (2005) studied the effects of duodenal switch surgery on hepatic function and steatohepatitis 6 mo post-operatively. Although there was a worsening of the liver enzymes AST ( $p < 0.02$ ) and ALT ( $p < 0.0001$ ) levels found at 6 mo after the surgery, normal levels the enzymes were achieved after 12 mo. More promisingly, there was an improvement with the severity of NASH with up to three grades and a 60% improvement in hepatic steatosis was seen 3 years post-operatively [46].

Another form of bariatric surgery is adjustable gastric band, where an inflatable device is placed around the superior aspect of the stomach with the intendment to decrease

food consumption and ultimately lead to sustained weight loss. Although there has been very limited literature found on the effects of gastric banding on NAFLD, weight loss is a significant factor which contributes to the reduction of hepatic steatosis. A systematic review has been conducted to demonstrate the amount of weight loss in cohorts of patients with gastric banding, gastric sleeve and gastric bypass [47]. Extracted from 24 studies and a total of 29 surgical subgroup populations, all types of bariatric surgery have caused short term weight loss. The short-term weight loss, measured as mean absolute change in BMI (kg/m<sup>2</sup>) at 6 mo, was -5.4 (-3.0, -7.8) after gastric band, -11.5 (-8.8, -14.2) after gastric sleeve, and -18.8 (-10.9, -26.6) after gastric bypass. Weight loss at 36 mo, also measured as mean absolute change in BMI (kg/m<sup>2</sup>), was -10.3 (-7.0, -13.7) after gastric band, -13.0 (-11.0, -15.0) after gastric sleeve, and -15.0 (-13.5 -16.5) after gastric bypass. Bariatric surgery has shown to be efficacious in achieving short-term weight loss at 36 mo, although it is imperative for more research to be established on long-term weight loss to understand the long-term efficacy of bariatric surgery [47].

BPD and Jejunal bypass are both types of malabsorptive surgery. A recent study by Yu *et al* (2019) demonstrated the effects of duodenal-jejunal bypass surgery on ameliorating NASH in diet-induced obese rats. It was found that duodenal-jejunal bypass improved NASH particularly by altering insulin sensitivity, inflammatory responses, HSC activity, and hepatocyte autophagy. Duodenal-jejunal bypass has shown to have a promising role of reducing NAFLD severity and preventing NASH progression. However, further trials on human subjects would be necessary to make more appropriate evidence-base conclusions. [48].

Biliopancreatic diversion alters the normal mechanisms of digestion by making the stomach smaller and diverting the course of food to bypass part of the small intestine with the desired outcome of patients absorbing fewer calories to achieve sustained weight loss. Kral *et al* (2004) studied liver biopsies on a cohort of 104 patients who have had a biliopancreatic diversion procedure to correct their metabolic syndrome. As

expected with sustained weight loss, in this study steatosis grades decreased, although 40% of the patients had a post-operative increase in mild fibrosis, 27% had a decrease in severe fibrosis, and no change in the remaining 33%. Hence, although 27% patients had a decrease in liver fibrosis, the majority (40%) had an increase [49]. Many factors affected fibrosis levels such as low serum albumin, low alcohol intake and menopausal status.

### **ENDOSCOPIC TREATMENTS OF NAFLD**

For some patients, significant weight loss can be difficult to achieve or maintain through lifestyle measures alone. Invasive interventions, such as bariatric surgery, may be contraindicated due to anaesthetic and/or surgical risks or patients may not meet BMI criteria for bariatric surgery. There are limited effects of pharmacotherapy on weight loss and no drug currently universally approved for the treatment of NAFLD, hence for some patients, less invasive interventions such as endoscopic treatments may be an ideal option to achieve weight loss. Innovative endoscopic procedures can also be used as a bridge to surgery by bringing the BMI within the accepted threshold for anaesthetic and/or bariatric surgery or for patients emphatically who do not want bariatric surgery.

#### **Intra-Gastric Balloon (IGB)**

In 2015, both Obera <sup>14</sup> (manufactured by Apollo endosurgery) and the ReShape Integrated Dual Balloon System (manufactured by ReShape medical) were approved by the FDA for use in the United States. However; in April 2020, the FDA updated its recommendations following post-approval studies on these liquid filled Intra-Gastric Balloons (IGB). Currently, the FDA recommends that all healthcare providers are aware of rare adverse effects such as acute pancreatitis secondary to hyperinflation and death. All patients should be made aware of these risks prior to undergoing IGB placement, so that they can make an informed decision.

A meta-analysis by Popov *et al* (2016) looked at the effect of IGBs on liver enzymes (50). 9 observational studies and one randomized trial were identified ( $n = 468$ ) and showed overall improvement in liver function tests [50]. <sup>2</sup> The duration of treatment with the IGB was 6 mo in all of the studies. The ALT decreased by  $-10.02\text{U/L}$  (95%CI,  $-13.2,-6.8$ ) with the BMI decreasing by  $-4.98\text{kg/m}^2$  (95%CI $-5.6,-4.4$ ) [40]. This was associated with improvement of hepatic steatosis, which was assessed with both fat fraction on MRI and histological NAS which was found to be <sup>8</sup> lower after 6 mo of IGB vs control with sham endoscopy and diet ( $2 \pm 0.75$  vs.  $4 \pm 2.25$ ,  $P = 0.03$ ) (50). Six of the studies reported adverse events, with vomiting being a feature in 6-10% of patients and in some of the patients this lead to removal of the balloon [50]. However, the studies in this meta-analysis have some limitations. Firstly, only one study included was an RCT with diet/sham endoscopy being the control arm. Secondly, in all of the studies, dietary recommendations were given to the participants therefore it is difficult to ascertain how much of an effect lifestyle change may have led to the improvement in weight and liver enzymes.

A paper published in clinical Gastroenterology and Hepatology (2020) looked at 21 patients (BMI >30) with early hepatic fibrosis, who underwent IGB placement [51]. This was an open-label prospective study and all patients underwent <sup>31</sup> MRE and endoscopic ultrasound with core liver biopsy at the time of IGB placement [51]. Follow up was after 6 mo with mean total body weight loss being at  $11.7\% \pm 7.7\%$  with NAS improved in 90% of patients [51]. Fibrosis was found to have improved in 50% of the patients by 1.5 stages with 42% of patients being found to have had normal liver stiffness [41]. Improvements were also seen in glycated haemoglobin (HbA1c) and waist circumference [51]. Interestingly, in this paper they applied the FDA criteria for NASH pharmacological endpoints at 6 mo at found that 50% of patients reached endpoints approved by the FDA. Furthermore, these findings surpass those found with pharmacotherapies including Liraglutide, Vitamin E, Pioglitazone and Obeticholic acid



which reached NASH resolution and fibrosis improvement endpoint at 18 mo in 12% and 23% of patients [51, 52]. In this study however, patients were prescribed a diet and exercise program over the 6-month study period which again may act as a cofounder. These studies do suggest that IGBs may have a role to play in the endoscopic management of NAFLD with short-term weight loss however, with no clear long-term data available and evidence to suggest “rebound” weight gain after the removal of these balloons the evidence to support its use as a definitive treatment for NAFLD remains inadequate.

### Endoscopic Sleeve Gastroplasty (ESG)

The overstretch endoscopic suturing system (Overstretch; Apollo Endosurgery, Austin, Tex) which was first reported in 2013 allows sleeve gastroplasty to be performed by placing full-thickness <sup>21</sup> sutures through the gastric wall from the pre-pyloric antrum to the gastro-oesophageal junction [53]. Performed using flexible-endoscopy, it has the advantage of being less invasive with no permanent visible scar and evidence suggestive of fewer complications. It also has the added benefit of a shorter hospital stay with same day discharge possible when compared to laparoscopic sleeve gastrectomy (LSG). As a novel procedure, further studies are still needed to ascertain benefit for NAFLD however there is now mounting evidence to support its use for obesity. Some studies have also shown improvement of HbA1c, reduction in blood pressure and improvement of gastroesophageal reflux disease (GERD) following ESG [54].

With regards to hepatic steatosis, liver enzymes and ESG, there is limited literature. A study by Sharaiha *et al* (2016) collected data from 91 patients who underwent ESG [55]. All patients had a BMI >30 and had failed non-invasive weight loss measures or had a BMI >40 and were not considered candidates for surgery [55]. At 12 mo after ESG,



patients were found to have statistically significant reductions in ALT ( $p < 0.001$ ) and metabolic components including HbA1c ( $P = 0.01$ ), systolic blood pressure ( $P = 0.02$ ), waist circumference ( $p < 0.001$ ) and serum triglycerides ( $P = 0.02$ ) [47]. No significant change was found in low density lipoprotein after *vs* before ESG ( $P = 0.70$ ) [55].

Although there are no results from RCTs looking at ESG and hepatic steatosis or NASH are available, two RCTs (NASH-APOLLO and TESLA-NASH) started in 2018 and 2019 respectively. NASH-APOLLO involves two parallel arms, placebo (sham endoscopy + lifestyle modification) or ESG with OverStitch® system (Apollo Endosurgery, Austin, TX, USA) + lifestyle modifications in patients with biopsy proven [NCT03426111]. TESLA-NASH is looking at comparing the efficacy and safety of ESG *vs* LSG in subjects with obesity and NASH [NCT04060368].

### COMPARISON BETWEEN BARIATRIC SURGERY AND BARIATRIC ENDOSCOPY

A case matched study comparing 54 ESG with 83 LSG patients showed that although at 30 days patients who underwent ESG achieved a greater % TBWL than LSG ( $9.8\% \pm 2.5\%$  *vs*  $6.6\% \pm 2.4\%$ ,  $p < 0.001$ ), at 6 mo patients who underwent ESG achieved a lower %TBWL ( $17.1\% \pm 6.5\%$  *vs*  $23.6\% \pm 7.6\%$ ,  $p < 0.01$ ) compared to LSG [56]. However, patients in the ESG group were found to have significantly less adverse events ( $5.2\%$  *vs*  $16.9\%$   $p < 0.05$ ) compared to LSG. The patients in the ESG group were healthier with less diabetes, hypertension and obstructive sleep apnea than the LSG group [56]. Interestingly, new-onset GERD was also found to be significantly lower in the ESG group ( $1.9\%$  *vs*  $14.5\%$ ,  $p < 0.05$ ) [56]. This is likely due to the fact that these patients had lost weight. A limitation to this study was that patients in the ESG group did undergo a weight management program post procedure, which may have resulted in a confounding bias.

Novikov *et al* (2018) performed a similar study comparing ESG with LSG and laparoscopic band for weight loss [57]. Similar results were seen with LSG achieving the greatest %TBWL (29.28 *vs* 13.30 *vs* 17.57%,  $P = 0.01$ ) compared to the LAGB and ESG respectively [57]. In patients with a BMI <40 kg/m<sup>2</sup>, %TBWL at 1 year were similar between ESG and LSG [57]. Adverse effects were the lowest in ESG group and ESG having the shortest stay [57].

### **BARIATRIC SURGERY IN CIRRHOSIS**

With no current approved pharmacological therapies available for the treatment of NAFLD, bariatric surgery is an option that one should consider. Klebanoff *et al* (2019) assessed <sup>26</sup> the cost-effectiveness of bariatric surgery in patients with NASH and compensated cirrhosis and concluded that bariatric surgery could be highly cost-effective [59]. Unfortunately, there is a high risk of morbidity and mortality post-surgery which has been reported to be as high as 30% post operatively with an 11.6% 30-day mortality in patients with cirrhosis. Hepatologists and Bariatric surgeons remain reluctant to consider surgery as a treatment option [60]. Not only are patients with cirrhosis at increased risk of complications post-surgery, but it has also been reported that this select group of patients are associated with a longer hospital stay [60]. Portal hypertension as a consequence of cirrhosis leads to specific risks of morbidity and mortality. Thrombocytopenia secondary to splenomegaly increases the risks of bleeding and a hyperkinetic circulation with hypalbuminaemia leading to ascites. This impairs wound healing and increases the risk of complications, including infection.

A case matched study published in 2013 evaluated the morbidity related to laparoscopic sleeve gastrectomy in patient with established cirrhosis and compared with non-cirrhotic patients [61]. Over a 9-year period, 13 patients with established cirrhosis undergoing laparoscopic sleeve gastrectomy (LSG) were included and matched with 26 non-cirrhotic patients [61]. The aetiology of cirrhosis in 93% of patients was secondary to NASH. Weight loss was found to be similar between the two groups

[61]. The overall complication rate in both groups was 7.7% *vs* 7.7% ( $P = 1$ ). However, a limitation to the study was that all 13 patients in the cirrhosis group had Child-Pugh A cirrhosis [61]. The paper concluded that LSG can be performed in patients with Child-Pugh A cirrhosis with no increased risk of post-operative complications [61].

Similar results were observed in a multicentre, retrospective study conducted by GOSEEN (Obesity group of the Spanish society of endocrinology and nutrition) [62]. 41 patients of which all but one had Child-Pugh A cirrhosis underwent bariatric surgery (68.3% sleeve gastrectomy) [62]. Total weight loss (%TWL) was  $26.33 \pm 8.3\%$  and  $21.16 \pm 15.32\%$  at 1 and 5 years [62]. Improvements were seen in liver enzymes, blood pressure and glycaemic control with 17% of patients having early postsurgical complications [62]. No patients died in the study. Although, there is some evidence to support bariatric surgery in patients with early (Child-Pugh A) cirrhosis if the benefits outweigh the risks there is currently lack of consensus among surgeons regarding safety of bariatric surgery and the best bariatric procedure in these patients. A systematic review was carried out and showed an acceptably higher overall risk of complications and perioperative mortality with bariatric surgery in cirrhotic patients [44].

11 Bariatric surgery in patients with advanced cirrhosis is associated with higher than usual risk of complications and mortality. In patients with NASH or significant fibrosis undergoing bariatric surgery, these overall risks highlight that surgeons must discuss the possibility of unexpected intraoperative findings of cirrhosis and agree on a course of action.

### UPCOMING PHARMACOLOGICAL AGENTS

Although there remains to be any licenced pharmaceutical treatments for NAFLD or NASH, some drugs are currently in clinical trials which do appear promising.

### Semaglutide

<sup>16</sup>  
In a 72 wk double-blind phase 2 clinical trial patients with biopsy confirmed NASH and fibrosis were treated with Semaglutide vs placebo [63]. 320 patients were randomly assigned to different doses of semaglutide vs 80 patients who received placebo [63]. The results <sup>3</sup> showed that treatment with Semaglutide resulted in a significantly higher percentage of patients with NASH resolution compared to placebo however the trial did not show a significant difference in terms of improvement of fibrosis stage [63].

### Resmetirom (MGL-3196)

<sup>36</sup>  
Resmetirom (MGL-3196) is a selective thyroid hormone receptor- $\beta$  agonist which is liver directed and designed to improve NASH by reducing lipotoxicity and enhancing liver fat metabolism [64]. In a 36 wk, phase 2, multicentre randomised, double-blind, placebo-controlled trial, treatment with Resmetirom showed a significant reduction in hepatic fat on both MRI-PDFF and liver biopsy after 12 and 36 wk compared to placebo [64]. The drug was well tolerated although there was a higher incidence of transient mild diarrhoea and nausea in the Resmetirom group [64]. <sup>27</sup>

### Tirzepatide

<sup>1</sup>  
Tirzepatide is a 39-amino acid synthetic peptide which has agonist activity at glucose-dependent insulintropic polypeptide (GIP) and GLP-1 receptors and is administered once weekly by subcutaneous (SC) injection [65]. In phase 2 clinical trials, treatment with Tirzepatide has been shown to reduce HbA1c and lead to weight loss [65]. There is currently a phase 2 clinical trial in progress to assess impact on non-alcoholic fatty liver disease.

## OUR EXPERIENCE WITH METABOLIC ENDOSCOPY

In a previous publication (Oben *et al* (2017)) we showed that IGB therapy is an efficacious non-surgical method of achieving weight loss in the short term [58]. We retrospectively examined the outcome in 135 IGB patients with obesity and NAFLD

who had received 1 to 3 IGBs Clinical and anthropometric data were analysed at 6 mo. There were significant improvements in ALT, GGT and HOMA-IR, the latter as a measure of insulin resistance, a key component of NAFLD. The mean reduction in weight and BMI was 11.3kg and 4.1kg/m<sup>2</sup> respectively, (p<0.01). The greatest amount of weight loss was seen at 6 mo. We found minor benefit from repeated IGB insertions. More recently we have been able to analyse data from all patients who underwent IGB insertion at St Thomas' hospital, London, from 2014 to 2018. We separated the data into 2014-2016 *vs* 2017-2018. The characteristics are available in table 2. Following our previous study which showed little benefit from repeated IGB insertions most patients only received one IGB. 127 patients underwent a total of 172 IGB insertions between 2014 and 2016. In comparison 60 patients underwent a total of 67 IGB insertions from 2017 to 2018.

Patients undergoing IGB insertions between 2014 and 2016 had a mean weight loss of 8.9kg, (95%CI 7.4-10.4kg), p<0.0001. Mean weight loss as %BW was 7.9% (95%CI 6.6-9.2%), p<0.0001 (Table 2).

In comparison, more weight loss was observed in patients undergoing IGB insertions between 2017 to 2018, with a mean weight loss of 10.2kg, (95%CI 7.5-11.9kg), p<0.0001. Mean weight loss as %BW was 9.1% (95%CI 7.5-10.6%), p<0.0001 (Table 3).

Our data shows that IGB can be a useful adjunct to dietary and lifestyle modification for achieving weight loss, in managing NAFLD.

## **CONCLUSION**

With the global rise in obesity, non-alcoholic fatty liver disease will continue to rise and poses a significant burden on healthcare systems. Liver fibrosis and cirrhosis associated with NAFLD is predicted to continue to increase over the next decades and become the commonest cause for liver transplantation. This poses a challenge. There is currently no licensed pharmacological treatment for NAFLD.



There is mounting evidence that bariatric surgery not only provides histological improvement in patients with NASH, but improvements are seen in other components of the metabolic syndrome including blood pressure and diabetes.

Moreover, with the lack of pharmacological treatments bariatric surgery remains a proven and viable option for all patients at risk of developing significant fibrosis. The involved numbers globally, however, mean that not all patients can be offered bariatric surgery.

Metabolic endoscopy is an evolving treatment option that may provide an alternative for patients who are either contraindicated to have surgery or who do not wish to undergo surgery. It can also be used as a “bridge” to surgery.

Innovative metabolic endoscopic procedures such as IGB and endoscopic sleeve gastropasty may be ideal for patients with obesity and NASH or with significant liver fibrosis who do not meet criteria for bariatric surgery. RCTs are now required to further identify the overall benefits for both bariatric surgery and metabolic endoscopic procedures.

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