REVIEW

Treating morbid obesity in cirrhosis: A quest of holy grail

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Abstract

The problem of obesity is increasing worldwide in epidemic proportions; the situation is similarly becoming more common in patients with cirrhosis which negatively affect the prognosis of disease and also makes liver transplantation difficult especially in the living donor liver transplantation setting where low graft to recipient weight ratio negatively affects survival. Treatment of obesity is difficult in cirrhosis due to difficulty in implementation of lifestyle measures, limited data on safety of anti-obesity drugs and high risk of surgery. Currently approved anti-obesity drugs have limited data in patients with cirrhosis. Bariatric surgery remains an option in selected compensated cirrhotic patients. Endoscopic interventions for obesity are emerging and are quite promising in patients with cirrhosis as these are minimally invasive. In present review, we briefly discuss various modalities of weight reduction in obese patients and their applicability in patients with cirrhosis.

Key words: Obesity; Intragastric balloon; Antiobesity drugs; Bariatric surgery; Cirrhosis

Core tip: The rising obesity problem is also associated with increased incidence of simultaneous obesity and cirrhosis. This is a particularly difficult subset of obese patients to treat as there is difficulty in implementation of lifestyle measures, limited data on safety of anti-obesity drugs and high risk of surgery. In present review, we briefly discuss various modalities of weight reduction in obese patients and their applicability in patients with cirrhosis.

INTRODUCTION

Obesity has been defined as abnormal or excessive fat accumulation that can lead to impairment of health. It's one of the most significant public health problems faced by people of industrialized countries and is rapidly

catching up in developing countries also. Worldwide obesity prevalence has almost doubled since 1980[1]. Obesity has reached epidemic proportions over the world and it is simultaneously associated with various comorbidities, namely diabetes mellitus, hypertension, and cardiac diseases[2]. In 2014, according to estimate more than 1.9 billion adults were overweight with 600 million likely obese. Approximately 39% of adults aged 18 years and above were overweight in 2014, and 13% were obese[3]. Due to various co-morbidities, obesity represents a very serious health problem worldwide. Obesity management is a unique challenge due to the rapid evolution of unfavourable lifestyles[4].

Obesity can be associated with cirrhosis as a virtue of non-alcoholic steatohepatitis (NASH), an important cause of cirrhosis, being a component of the metabolic syndrome and it can also exacerbate co-existing liver injury due to other causes and is associated with more risk of decompensation of cirrhosis[5]. The patho-physiology of NASH has been considered a "two hit" process[6]. The "first hit", hepatic steatosis, makes the liver susceptible to injury mediated by "second hits", like inflammatory cytokines/adipokines, oxidative stress, and mitochondrial dysfunction, leading to steatohepatitis and/or fibrosis[7]. Impaired hepatocyte proliferation progenitors due to cell death has been proposed as "third hit" in pathogenesis of non-alcoholic fatty liver disease[8]. Various cytokines/adipokines involved in NASH pathogenesis includes tumor necrosis factor-alpha, leptin, adiponectin, interleukin-6 (IL-6), *etc.*[9]. Fibrosis/cirrhosis represents the final common endpoint of pathway of almost all chronic liver diseases including NASH. Mechanisms for fibrosis include the secretion of profibrogenic cytokines (tumor growth factor-β, IL-6, IL-8, *etc.*) by the ductular reaction, as well as epithelial to mesenchymal transition of stellate cells to myofi-broblasts[10,11]. Steatosis is very commonly associated with hepatitis C, particularly with genotype 3. In chronic hepatitis C, obesity is associated with inflammation, steatosis, insulin resistance, faster progression of fibrosis, and nonresponse to treatment with interferon[12].

OBESITY AND CIRRHOSIS: THE CHALLENGES AND RATIONALE FOR MANAGEMENT

Obesity with cirrhosis is a complex problem. Once cirrhosis is decompensated, lifestyle measures are very difficult to implement and bariatric surgery becomes risky due to increased morbidity and mortality[13,14]. Phar-macological measures (drugs) have a very limited role in management of obesity, are not as effective as surgery and there is rebound weight gain once stopped. The limited drug arsenal available to treat obesity is not well studied in patients with liver disease. No safe anti-obesity drug in cirrhosis is available at the moment. Proportion of patients with NASH associated end stage liver disease as an indication for liver transplantation is increasing

gradually[15,16] and these patients are more prone for co-morbidities associated with NASH like coronary artery disease, diabetes, hypertension, dyslipidemia, metabolic syndrome and chronic kidney disease[17]. Obesity in cirrhosis becomes a multi-headed monster leading to more rapid worsening of liver disease and also makes liver transplantation difficult. There is difficulty in finding a suitable donor for morbidly obese patients due to risk of low graft to recipient ratio and subsequent risk of poor graft function and higher mortality in living donor liver transplantation (LDLT) programs which predominant from of liver transplantation in Asia[18]. Increased rates of complications and mortality, as well as decreased graft survival, have been reported in morbidly obese patients often discouraging transplantation in this population and have resulted in the exclusion of morbidly obese patients from liver transplantation at some centres[19]. With increasing number of non-alcoholic steatohepatitis associated end stage liver disease as an indication for liver transplantation, problem of morbid obesity before liver transplantation is going to rise[20].

There are multiple benefits of treating obesity in patients with cirrhosis. Firstly there is a reduction in risk of decompensation as studies have shown higher decompensation over time in overweight and obese cirrhotic[5]. Some patients may improve from compen-sated stage to lesser degree of fibrosis as shown by bariatric surgery studies[21]. This may avoid need for liver transplantation in many patients. Secondly reduc-tion in weight may improve their candidacy for liver transplantation by improving co-morbidities (like diabetes control), decreasing risk in surgery and improving their graft recipient weight ratio especially in LDLT settings. Thirdly there can be reduced incidence of hepatocellular carcinoma (HCC) as obesity is considered to be an independent risk factor for development of HCC[22].

In current review article we will discuss the various weight reductions strategies in brief and their applica-bility in patients with cirrhosis.

DIET, LIFE STYLE MODIFICATION AND EXERCISE IN THE MANAGEMENT OF OBESITY IN CIRRHOSIS

The recent worldwide increase in the population of obese individual is also seen in liver cirrhosis patients[23]. At present, in liver cirrhosis due to alcohol and chronic hepatitis C infection, nutritional intake is a spectrum ranging from being either sufficient or excessive[24,25]. Excessive nutrients has to be assessed in every patient, and the various nutritional parameters, like serum albumin and lean body mass, should be evaluated for the appropriate nutritional therapy. However, the amount of body weight reduction has not been evaluated properly in the obese liver cirrhosis patients. The addition of oral Branched chain amino acids (BCAA) granules to diet has been shown to reduce the incidence of HCC[23]. It has also been shown that oral BCAA supplementation

increases serum albumin levels[26]. The mechanism involved may be improved insulin sensitivity in muscle, increase in and reduced oxidative stress[27]. Thus, in obese liver cirrhosis patients, oral BCAA treatment is recommended in addition to correction of nutritional intake. The current epidemic of global obesity has created a new entity: The unique combination of sarcopenia and obesity, now commonly described as sarcopenic obesity[28]. A recent study has shown that sarcopenic obesity is more closely linked with insulin resistance than either sarcopenia or obesity alone[29].

Physical activity levels and also exercise capacity are generally lower in liver cirrhosis patients than in healthy controls[30,31]. Exercise is a key component of management of liver cirrhosis patients because it leads to increased calorie burning, increased skeletal muscle mass, along with exercise capacity, leading to improved quality of life. The advice regarding exercise is made complex in patients with cirrhosis as portal pressure has been shown to increase with moderate exercise (up to 30% of the maximum), which poses a risk for variceal bleeding[32]. The optimal exercise regimen in liver cirrhosis patients remains uncertain. Researcher's recommendation is walking 5000 or more steps every day with a caloric intake of 30 kcal/kg based on a survey done on compensated cirrhosis patients[31]. A randomized pilot study involving liver cirrhosis patients, mostly Child-Pugh A cirrhosis, examined the effect of exercise combined with leucine supplementation (10 g/d). The program included three sessions every week of one hour treadmill along-with cycle ergometry at 60%-70% of the maximum heart rate, over a total period of 12 wk. The intervention group had improved exercise capacity, shown by the 6-min walk test and the 2-min step test with associated improvement in quality of life parameters with no adverse events[33]. Aerobic exercise is expected to improve insulin resistance in patients with cirrhosis which is particularly important for obese patients[34,35]. Future studies will establish efficacious along with safe exercise regimen needed for liver cirrhosis patients.

DRUG THERAPY

Orlistat

Orlistat at a dose of 120 mg was approved by the Food and Drug Administration (FDA) in 1999 for the management of obesity in association with reduced calorie diet, and also to reduce the risk of regaining weight after previous weight loss. Orlistat was the first treatment for obesity that was not an appetite suppressant, but acted by interfering with the action of hormone lipase involved in fat digestion[36]. In one of the longest trials comprising of 3304 patients, 21% also having impaired glucose tolerance, were randomized to receive either placebo or orlistat. During the first year, weight loss was greater in the orlistat-treated group (11% compared with 6% in the placebo group)[37]. Despite being FDA-approved fewer than 10% patients take it for 1 year and less than 2% of patients for 2 years due

to poor compliance secondarily to side effects[38,39]. It is advisable to give vitamin supplements to patients treated with this drug. Severe liver injury has been reported rarely with a United States FDA review identifying 13 reports of severe liver damage[40]. Given the side effect profile it is unlikely to become a commonly prescribed drug in cirrhosis patients who may have malnutrition despite obesity.

Lorcaserin

Lorcaserin is a selective agonist of 5-hydroxytryptamine receptor 2C (5-HT2C), which is expressed in hypothalamic pro-opiomelanocortin (POMC)-producing neurons of central nervous system, the centre controlling appetite and satiety[41]. Lorcaserin causes activation of the 5-HT2C receptors which stimulates release of melanotropin-α, subsequently decreasing appetite through stimulation of melanocortin receptor 4[41]. Of significance is the low affinity lorcaserin has for other 5-hydroxytryptamine receptor subtypes, especially 5-HT2B, which has previously been associated with the development of valvular heart disease. Lorcaserin approval by FDA was largely based on two placebo-controlled trials in nondiabetic patients (BLOOM and BLOSSOM) along with a third smaller trial in adults with diabetes (BLOOM-DM)[42-44]. Lorcaserin caused a modest weight reduction of approximately 3.2 kg more than placebo. Adverse effects include headache, nausea, fatigue, and dizziness[45]. Lorcaserin should be discontinued if there is less than 5% weight reduction in 12 wk. No dose adjustment is required in patients with mild to moderate hepatic impairment. It has not been studied in patients with severe hepatic impairment and is not recommended in these groups of patients.

Phentermine/topiramate-extended-release

In 2012, the United States FDA approved a preparation of phentermine and extended-release topiramate for use in adults with a body mass index (BMI) $\geqslant$ 30 kg/m^2 or with BMI $\geqslant$ 27 kg/m^2 with associated comorbidity (hypertension, diabetes, dyslipidemia). Phentermine plus topiramate-extended-release (ER) was recommended for approval based largely on two phase 3 clinical trials (EQUIP and CONQUER)[46,47]. In the EQUIP trial (n = 1267) participants given the top dose *vs* placebo, the mean 1-year weight loss was 10.9% *vs* 1.6%[46]. In CONQUER trial (n = 2487) one-year mean weight loss was 8.1 kg (7.8%) with the recommended dose and 10.2 kg (9.8%) with the top dose *vs* 1.4 kg (1.2%) with placebo[47].

The labelling recommends against prescription in patients with recent or unstable cardiac or cerebrovascular disease, and suggests regular monitoring of resting heart rate. No dose adjustment is needed in patients with mild hepatic impairment. In patients with moderate hepatic impairment, the maximum dose is Phentermine/topiramate-ER 7.5 mg/46 mg once daily. Phentermine/topiramate-ER is not studied in patients with severe hepatic impairment where it has to be

Table 1 Newer weight reduction drugs in pipeline

Drug	Mechanism of action
Cetilistat	Gastrointestinal and pancreatic lipase inhibitor
Velneperit	Neuropeptide Y5 receptor inhibitor, appetite suppression
Tesofensine	Inhibition of serotonin, dopamine, and noradrenaline reuptake
Metreleptin	Leptin receptor agonist
Obinepitide	Dual neuropeptide Y2/Y4 receptor agonist
Beloranib	MetAP2 inhibition

MetAP2: Methionine aminopeptidase 2.

avoided[48].

Bupropion-naltrexone
In September 2014, a sustained release formulation of bupropion-naltrexone was approved by FDA[49]. Bupropion activates POMC neurons in the hypothalamus which gives downstream effects of appetite reduction and increased energy output. The POMC is regulated by endogenous opioids *via* opioid-mediated negative feedback. Naltrexone is a pure opioid antagonist, which further augments bupropion's activation of the POMC.

In a randomized trial of bupropion and naltrexone (varying doses) *vs* double placebo, weight loss was greater in those assigned to active treatment (mean change in body weight in low dose naltrexone and high dose naltrexone was -5% and -6.1% *vs* -1.3% in placebo arm)[50]. Compared with placebo, the combination of bupropion-naltrexone has been shown to reduce weight by approximately 4% to 5%[50-53]. Contraindications include uncontrolled hypertension, seizure history, eating disorders, simultaneously using other bupropion-containing products, chronic opioid use, and monoamine oxidase inhibitors use within last 14 d. Cases of hepatitis and clinically significant liver dysfunction have been seen in association with naltrexone use during naltrexone clinical trials and in post marketing reports of naltrexone use[54]. Thus the combination of bupropion-naltrexone doesn't looks too exciting for the patient of cirrhosis and in the absence of strong data for liver disease patients, shouldn't be prescribed.

Liraglutide
Liraglutide, is a long-acting glucagon-like peptide-1 analog, and a promising option for obese patients with type 2 diabetes. It is the most recent drug to be approved for obesity by FDA in December 2014. In diabetes trials, liraglutide (1.8 mg daily) was associated with a greater reduction in weight (2.0 to 2.5 kg) when compared with placebo or glimepiride[55]. In a randomized trial comparing liraglutide (1.2 to 3 mg), placebo, and open-label orlistat (120 mg orally three times daily) in 564 patients with a mean BMI of 35, weight loss increased with increasing doses of liraglutide, with the mean weight loss ranging from 4.8 to 7.2 kg[56]. Patients who were randomly assigned to receive any dose of liraglutide were found to lose significantly more weight compared to placebo (mean weight loss 2.8 kg). Patients taking the two highest doses of liraglutide (2.4 and 3.0 mg) lost significantly more weight than those assigned to orlistat (6.3, 7.2 and 4.1 kg, respectively)[56]. In a 56-wk SCALE Maintenance randomized study trial comparing liraglutide 3 mg once daily with placebo injection in 422 patients a greater proportion of patients maintained weight loss in the liraglutide group (81.4%) *vs* 48.9% in placebo group)[57]. Common side effects included nausea (37%-47%), vomiting (12%-14%), diarrhoea, reduction of blood sugar levels, and loss of appetite. Less common side effects included pancreatitis, renal impairment, and suicidal tendenciew. In rodent studies, liraglutide has been associated with benign and malignant thyroid C-cell tumors. Liraglutide is not recommended in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia 2A or 2B. Because of limited experience in patients with hepatic impairment, it must be used cautiously in patients with liver impairment. If data regarding safety becomes available it would an interesting drug given its potential to improve various cardio metabolic factors[58].

Antiobesity drugs: In the pipeline
Apart from the current approved drugs for treatment of obesity many other are in various stages of development. Endogenous cannabinoids which are ubiquitous lipid signalling molecules having both central and peripheral effects mediated by the specific receptors CB1 and CB2[59]. Compounds targeting the peripheral CB1 receptors selectively are under evaluation[60,61]. Various drugs which may hold promise in near future are listed in the table. Other drugs in various stages of development are summarized in the Table 1[62-67].

Overall there is hope of some drugs being available in near future. The role of combination polytherapy needs further evaluation due to paucity of efficacy and safety data in cirrhosis patients currently.

SURGERY
The number of obese patients awaiting organ transplantation is increasing in parallel with the increasing prevalence of obesity. For patients with advanced fibrosis and cirrhosis, historically, bariatric surgery was not advised or offered. Complications of bariatric surgery, including bleeding, gastrointestinal symptoms, nutritional or electrolyte abnormalities, and stomal stenosis, can be seen in 10% to 17% of patients without cirrhosis[68]. Bariatric surgery may be useful in cirrhosis patients needing LT who were denied evaluation primarily because of weight. Furthermore reduction in weight can lead to improvement in liver parameters reducing chances of decompensation over time.

Patients with cirrhosis undergoing surgery of any kind are placed at an increased risk of mortality from liver failure, renal failure, or even postoperative bleeding due to impaired coagulation. This risk depends on the

degree of liver dysfunction or model for end-stage liver disease scores[69]. The mortality rates from bariatric operations have been reported to be in the range of 0.28%-0.35%[14,70]. A large population-based study (*n* = 674900) has reported that patients with cirrhosis had higher in-hospital mortality rates than those without cirrhosis after bariatric surgery (1.2% *vs* 0.3%)[14].

Takata *et al*[71] reviewed 15 patients of end-stage organ failure, of which 6 with cirrhosis underwent laparoscopic sleeve gastrectomy (LSG). Complications were noted in 2 patients with cirrhosis but there was no mortality. The mean follow-up was 12.4 mo, and the mean excess weight loss noted was 33% for cirrhosis patients at 9 mo[71]. The LSG was selected instead of Roux-en-Y gastric bypass (LRYGB) in this study for the following reasons: (1) some evidence has shown previously that the operative time and overall morbidity are reduced compared with those with LRYGB[13]; (2) the remaining gastric tube remains endoscopically accessible in the case of variceal bleeding; (3) endoscopic access to the biliary system after liver transplantation is preserved; and (4) it is expected that intake and absorption of critical medications will not be significantly altered.

Lin *et al*[72] studied 26 pretransplant patients who underwent LSG. The mean age of patients was 57 years with 17 (65%) of patients being female. Six patients had end-stage renal disease, and 20 patients had end-stage liver disease. There were 6 postoperative complications but no death, the complications being two superficial wound infections, one staple line leak, one postoperative bleed, one transient encephalopathy, and one renal insufficiency that resolved. The mean excess weight loss at 1, 3 and 12 mo was 17%, 26% and 50% respectively[72]. This lead to liver transplantation in seven patients showing LSG is well tolerated, is technically feasible, and improves candidacy for transplantation.

Shimizu *et al*[73] prospectively reviewed 23 patients (12 with known cirrhosis and 11 with unknown cirrhosis). There were 14 females and 9 males with a mean age of 51.5 ± 8.3 and a mean body mass index of 48.2 ± 8.6 kg/m^2. Child-Pugh classes were A (*n* = 22) and B (*n* = 1). Procedures performed were LRYGB (*n* = 14), LSG (*n* = 8), and laparoscopic adjustable gastric banding (LAGB) (*n* = 1). No patients had liver decompensation after surgery. The patients lost 67.4% ± 30.9% of their excess weight at 12 mo follow-up and 67.7% ± 24.8% at 37 mo follow-up[73].

Most recently Pestana *et al*[74] reviewed 14 patients [11 patients underwent sleeve gastrectomy (78.6%) and 3 gastric bypass (21.4%)] with Child's A cirrhosis with or without portal hypertension. The mean patient age was 55.5 years, and 10 of 14 patients were women. At 1-year post surgery, only 1 of 8 patients who underwent follow-up ultrasound imaging showed steatosis. The bilirubin level above 2 mg/dL was seen in a patient one year post surgery. One patient developed encephalopathy at 2-year post-surgery. Bariatric surgery in patients with compensated cirrhosis even with mild portal hypertension seems well tolerated[74].

Woodford *et al*[75] studied 14 patients intraoperatively detected with cirrhosis undergoing LAGB. No patients had preoperative clinical evidence of decompensated liver disease. There was no operative mortality.

Table 2 reviews the various studies done on bariatric surgery in cirrhosis patients[71,73-78]. Overall the literature suggests that bariatric surgery is tolerated in compensated cirrhosis although with slightly higher but acceptable complication rate and should be offered to obese cirrhosis patients. This will delay progression of liver disease to decompensation and also increase the candidacy for transplantation in both living donor liver transplantation and dead donor liver transplantation setting.

ENDOSCOPIC INTERVENTIONS FOR MORBID OBESITY IN CIRRHOSIS

Endoluminal interventions performed through the gastro-intestinal (GI) tract using endoscope offers potential for a weight loss procedure which is safer and more cost-effective than the current laparoscopic approaches[79]. Endoscopic techniques try to mimic the anatomical features produced by bariatric surgery. There are mainly two types of endoscopic weight loss modalities - restrictive and malabsorptive. Restrictive procedures causes reduction of gastric volume through use of space-occupying prosthesis or through suturing/stapling devices, while malabsorptive procedures causes reduced absorption by preventing contact of food with the duodenum and proximal jejunum. Restrictive procedures include intragastric balloon insertion, endoluminal vertical gastroplasty, transoral gastroplasty and transoral endoscopic restrictive implant system, while malabsorptive procedure include duodenojejunal bypass sleeve. Gastroduodenojejunal bypass sleeve is combines both restrictive and malabsorptive features. Except for intragastric balloon, all the mentioned procedures are comparatively new, with no data on cirrhosis patients.

Intra-gastric balloon placement is minimally invasive modality for weight loss. While this procedure has a well-established role in patients without liver disease, data on cirrhosis is not there. A meta-analysis of intra-gastric balloon placement in general patients including 15 articles (3608 patients) showed weight loss of 14.7 kg, 12.2% of initial weight, 5.7 kg/m^2, and 32.1% of excess weight at 6 mo. Complications of intra-gastric balloon placement are uncommon and most common side effect is nausea and vomiting (8.6%)[80]. Other side effects included intolerance to the balloon which resulted in early removal, gastric ulcers and erosions, esophagitis, spontaneous deflation, persistent vomiting, gastroesophageal reflux and abdominal pain. However, severe complications are rare with a large Italian series of 2525 cases showing the following complications; 0.08% acute gastric dilatation, gastric perforation in 5 (0.19%, 4 of these had gastric surgery earlier), gastric obstruction in 0.76%, balloon rupture in 0.36%, esopha-

Table 2 Studies of bariatric surgery in cirrhotic patients

Ref.	Study characteristics	Cirrhosis diagnosis	Child pugh	Procedures	Complications	Liver decompensation	Mortality
Pestana *et al*[74] *n* = 14 F:M = 10:4	Mean age = 55.5 yr	Known cirrhosis	A = 14	SG = 11 RYGB = 3	0	1 (late HE)	0
Shimizu *et al*[73] *n* = 23 F:M = 14:9	Mean age = 51.5 yr Mean BMI = 48.2 kg/m^2 Mean stay = 4.3 d	12 preoperatively 11 intraoperatively	A = 22 B = 1	RYGB = 14 SG = 8 AGB = 1	8	0	0
Rebibo *et al*[78] *n* = 13 F:M = 7:6	Median age = 52 yr Median BMI = 46.3 kg/m^2	All intraoperatively	A = 13	SG = 13	2	1 (ascites)	0
Takata *et al*[71] *n* = 6 F:M = 4:2	Mean age = 52 yr Mean BMI = 49 kg/m^2	All preoperatively	A = 4 B = 2	SG = 6	2	1 (ascites) 1 (HE)	0
Dallal *et al*[76] *n* = 30 F:M = 20:20	Mean age = 50 yr Mean BMI = 52.6 kg/m^2 Mean hospital stay = 4 d	Diagnosed intraoperatively in 27 (90%)	A = 30	RYGB = 27 SG = 3	9	0	0
Kral *et al*[77] *n* = 14 F:M = 10:4	Mean age = 40 yr Mean BMI = 54 kg/m^2	All intraoperatively	NA	BPD = 14	2	2	2 (one late hepatic failure)
Woodford *et al*[75] *n* = 14 F:M = 10:4	Mean age = 52.5 yr Mean BMI = 38.9 kg/m^2	All intraoperatively	A or B	AGB = 14	2	0	0

RYGB: Roux-en-Y gastric bypass; SG: Sleeve gastrectomy; BPD: Bilio-pancreatic diversion; AGB: Adjustable gastric banding; HE: Hepatic encephalopathy; M: Male; F: Female; BMI: Body mass index.

gitis in 1.27% and gastric ulcer in 0.2%. They noted significant improvement of co-morbidities[81]. It should be noted that above meta-analysis and Italian study used BioEnterics intra-gastric balloon, the newer Spatz balloon provides option of gradual increase (or decrease) in balloon volume, thus should be associated with less complications and it can be kept for 1 year as compared to 6 mo duration for earlier. If dietary and lifestyle measures continued after balloon removal, these patients sustain initial weight loss. A Brazilian multicenter study of 483 patients showed that significant number of patients maintained their weight loss after balloon removal with a multidisciplinary program which involved clinical, psychiatric, exercise, and dietary therapy[82].

We published use of intragastric ballon in decompensated cirrhosis for the first time in 2012 as letter to editor. The 61-year-old patient had decompensated alcoholic liver disease (CTP score 9). His BMI decreased from 48.3 kg/m^2 to 39.2 kg/m^2 (resulting in a total of 24 kg weight loss) at 6 mo after intragastric balloon placement. His diabetic control also improved, HbA1c level decreasing from 9.2 to 5.4[83].

We have placed a total of 8 intragastric balloons (7 had decompensated cirrhosis) and five of them had successful liver transplantation (3 deceased donor liver transplantation and 2 LDLT), this data is submitted for publication elsewhere. None of these patients had any severe complication other than vomiting in initial few days. One patient didn't lose weight out of these 8 patients and in one patient we had to decrease initial volume of Spatz balloon due to persistent vomiting at day 7. Although intra-gastric balloon appears to be a promising modality for weight loss in decompensated cirrhosis,

it cannot be placed in all patients. Contraindications of intra-gastric balloon include severe coagulopathy, upper gastro-intestinal tract conditions with potential bleeding risks (large or high risk esophageal varices, gastric varices, ulceration), presence of eating disorders, history of prior gastroesophageal surgery, presence of autoimmune connective tissue disorder affecting GI tract, significant hiatal hernia, esophageal stenosis, GI motility disorders, unwillingness for supervised diet and behaviour modification program and allergy to Silicon (product information). In conclusion, there is plenty of data about use of intra-gastric balloon for weight loss in morbidly obese patients and it has proven to be a safe modality. However, its use in morbidly obese patients with cirrhosis who are awaiting liver transplantation has not been studied.

The endoscopic administration of botulinum toxin type A in gastric wall is thought to aid in weight reduction by inhibiting antral motility and slowing gastric emptying by inhibiting acetylcholine release at the neuromuscular junction causing local paralysis of muscle. In published randomized placebo controlled trials no statistically significant weight loss has been shown[84,85]. When fundal injections were also applied, significantly greater short-term weight loss, reduction in BMI and prolongation of gastric emptying was achieved compared with controls[86]. A recent meta-analysis by Bang *et al*[87] analysed a total of 115 patients in 8 studies. Wide area injection including the fundus or body rather than the antrum only and multiple injections (> 10) were associated with weight loss. The safety and efficacy of this approach needs to be studied in cirrhosis.

There has been a lot of enthusiasm in gastric elec-

trical stimulation (GES) and devices innervating the stomach for bariatric applications. The exact mechanisms of GES are largely unknown, but causes delayed gastric emptying and increased satiety[88]. Recently in January 2015 the Maestro Rechargeable System, was approved[89]. These devices are generally implanted through open or laparoscopic means, but electrical stimulation systems deployed endoluminally has shown to be feasible and safe[90,91].

CONCLUSION

There has been a worldwide rise in patients having obesity associated with cirrhosis. Obesity with cirrhosis is a double trouble leading to early decompensation and also making liver transplantation difficult. Weight reduction is generally more difficult in this group of patients. Lifestyle changes should include a diet of around 30 kcal/kg and walk of greater than 5000 steps/d but optimal safe exercise regimen is unknown.

Among the current FDA approved anti-obesity drugs (orlistat, phenteramine/topiramate-ER, lorcaserin, naltrexone-bupropion ER and liraglutide) none are well studied in patients with cirrhosis but lorcaserin and liraglutide have similar pharmacokinetics in patients with mild hepatic impairment and are not contraindicated.

Bariatric surgery can be relatively safely performed in compensated cirrhosis patients with a slightly higher but acceptable complication rate.

Role of endoscopic intervention for management of obesity in cirrhosis especially intragastric balloon placement is evolving but promising and seems feasible even in those with decompensated cirrhosis.

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