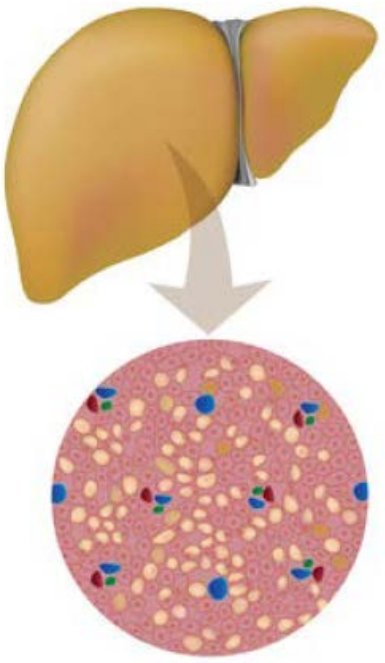
ORBERA365™ and the management of NAFLD

Orbera365 managed weight loss system

apollo endosurgery

Non-alcoholic fatty liver disease (NAFLD) incidence rapidly increasing

- NAFLD incidence rate is rapidly increasing globally; reflecting the growth rate of the obesity epidemic.



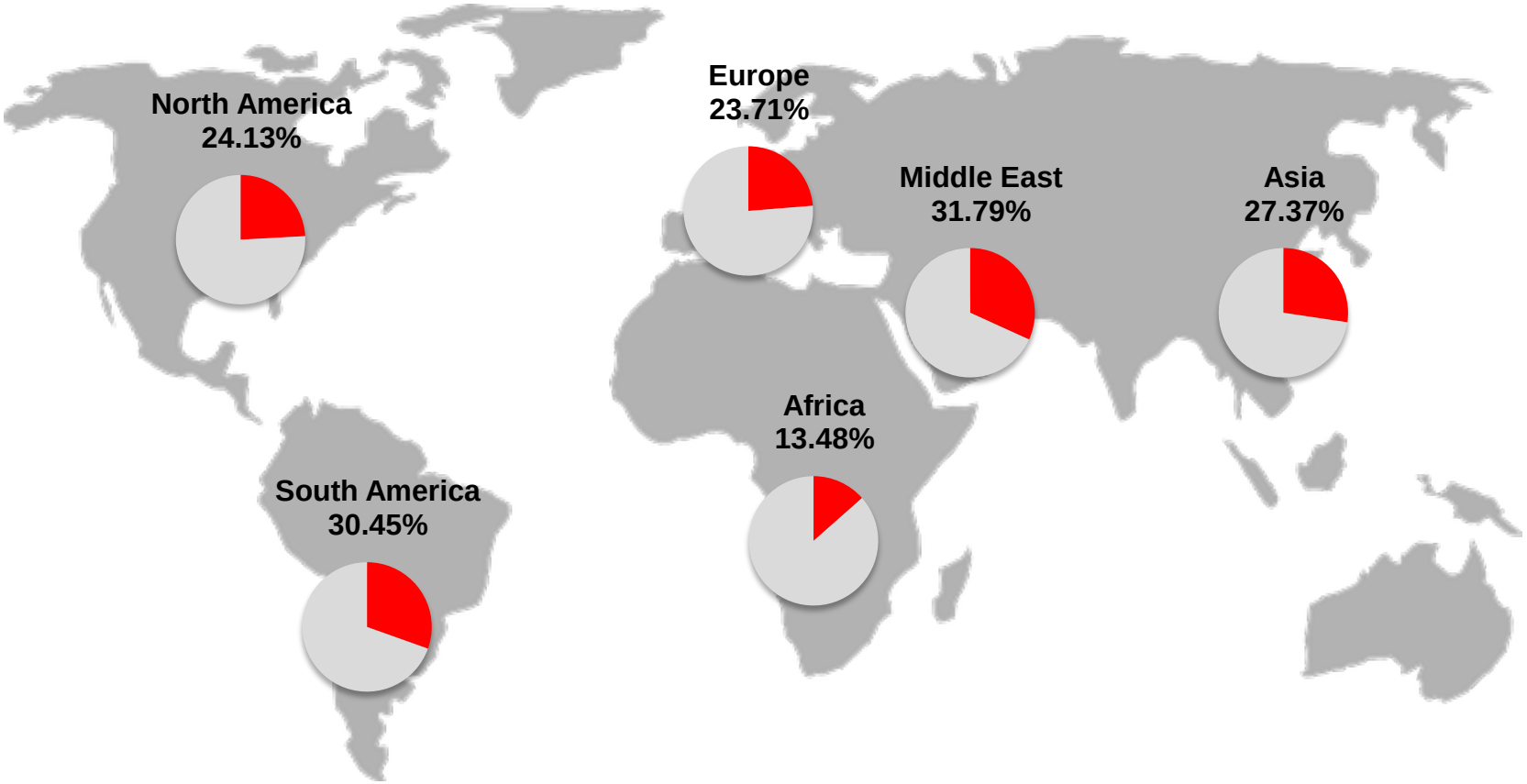
NAFLD affects up to 70% of obese patients, and is strongly linked to metabolic syndrome.

NAFLD is on a trajectory of becoming the leading indication for liver transplantation in the next decade.

1) An Overview of Dietary Interventions and Strategies to Optimize the Management of Non-Alcoholic Fatty Liver Disease. Diseases. 2017 Oct 22;5(4)

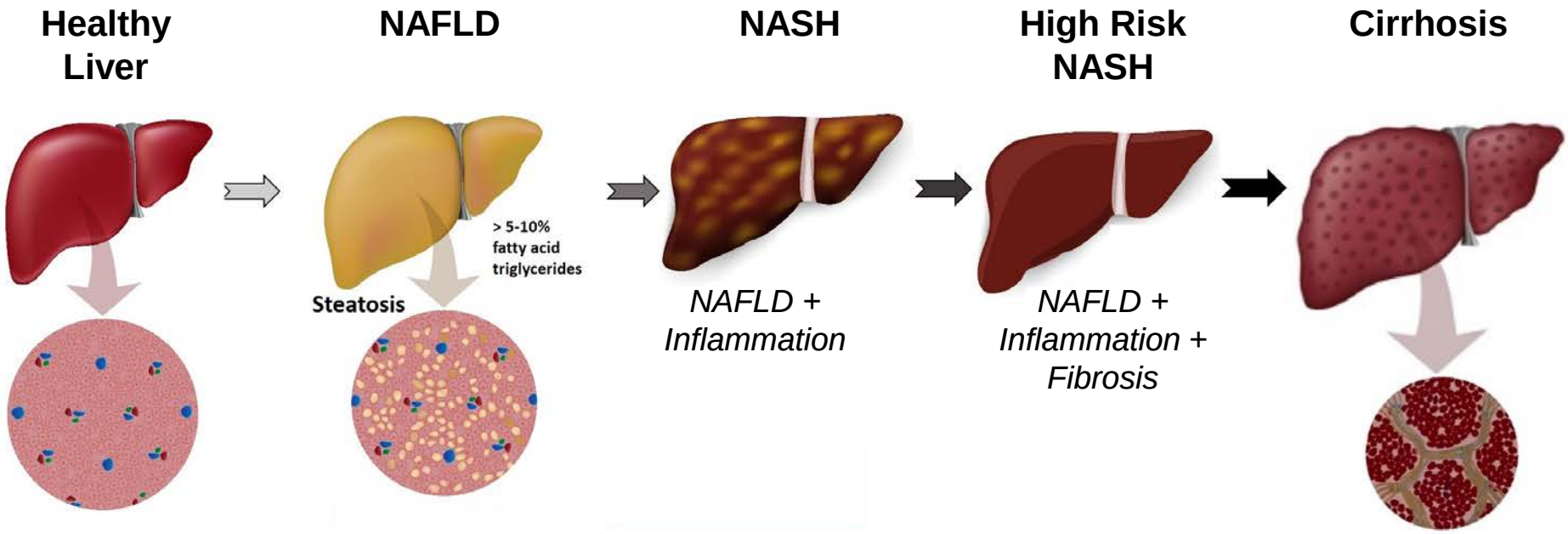
NAFLD is having a global impact

Global incidence rate of NAFLD



1) Contribution of Alcoholic and Nonalcoholic Fatty Liver Disease to the Burden of Liver-Related Morbidity and Mortality. Gastroenterology. 2016 Jun;150(8):1778-85.

If left untreated, NAFLD frequently progresses to NASH, Cirrhosis or Cancer



30 - 40%
of NAFLD patients progress to NASH in 6 years

10-30% of NASH patients progress to Cirrhosis

2-6% of NAFLD patients develop hepatocellular carcinoma

Few treatment options for NAFLD

✗ ***No approved pharmacotherapy***

✗ ***No approved procedures / devices***

Primary Treatment: Weight Loss / Lifestyle Modification[1]

Target: 7-10% Total Body Weight Loss & Maintain

1) An Overview of Dietary Interventions and Strategies to Optimize the Management of Non-Alcoholic Fatty Liver Disease. Diseases. 2017 Oct 22;5(4)

NAFLD Guidelines

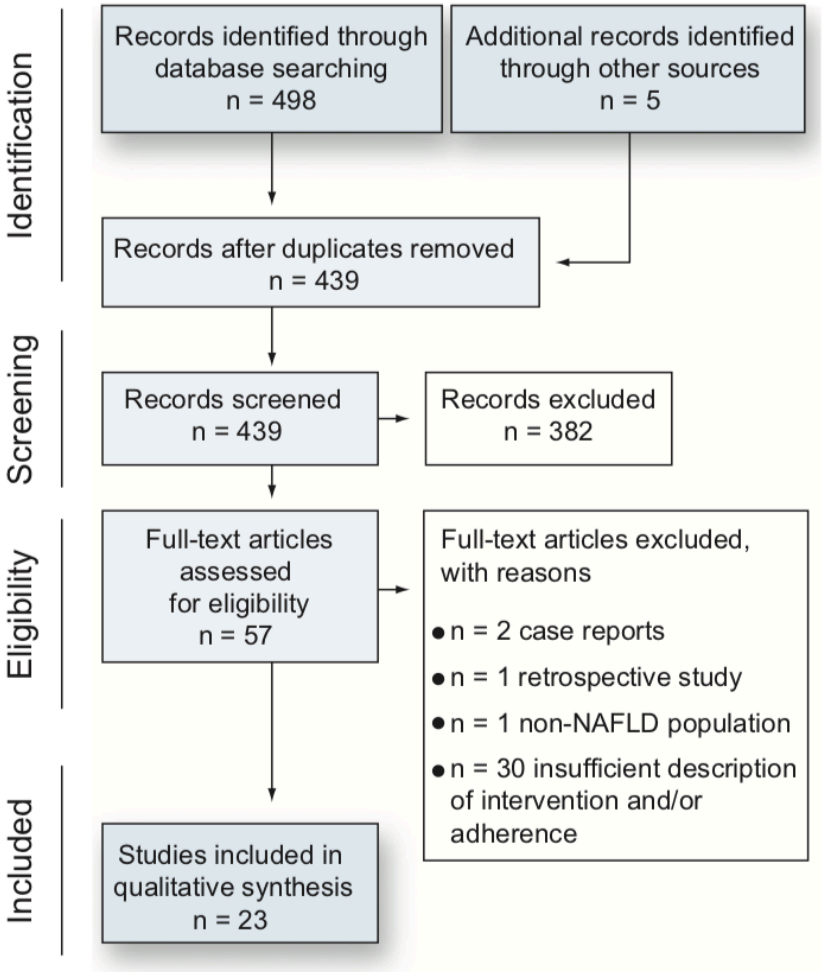
EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease☆

Area	Suggested intervention
Energy restriction	• 500-1000 kcal energy defect, to induce a weight loss of 500-1000 g/week
	• 7-10% total weight loss target
	• Long-term maintenance approach, combining physical activity according to the principles of cognitive-behavioural treatment
Macronutrient composition	• Low-to-moderate fat and moderate-to-high carbohydrate intake • Low-carbohydrate ketogenic diets or high-protein
Fructose intake	• Avoid fructose-containing beverages and foods
Alcohol intake	• Strictly keep alcohol below the risk threshold (30 g, men; 20 g, women)
Coffee drinking	• No liver-related limitations
Exercise/physical activity	• 150-200 min/week of moderate intensity aerobic physical activities in 3-5 sessions are generally preferred (brisk walking, stationery cycling) • Resistance training is also effective and promotes musculoskeletal fitness, with effects on metabolic risk factors • High rates of inactivity-promoting fatigue and daytime sleepiness reduce compliance with exercise

7-10% TBWL Target

Long-term maintenance approach

Meta-analysis of lifestyle interventions for NAFLD highlights the benefits of weight loss



- Strong correlation between weight loss and reduction of intrahepatic triacyglycerol concentration (IHTAG)
- ***Weight reductions of 4–14% resulted in statistically significant reductions in IHTAG (35–81%)***
  - Most rapid weight loss results with: Low (800–1800 kCal/day), very low-calorie diets (<800 kCal/day), and carbohydrate restriction (20–50 g/d)
- Greatest limitation is the variability in program adherence and the weight loss results of any of the programs

1) Lifestyle interventions for the treatment of non-alcoholic fatty liver disease in adults: A systematic review. Journal of Hepatology 2012 vol. 56 j 255–266.

Weight loss one of the most effective treatments for NAFLD

Multiple studies have shown weight loss is very effective:

- *75% remission rate* among NAFLD patients who lost >5% TBWL.[1]
- Weight loss of at least 5% TBLD (ideally 10% TBWL) through lifestyle changes demonstrated resolution of NAFLD or *improvement of fibrosis*
- >7% body weight loss has been shown to reduce fibrosis, and so referral to weight-management specialists for those patients with a BMI >30 is encouraged[2]

While weight loss is effective it is difficult to achieve,

>50% of patients fail to meet weigh loss targets[3]

1) Predictors for incidence and remission of NAFLD in the general population during a seven-year prospective follow-up. J Hepatol. 2012 May;56(5):1145-51.
2) Mistakes in nonalcoholic fatty liver disease and how to avoid them. October 19, 2017 By: Sarah A. Townsend and Philip N. Newsome – UEG publication
3) A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease. Hepatology. 2010 Jul;52(1):79-104.

ORBERA365:
Effective Non-surgical weight loss

ORBERA365™ is an effective weight loss option that fills the gap

- ✓ ***10-18% TBWL in 6 months***
- ✓ **15-20 minute, non-surgical procedure**
- ✓ **NOW with *12 months* of therapy to help patients maintain weight loss**

Globally proven with real world results

277,000

Devices placed worldwide[2]

#1

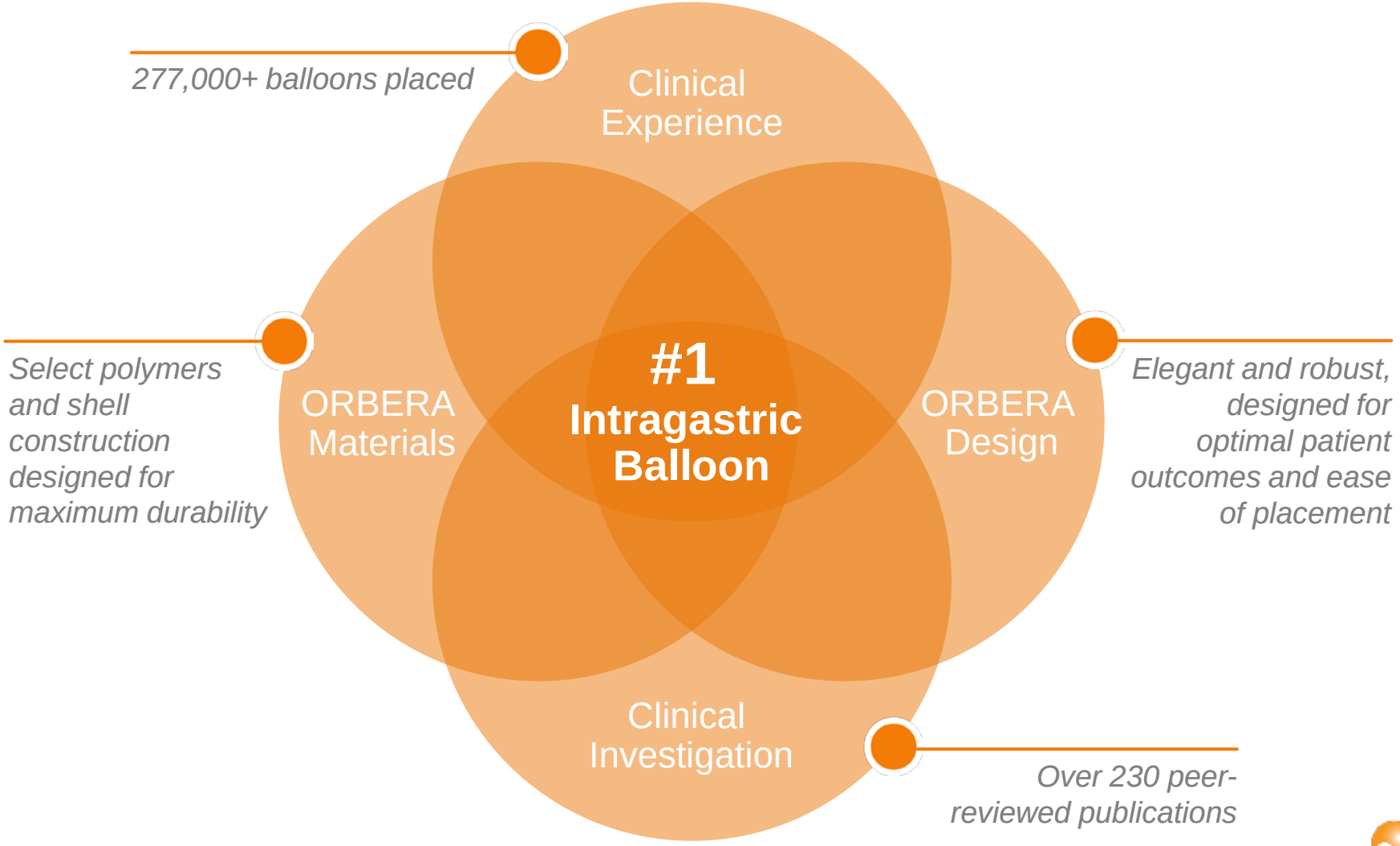
Most frequently used intragastric balloon around the world

365

Extended Support

Up to 12 Months

ORBERA:
#1 Weight Loss Balloon Around the World



Launched in 2017, ORBERA365™ expands the benefits of the #1 IGB

#1

Weight Loss Balloon

- 20+ year experience
- 277,000+ distributed
- 230+ published studies

365

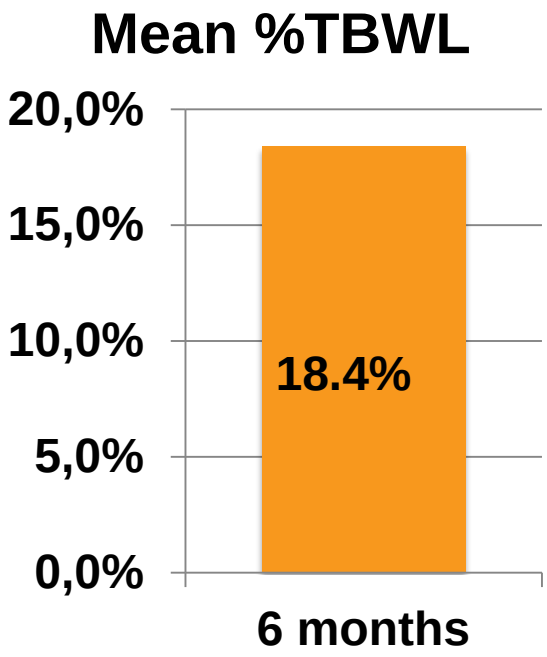
Extended Support

- Up to 12 months
- Expand offerings
- Weight maintenance

Orbera365™
managed weight loss system

Long and safe clinical history
Experience with 32,735 ORBERA

Significant Weight Loss



Experienced practices are achieving 58% greater weight loss than the FDA Pivotal Study

Strong Safety Profile

2.0%

Adverse Event Rate

Lowest rate of adverse events

Very Low Early Removal Rate

2.5%

Early Removal Rate

Few early removals in experienced practices

[4] Galvao Neto et al. **Brazilian Intragastric Balloon Consensus Statement (BIBC): practical guidelines based on experience of over 40,000 case“** SOARD, 2017

Effective rapid and Long-term weight loss maintenance

Rapid Weight Loss

- 3.1x the weight loss of diet & exercise alone
- patients tend to lose 10-15 Kg

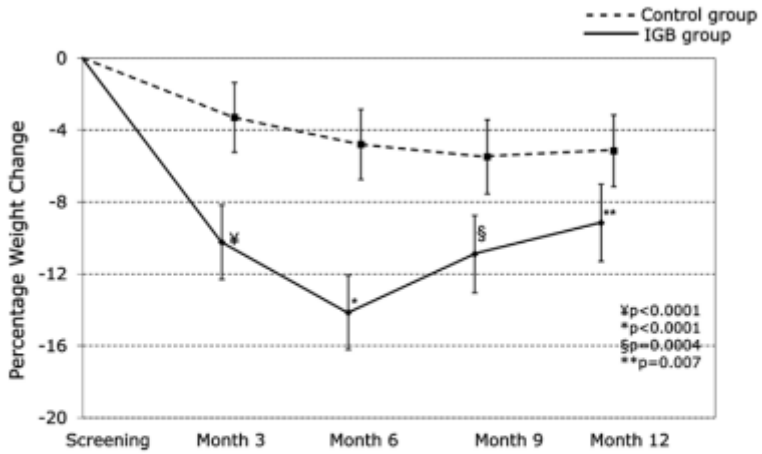


FIGURE 2 Percentage weight loss for the two treatment groups over the 12 month period of the study.

Long Term Weight Loss

- Meta-analyses indicated ORBERA IGB met leading US Bariatric & GI Society thresholds to use for primary obesity management and bridge to obesity surgery.
- 17 studies (1683 patients) had mean *%EWL of 25.44% at 12 months*
  - Exceeding their criteria of 25% EWL threshold as a primary obesity therapy.

[8] Abu Dayyeh, Kumar, Sullivan, Thompson et al. **"ASGE Bariatric Endoscopy Task Force systematic review and meta-analysis assessing the ASGE PIVI thresholds for adopting endoscopic bariatric therapies"** 2015 GASTROINTESTINAL ENDOSCOPY

Intragastric Balloons: Clinical data with Fatty Liver Disease

Intragastric Balloon Reduces Liver Volume in Super-Obese Patients[9]

- **Obese Patients: Surgery in patients with super-obesity (BMI ≥50) involves technical difficulties that are related, among other factors, to increased liver volume**
- **Intragastric Balloon: Intragastric balloons were used in these patients as means of reducing liver volume, excess weight and the risks of subsequent surgery**

In patients with super-obesity, preoperative treatment with intragastric balloon considerably reduces liver volume [9]

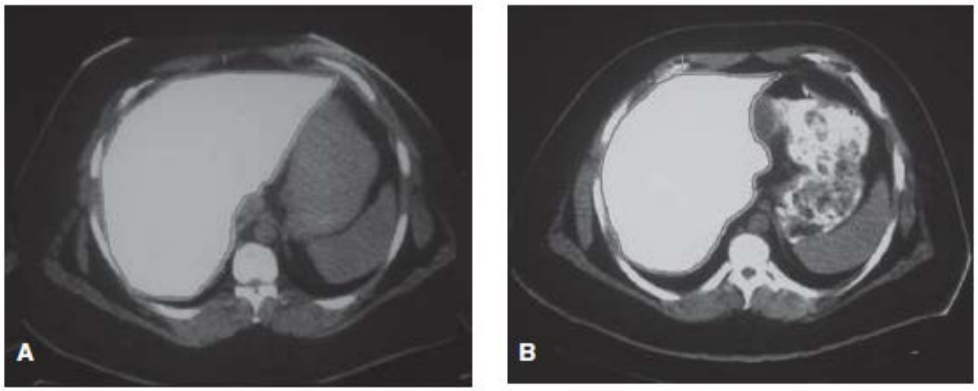


Figure 2. CT before intragastric balloon (A) and after 6 months (B) for measurement of reduction in liver volume.

9 Frutos et al. **Intragastric Balloon Reduces Liver Volume in Super-Obese Patients, Facilitating Subsequent Laparoscopic Gastric Bypass**. Obesity Surgery, 17, (2007) 150-154

Multiple studies have investigated impact of IGB induced weight loss on NAFLD / NASH

- Meta-analysis reviewed evaluating the impact of 6mth ORBERA / BIB for the management of NAFLD / NASH
  - 11 studies / 548 patients
  - Studies included: 7 case series, 3 case–control studies and 1 RCT with diet/sham endoscopy as the control arm
- Across the studies 6 month IGB treatment was able to deliver significant weight loss in this population with a mean BMI decrease of -4.98 kg/m2 (-5.6,-4.4)
- More importantly, studies demonstrated significant improvements in a number of key fatty liver indicators: Liver Enzymes, Hepatic steatosis and histological activity

Effect of Intragastric Balloons on Liver Enzymes: A Systematic Review and Meta-Analysis. Dig Dis Sci. 2016 Sep;61(9):2477-87

Multiple studied have investigated impact of IGB induced weight loss on NAFLD / NASH

Liver Enzymes

Significant reduction in liver enzymes

- ALT: -10.02 U/l *(95% CI, -13.2, -6.8)*
- GGT: -9.82 U/l *(95% CI, -12.9, -6.8)*

Hepatic steatosis

Improved after 6 mth of IGB treatment

- MRI / fat fraction: 16.7 ± 10.9 to 7.6 ± 9.8, p = 0.003),
- Ultrasound / severe liver steatosis: 52% to 4 %, p = 0.0001)

Histological Activity

NAFLD activity score was lower with IGB vs. sham endoscopy at 6 months

- 2 ± 0.75 vs. 4 ± 2.25, p = 0.03

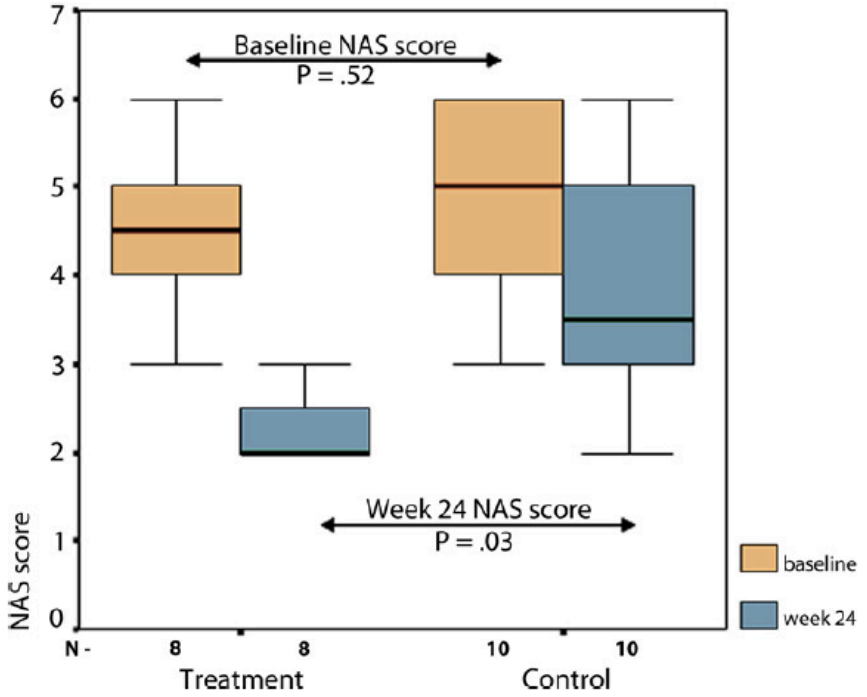
Effect of Intragastric Balloons on Liver Enzymes: A Systematic Review and Meta-Analysis. Dig Dis Sci. 2016 Sep;61(9):2477-87

Pilot Study specifically evaluated impact of ORBERA on NAFLD activity score

- Randomized sham controlled study that compared ORBERA + Diet / Exercise (n=8) vs. Sham + Diet / Exercise endoscopy (n=10)
- Liver histology assessed before placement and after balloon removal

NAFLD Activity Score

lower in ORBERA-treated compared with sham-treated (2 [0.75] vs 4 [2.25]; P=0.03)



Significantly lower NAFLD activity score with ORBERA Treatments

Mayo Clinic evaluation of ORBERA in NASH (DDW 2018)

- 6 month study with histologic and metabolic assessment of NASH before and after ORBERA balloon placement / removal (n=21)
- Significant weight loss with 80% of patients achieving ≥7%TBWL, recommended weight loss target for NASH. (Mean weight loss: 12.8%TBWL)

Resolution of NASH

- **65% of patients achieved resolution of NASH (NAFLD Activity Score ≤1)**
- **80% of patients had a ≥2 point improvement in NAFLD activity score**
- **15% had tissue evidence indicating regression of fibrosis (scarring)**

Metabolic Improvements

- HbA1c - decreased from 7.5±0.4 to 6.3±0.3; p=0.004)
- Central obesity / waist circumference - decreased by 8.6±13 cm; p=0.02

Weight loss with ORBERA resulted in significant regression of the inflammation and fibrosis of the liver

Intragastric Balloons: Patient Selection Considerations

What patients may benefit from IGB induced weight loss

- **Target Patients:**
  - NAFLD
  - compensated hepatic insufficiency
- **Exclusions:**
  - Acute hepatic insufficiency / end stage issues (i.e. ascites, uncorrectable coagulopathy with thrombocytopenia (<40,000), etc)
  - Portal hypertension
  - Varices – no gastric varices and no esophageal varices larger than grade 1
  - Delayed Gastric Emptying (delayed or abnormal)– screening with breath test or similar