Overview of Current literature on ESG

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Obesity and its comorbidities as you all know is a major health concern in the US and worldwide. In the US the percentage of the population with class/grade I obesity (bmi 30-34.9) is 20.6%, class II (bmi 35-39.9) is 8.8%, class III (bmi $\geq$ 40) is 6.9%.[1] 69.5% of the population has a bmi over 25. 29.4% of the population has a bmi between 30-39.9. Traditionally bariatric surgery has been focused on patients with a bmi of 40 or above, which is 6.9% of the population, and an unknown percentage of the population who have a bmi of 35-39.9 with comorbidities. Class I and Class II patients have been underserved with traditionally less effective medical therapies, however make up a much larger percentage of patients than Class III patients. According to the ASMBS updated position statement on bariatric surgery in class I obesity (BMI 30-35 kg/m^2) from 2018, "Access to bariatric surgery should not be denied to a patient with class I obesity associated to significant obesity-related co-morbidity simply on the basis of the BMI level…"[2] Although the risk associated with traditional bariatric surgery has dramatically decreased with more experience, better training and improved technology, it is not insignificant which has spurred significant research in to less invasive modalities to treat obesity, specifically Endoscopic Bariatric Therapies (EBTs). There are a myriad of EBTs available today as outlined by Dayyeh.[3]

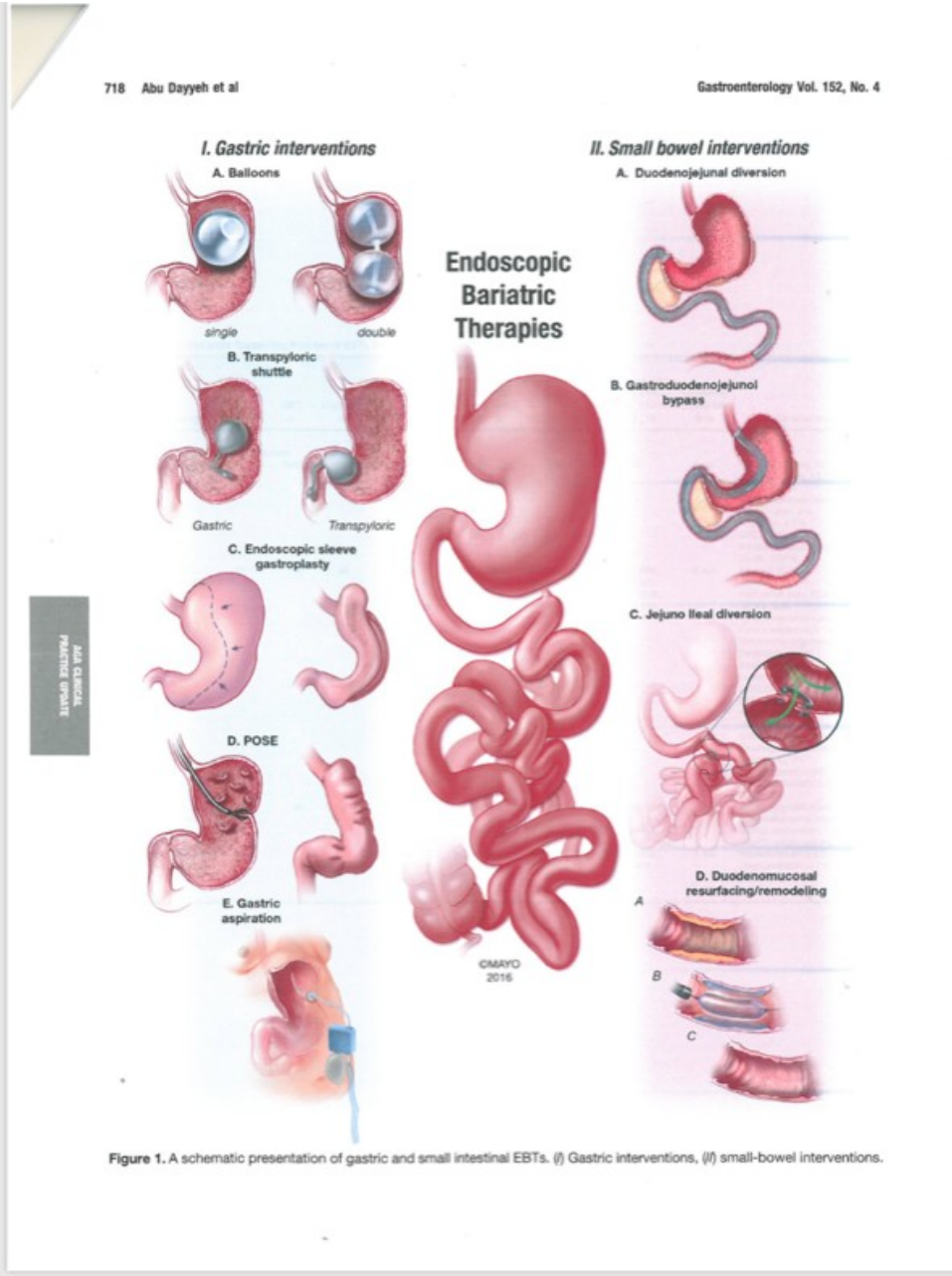

Figure 1. A schematic presentation of gastric and small intestinal EBTs. (*I*) Gastric interventions, (*II*) small-bowel interventions.

In order to, "provide a framework for, and a pathway towards, the development, investigation, and adoption of safe and effective endoscopic bariatric therapies (EBT),"[4] The American Society for Gastrointestinal Endoscopy (ASGE) and the American Society for Metabolic and Bariatric Surgery (ASMBS) jointly wrote a White paper, "A pathway to endoscopic bariatric therapies"[4] through the ASGE/ASMBS Task Force on Endoscopic Bariatric Therapy in 2011. In this White paper the "Potential indications for EBT" include 1. Primary therapy, 2. Early intervention/preemptive obesity therapy, 3. Bridge therapy and 4. Metabolic therapy. Grading the endpoints/outcomes of Endoluminal Interventions were defined including weight loss, safety, efficacy, durability and altered anatomy. Furthermore, the Task force states, "If this approach is developed and shown to be feasible, safe, and effective, endoscopic therapy may be appropriate for intervention to individuals with lower classes of obesity (i.e. Class I, bmi 30-34.9)."[4] As a direct result of this White paper, the ASGE established the PIVI

Initiative in 2012.[5] PIVI standing for Preservation and Incorporation of Valuable Endoscopic Innovations. At inception the PIVI Committee consisted of members of the ASGE/ASMBS Task Force on Endoscopic Bariatric Therapy:

Gregory G.Ginsberg, MD, Chair

Bipan Chand, MD, Co-Chair

Gregory A. Cote, MD

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Christopher C. Thompson, MD

Subsequent to the White paper in 2011 and the PIVI Initiative in 2012, the PIVI thresholds have been adopted by the ASGE and ASMBS as valid and an evidenced based way in which to evaluate EBTs. "Once endoscopic technologies meet an established PIVI threshold, those technologies are appropriate to incorporate into clinical practice presuming the appropriate training in that endoscopic technology has been achieved."[5] A summarized version of the PIVI thresholds is below:

- EBT intended as primary intervention in Class II/III should achieve a minimum of 25% Excess Weight Loss (EWL) measured at 12 months
- This goal will vary depending on the category or intent of endoscopic procedure (primary, early/preemptive, bridge, metabolic)
- EBT should be compared to a second treatment group, not Sham
- In addition, the %EWL difference between primary EBT and control group should be at least 15% and statistically significant
- 5% Total Body Weight (TBW) lost is the minimum threshold for non-primary EBT
- Risk with EBT $\leq$ 5% for serious adverse events
- If a low risk EBT proves to have significant impact on one or more obesity-related comorbidities, the threshold for intervention may extend to Class I Individuals (BMI 30-34.9)

Dayyeh et al in 2015 published the most comprehensive evaluation of EBTs to date in, "ASGE Bariatric Endoscopy Task Force systematic review and meta-analysis assessing the ASGE PIVI thresholds for adopting endoscopic bariatric therapies."[6] In this study 3 EBTs were assessed, the Orbera Intragastric ballon (IGB), Apollo Endoscopic Sleeve Gastroplasty (ESG) and the EndoBarrier duodenal-jejunal bypass sleeve (DJBS). The meta-analysis results indicated that the IGB met the PIVI thresholds for both primary and nonprimary bridge obesity therapy. %EWL at 12 months was 25.44%. %EWL over controls was 26.9%. %TBWL at 12 months was 11.27%, exceeding the 5% threshold for nonprimary (bridge) obesity therapy. The DJBS did meet %EWL PIVI threshold at 12 months with 35% EWL however failed to meet 15% EWL over controls. More data from the pivotal trial for DJBS was pending at the time of publication. Unfortunately, there was not sufficient data to evaluate the ESG as there were only 2 studies with 6 month follow-up at the time of its publication.[18,19] This is because ESG has only been performed since 2014. Fortunately, there have been numerous peer reviewed journal articles since

2015 that support the efficacy and safety of ESG, in which ESG meets PIVI threshold criteria for primary and nonprimary treatment and exceeds %EBW accomplished with IGB. Had These following studies been available in 2015, the Task Force would have come to the same conclusion for ESG as they did for the IGB.

Algahtani in 2019 in "Short-term outcomes of endoscopic sleeve gastroplasty in 1000 consecutive patients"[7] reported a n=1000, %TBWL of 15.0% and %EWL of 67.5% at 12 months. Severe adverse events were 1.9% with no mortality.

Morales in 2018 in "Modified endoscopic gastroplasty for the treatment of obesity"[8] reported n=148, %TBWL at 12 months and 18 months respectively at 17.53% and 18.5% and 1 severe adverse event of 0.67%, which was a bleed not requiring transfusion, with no mortality.

Saumoy in 2018 in "A single-operator learning curve analysis for the endoscopic sleeve gastroplasty"[9] reported a n=128, %TBWL at 12 months of 15.8% with a serious adverse event rate of 1.5% with no mortality.

Fayd in 2018 in "Endoscopic sleeve gastroplasty versus laparoscopic sleeve gastrectomy: a case-matched study"[10] reported n=54 for ESG, %TBWL at 6 months of 17.1% and an adverse event rate of 5.2%, compared to and adverse event rate of 16.9% for standard sleeve gastrectomy, with no mortality

Satoretto in 2018 in "Endoscopic Sleeve Gastroplasty (ESG) is a Reproducible and Effective Endoscopic Bariatric Therapy Suitable for Widespread Clinical Adoption: a Large, International Multicenter Study"[11] reported a n=112, %TBWL and %EWL at 6 months of 14.9% and 86.5% with an adverse event rate of 2.7% with no mortality

Novikov in 2018 in "Endoscopic Sleeve Gastroplasty, Laparoscopic Sleeve Gastrectomy, and Laparoscopic Band for Weight loss: How Do They Compare?"[12] reported a n=91for ESG, %TBWL at 12 months of 17.6%. Adverse events were significantly lower for ESG compared to LSG or LAGB, with no mortality.

Lopez-Nava in 2017 in "Endoscopic Sleeve Gastroplasty for Obesity Treatment: Two Years of Experience"[13] reported a n=154, %TBWL and %EWL at 24 months of 19.5% and 60.4% with no adverse events and no mortality.

Sharaiha in2017 in "Sleeve Gastroplasty Significantly Reduces Body Mass Index and Metabolic Complications in Obese Patient"[14] reported a n=91, %TBWL at 24 months of 20.9% with 1 serious adverse event = 1.1% and no mortality. At 12 months there were statistically significant reductions in comorbidities measured by A1c, Systolic blood pressure, waist circumference, ALT and triglycerides.

Jain in 2017 wrote a comprehensive review of published data on ESG in "Endoscopic Sleeve Gastroplasty-A New Tool to Manage Obeisty"[15] in which he reviewed 9 articles with a total n =281. All met PIVI thresholds with a serious adverse event rate of 1.1% with no mortality.

Lopez-Nava in 2017 in "Endoscopic Sleeve Gastroplasty for Obesity: a Multicenter Study of 248 Patients with 24 Months Follow-up"[16] reported a n=248, %TBWL at 24 months of 18.6% with a serious adverse event rate of 2.0% with no mortality.

Lopez-Nava in 2015 in "Endoscopic sleeve gastroplasty with 1-year follow up: factors predictive of success"[17] reported a n=25, %TBWL and %EWL at 12 months of 18.7% and 54.6% with 0 adverse events and no mortality.

The reporting of weight loss as either %TBWL vs %EWL is granted, not consistent and most bariatric surgeons are used to weight loss expressed as %EWL. The difference stems from how weight loss is expressed in the literature for medical weight loss, which is usually %TBWL. Most medical therapies do not exceed %TBWL of 5% at 12 months. As EBTs seem to be some what of a bridge between medical therapy and traditional surgical treatment there has been a mixing of the way weight loss is reported. As a result, the PIVI thresholds define weight loss as both %TBWL and %EWL. When reviewing studies reporting only %TBWL, %EWL can be estimated rather simply. 20%TBWL is approximately 50%EWL. 15%TBWL is approximately 38%EWL. In all the studies listed above, the 12 month %TBWL is equal to or greater that 15% which means %EWL is equal to or greater than 38% for ESG. The PIVI threshold for EBT as a primary intervention is 25%EWL at 12 months, therefore all studies with 12 month follow up show ESG meets PIVI thresholds for primary therapy. No mortalities associated with ESG have been reported worldwide and an average serious adverse event range far below 5% also meets PIVI thresholds for appropriateness for incorporation into clinical practice.

Further guidelines for incorporation of EBTs in clinical practice have been outlined by the ASGE in their position statement of 2015.[21] The recommendations are very similar to that put forth by the MBSQIP of the ASMBS. A bariatric practice already practicing within a MBSQIP certified bariatric program, easily meets the criteria put forth in this position statement, especially for surgeons experienced in advanced endoscopic procedures due to these practices already offering a full line of weight loss options, with in house dietician follow up and comprehensive multidisciplinary services.

I have been in communication with Apollo, the manufacturer of the Overstitch device used to accomplish ESG. According to them from 2014 through 2018, 5,000 ESGs have been performed worldwide. Of those, 1,400 were performed in the US. Any adverse event or serious adverse event that occurs associated with their Overstitch device in the US is reported to the FDA on a mandatory basis. The FDA's data base can easily be searched for adverse events associated with any FDA approved product through there Manufacturer and User Facility Device Experience (MAUDE) database.[20] If you were to query their database you will find 18 total adverse events associated with the Overstitch device since 2014.[22] I reviewed all 18 adverse and serious adverse events. 7 of those events reported are associated with ESG, however the number should actually be 6 as one adverse event was reported twice, once by the facility and once by the physician. Of the estimated 1400 ESGs done in the US from 2014 to present, only 6 adverse events have been reported, with no mortality. It can be reasonably argued therefore that the safety profile of ESG, as well as multiple recent peer reviewed publications showing PIVI thresholds being met by ESG, places ESG in the category of extremely safe EBT appropriate for integration into clinical practice for the treatment of all classes of obesity.

The ASMBS website has no position statement on ESG other than their position statement on EBTs in general in their last position statement "Emerging Endosurgical Interventions for Treatment of Obesity" published in 2009 and reviewed in 2013, which badly needs updating. Sadly, the references cited for this position statement are from 1991 to 2008. It appears the reviewer who stated that the statement

needs no updating was not aware of the ASMBS's own involvement in defining and evaluating EBTs with the ASGE as there is no mention of the White paper or the PIVI initiative published in 2011 and 2012. If we appropriately evaluate ESG under the guidelines put forth by the ASGE/ASMBS Task Force on Endoscopic Bariatric Therapy, the thresholds for safety and efficacy have been met by ESG and it is acceptable to incorporate into clinical practice.

ESG has less weight loss than traditional sleeve gastrectomy and should not be evaluated as a surgery as it is not. It is an EBT and should be judged by the criteria set forth by the ASGE/ASMBS for evaluating EBTs.

The ESG is not covered by any health plan. The IGB is also not covered by any health plans in the US however it is procedure acceptable to be incorporated into clinical practice as it meets PIVI thresholds as outlined by the ASGE/ASMBS and is FDA approved, as is the ESG. IGB is also performed only on a self-pay basis.

ESG also meets PIVI thresholds and has a much higher %TBWL and %EWL compared to IGB which is removed after 6 months as mandated by the FDA. ESG is being offered in a growing number of facilities on a self-pay basis.

All bariatric surgeries were also not covered by insurances initially. That being said; ESG is not surgery, it is an EBT and due to the reduced risk and cost it potentially serves a much larger population of patients (class I and II obesity) as compared to the population (class III obesity) served by traditional bariatric surgery.

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