Pantelis *et al. Metab Target Organ Damage* 2023;3:17
DOI: 10.20517/mtod.2023.27

Metabolism and Target Organ Damage

Opinion

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Metabolic bariatric surgery in face of new anti-obesity medications-10 + 1 challenges

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How to cite this article: Pantelis AG, Lapatsanis DP. Metabolic bariatric surgery in face of new anti-obesity medications-10 + 1 challenges. *Metab Target Organ Damage* 2023;3:17. https://dx.doi.org/10.20517/mtod.2023.27

Received: 22 Jul 2023 **First Decision:** 8 Sep 2023 **Revised:** 21 Sep 2023 **Accepted:** 11 Oct 2023 **Published:** 16 Oct 2023

Academic Editor: Wah Yang **Copy Editor:** Dan Zhang **Production Editor:** Dan Zhang

INTRODUCTION

Obesity is a chronic, progressive, multifactorial, and multistage disease[1-4]. Although difficult to define, disease is any condition that disrupts homeostasis and well-being[5]. Obesity disrupts homeostasis and well-being on many levels and in many ways, but for purposes of systemization, the obesity-related complications and barriers broadly fall into one (or more) of the following categories (conveniently characterized as the "M & Ms of obesity", according to the obesity management expert Dr. Arya Sharma): mechanical, metabolic, mental, and monetary[6]. Mechanical problems include all those issues that healthcare providers usually overlook but constitute the most important barriers for people suffering from obesity to living a healthy and quality life: chronic pain, osteoarthritis, gastroesophageal reflux and esophageal stasis, obstructive sleep apnea (OSA), urinary incontinence, intertrigo, idiopathic intracranial hypertension (previously known as pseudotumor cerebri), and plantar fasciitis, to name a few. Metabolic complications are the most notorious among healthcare providers and patients alike and comprise type 2 diabetes mellitus (T2DM), hypertension (HTN), dyslipidemia (DLP), metabolic dysfunction-associated steatotic liver disease (MASLD -previously termed non-alcoholic fatty liver disease or NAFLD)[7], cholelithiasis and cholecystitis, polycystic ovary syndrome (PCOS), infertility, and cancer (with sufficient evidence for at least 14 types of malignancy, including, in descending order of relative risk, endometrial cancer (7.1x), esophageal adenocarcinoma (4.8x), carcinoma of the gastric cardia and hepatocellular

carcinoma (both 1.8x), *etc.*[8-9]. Mental issues cover almost the wholeness of psychiatric disorders, including mood, anxiety, attention deficit, sleep, personality, addiction, psychotic, and cognitive disorders. Ultimately, monetary barriers associated with obesity are related to limited educational opportunities, unemployment, low income, disability, life, and health insurance issues, dependence on bariatric furniture and aids, oversized clothing, and futile expenses on weight loss programs.

Only recently has obesity been officially and broadly recognized (by WHO, AMA, and World Obesity Federation, to name a few bodies) as a disease rather than a disorder, a behavioral abnormality, or an individual's body choice[2,10-12]; nevertheless, this has paved the way for novel modalities and sustainable treatment options in the spectrum of its management. Among the treatment options for obesity, metabolic bariatric surgery (MBS) has been acknowledged as the most effective to date, with a favorable safety profile and reliable long-term outcomes regarding both weight loss and control of associated health problems[13-17]. Recently, a revolution has taken place in the field of obesity management with the advent of anti-obesity drugs, particularly the newer anti-obesity medications (NAOMs)[18]. Relevant literature is increasing exponentially and pertinent research is progressing vigorously, with different pathophysiologic mechanisms being addressed in the process. For the purposes of this article, we will focus on the use of the approved and commercially available medications glucagon-like peptide receptor agonists (GLP-1 RAs) liraglutide and semaglutide, as well as the dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 RA tirzepatide for weight loss. The main body of evidence for these medications stems from bundles of seminal studies, namely SCALE for liraglutide, STEP, SUSTAIN, and PIONEER for semaglutide, and SURMOUNT and SURPASS for tirzepatide. Are NAOMs threatening the long-standing prestige of MBS as our best weapon in the fight against obesity? Are they all about hype rather than hope? As usually happens in science, the truth lies somewhere in between. We will attempt to crystallize the current status of NAOMs compared to MBS through eleven established, emerging, and potential challenges.

NAOMS ARE AT LEAST AS EFFECTIVE AND SUSTAINABLE AS MBS FOR WEIGHT LOSS

Although overweight and obesity are defined by the WHO as "abnormal or excessive fat accumulation that presents a risk to health", the metrics implemented to quantify them are body weight and body mass index (BMI). These are inaccurate measures of body fat content: they do not measure body fat percentage and distribution, they do not account for geographical and racial discrepancies, they do not take the rest of the body tissues into consideration, and they do not constitute global assessments of metabolic health[19-22]. Regardless of their imperfections, weight and BMI can be easily measured and calculated, so their clinical use is widespread. In addition, BMI is the metric that the recently updated joint ASMBS-IFSO guidelines have endorsed as a tool for obesity classification and decision-making[23]. Moreover, the majority of relevant studies have quantified the bariatric effect of each intervention based on weight, BMI, and their derivatives, including ideal weight, percentage total weight loss (%TWL), percentage excess weight loss (%EWL), percentage excess BMI loss (%EBMIL), and so forth, in an attempt to standardize outcomes and allow for comparisons[24]. A simple measure of weight loss is of paramount importance for one more reason: to help patients (and even involved healthcare providers) set clear goals. This is of pivotal significance when attempting to benchmark an individual's performance in the course of their long journey towards losing weight and gaining health[25].

In order to determine bariatric effectiveness, we need to define "how much" and "for how long". In other words, we need to set objective and countable measurements regarding the amount of weight lost and the timing of the observed weight loss after a bariatric intervention. Regarding the former, a favorable weight loss response is considered a %TWL ≥ 20% and a %EWL ≥ 50%[26]. According to those, 97% of patients who have been submitted to bariatric surgery are expected to have a %TWL ≥ 20% by 1-2 years postoperatively

and 70.3% of patients to have maintained this weight loss at 10 years. Likewise, 93% of patients are expected to have experienced a %EWL ≥ 50% at 1-2 years and 61.8% to have maintained it at 10 years[26].

Claiming that MBS is effective for losing weight would be a self-referential statement. What is important is to examine the sustainability of the bariatric effect. Indeed, several studies have shown that bariatric operations offer long-term weight loss. Two seminal multicentric randomized trials on the most widely performed bariatric operations, SLEEVEPASS and SM-BOSS, have shown that laparoscopic sleeve gastrectomy (LSG) leads to a mean %EWL of 49% (95%CI 45%-52%) at 5 years, %EBMIL of 61.1% at 5 years, and %EWL of 43.5% (95%CI 39.8%-47.2%) at 10 years. The results for Roux-en-Y gastric bypass (RYGB) were even more favorable (although with no statistical significance), with a mean %EWL of 57% (95%CI 53%-61%) at 5 years, a %EBMIL of 68.3% at 5 years, and a %EWL of 51.9% at 10 years[27-29]. Furthermore, a systematic review and meta-analysis of all bariatric procedures showed a %EWL range of 45.9%-58.3%, depending on the procedure[30]. Similarly favorable results on %EWL have been published from the ASMBS: 65% for RYGB (42%-93%, n = 2,988), 58% for LSG (40%-86%, n = 953), and 66% for duodenal switch (DS; n = 50) at 5 years; 59% for RYGB (52%-82%, n = 795), 53% for LSG, 68% for biliopancreatic diversion (BPD; 63%-78%, n = 99), and 81% for DS (73%-94%, n = 344) at 10 years; and 51% (49%-59%) at 14 years for RYGB, 28% (28%-31%) for LSG at 25 years, and 69-71% for BPD/DS at 14-20 years[31]. Eventually, according to a very recent report of 7,755 post-bariatric patients (LSG = 3,791; RYGB = 3,964), who were followed for 3 years, a %EWL of 61.9% was observed for LSG and 69.5% for RYGB (P = 0.638)[32].

Even more promising results have been published for newer procedures, such as one-anastomosis gastric bypass (OAGB) and single anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S): mean %EBMIL of 81.8% ± 23.6% at 5 years and 62.3% ± 23.4% at 8 years for OAGB[33], mean %TWL of 33.4% ± 23.4% and %EWL of 64.1% ± 24.6% at 10 years for OAGB[34], and %TWL of 38% with %EWL of 87% at 5 years, along with %TWL of 34% and %EWL of 80% at 10 years for SADI-S[35]. A comparative study showed that, at 5 years, the %TWL was 40.8% for OAGB, followed by 37.2% for RYGB, and 35.1% for LSG. However, the follow-up rate at 5 years for this study was only 52%[36].

Conversely, there have been reports claiming that at 10 years postoperatively, the outcomes for LSG and adjustable banding (AGB) are equated at a %TWL of about 22%[37]. Additionally, a very recent monocentric study found that only 27.7% of patients who had been submitted to LSG maintained a %EWL ≥ 50%, whereas the mean %EWL at 10 years was only 35.9%, thus resulting in 80.5% of patients who experienced inadequate weight loss in the long run[38]. Indeed, bariatric failure, i.e., insufficient weight loss (IWL) and weight regain (WR), constitutes a very tangible mishap potentially affecting any bariatric surgery, with WR reaching 27.8% ≥ 7 years after LSG and 3.9% at 3-7 years post-RYGB[39]. WR occurs for a series of reasons, including neuro-hormonal mechanisms, non-adherence to postoperative nutritional and physical activity schemes, and technical issues (pouch and stomach dilatation, gastro-gastric fistula, *etc.*). Collectively, these negative outcomes underline the necessity of continuous effort on behalf of the patients, meticulous follow-up on behalf of the physicians, and further stress that obesity is a chronic disease rather than a time-confined condition[40,41].

Available NAOMs feature GLP-1 and its receptor as the pivotal players in exerting their biological effects. However, it has long been known that GLP-1 also plays a central role in orchestrating the metabolic and bariatric effects of relevant operations, along with other hormones such as leptin, ghrelin, and peptide YY, to name a few. An extensive analysis of the pathophysiology of GLP-1 and other incretins and anti-incretins is beyond the scope of this article but can be retrieved from other sources[42-44]. Nevertheless, it should be mentioned that the net biological effect of naturally occurring (endogenous) GLP-1 in humans is

primarily on the brain, where it acts to suppress appetite (in the brainstem and hypothalamus) and inhibit gastrointestinal motility and secretion (via parasympathetic inhibition)[45]. This is presumably the case with GLP-1 in the context of metabolic bariatric surgery, given that the anatomical alterations implemented by different procedures collectively lead to an increase in (endogenous) GLP-1. On the contrary, exogenous GLP-1 features a much more prominent impact on the pancreas (and other peripheral tissues), as well as the central nervous system, thus having a dual action on glycemic control and appetite, respectively. These differences are schematically represented and further analyzed in detail in Figure 1.

Clinically, NAOMs have been extensively studied in their respective seminal research. The bariatric effects of liraglutide, the oldest among the GLP-1 RAs, have been investigated in the context of the multinational randomized SCALE bundle of studies. The %TWL with 3.0 mg of liraglutide subcutaneously once daily ranged from 6% in diabetic patients to 8.4% in non-diabetic patients suffering from overweight and obesity during a 56-week follow-up period[51,52], while it reached 6.1% at 160-week follow-up[53]. The percentage of patients who reached a %TWL ≥ 5% ranged from 54.3%-63.2%, and those with a %TWL ≥ 10% ranged from 25.2%-33.1%. The equivalent bundle of seminal, multinational, randomized trials for semaglutide at a dose of 2.4mg administered subcutaneously once weekly are the STEP 1-5 studies, with a %TWL range of 7.9%-16%, depending on the presence (STEP-2) or absence (STEP-1) of T2DM[54,55], combination with intensive behavioral therapy (STEP 3)[56], weight loss maintenance[57], or long-term follow-up (104 weeks in STEP-5 *vs.* 68 weeks in STEP 1-4)[58]. The percentage of patients who had a %TWL ≥ 5% ranged from 57.1%-88.7%, whereas those with a %TWL ≥ 10% ranged from 28.7%-79%. Overall, GLP-1 RAs resulted in a mean difference of -7.1 Kg (95%CI -9.2 to -5.0) compared to control groups, according to a recent meta-analysis[59], and in a weighted mean difference of -5.39 Kg (95%CI -6.82 to -3.96) compared to placebo, according to another[60].

The bariatric efficacy of subcutaneous tirzepatide once weekly has been demonstrated in the SURMOUNT-2 study for diabetic patients (body weight loss ranging from 7.0-9.5 Kg) and the SURMOUNT-1 study for non-diabetic[61,62]. The latter demonstrated a %TWL ranging from 15%-20.9%, depending on the dose (5, 10, or 15 mg); those who reached a %TWL ≥ 5% range from 85.1%-90.9%, those who reached a %TWL ≥ 10% range from 68.5%-83.5%, and those who reached a %TWL ≥ 20% range from 30.0%-56.7%[62]. Interestingly, tirzepatide has proven to be superior to semaglutide once weekly regarding weight loss in patients with T2DM, according to the SURPASS-2 trial[63]. The weight loss that accompanies tirzepatide has been characterized as "staggering", given that up to 2/3 of participants achieved a reduction of body weight ≥ 20% at 72 weeks of follow-up, and has been compared to 17% mean weight loss that accompanies gastric banding (a procedure that has largely been abandoned worldwide), 25% mean weight loss for LSG, and 33% mean weight loss for RYGB[64]. Lastly, when all commercially available NAOMs were compared, weekly tirzepatide 10 mg and 15 mg led to a better bariatric outcome than weekly semaglutide 2.4 mg, daily semaglutide 0.4 mg, and liraglutide 3 mg, according to a recent network meta-analysis[65].

From a quick overview of the aforementioned outcomes on weight loss between MBS and NAOMs, it is easy but important to understand two outstanding characteristics: the lack of standardized reporting on weight loss and the lack of long-term results as far as NAOMs are concerned. Henceforth, no direct comparisons can be made at this point based on this data. Nevertheless, there are a couple of studies that directly compare the bariatric effects of liraglutide against those of MBS. In the oldest one, there was a 38 Kg weight loss 1 year post-bariatric surgery *vs.* 5 Kg over the same period for liraglutide[66]. In the more recent one, there was a %EBMIL of 32% for LSG *vs.* 24% for liraglutide with intensive lifestyle modification (ILM) *vs.* 14% for ILM alone[67]. Both these studies were underpowered (31 and 75 patients, respectively). More recently, a meta-analysis found that the mean difference in weight between bariatric surgery and GLP-1 RAs

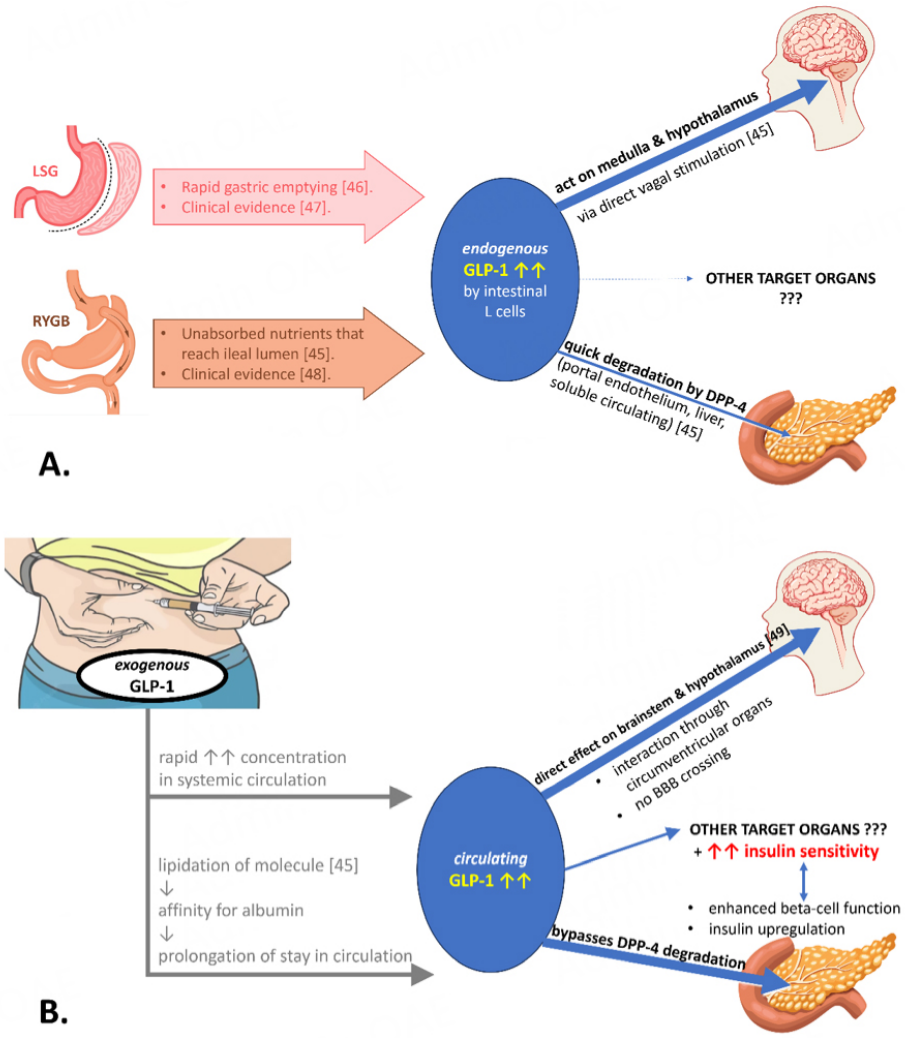

Figure 1. A simplified graphic demonstrating the differences between endogenous and exogenous GLP-1. (A) Taking sleeve gastrectomy (LSG) and Roux-en-Y gastric bypass (RYGB) as the archetypal examples of metabolic bariatric operations, both procedures lead to a net increase of endogenous GLP-1 with different mechanisms: LSG via rapid gastric emptying and RYGB due to the presence of undigested nutrients in the intestinal lumen in segments rich in L-cells, such as the ileum[45,46]. This has also been demonstrated clinically[47,48]. Consequently, GLP-1 that is secreted by intestinal L-cells is rapidly degraded by dipeptylpeptidase-4 (DPP-4) in the endothelium of the portal circulation and in the liver, as well as by a soluble circulating moiety of DPP-4. Simultaneously, GLP-1 interacts with afferent vagal fibers that transmit the signal to the brainstem and the hypothalamus. The net effect is that after MBS, endogenous GLP-1 primarily acts on the brain to inhibit appetite, while only 10% of the secreted GLP-1 reaches the pancreas; (B) Exogenously administered GLP-1, as the one contained in NAOMs, is readily available in systemic circulation, bypassing portal circulation and the deleterious effects of DPP-4. Additionally, these pharmaceutical molecules have undergone lipidation, which facilitates binding with albumin and prolongs their presence in the bloodstream. Consequently, they achieve robust glycemic control via direct action on the pancreas, where they increase insulin synthesis and secretion and enhance beta-cell function[49]. In the meantime, exogenous GLP-1 maintains its ability to act on the brainstem and hypothalamus by direct action. Although these molecules do not cross the blood-brain barrier (BBB), they exert their action through the circumventricular organs and several select sites adjacent to the ventricles[50]. Beyond the pancreas and the brain, GLP-1 has pleiotropic effects on several other tissues, the role of which has only recently started being elucidated. Among these effects, increased insulin sensitivity, either by direct action on target organs or secondary to weight loss, might act synergistically with enhanced beta-cell function and insulin upregulation in the pancreas, collectively improving metabolic control.

was -22.68 Kg (95%CI -31.41 to -13.96) for randomized trials and -25.1 (95%CI -40.61 to -9.60) for observational studies, whereas the respective figures for BMI were -8.18 Kg/m^2 (95%CI -11.59 to -4.77) and -10.60 Kg/m^2 (95%CI -17.22 to -3.98), respectively[68].

To sum up, there are some issues that need to be addressed and resolved by future research. First, there needs to be uniform reporting on bariatric outcomes, since NAOM studies only mention weight loss and %TWL, whereas bariatric studies additionally refer to %EWL (with or without %EBMIL), which generally represent more objective metrics. Second, current evidence on NAOMs stems from randomized (i.e., "idealized") trials, which mainly address their *efficacy*, whereas bariatric operations have also been tested in real-time conditions, enabling the assessment of their *effectiveness*, i.e., how well these operations work in practice. Third, NAOMs need to be tested against the challenge of time, given that the longest-term relevant study lasted only 160 weeks, whereas long- and very long-term outcomes are available for MBS. Last but not least, the implementation of a better metric than BMI, which can differentiate lean body mass from visceral fat, applies not only to bariatric studies but also to ones involving NAOMs, since all relevant seminal trials have shown that these drugs also contribute to lean body mass loss[69].

NAOMS ARE AS EFFECTIVE AS MBS (OR EVEN MORE) FOR IMPROVING (AND EVEN RESOLVING) DIABETES (AND OTHER ASSOCIATED HEALTH PROBLEMS)

The superiority of MBS over conventional treatment and lifestyle modifications in controlling T2DM has been demonstrated in multiple randomized studies[70-74], with a cumulative 3-year remission rate of 37.5% with surgery *vs.* 2.6% with medical or lifestyle interventions[75]. According to a recent meta-analysis of 12 relevant studies, the odds ratio of T2DM remission for bariatric surgery compared to control was 0.06 (95%CI 0.02-0.25), whereas the respective OR for complete and prolonged remission was 0.12 (95%CI 0.02-0.72)[76]. Most importantly, T2DM remission, which occurs with virtually all bariatric operations, has proven to be sustainable, with 5-year outcomes showing remission rates of 19% for AGB, 23% for LSG, 29%-37% for RYGB, and 63% for BPD *vs.* 0%-5% for non-surgical interventions, depending on the study[15,77,78], and 10-year outcomes showing remission rates of 25% for RYGB and 50% for BPD *vs.* 5.5% for medical therapy[17]. Additionally, a recent meta-analysis of 31 trials (1,906 patients in total) on complete or partial remission of T2DM showed that, compared to RYGB, LSG had a similar 5-year remission rate (OR 1.08, 95%CI 0.59-1.97), OAGB was superior (OR 3.71, 95%CI 1.16-12.55), while medical treatment was inferior (OR 0.05, 95%CI 0.02-0.13)[79]. This has been pretty much the evidence that has led to the establishment of the term "metabolic bariatric" surgery instead of simply "bariatric" to characterize the array of operative options that combat obesity along with its metabolic sequelae[80]. The only statistically significant mechanism by which glycemic control and T2DM remission seem to be achieved after MBS is via the increase of postprandial levels of GLP-1[81].

For NAOMs, the situation regarding diabetes control has been more straightforward since these medications were initially intended for the treatment of T2DM. This effectiveness has been shown in multiple systematic reviews and meta-analyses, in the context of which liraglutide, semaglutide (both injectable and oral forms), and tirzepatide demonstrated better glycemic control than conventional T2DM therapy[82-85]. Most importantly, NAOMs have shown effectiveness against other components of metabolic syndrome, such as cardiovascular events, OSA, MASLD, *etc.*[86-89]. By analogy, Aminian *et al.*, in one of their seminal studies, have shown that among patients living with obesity and T2DM, MBS was associated with significantly lower major cardiovascular events and reduced all-cause mortality (HR 0.59, 95%CI 0.48-0.72) compared to nonoperative management[90]. Interestingly, no direct comparisons between NAOMs and MBS have been made or have been possible so far regarding glycemic control and resolution of T2DM, perhaps because surgery has not been established as a standard of care for T2DM by patients and (most) healthcare providers alike. But on the other hand, would it be useful to compare NAOMs and MBS instead of evaluating their synergistic or complementary effects in the persevering battle against "diabesity"?

NAOMS ARE SAFER THAN MBS

MBS has become equally safe or even safer than most "routine" laparoscopic operations. The accumulation of experience, the use of laparoscopic techniques almost exclusively, the implementation of quality control programs, and the accreditation of bariatric surgeons by official bodies have been the main contributors to this[91]. In the immediate postoperative period (i.e., within 30 days), the most frequently encountered and clinically important complications are hemorrhage (0.7%), wound infection (0.5%), urinary tract infection (0.3%), venous thromboembolism (VTE -0.3%) and leak (0.2%), with an overall mortality rate of 0.11%, readmission rate of 4.21%, and reoperation rate of 1.35%, according to an ASMBS-NSQIP quality review of more than 135,000 post-bariatric patients[92]. On a comparative basis, LSG seems to be the safest, followed by OAGB, SADI-S, and finally RYGB[93-95]. Hypoabsorptive procedures, especially RYGB, are notorious mostly for long-term complications, particularly those related to malabsorption and micronutrient deficiencies[96]. This is among the reasons why minimally hypoabsorptive procedures such as OAGB and SADI-S have gained popularity lately.

A common motif among NAOMs is that they feature a dose-dependent bariatric effect, which comes at the cost of equally dose-dependent adverse manifestations. This is documented in all seminal trials (SCALE, STEP, SURMOUNT, and SURPASS), and most adverse events involve transient, non-specific, mild-to-moderate gastrointestinal disturbances (nausea, vomiting, abdominal cramps, constipation, diarrhea)[53,62,97,98]. Certain concerns have been raised about the relationship between liraglutide and acute pancreatitis[99]. In this context, it has been shown that liraglutide causes a dose-dependent elevation in amylase and lipase, but this does not warrant routine monitoring in otherwise asymptomatic patients. Gallstone formation and biliary disease, primarily or secondary to weight loss, may also contribute to this condition[100]. Interestingly, with this respect, there has been a recent publication of 36 cases of acute cholecystitis associated with the use of GLP-1 RAs reported by the Federal Drug Administration (FDA) after commercial approval of the respective NAOMs[101]. Another absolute contraindication for this category of drugs is a family history of thyroid cancer, particularly the aggressive form of medullary thyroid carcinoma (MTC, and consequently MEN2A syndrome)[53]. Even more concerning, however, is the fact that a recent analysis demonstrated that long-term use of GLP-1 RAs increases the risk of thyroid cancer (adjusted hazard ratio – aHR 1.58; 95%CI 1.27-1.95) and MTC (aHR 1.78; 95%CI 1.04-3.05)[102]. Another alarming adverse effect of NAOMs is suicidal ideation, based on recent reports[103]. No causal relationship has been shown so far, but the central-acting properties of these mediations could potentially explain this kind of treatment complication. In this context, the European Medicines Agency (EMA) has prompted monitoring of these medications regarding suicide risk, and its review is expected to be completed in November 2023[103]. It is worth mentioning, however, that similar correlations have been found between self-harm/suicidal ideation and bariatric surgery at a rate of 2.7/1000 patients (i.e., almost double the risk of BMI-matched controls)[104]. Consequently, it remains elusive whether this complication should be attributed to the drugs themselves, the weight loss, or the so-called "gut-brain connection"[105,106].

NAOMS RESULT IN BETTER COMPLIANCE THAN POST-BARIATRIC FOLLOW-UP

Bariatric surgery is certainly not the end of the road but the beginning of an enduring effort for a patient living with obesity to regain their health. One of the pivotal steps in the continuum of obesity management is the follow-up after MBS, at least in the short term[107]. Indeed, adherence to long-term follow-up has been shown in several studies not to be significantly associated with sustainable weight loss[108,109]. On the other hand, compliant post-bariatric patients typically present with non-resolving obesity-related health problems and vitamin deficiencies, as compared to their non-adhering peers[108]. It seems that more important than adherence to follow-up is the implementation of pre- and postoperative educational programs, the individualized management of each patient by a multidisciplinary team, and the active involvement of

primary care providers[41,110].

The situation of compliance with NAOMs is not much different, but for other reasons. According to a recent report, only 1/3 of patients prescribed semaglutide 2.4 mg weekly were still taking it one year after its onset[111]. The cause is multifactorial: the high cost accompanied by burdensome insurance coverage, the high demand that has led to significant supply shortages, and the increasing incidence of side effects that accompany widespread use are all in part responsible for non-compliance in the long run[112]. The need for daily (or even weekly) injections is also confronting, but the introduction of newer preparations in swallowable form (like oral semaglutide) could effectively address this issue[113]. In any case, withdrawal of NAOMs leads to (rebound?) regaining two-thirds of weight lost and elimination of cardiometabolic benefits within one year[114]. Consequently, the concept of obesity as a disease needs to be consolidated by all involved parts (insurance bodies, pharmaceutical companies, healthcare providers, and patients) in order to safeguard the long-term compliance of NAOMs.

NAOMS WILL BENEFIT MANY MORE PATIENTS THAN SURGERY

This is one of the most controversial statements regarding NAOMs because it has two levels of comprehension. On the one hand, it signifies the "democratization" of access to effective treatments against obesity without the need for major anatomical changes and physiological stress as the ones accompanying surgery. On the other hand, however, as it has been stressed by insurance market experts and certain stakeholders, their cost is additive and will impose an unsurpassable burden on health systems and insurance companies. This additive cost owes to 3 components: (1) the high selling price of the medications themselves, which is something to be expected for any novel pharmaceutics with such an impressive efficacy; (2) the need for long-term administration, which is also a feature of all treatments for chronic conditions; (3) the high demand on behalf of the public, given that NAOMs constitute effective solutions to a disease with a high prevalence worldwide[115]. Contrary to what usually happens for other chronic conditions' medications, however, the UK has suggested only 2-year coverage for NAOMs, based on an estimated annual cost of 13,618 USD per payer[116]. The scientific support behind this is that longer-term studies are needed to determine how the pleiotropic positive impact of NAOMs on body weight, waist circumference, glycemic control, blood pressure, kidney function, and liver steatosis translate into clinical benefit[117]. Even the postulated high cost of NAOM therapy is not uniform across different drugs: according to a recent report, the therapy with semaglutide was estimated to be > 5,000 USD more expensive than that of liraglutide in absolute numbers (22,878 *vs.* 17,585 USD), whereas the cost-needed-to-treat per 1% weight reduction was 3,256 for liraglutide *vs.* 1,845 for semaglutide[118].

Similar queries had been submitted in the early days of MBS[119]. The cost-effectiveness of bariatric surgery has been repeatedly confirmed in multiple studies to date and has been validated in large-scale models and comprehensive meta-analyses[120,121]. The cost-effectiveness of MBS might differ among procedures and populations, but it has withstood the test of time.

NAOMS NEED TO BE HELD BEFORE SURGERY TO OPTIMIZE PATIENT SAFETY-HOW IS THIS RELATED TO BARIATRIC SURGERY?

Another hot topic on the use of NAOMs, which corresponds to their side effects but also is intrinsically related to their perioperative management and thus directly connected to any elective surgery, including MBS, is the need to hold them because of delayed gastric emptying (DGE) and retained solid gastric contents. GLP-1 analogs have a known mechanism of DGE, which can be triggered even after a single dose. Interestingly, it may attenuate after multiple doses in healthy individuals, whereas in diabetic patients, this effect may persist in the long run[122]. This might have direct implications for elective surgery, as it has been

shown on a case-report basis[123]. In case a patient living with obesity who is already taking GLP-1 RAs decides to undergo MBS, this might have several sequelae. Firstly, DGE poses a risk for aspiration of gastric contents. Then, the presence of solid gastric contents might lead to incomplete gastric evacuation, adding to the perplexity of bariatric surgery (suboptimal volume reduction of the stomach or gastric pouch, increased intraluminal pressure, and thickened gastric tissue). This, in turn, might lead to an increased risk of equipment failure and subsequent manifestation of postoperative complications (hemorrhage, leak). This might be a rare-case scenario at the moment, but the time of combined management of obesity with both NAOMs and MBS is not so distant. Of course, everything remains to be validated in clinical practice.

NAOMS CANCEL THE "FOOD NOISE", WHEREAS MBS DOES NOT

People living with obesity frequently complain that they constantly think about their next meal and that they "live to eat instead of eating to live"[124]. This constant "food noise" has not enjoyed a proper definition or quantification metric so far, but it is a very tangible problem, even after MBS. Indeed, post-bariatric patients who present to their scheduled follow-up visits more often than not complain of this "constant hunger", which sometimes is responsible for bariatric failure (IWL and WR). The underlying mechanism remains elusive, but hedonic pathways may be implicated in its pathophysiology[18,125]. This constant craving for food seems to be abated by both semaglutide and tirzepatide, a feature that highlights the central actions of their GLP-1 agonistic effects. Although this cancellation of the "food noise" has not been documented after MBS, the prevalence of food addiction was reduced by more than half after surgery (preoperative: 32%, 95%CI 27%-37%; postoperative: 15%, 95%CI 12%-18%), according to the most recent relevant meta-analysis[126]. In this context, NAOMs could serve as invaluable adjuncts after bariatric surgery, aiding patients in maintaining their maximum bariatric outcomes without relapsing to pathologic eating behaviors.

NAOMS CURB ADDICTIONS, WHEREAS MBS TRIGGERS THEM

MBS is notoriously connected to alcohol use disorders (AUD) and abuse of other substances. Post-MBS alcohol misuse, abuse, or dependence ranges from 1.3%-28.4%, depending on the study[127]. According to the most recent systematic review, after bariatric surgery, a patient is almost three times more likely to develop alcohol abuse as compared to the preoperative period[128]. The underlying etiopathogenesis remains largely unknown, but several mechanisms have been proposed, including direct effects of gut peptides on centers in the brain, altered alcohol pharmacokinetics, genetics, epidemiological factors, past and family history of alcohol abuse, social factors and supportive systems, *etc*.[127]. The attractive theory of "addiction transfer" (*aka* cross-addiction, addiction shift, symptom substitution) has been investigated as a potential mechanism, in the context of which bariatric patients practically exchange their addiction to food with another type of addiction, including alcohol, illicit drugs, and opioid medications[129]. This may be mediated by a dysregulation in the dopamine reward processing system, either directly or via ghrelin and other hormones[106]. One of the main drawbacks of this theory is that it takes food addiction for granted in those suffering from obesity, whereas this entity is multifactorial and rather more complex. Indeed, food addiction ranges from 14%-58% preoperatively and falls dramatically to 2%-14% after MBS[130]. Interestingly, food addiction pre- or postoperatively is not significantly correlated with the bariatric outcome, but it is associated with a broad spectrum of psychopathology[131]. Additionally, AUD tends to develop 1-2 years post-MBS, whereas one would expect it to manifest itself shortly after the operation. Eventually, there is heterogeneity of AUD among different types of bariatric surgery, with those who have undergone RYGB being more susceptible (OR 1.83, 95%CI 1.51-2.21)[128]. Even more concerning is the increased risk of self-harm and suicide after MBS, with a prevalence of 2.7 cases per 1,000 patients (95%CI 1.9-3.8 per 1,000 patients) for suicides and 17 per 1,000 patients (95%CI 10-30 per 1,000 patients) for suicide/self-harm attempts, according to a meta-analysis[104].

With the widespread use of NAOMs, additional benefits have emerged beyond their effectiveness on weight loss and control of T2DM, including loss of interest in addictive behaviors like alcohol abuse, smoking, nail biting, *etc*.[132]. Relevant reports remain scarce, but the confirmation of this effect would warrant further investigation of the role of GLP-1 in central pathways of the reward system. One experimental study in monkeys has shown that liraglutide, and to a lesser extent exenatide (another GLP-1 RA), significantly reduce alcohol consumption without adverse effects on emesis or water intake[133]. According to another study in humans, exenatide does not significantly reduce heavy drinking, but causes significant attenuation of the reactivity to alcohol, as observed through functional MRI, in specific parts of the brain pivotal for drug reward and addiction (ventral striatum and septal area)[134]. These potentially beneficial effects of NAOMs on AUDs prompt the need for synergy with MBS in the post-bariatric setting.

MBS REQUIRES SPECIAL TRAINING, RESOURCES, AND INFRASTRUCTURES; NAOMS DO NOT

Bariatric surgery is a specialized task of advanced laparoscopic upper gastrointestinal (GI) surgery. For this reason, it requires both proficiency and dexterity in upper GI surgery and postgraduate training in an array of specific bariatric procedures. Beyond the operative skills, bariatric surgeons are supposed to be equipped with escalating levels of knowledge and skills on obesity and its pathophysiology, principles of management, principles of diagnostic and interventional endoscopy, ethics and professionalism, comprehensive medical evaluation of patients living with obesity, and bariatric candidates with consultation capability in lifestyle modifications (including but not limited to nutrition and physical activity), competence in the medical management of obesity, and so forth[135]. This can (and should) be achieved in the form of official fellowships, courses, and workshops, each process of which bears its own requirements in terms of curriculum, infrastructure, expenses, and working hours. An extensive reference of the available programs in each health system is beyond the scope of this article. What should be underlined, however, is that organized training (as opposed to the empirical and sporadic performance of bariatric surgery) is *sine qua non*, in order to provide safe, effective, and sustainable bariatric services, as it has been shown after the implementation of relevant programs in different parts of the world[136-138]. Having said that, accreditation does not ensure patient safety, as pertinent evidence is contradictory[139-140].

The medical management of obesity, in the context of which NAOMs are prescribed, seems more straightforward. Nevertheless, specialized training in the management of patients living with obesity is not only desirable but also mandatory, given the pluralistic nature of the disease. The Strategic Centre for Obesity Professional Education (SCOPE®) program under the auspices of the World Obesity Federation constitutes the "international gold standard" (as per the organization's own declaration) for healthcare providers' training in obesity and the only one that provides relevant certification following online module attendance and assessment[141]. Several other programs and seminars are available at local and regional levels. Obviously, the learning curve and required time are not the same as excelling bariatric techniques, but NAOMs, their pathophysiologic consequences and their complications are supposed to be addressed in a setting of relevant expertise.

MBS REINFORCES THE STIGMA OF OBESITY, WHEREAS NAOMS FACILITATE THE "CHRONIC DISEASE" CONCEPT

Disease stigma is a social phenomenon that results from "misconceptions and biases" that end up in a vicious circle of "exacerbating suffering on individuals with diseases"[142], as it has diachronically happened with cholera, leprosy, tuberculosis, syphilis, drug addiction, mental illness, HIV/AIDS, *etc*.[143]. The weight/obesity stigma is promoted by media and the entertainment industry, where the stereotype of lean people being clever, kind, generous, beautiful *vs*. "obese" being rude, aggressive, retarded is reproduced; it

constitutes one of the main reasons for bullying among the youth; it inculcates "explicit and implicit" bias among healthcare professionals, as "obese" patients are considered non-compliant or negligent about their health; it results in workplace discrimination and so forth[142]. The caveat is that the weight stigma may lead to a social automatism in the context of which patients living with obesity promote their condition as a personal choice, thus demoting the significance of the problem and its sequelae and perpetuating its root causes.

The obesity stigma is inherently connected to but (should be) differentiated from the stigma towards bariatric surgery, which in part may justify the reason why, although MBS remains the most effective option for the treatment of obesity, its penetrance is only 0.1%-2% among eligible individuals worldwide[144]. Interestingly, an initiative to investigate the perceptions and consequences of this stigma has recently been launched on a multinational basis[144]. One of the aspects of the "bariatric stigma" is the quick loss of weight that is accompanied by a variable time of absence from work and social interactions for the purposes of perioperative optimization and postoperative recovery. On the contrary, pharmacotherapy with NAOMs can be kept confidential more easily and weight loss is effective but more gradual. Additionally, as new pharmaceutical forms are introduced into clinical practice, like once-weekly subcutaneous injections instead of daily ones, or even NAOMs in the form of pills, the concept of obesity as a chronic disease can be fostered more easily. It is important to realize that this change in point of view could not only weaken the obesity stigma but, concomitantly, the bariatric surgery stigma as well, as it will be easier to promote (on behalf of obesity experts) and accept (on behalf of non-specialist healthcare providers, patients and the society) surgery as part of an integrated healthcare plan rather than an isolated invasive intervention aiming to improve body image.

COMBINING NAOMS WITH MBS-TOWARDS AN INTEGRATED STRATEGY FOR THE MANAGEMENT OF OBESITY

This article/mini-review focused on semaglutide, liraglutide, and tirzepatide. Multiple novel drugs are underway in the phase of development, clinical trials, or pending license for commercial use, including GLP-1 glucagon dual agonists, novel GIP/GLP-1 dual agonists, GIP/GLP-1/glucagon triple agonists, GIP RAs, novel GLP-1 RAs, glucagon analogs, leptin sensitizers, neuropeptide Y receptor type 2 (Y2R) agonists, amylin/calcitonin dual agonists, amylin analogs, drugs targeting the ghrelin pathway, mitochondrial uncouplers, appetite suppressants, *etc*.[125]. A few examples: survodutide, a dual GLP-1/glucagon RA, led to ≥ 20% weight loss in almost 40% of patients with obesity and without T2DM in a phase 2 trial[145]; retatrutide, a triple GIP/GLP-1/glucagon RA safely led to ≥ 5% weight loss in all participants and 24% weight loss on average at 48 weeks from its initiation[146,147]. Not only new drugs with novel mechanisms of action, but also drugs with different pharmacokinetics are under investigation. For example, orforglipron is an oral GLP-1 RA which, in contrast to oral semaglutide, is non-peptide, consequently not disintegrated in the gastrointestinal tract, a feature with direct implications to its bioavailability[148]. Daily orforglipron resulted in mean weight loss of 8.6%-12.6%, depending on dose, over a period of 36 weeks in a phase 2 trial[149].

It is understandable that new preparations aim for improved efficacy (i.e., more weight loss) with minimization of adverse effects and involvement of multiple molecular pathways. Does this mean that a crucial singularity will soon be reached beyond which the efficacy of NAOMs will be greater than the effectiveness of MBS? Simply put, will drugs substitute surgery for the treatment of obesity? Throughout the text, it has been shown that there are multiple levels that need to be addressed with this rapport. Most importantly, we have demonstrated that obesity is a multifactorial and multistage disease that needs to be addressed on an individualized basis with a combination of approaches by a multidisciplinary team. Do these terms sound familiar? At this point, we will attempt to answer with an analogy from the medical field.

Cancer is also a multifactorial and multistage disease, and its management is effectuated by a multidisciplinary team of experts with a multitude of therapeutic options, i.e., chemotherapy, radiotherapy, oncologic surgery, immunotherapy, hormone therapy, *etc*. The prognosis for several cancer types has improved significantly over the years, not only because new drugs have been invented, but primarily after the establishment of the tumor board as a mandatory component of the treatment of the oncologic patient[150]. This, along with the incorporation of long-known anatomical concepts into operative surgical perspective and the customization of therapy to disease stage and type, patient comorbidities, sociodemographic factors, *etc*., has revolutionized current cancer management[150-152]. Some first steps have been taken towards the direction of treating obesity in a similar way, such as staging obesity with the use of the Edmonton Obesity Staging System and evaluating its association with weight loss[153], or employing NAOMs as adjuvant therapy for weight regain and relapse of T2DM following MBS[154-157]. However, this is not a task that will materialize overnight, as it requires organizational and cultural changes, teamwork among a diverse body of healthcare providers within their local and regional organizations, and leadership by health managers.

From all the above challenging topics, it has been made clear that surgery and new anti-obesity treatments are not meant to exist competitively but rather synergistically. More available treatment options will multiply choices for our patients, improve our understanding of obesity as a disease, and fortify our arsenal in the enduring fight against one of the most impactful ongoing pandemics. All these remain to be proven in practice and endure the relentless test of time.

DECLARATIONS

Authors' contributions

Study concept and design: Pantelis AG, Lapatsanis DP
Data acquisition and manuscript preparation: Pantelis AG
Manuscript review and editing: Lapatsanis DP

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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