Arthroplasty Today 27 (2024) 101327

Contents lists available at ScienceDirect

Arthroplasty Today

journal homepage: http://www.arthroplastytoday.org/

Special Issue: Highlights from the Young Arthroplasty Group (YAG) of AAHKS. Edited by Anna A.R.Cohen-Rosenblum

Glucagon-Like Peptide Receptor-1 Agonists Used for Medically-Supervised Weight Loss in Patients With Hip and Knee Osteoarthritis: Critical Considerations for the Arthroplasty Surgeon

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ARTICLE INFO

Article history:
Received 11 September 2023
Received in revised form
8 December 2023
Accepted 27 January 2024
Available online 28 June 2024

Keywords:
GLP-1 agonists
Total joint arthroplasty
Perioperative considerations

ABSTRACT

Patients with morbid obesity and concomitant hip or knee osteoarthritis represent a challenging patient demographic to treat as these patients often present earlier in life, have more severe symptoms, and have worse surgical outcomes following total hip and total knee arthroplasty. Previously, bariatric and metabolic surgeries represented one of the few weight loss interventions that morbidly obese patients could undergo prior to total joint arthroplasty. However, data regarding the reduction in complications with preoperative bariatric surgery remain mixed. Glucagon-like peptide receptor-1 (GLP-1) agonists have emerged as an effective treatment option for obesity in patients with and without diabetes mellitus. Furthermore, recent data suggest these medications may serve as potential anti-inflammatory and disease-modifying agents for numerous chronic conditions, including osteoarthritis. This review will discuss the GLP-1 agonists and GLP-1/glucose-dependent insulinotropic polypeptide dual agonists currently available, along with GLP-1/glucose-dependent insulinotropic polypeptide/glucagon triple agonists presently being developed to address the obesity epidemic. Furthermore, this review will address the potential problem of GLP-1-related delayed gastric emptying and its impact on the timing of elective total joint arthroplasty. The review aims to provide arthroplasty surgeons with a primer for implementing this class of medication in their current and future practice, including perioperative instructions and perioperative safety considerations when treating patients taking these medications.
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Introduction

The global obesity pandemic

Obesity is an ever-worsening global pandemic. In 2016, the World Health Organization estimated 1.9 billion adults were overweight, with 650 million being obese [1] (Table 1). Most alarmingly, the number of obese adults has tripled since 1975 due to several factors, including the widespread consumption of ultra-processed foods, relative food pricing and availability, changes in daily energy expenditure, and a complex array of socioeconomic factors [5-7]. In the United States, obesity is endemic as approximately 40%-45% of adults have some form of obesity, with 9% of individuals being morbidly obese [8,9]. The increased prevalence of obesity has wide-reaching economic and health-care implications [10]. For instance, heart disease, the leading cause of death in the United States, is associated with obesity and other obesity-related comorbidities, including high blood pressure, increased low-density lipoprotein (LDL) cholesterol, diabetes, metabolic syndrome, and physical inactivity [11,12]. The societal importance of addressing the obesity epidemic cannot be overstated.

Obesity and total joint arthroplasty

The obesity epidemic has profoundly affected the field of arthroplasty. In particular, obesity has played a substantial role in

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https://doi.org/10.1016/j.artd.2024.101327
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Table 1
The World Health Organization (WHO) 2019 obesity classification system and other commonly used terminology to describe categories of weight [1-4].

WHO classification	Body mass index (kg/m^2)	Alternate names & past terminology	Body mass index (kg/m^2)
Overweight	25-29.9	Overweight	25-29.9
Class I obesity	30-34.9	Obese	≥30 or 30-34.9
Class II obesity	35-39.9	Severe obesity	35-39.9
Class III obesity	≥40	Morbid obesity	≥40 or 40-49.9
		Super obesity	≥50 or 50-59.9
		Super super obesity	≥60

the increased demand for total knee and hip arthroplasty utilization in recent years, particularly among younger patients [13]. The risk of developing knee osteoarthritis is approximately fourfold for obese men and fivefold for obese women [14]. Moreover, patients with a body mass index (BMI) >40 kg/m^2 are 8.5 times more likely to experience debilitating end-stage osteoarthritis and request a total hip arthroplasty compared to matched non-obese individuals [15]. Furthermore, by 2029, approximately 46% of the general population is projected to be obese, with approximately 69% of all primary total knee arthroplasty surgeries and 55% of all primary total hip arthroplasty surgeries projected to be performed in obese patients [16,17].

The increasing utilization of total joint arthroplasty in a rapidly growing obese population has several important considerations. In 2013, The American Association of Hip and Knee Surgeons recognized the importance of weight and medical optimization in patients with a BMI >40 kg/m^2 due to the heightened risk of perioperative complications [18]. Obese patients have a higher risk of perioperative complications such as poor wound healing, deep infection, respiratory complications, venous thromboembolism, increased total cost of care, prolonged hospital length of stay, component malposition, aseptic loosening, and need for subsequent revision compared to non-obese patients [10,19-22]. Using prospectively collected data obtained from a single-institution joint registry, Wagner et al. found that for every unit increase in BMI above 35 kg/m^2, there is an approximate 8% increase in the relative risk of deep infection following total knee arthroplasty [19,20]. For every unit increase in BMI above 25 kg/m^2, there is an approximate 9% increase in the relative risk of deep infection following total hip arthroplasty [19,20]. The increased risk associated with obese patients has led many surgeons to implement a BMI = 40 kg/m^2 cutoff, above which patients are often denied elective total hip and total knee arthroplasty surgeries. While these BMI thresholds are often implemented to minimize complications, the effect of this practice often limits access to potential complication-free surgery in many patients if rigid BMI eligibility thresholds are applied [23-26]. As such, great efforts have been implemented to assist patients in weight loss and to medically optimize patients who are overweight and obese as a means to provide arthroplasty to this high-risk population.

Limitations of metabolic and bariatric surgery

Metabolic and bariatric surgeries have gained popularity in the United States, increasing year over year in the past decade, with approximately 250,000 cases having these procedures performed in 2019 alone [27]. However, bariatric surgery as a risk-mitigation tool before total knee and hip arthroplasty has had mixed results in the literature [28-31]. Springer et al. performed a systematic review and meta-analysis and found that bariatric surgery improves gait mechanics, enhances joint function, and ameliorates pain in morbidly obese patients with osteoarthritis [31]. However, the authors concluded that "... evidence for supporting bariatric surgery before total joint arthroplasty is limited to retrospective reports with conflicting results." Yan et al. performed a meta-analysis comparing morbidly obese patients with prior bariatric surgery to morbidly obese patients without a prior bariatric surgery [28]. The authors assessed 166,047 patients who underwent total knee arthroplasty and found similar rates of short-term complications and revisions but higher rates of blood transfusion, infection at longer-term follow-up, and long-term all-cause revision rates among patients who underwent bariatric surgery. In a similar study, Li et al. performed a meta-analysis of 38,728 total hip and total knee arthroplasty patients and compared patients who underwent bariatric surgery prior to total hip and total knee arthroplasty to morbidly obese patients who did not undergo a bariatric surgery [30]. There were lower rates of medical complications, decreased operative time, and shorter lengths of stay among patients who underwent prior bariatric surgery. However, there were no differences in rates of superficial wound infection or venous thromboembolism and no benefits of bariatric surgery related to long-term dislocation rates, periprosthetic joint infection, periprosthetic fracture, and overall rates of revision surgery. Notably, conclusions from the aforementioned meta-analyses are limited by a lack of high-quality prospective randomized data.

Recently, Dowsey et al. performed a prospective randomized controlled trial of 82 patients, of which 41 were randomized to undergo bariatric surgery prior to total knee arthroplasty, and found lower rates of complications in the bariatric surgery group [32]. However, the lower complication rates were due, in large part, to the number of patients who decided to forego surgery because of symptom improvement, as 12 patients in the bariatric surgery and 2 patients in the control group never underwent elective arthroplasty. Moreover, this study was not powered to detect differences in periprosthetic joint infection, nor did the authors assess long-term revision rates. The SWIFT trial (Surgical Weight Loss to Improve Functional Status Trajectories Following Total Knee Arthroplasty) is a prospective case-control trial that is currently enrolling obese patients considering total knee arthroplasty to assess perioperative outcomes and long-term complication rates among patients undergoing bariatric surgery prior to arthroplasty compared to patients who proceed with arthroplasty without a prior weight-loss surgery [33]. This trial began enrollment in 2016 and, as of February 2023, has only enrolled approximately 300 of the 500 target patients. Hopefully, this study will provide valuable data to help elucidate the role of bariatric surgery before elective arthroplasty among the obese population.

Past weight-loss pharmacotherapy

In the past, medically supervised weight-loss pharmacotherapy has had disappointing results. Various medication classes, such as anorectic stimulants and lipase inhibitors, have facilitated preoperative weight loss. However, these drugs have largely been abandoned because of their unfavorable safety profiles. Stimulant-based anorectic drugs like phentermine and diethylpropion gained

Table 2
Weight loss mechanisms of action of GLP-1, GIP, and glucagon stratified by organ system.

Organ system	Function	GLP-1	GIP	Glucagon
Pancreas	Insulin secretion	↑↑ [54,55]	↑↑ [56]	↑↑ [57]
	Insulin biosynthesis	↑↑ [58-61]	↑↑ [62]	Unknown
	β-Cell proliferation	↑↑ [58-61]	↑↑ [62]	↑/↔ [63]
	β-Cell apoptosis	↓↓ [54,55]	↓↓ [62]	Unknown
Stomach	Gastric emptying	↓↓ [64,65]	↓/↔ [66]	↓↓ [67]
	Gastric acid secretion	↓↓ [68]	↓/↔ [66,69]	↓↓ [70]
Liver (indirect effects)	Glucose production	↓ [62]	↓/↔ [62,71]	↑↑ [62]
Brain	Satiety	↑↑ [72-75]	↑/↔ [76]	↑↑ [77]
	Hunger	↓↓ [78-82]	↓/↔ [83]	↓ [84,85]
Adipose	Lipogenesis	↑ [86]	↑↑ [87,88]	↓↓ [89,90]
	Lipolysis	↑ [86]	↓/↔ [91]	↑/↔ [92]
Skeletal muscle	Glucose uptake	↑/↔ [62,93]	↓/↔ [94]	↔ [95]
	Glycogenolysis	↓/↔ [96]	↔ [94]	↔ [97]

Two arrows denote a notable positive or negative effect, one arrow denotes a mild to moderate effect, and a horizontal arrow indicates no notable effect.

traction in the 1960s for appetite suppression, but cardiovascular concerns relating to their sympathomimetic properties hindered widespread utilization [34-37]. Fen-Phen (fenfluramine-phentermine, Wyeth Pharmaceuticals), a popular weight loss drug in the 1990s, was withdrawn from the market in 1997 because of its association with life-threatening valvular heart disease [38]. Orlistat, approved in 1999, functions as a gastrointestinal lipase inhibitor. However, suboptimal weight loss efficacy and concerns regarding drug-drug interactions, micronutrient deficiency, and gastrointestinal side effects have limited the drug's appeal and widespread utilization [39-42]. Combination naltrexone-bupropion (Contrave, Orexigen Therapeutics, Inc.), a more recent medication approved in 2014, combines an opioid receptor antagonist with a norepinephrine-dopamine reuptake inhibitor [43]. However, clinical studies have demonstrated non-superior weight-loss efficacy compared to previous stimulant-derived medications [44]. Furthermore, risks relating to seizures, drug interactions, and cardiovascular side effects have tempered enthusiasm for these medications [43]. As such, medically supervised weight loss, until recently, has generated limited enthusiasm as a means to address the obese osteoarthritic patient pursuing elective total joint arthroplasty.

Glucagon-like peptide-1 receptor agonists

Recent clinical data regarding incretin-based pharmacotherapeutic agents have led to a newfound enthusiasm for medically supervised weight loss. The recent phase 3 weight-loss data from semaglutide, liraglutide, and tirzepatide has changed the medically supervised weight-loss landscape given the safety and efficacy of this class of medications [45-47]. Semaglutide and liraglutide are glucagon-like peptide-1 (GLP-1) receptor agonists, and tirzepatide is both a GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor dual agonist, now being used extensively for medically supervised weight loss. Not surprisingly, these medications have gained popularity, becoming ubiquitous in the media and social media platforms to the extent that drug manufacturers are struggling to meet the surging demand [48]. To further generate enthusiasm, several clinical guidelines recommend adjunctive pharmacotherapy in addition to lifestyle modifications, such as diet and exercise, acknowledging the challenge of substantial and sustained weight loss in the obese population [49-51]. As such, the use of GLP-1 receptor agonists and dual-receptor agonists will continue to affect a larger proportion of total joint arthroplasty patients in the future. This review seeks to provide an overview of this class of weight-loss medications, including the mechanism of action, health benefits, side effects, and perioperative considerations, while also emphasizing safety concerns for the arthroplasty surgeon.

Mechanisms of action

GLP-1 and GIP are incretin peptides released by the gastrointestinal tract in response to oral nutritional intake [52]. These peptide hormones work in concert to stimulate insulin secretion and are responsible for the "incretin effect," whereby patients experience a 2- to 3-fold increase in insulin in response to orally ingested glucose compared to intravenous glucose [53]. GLP-1 receptor and GIP receptor agonists are recognized for their multifaceted influence on blood glucose levels and weight reduction through several interconnected mechanisms (Table 2). Specifically, GLP-1 receptor agonists assist in weight loss through 5 distinct mechanisms: (1) increasing insulin biosynthesis and secretion, (2) decreasing hunger, (3) promoting satiety, (4) delaying gastric emptying, and (5) decreasing meal-stimulated gastric acid secretion [98].

Most notably, GLP-1 agonists act directly on the pancreas to promote glucose-dependent insulin secretion, improve glucose sensitivity in glucose-resistant β-cells, and facilitate glucose transport through the upregulation of glucokinases and glucose transporters [62,99]. While the exact mechanism remains unknown, GLP-1 agonists may also inhibit glucagon secretion and stimulate somatostatin via a proposed direct GLP-1 receptor interaction with α and δ cells, respectively [100,101].

The effects of GLP-1 further extend to the central and peripheral nervous systems. As small molecules capable of crossing the blood-brain barrier, GLP-1 agonists act directly on hypophyseal neurons to regulate homeostatic functions, including decreasing hunger and promoting satiety [58,102-104]. While the central impact that GLP-1 agonists have on satiety is well established, it remains unclear

Table 3
Pharmacological agents approved by the FDA.

Drug name	Receptor activity	Dosage frequency	Route	Brand name	Weight loss ranges
Liraglutide	GLP-1	Once daily	Subcutaneous	Victoza Saxenda	The Satiety and Clinical Adiposity - Liraglutide Evidence in individuals with and without diabetes (SCALE) trial mean percent weight loss at 56 weeks on liraglutide 3.0 mg: 8.0% [113]
Semaglutide	GLP-1	Once weekly	Subcutaneous	Ozempic	STEP 2 Trial mean percent weight loss at 68 weeks on semaglutide 1-2.4 mg: 7.0-9.6% [114]
				Wegovy	STEP 8 Trial mean percent weight loss at 68 weeks on semaglutide 2.4 mg: 15.8% [115]
			Oral	Rybelsus	OASIS I Trial mean percent weight loss at 68 weeks on semaglutide 50 mg: 15.1% [116]
Tirzepatide	GLP-1 and GIP	Once weekly	Subcutaneous	Mounjaro Zepbound	SURMOUNT 1 Trial mean percent weight loss at 72 weeks on tirzepatide 5-15 mg: 15.0%-20.9% [46]

Table 4
Pharmacologic agents currently in clinical trials.

Drug name	Receptor activity	Dosage frequency	Route	Weight loss ranges
Retatrutide	GLP-1, GIP, and glucagon	Once weekly	Subcutaneous	Retatutride Phase 2 Obesity Trial mean percent weight loss at 48 weeks on retatrutride 1-12 mg: 8.7%-24.2% [118]
Pemvidutide	GLP-1 and glucagon	Once weekly	Subcutaneous	MOMENTUM Phase 2 Trial mean percent weight loss at 24 weeks on pemvidutide 1.2-2.4 mg: 7.3%-10.7% [119]
Cotadutide	GLP-1 and glucagon	Once daily	Subcutaneous	Cotadutide Phase 2b Trial mean percent weight loss at 54 weeks on cotadutide 100-300 μg: 3.7%-5.0% [120]
Orforglipron	GLP-1	Once daily	Oral	Orforglipron Phase 2 Trial mean percent weight loss at 36 weeks on orforglipron 12-45 mg: 9.4%-14.7% [121]
Danuglipron	GLP-1	BID	Oral	Danuglipron Phase 2b Trial mean percent weight loss at 16 weeks on danuglipron 10-120 mg: 0.06%-4.60% [122]

whether this effect is centrally mediated or more strongly related to delayed gastric emptying [62].

Within the stomach, GLP-1 receptor agonists decrease meal-stimulated gastric acid secretion and delay gastric emptying through several complex mechanisms [62]. The increased food transit times associated with GLP-1 receptor agonists come with several significant benefits, including promoting meal-time satiety and reducing postprandial blood glucose levels [105,106]. The culmination of these effects, termed the "ileal break," underscores the efficacy of this medication class in promoting weight loss [107,108].

While additional GLP-1-dependent effects have been proposed relating to glucose and lipid metabolism, including lipolytic effects in adipocytes and insulin-independent suppression of hepatic glucose production, the literature remains divided regarding the contributions of these other mechanisms of action to weight loss [62,86,109-112].

Weight-loss efficacy

Commercially available drugs

Three GLP-1 agonists have obtained Food and Drug Administration (FDA) approval for treating diabetes mellitus and obesity (Table 3). Liraglutide and semaglutide are utilized for diabetes mellitus, marketed as Victoza (Novo Nordisk, Bagsværd, Denmark) (0.6 mg-1.8 mg) and Ozempic (Novo Nordisk, Bagsværd, Denmark) (0.25 mg-2 mg), respectively. These medications are rebranded at higher doses as Saxenda (Novo Nordisk, Bagsværd, Denmark) (0.6 mg-3 mg) and Wegovy (Novo Nordisk, Bagsværd, Denmark) (0.25 mg-2.4 mg) and have gained approval for weight loss with or without diabetes mellitus. The first dual-receptor agonist, tirzepatide, is available for treating diabetes mellitus and obesity, marketed as Mounjaro (Eli Lilly and Company, Indianapolis, IN) (2.5 mg-15 mg) and Zepbound (Eli Lilly and Company, Indianapolis, IN) (2.5 mg-15 mg), respectively. Currently, GLP-1 receptor agonists are indicated for weight loss for patients who have a BMI $\geq$30 kg/m^2 or a BMI $\geq$27 kg/m^2 plus one obesity-related comorbidity. No BMI criteria exist with regard to prescribing GLP-1 agonists in diabetic patients.

Several large clinical trials have documented the weight loss efficacy of these medications. A brief summary of these results will be outlined below as more detailed weight loss results of GLP-1 receptor agonists have been discussed in a review we recently authored [117]. The Satiety and Clinical Adiposity - Liraglutide Evidence in individuals with and without diabetes (SCALE) trial, published in 2015, reported that weekly subcutaneous liraglutide 3.0 mg resulted in up to 8.0% average weight loss at 56 weeks [47]. In 2022, the STEP 8 trial found that weekly subcutaneous semaglutide 2.4 mg resulted in an average 15.8% total body weight loss at 68 weeks [115]. In 2023, the OASIS I trial revealed daily dosing of oral semaglutide 50 mg led to an average 15.1% total body weight loss at 68 weeks [116]. The SURMOUNT 1 trial, published in July 2022, found that weekly dosing of tirzepatide led to an average 15.0% total body weight reduction at 72 weeks, with the lowest dosage of 5 mg, peaking at 20.9% weight loss for the highest dose of 15 mg [46].

Drugs in development

Several GLP-1 agonists are currently in various stages of clinical trials: retatrutide, pemvidutide, cotadutide, danuglipron, and orforglipron (Table 4). While all these medications have demonstrated the ability to enact clinically significant weight loss, orforglipron, and retatrutide have displayed particular promise. Orforglipron is a novel non-peptide small-molecule GLP-1 receptor agonist with notable weight loss results from phase 2 trials and a safety profile similar to other incretin-based therapies [121]. Preliminary 36-week findings have demonstrated weight loss of 14.7% of total body weight at the highest dose, marking a promising future for oral incretin-based therapies in medical weight management. Furthermore, the non-peptide structure of this medication may provide a more cost-effective alternative to the more costly peptide-based medications currently on the market [123]. Retatrutide is an investigational GLP-1/GIP/glucagon triple agonist currently in phase 3 trials for treating obesity. This peptide has shown significant promise in medical weight optimization by combining the anorectic effects of GLP-1 and GIP with the enhanced energy expenditure of glucagon [124]. At 48 weeks, participants on the highest dose of retatrutide achieved a remarkable bodyweight loss of 24.2% [118].

Table 5
Health benefits of GLP-1 agonists.

GLP-1 agonists	
Non−weight-loss benefits	
Glycemic control	Lowers blood sugar Stimulates insulin secretion Stimulates insulin biosynthesis Increases insulin sensitivity Suppresses glucagon
Cardiovascular	Lowers blood pressure Increased cardiac output Lowers risk of stroke Lowers risk of myocardial infarction Lowers risk of mortality
Lipid profile	Lowers LDL Increases HDL Lowers triglyceride levels

Table 6
Non–weight-loss mechanisms of action of GLP-1, GIP, and glucagon stratified by location of action.

Organ system	Function	GLP-1	GIP	Glucagon
Bone	Bone remodeling	↑ [132]	↔ [133,134]	Unknown
Brain	Neuroprotection	↑/↔ [135]	↔ [62]	↑↑ [136]
Heart	Cardioprotection	↑ [137]	Unknown	↔ [138]
	Cardiac function	↑/↔ [139-142]	Unknown	↑ [143]
Joint	Synoviocyte protection	↑ [144]	Unknown	Unknown
	Chondrocyte protection	↑ [145]	↑ [146]	Unknown

Two arrows denote a notable positive or negative effect, one arrow denotes a mild to moderate effect, and a horizontal arrow indicates no notable effect.

Other health benefits

Lipid profile

These medications have a profound impact on the lipid profile, increasing high-density lipoprotein (HDL) and LDL among patients taking these medications (Table 5). Patients taking semaglutide weekly for 68 weeks saw an average 5% increase in HDL levels and a 3% decrease in LDL [45]. Similarly, patients taking tirzepatide for 72 weeks saw their HDL increase on average by 8.0 mg/dL (95% confidence interval [CI] 6.9-9.1 mg/dL) and their LDL decrease by −5.8 mg/dL (95% CI −6.9 to −4.6 mg/dL) [46]. Retatrutide, although still not approved by the FDA, showed a 3.5-mg/dL increase in HDL and a −24.3-mg/dL decrease in LDL at 48 weeks in the highest dose group [118]. However, the effects of HDL reductions for patients on retatrutide were only observable after 24 weeks.

Cardiovascular health

Mounting evidence suggests GLP-1 receptor agonists may be beneficial for cardiovascular health, independent of associated weight reduction, improvement in systolic and diastolic blood pressure, and improvements in patient lipid profile. In a nondiabetic hypertension mouse model, liraglutide treatment reversed cardiac hypertrophy, vascular fibrosis, and endothelial dysfunction, while decreasing oxidative stress and vascular inflammation in a direct GLP-1 receptor–dependent manner [125]. Marso et al. randomized 3297 diabetic patients to receive semaglutide or placebo for 104 weeks and found similar rates of myocardial infarction (2.9% semaglutide vs 3.9% placebo, $P = .12$) but lower rates of stroke (1.6% semaglutide vs 2.7% placebo, $P = .04$) in the GLP-1 receptor agonist group [126]. Marso et al. also conducted a double-blind prospective randomized trial involving 9340 patients with type 2 diabetes at increased risk of cardiovascular disease [127]. These patients were randomly assigned to receive either liraglutide or a placebo. At a median follow-up of 3.8 years, patients on liraglutide had a lower risk of reaching the composite endpoint of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes (hazard ratio [HR] 0.87, 95% CI 0.78-0.97, $P = .01$). Kristensen et al. performed a meta-analysis of prospective randomized placebo-controlled trials, including studies with a minimum of 500 patients who received either a GLP-1 receptor agonist or placebo [128]. The authors pooled 7 trials with 56,006 patients and found a 12% relative risk reduction in major adverse cardiac events (HR 0.88, 95% CI 0.82-0.94, $P < .001$). The SELECT trial was designed to investigate the effectiveness of semaglutide in reducing cardiovascular risks among obese, nondiabetic individuals [129]. Lingvay et al. randomized 17,605 patients with a history of myocardial infarction, stroke, or peripheral vascular disease to receive weekly subcutaneous semaglutide 2.4 mg or placebo [129]. Preliminary results found patients receiving semaglutide had a 20% reduction in the risk of major adverse cardiovascular events compared to the placebo cohort at up to 5-year follow-up [130]. These cardiovascular benefits are likely multifactorial and related to weight reduction, lower blood pressure, decreased inflammation, vascular endothelial health, and diminished atherosclerosis progression [131]. These findings underscore the profound impact of GLP-1 agonists on cardiovascular health (Table 6). Furthermore, they suggest this class of medications may revolutionize the medical management of obesity by serving the dual purpose of being cardioprotective.

Mortality

The mortality benefits of GLP-1 receptor agonist treatment warrant a separate discussion. In the aforementioned meta-analysis by Kristensen et al., patients on a GLP-1 receptor agonist had a lower risk of death from cardiovascular causes (HR 0.88, 95% CI 0.81-0.96, $P = .003$) [128]. Chen et al. assessed 27,279 patients with type 2 diabetes and chronic kidney disease and compared patients receiving a GLP-1 receptor agonist to patients receiving a dipeptidyl peptidase-4 inhibitor [147]. Patients receiving GLP-1 receptor agonists experienced a lower rate of all-cause mortality (HR 0.79, 95% CI 0.63-0.98), which was notably not driven by differences in rates of major cardiac events. To date, most of the data demonstrating a lower risk of mortality among patients taking GLP-1 receptor agonists were identified in patients with comorbidities such as type 2 diabetes mellitus and chronic kidney disease. However, limited mortality data exist among the overweight and obese population taking this class of medication for medically supervised weight loss.

Direct effects on joint health

Recent evidence suggests GLP-1 receptor agonists may play an important role in regulating inflammation in the osteoarthritic joint [86,148]. Notably, the GLP-1 receptor is present in human articular cartilage and the synovial membrane [144,149]. In an osteoarthritis mouse model, Meurot et al. found that liraglutide displayed potent analgesic and anti-inflammatory effects [144]. These authors confirmed their *in vivo* findings by performing *in vitro* studies and found liraglutide treatment led to a decrease in several pro-inflammatory cytokines implicated in the progression and pathogenesis of osteoarthritis including nitrite, prostaglandin E2, and interleukin 6. Chen et al. found that liraglutide provided *in vivo* anti-apoptotic effects on chondrocytes in an osteoarthritis mouse model by preventing apoptosis induced by interleukin 1β [145]. These authors also noted decreased levels of interleukin 6 and tumor necrosis factor-alpha and a decrease in the breakdown of the extracellular cartilage matrix in response to liraglutide. These findings underscore the potential utilization of GLP-1 receptor agonists as disease-modifying agents for the osteoarthritic joint [149].

In a clinical study, Zhu et al. assessed patients in the Shanghai Osteoarthritis Cohort, a prospective, observational, multicenter cohort of over 40,000 adults with osteoarthritis [150]. The authors found patients taking GLP-1 receptor agonists for a minimum of 2 years had significantly decreased Western Ontario and McMaster Universities Arthritis Index scores and lower analgesic consumption than those not taking GLP-1 receptor agonists. Furthermore, patients taking GLP-1 receptor agonists demonstrated decreased cartilage loss (-0.05 ± 0.08 mm/y vs -0.07 ± 0.10 mm/y, $P = .026$) as measured by magnetic resonance imaging and a lower incidence of knee surgery than patients not treated with GLP-1 receptor agonists. Surprisingly, the association between GLP-1 receptor agonist exposure and cartilage loss was not mediated by weight loss, leading the authors to postulate that GLP-1 receptor agonists may have disease-modifying behaviors. These data suggest that in

Table 7
Documented side effect profile of GLP-1 receptor agonist medication class.

GLP-1 agonists	
Side effect profile	
Common	Nausea
	Vomiting
	Diarrhoea
	Abdominal pain
	Constipation
Infrequent	Acute gallbladder disease
	Hypoglycemia
	Acute kidney injury
	Headache
Rare	Pancreatitis
	Angioedema
	Diabetic retinopathy
	Hypersensitivity reactions

addition to symptom improvement from mechanically offloading the joint secondary to weight loss, GLP-1 receptor agonists may provide a direct anti-inflammatory and analgesic effect at the cellular level and may serve as disease-modifying agents (Table 6).

Side effects

Several large prospective randomized controlled trials have highlighted the overall safety of these medications with limited side effect profiles. The most common side effects are gastrointestinal, such as nausea, vomiting, diarrhea, and constipation, with 9%-26% of patients experiencing these digestive side effects [151-153] (Table 7). These side effects are typically dose-dependent and diminish with ongoing treatment after the dose-escalation phase of these medications has been completed. However, digestive symptoms have led to early cessation in 3%-21% of patients [115,121,152,154,155]. Pancreatic side effects, including pancreatitis and pancreatic cancer, initially garnered significant attention from the media and several authors [156]. However, post-market reassessment by the FDA and European Medicines Agency and large-scale meta-analyses of over 1 million patients have concluded that the current data do not support a link between incretin therapy and pancreatic side effects [157-159]. Despite these analyses, a history of pancreatitis remains a contraindication for GLP-1 use. Multiple endocrine neoplasia type 2 and a history of medullary thyroid cancer, a rare tumor commonly associated with Multiple endocrine neoplasia type 2, are other contraindications for GLP-1 therapy [160]. Other infrequent or rare side effects associated with incretin-based therapy include gallbladder disease, acute kidney injury, hypoglycemia, allergic hypersensitivity reactions, angioedema, injection site reactions, and headache [152]. When taken together, incretin-based therapy for weight loss appears to be both safe and efficacious in treating obesity. However, perioperative safety has recently garnered further consideration, particularly among patients undergoing elective surgery such as total hip and total knee arthroplasties.

Perioperative considerations

Risk of pulmonary aspiration during anesthesia

Increased attention has been turned to the safety of this class of medications in the perioperative period due to concerns of increased risk of aspiration due to delayed gastric emptying. However, insufficient data have led to several anesthesia editorials and guidelines presenting opposing conclusions [161-163]. Hulst et al. argued that it is not practical to discontinue long-acting GLP-1 agonists like semaglutide perioperatively as this would require discontinuation of the medication 3 to 4 weeks before surgery due to the half-life of the medication, which would have the potential to alter glycemic control in a way that may make surgery unsafe [163]. In contradistinction, Jones et al. acknowledged the lack of conclusive data linking GLP-1 agonists to the risk of aspiration but nonetheless recommended that these medications be held for 3 weeks prior to surgery as a precautionary measure [161]. These authors suggest bridging with a shorter-acting GLP-1 agonist among patients with diabetes mellitus to minimize the risk of altering perioperative glycemic control. Most recently, in June of 2023, the American Society of Anesthesiologists released consensus-based guidelines, recommending weekly-dosed GLP-1 receptor agonists be withheld for 1 week before surgery [162]. However, all 3 guidelines acknowledge a limitation in the available data.

The aforementioned concerns from the anesthesia community warrant serious consideration. Intraoperative aspiration due to delayed gastric emptying has been reported using semaglutide in multiple case reports [161,164]. Furthermore, several reports have identified residual gastric contents during esophagogastroduodenoscopy among patients using semaglutide [165-168]. Silveira et al. assessed 404 esophagogastroduodenoscopies, of which 33 (8.2%) were on semaglutide and 371 (91.8%) were not on semaglutide or any other GLP-1 receptor agonist [168]. The authors found residual gastric contents in 8 (24.2%) patients on semaglutide and 19 (5.1%) not taking semaglutide ($P < .001$) despite appropriate fasting duration (>2 hours for clear fluids, >8 hours for solid foods). Notably, digestive symptoms such as nausea, vomiting, dyspepsia, and abdominal distension were associated with an increased risk of residual gastric contents (OR 3.56, 95% CI 2.2-5.78). These studies raise concerns about an increased risk of aspiration among patients taking GLP-1 receptor agonists.

In the absence of conclusive evidence, the authors of this review have several recommendations the arthroplasty surgeon should consider. First, the risk of perioperative aspiration is likely dose, duration, and medication dependent. Patients taking higher doses of GLP-1 receptor agonists, particularly during the early dose-escalation phase, have higher rates of nausea and vomiting from a more substantial delay in gastric emptying. During this phase of treatment, patients with these symptoms are likely at higher risk of aspiration [168]. Conversely, it stands to reason that patients taking lower doses for a longer duration, particularly patients who have completed the dose-escalation phase, may be at lower risk of aspiration. As such, the arthroplasty surgeon should consider delaying elective total joint arthroplasty until a patient has completed the dose-escalation phase and has complete resolution of their digestive symptoms, including nausea, vomiting, and dyspepsia. For medications such as semaglutide or tirzepatide, this would mean a minimum of a 4- to 5-month and a 2- to 6-month titration periods, respectively [169,170]. Second, for patients on these medications for weight loss (ie, patients not taking these medications for glycemic control), surgeons should consider holding weekly dosed medications for 1-3 weeks in coordination with their anesthesia team and the prescribing internist, endocrinologist, or bariatrician [161,162]. While this may not be necessary for all patients, particularly those on lower doses for more extended durations with no digestive symptoms, this should be considered out of an abundance of caution until higher-quality data have informed more detailed clinical practice guidelines. Third, the type of medication may also play a role in the risk of aspiration, as the GIP receptor appears to have a weaker effect on delaying gastric emptying [145]. As such, medications such as tirzepatide, which has a stronger affinity for the GIP receptor than the GLP-1 receptor,

may be safer in the perioperative period, mitigating the risk of aspiration [46,171]. Fourth, for patients on these medications, consider point-of-care gastric ultrasound, which can be performed in the preoperative holding area to assess for the presence of gastric contents [172,173]. If gastric contents are identified, a rapid induction intubation can be performed with nasogastric tube evacuation, or the patient's surgery can be delayed. As total joint arthroplasty is an elective procedure, the decision to proceed with surgery should be made through shared decision-making with the patient and the anesthesia team. Since GLP-1 agonists are rising in popularity among patients, it behooves all surgeons to check if their patients are taking these agents when surgery is scheduled. In the future, well-designed studies are required to answer questions regarding the perioperative risk of aspiration related to medication type, dose, duration, preoperative fasting duration, and screening guidelines.

Malnutrition

As with all weight loss strategies, concerns about malnutrition and catabolism should be considered, particularly in the setting of rapid weight loss. While there is no evidence to support malnourishment solely caused by GLP-1 receptor agonists, patients on these medications who aggressively attempt to lose weight may enact behavioral changes like extreme dieting or caloric deprivation that may place them at increased risk of perioperative complications. Rapid weight loss in this population may lead to a decrease in muscle mass and compromise bone density, eventually leading to sarcopenia with ongoing gradual loss of muscle mass and strength over time. Concerns regarding perioperative risk may be addressed by waiting until a patient has reached a stable weight (ie, avoid elective arthroplasty during a dramatic weight loss interval), selective preoperative screening of nutrition markers such as albumin or total lymphocyte count, and perioperative counseling to inform patients that extreme perioperative caloric deprivation may be deleterious [174,175].

Rebound weight gain

As with any weight loss strategy, concerns about rebound weight gain are an issue for patients treated with a GLP-1 receptor agonist after medication discontinuation. This is of particular concern for arthroplasty surgeons, as body mass is predictive of long-term revision rates and implant durability, even among patients who avoid early postoperative complications [176]. Rapid weight loss may place patients at risk of sarcopenia, which may lead to a decrease in the basal metabolic rate as lean muscle mass decreases, predisposing patients to long-term weight recidivism after medication discontinuation [177].

To quantify the degree of rebound weight gain, Rubino et al. performed a prospective, double-blind, placebo-controlled withdrawal study by randomizing 902 patients treated with a 20-week course of subcutaneous semaglutide to either transition to a placebo or continued semaglutide for an additional 48 weeks [178]. At the 20-week run-in randomization point, the mean weight reduction was 10.6% across both groups. Patients randomized to the placebo group re-gained weight during the 48-week continuation phase for a net weight loss of 5.2% at the conclusion of the 68-week trial period compared to the semaglutide continuation group, which lost additional weight during the 48-week continuation phase for a net weight loss of 18.2%. Wilding et al. assessed 327 patients who had completed either a 68-week course of once-weekly subcutaneous semaglutide or placebo and followed both groups of patients for an additional 1-year interval after intervention discontinuation [179]. At the end of the 68-week treatment period, patients taking semaglutide lost an average of 17.3% of their body weight compared to 2.0% in the placebo group. After the 1-year discontinuation phase, the semaglutide group regained 11.6% of their body weight while the placebo group regained 1.9% for a net loss of 5.6% and 0.1%, respectively, at the end of the 120-week study period.

While the incomplete rebound weight gain observed in both trials is promising, more research is necessary to determine if longer-term maintenance therapy is beneficial in maintaining more substantial long-term weight loss. Furthermore, physicians and patients together may employ strategies, such as appropriate post-withdrawal nutrition, resistance-based training, and the gradual weaning of GLP-1 agonists, particularly in patients on higher doses, to proactively combat the problem of weight recidivism.

Conclusions

GLP-1 and dual-receptor agonists have demonstrated marked weight loss among overweight and obese patients, providing a potential risk-mitigating clinical pathway toward elective total joint arthroplasty surgery. These medications have become ubiquitous given their efficacy in managing weight loss, favorable safety profile compared to previous weight-loss strategies, and other associated health benefits. Orthopedic surgeons should partner with internists, endocrinologists, or family medicine doctors to consider GLP-1 agonist therapy when treating overweight and obese patients who are incapable of achieving clinically meaningful weight loss with diet and exercise alone. Further research is required to determine how long the different GLP-1 agonists must be stopped before total joint arthroplasty. Consultation between arthroplasty surgeons and anesthesiologists is necessary to safely manage these patients.

Conflicts of interest

J.R.L. receives royalties from and is a consultant for DePuy: A Johnson & Johnson Company; has stock or stock options in BD Surgiphor and Hip Innovations Technologies; receives financial or material support from Saunders/Mosby-Elsevier; and is a member of American Academy of Orthopaedic Surgeons, Hip Society, Musculoskeletal Transplant Foundation, and Western Orthopaedic Association. N.D.H. receives royalties from Corin U.S.A., is a paid consultant for Intellijoint Surgical, MicroPort Orthopedics, Corin U.S.A., and Zimmer; has stock or stock options in Intellijoint Surgical; and is a member of American Academy of Orthopaedic Surgeons, American Joint Replacement Registry, and American Association of Hip and Knee Surgeons. All other authors declare no conflicts to disclose.

For full disclosure statements refer to https://doi.org/10.1016/j.artd.2024.101327.

CRediT authorship contribution statement

Nathanael D. Heckmann: Conceptualization, Formal analysis, Investigation, Supervision, Writing – original draft, Writing – review & editing. **Ryan Palmer:** Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Cory K. Mayfield:** Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Gligor Gucev:** Formal analysis, Supervision, Writing – review & editing, Conceptualization. **Jay R. Lieberman:** Formal analysis, Supervision, Writing – review & editing, Conceptualization. **Kurt Hong:** Conceptualization, Formal analysis, Supervision, Writing – review & editing.

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