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ABOUT COVER

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EDITORIAL

Surgical or medical treatment of obesity-associated type 2 diabetes-an increasing clinical conundrum

Ryan J Jalleh, Karen L Jones, Md Shahidul Islam, Lu Cai, Michael Horowitz

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Abstract

In this editorial, we comment on the article by He *et al*, specifically in relation to the efficacy of bariatric surgery *vs* glucagon-like peptide-1 receptor agonist (GLP-1RA) therapy in the management of type 2 diabetes (T2D) associated with obesity. Bariatric surgery has now also been shown to be safe and effective in pre-teens and teenagers with obesity and T2D, but information on newer GLP-1RAs in these groups is predictably limited. In older individuals (age > 65 years), both bariatric surgery and GLP-1RA therapy improve cardiovascular outcomes. Bariatric surgery is not infrequently associated with post-operative postprandial hypoglycemia, which is not the case with GLP-1RAs and, paradoxically, there is evidence that GLP-1RAs may reduce both the frequency and severity of postprandial hypoglycemia. Comparative trials of the long-term efficacy of bariatric surgery and GLP-1RAs are indicated.

Key Words: Glucagon-like peptide-1; Glucagon-like peptide-1 receptor agonist; Obesity; Diabetes; Weight loss; Bariatric surgery; Metabolic surgery; Hypoglycemia

Core Tip: Glucagon-like peptide-1 receptor agonist-based therapy should be considered for the remission of type 2 diabetes and weight loss as an alternative to bariatric surgery.

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INTRODUCTION

The informative review by He *et al*[1], addresses the relevance of bariatric surgery to the management of type 2 diabetes (T2D) in adults with obesity and its potential application to other cohorts–older people (> 65-70 years) and children (< 16 years) who have T2D, obesity in type 1 diabetes (T1D) and in T2D when body weight is normal. They also addressed the long-term adverse sequelae of bariatric surgery, particularly post-bariatric surgery hypoglycemia (PBSH)[2]. A recent study[3] has confirmed the efficacy of different forms of bariatric surgery [predominantly Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy] compared with traditional medical/lifestyle management in producing sustained improvements in glycemic control (including T2D remission) associated with the maintenance of substantial weight loss and amelioration of diabetic microvascular complications. It can no longer be disputed that bariatric surgery (now often referred to as 'metabolic surgery') is the most effective approach to the treatment of T2D associated with obesity[4]. That lifestyle approaches usually fail in the long-term, so that weight loss is often modest and weight regain is very common, is not surprising and, at least in part, attributable to potent neural/hormonal mechanisms that favor an increased energy intake and diminished energy expenditure[5]. Limitations of bariatric surgery are, for the main part, predictable–it is an invasive procedure, costly, not applicable on a population basis, requires life-long follow up (particularly to monitor for nutritional deficiencies) and is usually associated with adverse effects that are, not infrequently, major. It is also appreciated that the improvement in glycemic control in T2D occurs very soon after bariatric surgery and is, accordingly, not solely attributable to weight loss per se[6]. After most forms of bariatric surgery, but particularly RYGB, gastric emptying and small intestinal transit are accelerated markedly[7] to increase secretion of the 'incretin' hormone, glucagon-like peptide-1 (GLP-1)[6]. The latter is likely to be central to the improvements in glycemic control and reduction in body weight induced by bariatric surgery, but also pivotal to the etiology of PBSH[8]. It is, therefore, not surprising that the advent of agonists of GLP-1, used widely in the management of T2D and obesity with and without diabetes, now provides a therapeutic alternative to bariatric surgery for the first time.

DEVELOPMENT OF GLP-1 RECEPTOR AGONISTS FOR THE MANAGEMENT OF OBESITY

The development of GLP-1 receptor agonists (RAs) followed the recognition that GLP-1, released from the small intestine in response to the presence of nutrients, was an 'incretin' hormone, so that it stimulated insulin (and also, suppressed glucagon) potently and in a glucose-dependent manner. It was shown subsequently, that even in low concentrations, GLP-1 also slowed the rate of gastric emptying substantially, thereby contributing to the reduction in postprandial glucose excursions[9]. Because of its short plasma half-life (about 2 minutes), GLP-1RAs resistant to proteolytic degradation were developed for the management of T2D. With 'first generation' compounds (*e.g.* exenatide twice daily), lowering of glucose in T2D was also found to be associated with modest effects to reduce appetite and weight–the latter on average by approximately 10%[10]. This observation, coupled with the demonstration of cardiovascular and renal protective effects, stimulated the evaluation of 'second generation' GLP-1RAs (*e.g.* liraglutide) in higher doses than those used in T2D, for the management of obesity without T2D, with a resulting increased weight loss of approximately 15% [11]. More potent GLP-1RAs, such as subcutaneous semaglutide, were then developed. Recently, co-agonists where a 'third generation' GLP-1RA has been combined with another hormone(s) [glucose-dependent insulinotropic polypeptide (GIP), amylin and glucagon] have been developed. Tirzepatide, a co-agonist of GLP-1 and GIP receptors, is now widely available and induces weight loss of > 20%[12], albeit a little less in individuals with T2D compared to those with obesity without diabetes. Triple agonists (*e.g.* GLP-1, GIP and glucagon) are currently in development[13]. The majority of GLP-1RAs, alone or in combination, are usually administered subcutaneously once a week. However, an oral formulation of semaglutide, administered daily, has recently become available for the management of T2D and is currently being evaluated in a higher dose for use in obesity management[14]. Furthermore, non-peptide small molecule GLP-1RAs (*e.g.* orforglipron) are in late development[15]. It should be appreciated that adherence with GLP-1RAs in the longer term is suboptimal and their use is not infrequently compromised by gastrointestinal adverse effects and cost[16]. However, while future studies are required to determine their safety and long-term efficacy, it is clear that GLP-1RAs may now represent an alternative to bariatric surgery for the management of obesity with, or without, concomitant T2D.

USE OF GLP-1RA IN PEDIATRIC AND OLDER POPULATIONS

He *et al*[1] review the evidence relating to the safety and efficacy of bariatric surgery in youths (< 18 years) and older individuals (> 65-70 years)[1]. While there may be a role of bariatric surgery in the management of obesity in pre-teens and teens with severe obesity (body mass index > 40)[17], long-term, prospective studies are required to guide the management of childhood obesity. In older individuals, bariatric surgery has now been shown to be safe and effective at reducing weight, with concomitant improvements in cardiovascular health and quality of life[1].

As with bariatric surgery, there is much less information about the effect of GLP-1RAs in individuals < 18 years or > 65-70 years of age. Currently, there are three subcutaneous GLP-1RAs approved for treatment of youths aged 10–18 years with T2D that have been shown to improve glycemic control: Liraglutide, extended release exenatide and dulaglutide [18]. In youths with obesity (without T2D), aged 12–18 years, GLP-1RAs can now be used for weight management, although the observed reductions in mean weight were modest (4.9 kg), apart from semaglutide, which showed a mean weight loss of 17.7 kg in one study[19]. The long-term efficacy and safety of GLP-1RA therapy in youths requires further study.

While in older people, GLP-1RA therapy has been associated with improved cardiovascular outcomes[20], their use must be balanced against potential deleterious effects. Although with liraglutide, no decline in bone mineral density was observed after 2 years of treatment[21], subcutaneous semaglutide was associated with a reduction in bone mineral density after 1 year of treatment[22]. However, the combination of GLP-1RA therapy with exercise may potentially preserve bone mineral density[23]. Studies are required to address this issue more comprehensively and to also determine whether there is an increase in fracture risk. Muscle loss is an inevitable sequelae of weight loss and there is appropriate concern that due to their effects to reduce energy intake and muscle mass significantly[24,25]. GLP-1RAs have the potential to exacerbate sarcopenia and/or malnutrition. Accordingly, as is the case with bariatric surgery, judicious use of GLP-1RAs in this population is essential at present

In the elderly, there is a high rate of cessation of therapy after 2 years which is likely to reflect, at least in part, adverse effects or cost[16]. Symptoms such as constipation may occur with more prolonged treatment[26]. There is also a suggestion that possible effects such as small bowel obstruction, albeit rare, may occur more frequently with prolonged treatment, with evidence that the highest risk is after 1.6 years of therapy[27].

GLP-1 AND POST BARIATRIC SURGERY HYPOGLYCEMIA

In prospective studies[28,29], about a quarter of patients following RYGB experience PBSH and approximately 7% required hospital admission because of severe hypoglycemia (< 3.1 mmol/L)[28]. GLP-1RA therapy, in isolation, is not associated with hypoglycemia[30,31], which is not surprising given the glucose-dependency of insulin stimulation. However, there is a risk of hypoglycemia when GLP-1RAs are used concurrently with insulin or sulphonylureas, which may, potentially, be increased[32,33]. The underlying mechanism of PBSH is complex and incompletely defined but may, in part, relate to rapid delivery of nutrients to the small intestine to result in exaggerated GLP-1 and insulin responses [34]. We have reported that in individuals with PBSH following RYGB, the postprandial GLP-1 and insulin responses are greater than in those without PBSH[8]. It is, accordingly, not surprising that a GLP-1 receptor antagonist, avexitide, has been associated with reductions in postprandial hypoglycemia and is in development for its management[35]. Small trials and case reports also indicate of a reduction in the frequency of PBSH with GLP-1RA therapy, which is intuitively surprising[36]. The mechanism(s) underlying the apparently paradoxical reduction in the frequency of hypoglycemia after both agonism or antagonism of the GLP-1 receptor remain to be determined but may relate to a slowing of small intestinal transit and/or suppression of the postprandial rise in glucose, to thereby attenuate the insulinemic response.

CONCLUSION

GLP-1RAs, particularly newly developed drugs, clearly have the potential to represent an alternative to surgery for the long-term management of T2D associated with obesity in adults < 65 years. In individuals with substantial comorbidity or those who wish to avoid an invasive procedure, they now represent a reasonable alternative to surgery. Bariatric surgery and GLP-1RAs may both be effective options for the management of diabetes and obesity in youths and older individuals. Further studies are, however, required to determine the safety and efficacy of both treatments in childhood obesity.

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FOOTNOTES

Author contributions: Jalleh RJ wrote the original draft; Jones KL, Islam MS, Cai L reviewed and edited it; Horowitz M was the senior author and provided supervision and validation of the writing.

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