

Obesity and GLP-1 RAs

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In this issue of the *Journal of Investigative Medicine*, Singh *et al* review the important addition of the glucagon-like peptide-1 receptor agonists (GLP-1 RAs) for the treatment of obesity and specifically discuss semaglutide for weight management. Despite the dire and costly outcomes of obesity, the USA and much of the world have failed for years to practice healthy eating and exercise. The 2017–2018 National Health and Nutrition Examination Survey (NHANES) estimated that 42.5% of US adults aged 20 and over have obesity and an additional 31.1% are overweight, impacting 73.6% of the adult population.¹

Having excessive weight has now become the “norm” with those overweight or obese far exceeding those of appropriate body weight. As discussed in this review, obesity is of critical concern because it contributes to the development of the top two leading causes of death, heart disease and cancer,² as well as a host of other medical conditions such as diabetes and hypertension. For 2020, COVID-19 was the third most common cause of death² and obesity is a known risk factor for mortality from COVID-19 as well.³ Effective treatments have been lacking. A multitude of diets have come and gone with high dropout rates and very poor long-term weight loss sustainability. A recent meta-analysis with 21,942 patients showed a minimal weight loss of 2.0 kg compared with the usual diet for up to 12 months, with trivial differences between diets.⁴ Consequently, treatment with medications and surgical options have now come to the forefront. Usually, surgery is reserved for those with the most excessive obesity due to the invasive nature and side effects, leaving the vast majority of the population with limited medical options to reduce weight. For long-term weight management, orlistat, phentermine/topiramate, and naltrexone/bupropion have been available since 1999, 2012, and 2014, respectively, but have not had widespread use due to cost and concerns over safety and efficacy.⁵

The most recent class of medication, the GLP-1 RAs, has been a welcome addition to our armamentarium to treat obesity. Initially designed for glucose lowering, recently their indication has been expanded to include weight reduction in non-diabetic populations. There is extensive experience with GLP-1 RAs with diabetes and these medications have

now become first-line therapies for long-term diabetes treatment not only for their glucose lowering but also due to their improvement in cardiac and renal outcomes.⁶ GLP-1 RAs approved for treatment of obesity without diabetes, liraglutide and now semaglutide, have shown good tolerability with limited side effects, mainly nausea and vomiting, and excellent weight reduction especially in combination with behavioral modification.^{7–9} As noted by the authors, unfortunately GLP-1 RAs are currently expensive and not well-covered by insurance. Weight loss is associated with lower mortality and a decreased risk of diabetes, high blood pressure, hyperlipidemia, cardiovascular disease, and obstructive sleep apnea.¹⁰ Therefore, making these medications more affordable, as well as increasing research to develop additional weight loss medications, is essential.

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