GLP-1-based therapies for the treatment of resistant hypertension in individuals with overweight or obesity: a review

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Summary

Despite the availability of a wide range of antihypertensive agents, a significant proportion of individuals with resistant hypertension (RHTN) struggle to achieve blood pressure (BP) control. Obesity ranks among the most significant modifiable risk factors for RHTN, with 56–91% of patients with RHTN classified as overweight or obese. Glucagon-like peptide-1 receptor agonist (GLP-1 RAs) are a class of anti-obesity medications that have recently demonstrated efficacy in reducing BP and improving cardiovascular (CV) outcomes in individuals with overweight or obesity. Among the available GLP-1-based therapies, liraglutide, semaglutide, and tirzepatide have been approved for chronic weight management in this population. Tirzepatide, a dual GLP-1 and glucose-dependent insulinotropic polypeptide receptor agonist, has the greatest effect on weight loss and BP reduction compared to GLP-1 RAs alone. To our knowledge, no trials have directly evaluated the effect of GLP-1 RAs or dual GLP-1/GIP receptor agonists on RHTN management. In this review article, we propose that targeting weight loss through GLP-1-based therapies should be explored as a treatment option for individuals with RHTN who are overweight or obese.

Keywords: Glucagon-like peptide-1-based therapies; Resistant hypertension; Weight loss; Blood pressure; Obesity; Overweight

Introduction

Hypertension remains the leading modifiable risk factor for many adverse cardiovascular (CV) events, including stroke, heart failure, and death worldwide.[1] An estimated 10–30% of adults with hypertension have resistant hypertension (RHTN), which is associated with a 50% higher risk of adverse CV events and end-organ damage.[1–5] According to the American College of Cardiology/American Heart Association clinical practice guidelines, RHTN is defined as:

"[…] above-goal elevated blood pressure (BP) in a patient despite the concurrent use of 3 antihypertensive drug classes, commonly including a long-acting calcium channel blocker, a blocker of the renin-angiotensin system (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker), and a diuretic. The antihypertensive drugs should be administered at maximum or maximally tolerated daily doses. […] Nonadherence in taking prescribed antihypertensive medications must also be excluded before [RHTN] is diagnosed."[6] *(p.1)*

The BP goal of treatment for the majority of adults with RHTN is <130/80 mmHg.[4,6] Despite the availability of a wide range of antihypertensive medications, 45–82% of individuals with apparent RHTN struggle to achieve BP control.[7,8] Apparent RHTN refers to individuals who meet the criteria for RHTN but lack confirmed adherence to medication, proper dosing, or have not undergone out-of-office BP monitoring to exclude the white-coat effect.[6] Even among those with true RHTN, the rate of medication non-adherence remains high.[9] This is attributable to the large pill burden, dosing complexity, expense, and high frequency of adverse reactions with multidrug antihypertensive regimens.[9] Thus, an investigation of more effective treatment regimens for RHTN is warranted.

Common risk factors for RHTN include older age, obesity, chronic kidney disease, black race, and diabetes mellitus.[8,10,11] Obesity ranks among the most significant

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modifiable risk factors, with 56–91% of patients with RHTN being overweight (body mass index [BMI] ≥ 25 kg/m^2) or obese (BMI ≥ 30 kg/m^2).[8,12–14] Obesity is also significantly associated with a higher likelihood of exhibiting non-adherence to antihypertensive medications and developing comorbidities and CV disorders.[12,13] It is likely that as the prevalence of obesity continues to increase,[15] RHTN will also increase unless obesity is effectively treated. Current management of RHTN recommends maximizing lifestyle interventions that promote weight loss as an effective method to improve BP in individuals with overweight or obesity.[4,6] However, long-term weight loss maintenance is challenging with lifestyle modification alone, and weight regain is common.[16,17] Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) promote greater weight loss, BP reduction, and improved CV outcomes compared to lifestyle modification. In this review article, we propose that targeting weight loss pharmacologically through GLP-1-based therapies offers a promising treatment option for individuals with RHTN who are overweight or obese.

Link between obesity and RHTN

The pathophysiological mechanisms linking overweight or obesity, especially visceral adiposity, to RHTN are complex and not completely understood. The main mechanisms are hyperaldosteronism,[18] systemic inflammation,[19] increased renin-angiotensin-aldosterone system (RAAS) activity, sympathetic nervous system hyperactivity,[20] oxidative stress,[21] and insulin resistance.[22]

Hyperaldosteronism is found in approximately 20% of individuals with RHTN.[18] In a cross-sectional analysis of 2170 patients with RHTN, it was shown that BMI positively correlates with 24-h urinary aldosterone levels.[18] Moreover, weight loss in individuals with obesity and hypertension results in a decrease in plasma aldosterone concentration and systolic BP (SBP) reduction.[23] Data from a study conducted on animal models with induced obesity indicates that leptin, an adipokine, increases sympathetic activity and directly regulates adrenal aldosterone secretion independently of the systemic RAAS.[24]

Insulin resistance and oxidative stress are typically observed in individuals with increased visceral adiposity.[22] Obesity-induced insulin resistance contributes to overactivation of both the RAAS and sympathetic nervous system, causing impairment in natriuresis, increased renal sodium retention, and extracellular volume expansion.[22] Ultimately, dysregulation of these processes can lead to RHTN.[20,22]

Current pharmacological management of RHTN

Spironolactone, a steroid mineralocorticoid receptor antagonist, is currently recommended as the fourth line agent for RHTN. The PATHWAY-2 Trial demonstrated that spironolactone was superior to the beta blocker bisoprolol, alpha blocker doxazosin, and placebo for lowering BP in RHTN.[25] On average, spironolactone reduced SBP by 4.5 mmHg more than bisoprolol, 4.0 mmHg more than doxazosin, and 8.7 mmHg more than placebo.[25] However, spironolactone's dose-limiting adverse effects, such as hyperkalaemia and gynecomastia, have prompted the investigation of novel fourth line medications in individuals with RHTN. Instead of using a fourth line antihypertensive agent, we suggest targeting weight management with GLP-1-based therapies among individuals with RHTN.

Targeting weight loss in RHTN

Several studies have proven weight loss to be effective at improving BP control in individuals with hypertension, achieved through diet and lifestyle modification, pharmacotherapy, and bariatric surgery.[26–29]

Lifestyle modification

Among individuals with hypertension, lifestyle modifications, including weight loss, low caloric diets, reduced intake of dietary sodium and alcohol, and increased physical activity, are recommended as first line therapy.[4,30] The same recommendations are applicable to individuals with RHTN, despite the limited evidence on the effectiveness of nonpharmacological weight management in this population. The TRIUMPH Trial assessed the impact of lifestyle modification in patients with RHTN.[31] Individuals (n = 140) with a mean BMI of 36 kg/m^2 were randomized to either an intensive four month program of dietary counselling, behavioural weight management, and exercise (C-LIFE) or a single 1 h counselling session (SEPA). In the C-LIFE arm, even modest decreases in BMI (–2.3 kg/m^2) were associated with substantial reductions in SBP (–12.5 mmHg) and diastolic BP ([DBP] –5.9 mmHg) compared to the SEPA arm (–1.3 kg/m^2; –7.1 mmHg; –3.7 mmHg, respectively). The BP reductions attained through lifestyle modification in the TRIUMPH Trial were comparable to those observed with fourth line antihypertensive medications, suggesting that even modest weight loss (5–10% of body weight) could significantly lower BP in individuals with RHTN. A 2023 pilot study (n = 50) evaluated the effect of intensive lifestyle interventions on BP reduction in patients with RHTN.[32] Ambulatory BP monitoring (ABPM) data showed a substantial mean reduction in 24-h SBP (–14.0 mmHg) and DBP (–8.5 mmHg) at 6 months. Decreases in BMI, medication burden, and CV risk markers were also observed. However, these studies lack data on the extent to which lifestyle intervention alone can sustain long-term weight loss in individuals with RHTN.[31,32]

Pharmacological interventions

To our knowledge, pharmacological interventions for weight management have not been specifically tested in patients with RHTN, but there is some evidence of their effect in people with hypertension.[26,33] A 2021 Cochrane review assessed the long-term effects of pharmacologically induced weight loss on SBP and DBP among individuals with hypertension and BMI ≥ 27 kg/m^2 [26] Six RCTs (n = 12,724) with a range of follow-up from six to 13 months were included. Orlistat was associated with greater SBP (–2.6 mmHg) and DBP (–2.0 mmHg) reductions compared to placebo. Phentermine/topiramate also led to placebo-adjusted reductions in SBP (–2.0 to –4.2 mmHg) and DBP (–1.3 to –1.9 mmHg).[25] In 2024, a network meta-analysis including 31 RCTs (n = 35,458) showed that GLP-1-based agents were associated with the largest relative BP reductions compared to placebo in individuals who are overweight or obese.[34] Among them, tirzepatide led to the largest decreases in SBP (–6.45 mmHg) and DBP (–3.64 mmHg).[34]

GLP-1-based therapies for chronic weight management

GLP-1 RAs mimic the incretin hormone GLP-1, triggering insulin secretion in response to oral glucose intake, targeting the hypothalamus to increase satiety, and delaying gastric emptying.[33] These agents were initially developed for glycaemic control among patients with type 2 diabetes.[4,35] In 2014, the United States Food and Drug Administration approved the first GLP-1 RA, liraglutide, as an adjunct to lifestyle modification for chronic weight management.[36] Only three GLP-1-based agents are currently approved in individuals without diabetes who are obese or high risk overweight (BMI ≥ 27 kg/m^2) with at least one related comorbidity, such as hypertension.[4,35] These include liraglutide (Saxenda™), semaglutide (Wegovy™), and tirzepatide (Zepbound™).

Antihypertensive effect of GLP-1-based therapies

Mechanisms of BP reduction beyond weight loss. The antihypertensive effect of GLP-1-based therapies is mediated through multiple pathways.[37] Based on results from preclinical studies, the proposed mechanisms include direct actions on: central and peripheral nervous system to counteract sympathoexcitation[38,39]; kidneys to induce natriuresis[37,40–42]; and endothelial cells to promote vasodilation.[43,44] Sustained GLP-1 receptor activation decreases BP via activation of brainstem catecholamine neurons to attenuate sympathetic nerve activity in spontaneously hypertensive rats.[38] In the peripheral nervous system of spontaneously hypertensive rats, decreased expression of GLP-1 receptor activity in the carotid body is associated with sympathetic hyperactivity.[39] By activating GLP-1 receptors, GLP-1 RAs can counteract sympathetic hyperactivity, thereby reducing BP.[39] Moreover, GLP-1 RAs inhibit the Na^+/H^+ exchanger NHE3 in the renal proximal tubules, reducing sodium reabsorption and preventing volume expansion.[40] GLP-1 RAs have also been found to inhibit the local RAAS and counteract the actions of angiotensin II on the kidneys.[37,41,42] Notably, their beneficial effect on BP seems to occur, at least partially, independently of weight loss.[37–42] Based on this evidence, we believe that GLP-1-based therapies offer a potential alternative for RHTN management in individuals who are overweight or have obesity.

Evidence from RCTs. Liraglutide, the first GLP-1 RA approved for chronic weight management, leads to BP reductions in individuals with overweight or obesity. The SCALE Obesity and Prediabetes Trial randomized 3731 individuals in a 2:1 ratio to receive once daily liraglutide 3.0 mg or placebo.[45] Compared to placebo, liraglutide led to 5.6 kg reduction in body weight at week 56. Liraglutide treatment was associated with placebo-adjusted reductions in cardiometabolic risk factors, including waist circumference (–4.2 cm), SBP (–2.8 mmHg), and DBP (–0.9 mmHg). Furthermore, a meta-analysis of 12 trials with 8249 individuals demonstrated that liraglutide reduces body weight (–3.4 kg), BMI (–1.5 kg/m^2), SBP (–3.1 mmHg), and DBP (–1.0 mmHg) compared to placebo.[46]

Semaglutide 2.4 mg administered once weekly also reduces BP and improves CV outcomes in individuals with overweight or obesity. In the STEP-1 Trial, the use of semaglutide resulted in a placebo-adjusted body weight change of –12.4% at 68 weeks, with significant reductions in SBP (–5.1 mmHg) and DBP (–2.4 mmHg).[47] Among semaglutide-treated individuals, 36.1% were hypertensive at baseline, with 20% stopping and 14% reducing the number of antihypertensive medications required, compared to 11% and 5% in placebo-treated individuals, respectively.[47] A meta-analysis of six trials with 4744 individuals demonstrated that semaglutide had a greater effect on BP reduction compared to placebo, with placebo-adjusted reductions in SBP (–4.83 mmHg) and DBP (–2.45 mmHg) in individuals with overweight and obesity.[48] Furthermore, the SELECT Trial directly evaluated the impact of semaglutide on CV risk reduction in adults who are overweight or obese with pre-existing cardiovascular disease.[49] Among 17,604 individuals, the use of semaglutide resulted in a 20% reduction in the risk of major adverse CV events (MACE), including CV death, myocardial infarction, and stroke. Semaglutide was also associated with placebo-adjusted reductions in SBP (–3.3 mmHg) and body weight (–8.5%), suggesting that even small BP changes with GLP-1 RAs translate into reductions in MACE. Most recently, the STEP-HFpEF DM Trial demonstrated that semaglutide is also beneficial for patients with obesity-related heart

failure and type 2 diabetes, leading to larger reductions in heart failure-related symptoms and physical limitations than placebo at 1 year follow-up.[50] The results of this study add to the previously reported findings of the SELECT Trial, suggesting that semaglutide has the potential to treat a wider range of obesity-related conditions, including RHTN.

Tirzepatide, a dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) agonist, exhibits synergistic effects on reducing appetite, boosting metabolic function, and decreasing food intake.[51] In the SURMOUNT-1 Trial, once weekly subcutaneous tirzepatide conferred dose-dependent weight reduction up to 20.1% at 72 weeks.[51] A sub-study of SURMOUNT-1 evaluated the effect of tirzepatide on 24-h ABPM at week 36.[52] Among 600 individuals, tirzepatide reduced SBP from baseline by 7.4 to 10.6 mmHg compared to placebo. The real effect of tirzepatide on BP may be even more pronounced, given that only 30% of the participants reported hypertension at baseline.[52] Moreover, tirzepatide's BP-lowering effect was found to be partially independent of weight loss, suggesting that alternative pathways may be involved in BP reduction with GLP-1-based therapies. The results from the SURMOUNT-1 Trial suggest that tirzepatide's clinical benefits may extend beyond weight loss and may include independent effects on BP reduction, which warrants an investigation in RHTN treatment.

Several promising new GLP-1-based medications, while not yet commercially available, have demonstrated even greater weight-reducing and BP-lowering effects in individuals who are overweight or obese. Retatrutide is a triple GLP-1, GIP, and glucagon (GCG) receptor agonist that demonstrates dose-dependent reductions in body weight and BP.[53] In a recent phase II trial, retatrutide treatment for 48 weeks led to SBP and DBP reductions up to 12.1 and 8.1 mmHg, respectively.[53] Retatrutide treatment also resulted in dose-dependent discontinuation of at least one antihypertensive medication, up to 41% in the retatrutide 8.0 mg arm.[53] Phase II trials of another molecule called JNJ-64565111, a dual GLP-1/GCG co-agonist, also led to clinically significant SBP (–9.5 mmHg) and DBP (–4.1 mmHg) reductions at week 26.[45]

Common adverse events (AEs) with GLP-1-based therapies include mild-to-moderate gastrointestinal (GI) symptoms, nasopharyngitis, headache, and upper respiratory tract infection.[54] In a meta-analysis of 4 trials with 3087 individuals, AEs were commonly reported in both semaglutide and placebo arms.[54] GI symptoms (nausea, vomiting, constipation, dyspepsia, and diarrhoea) were the most common AEs, with 77.2% in the semaglutide arm and 52.2% in the placebo arm.[54] However, only 6.5% of individuals in the semaglutide arm discontinued treatment due to AEs. The rate of serious AEs (SAEs) and death were low (9.4% in semaglutide vs 6.6% in placebo) across all trials. Another meta-analysis reported no significant difference between GLP-1-based therapies and placebo in the overall incidence of AEs, despite a statistically significant increased risk of GI side effects compared to placebo.[34] It should be noted that some individuals might not achieve significant weight loss with GLP-1-based agents, but the rate of poor responders (less than 5% body weight reduction) is below 17%.[47,51,55]

GLP-1-based therapies, adherence, and medication burden

We expect GLP-1-based therapies to also decrease medication non-adherence in people with RHTN.[9] In a meta-analysis of 24 studies with 68,313 individuals, the prevalence of antihypertensive medication non-adherence in patients with apparent RHTN was 31.2%.[56] The prevalence of non-adherence ranged from 3.3% to 86.1% depending on the method of assessment used.[56] Conversely, the STEP-1, SELECT, and SURMOUNT Trials investigating GLP-1-based therapies in individuals who are overweight or obese report adherence rates as high as 81%.[47,49,52] Unlike standard antihypertensive agents, GLP-1-based therapies offer a dual benefit of weight loss and BP reduction, which may appeal to many people. This dual benefit can provide a compelling incentive for patients to adhere to their medication regimen. Moreover, the once-weekly injectable options like tirzepatide or semaglutide may be more convenient and less burdensome for some patients compared to a daily oral medication regimen.[57,58]

It is likely that GLP-1-based therapies would lead to a reduction in patients' antihypertensive medication burden. On average, individuals with RHTN are treated with five to six antihypertensive agents daily.[9] Among them, co-morbidities are highly prevalent, posing a risk of potentially harmful drug–drug interactions.[59] It has been shown that tirzepatide and semaglutide are linked with the reduction in the number of antihypertensive medications in individuals who are overweight or obese and have hypertension.[34–36] Improvements in BP levels with semaglutide were maintained despite a parallel relative reduction in antihypertensive medication use.[60] These findings demonstrate that GLP-1-based therapies have the capacity to reduce treatment burden in individuals with RHTN, which may lead to improvements in medication adherence and BP control.

Bariatric surgery

The effects of bariatric surgery on BP and hypertension management have also been studied.[61] In the GATEWAY Trial, 100 patients with obesity and hypertension were randomly assigned to Roux-en-Y gastric bypass (RYGB) plus antihypertensive medical therapy (MT) or antihypertensive MT alone.[62] The primary outcome was reduction of at least 30% of the total antihypertensive medications while maintaining controlled BP. After 5 years of follow-up, 86.5% of patients in the RYGB arm reached the primary outcome

Search Strategy and Selection Criteria

Data for this review article were identified through searches of PubMed, Google Scholar, and clinicaltrials.gov using the search terms "resistant hypertension," "resistant hypertension management," "obesity," "overweight," "glucagon-like peptide-1 receptor agonist," "glucagon-like peptide-1-based therapies," "liraglutide," "semaglutide," "tirzepatide," "blood pressure control," "lifestyle modification," "pharmacological interventions," "bariatric surgery," and "randomized controlled trial." The search period covered the years of inception to May 2024. The final reference list was generated based on originality and relevance to the broad scope of this review.

compared to only 12.5% in the MT arm.[62] At 5 years follow-up, ABPM revealed no differences in mean 24-h SBP (123.4 mmHg) and DBP (78.11 mmHg) between the two groups. However, 46.9% of individuals in the RYGB arm discontinued their antihypertensive medical treatment compared to only 2.4% in the MT arm.[62] The prevalence of RHTN in the RYGB arm was reduced from 10.0% at baseline to 0% after 5 years while MT had no effect (16.0% vs 15.2%).[62] Despite its promising effect on RHTN, bariatric surgery is reserved only for patients with severe obesity (BMI $\geq$ 40 kg/m^2) due to its invasiveness and high risk of complications.[63] These include marginal ulceration, gastro-gastric fistula, small bowel obstruction, dumping syndrome, nutritional complications, and deficiencies in B12, iron, and calcium.[63]

In this review article, we propose that GLP-1-based therapies, which have been associated with BP reductions, present a promising therapy option for individuals with RHTN who are overweight or obese. First, we hypothesize that the BP reductions from GLP-1 RA-assisted weight loss would be even more significant in individuals with RHTN, given their typically higher BP levels at baseline. Second, GLP-1-based therapies may also improve CV outcomes in individuals with RHTN who are overweight and obese, reducing CV risk and possibly improving their quality of life. Third, we believe that their use will also improve medication adherence in individuals with RHTN. Finally, we expect the effect of GLP-1-based therapies on weight loss and BP might be associated with reduced medication burden.

We need robust clinical trials designed to assess the efficacy, safety, and long-term CV effects of GLP-1-based treatments among individuals with RHTN who are overweight or obese. It would be valuable to assess whether any reductions in BP would persist upon GLP-1 RA discontinuation or weight regain, and whether the achieved effect on BP is independent of weight loss. Moreover, GLP-1-based therapies should be studied in combination with common antihypertensive medications in individuals with RHTN to test their potential to simplify antihypertensive management.

Conclusion

GLP-1-based therapies may provide a holistic approach for treating individuals with RHTN who are overweight or obese. Liraglutide, semaglutide, and tirzepatide have shown BP reductions comparable to many antihypertensive medications but with the added benefit of improved CV outcomes and medication adherence. Although not yet commercially available, novel GLP-1-based agents are now demonstrating even greater BP-lowering effects. GLP-1-based therapies should be strongly considered in the treatment of individuals with RHTN who are overweight or obese, especially since sustained weight loss may lead to reduced CV risk, the successful withdrawal of antihypertensive medications, and improved medication adherence.

Contributors

CJ: methodology, literature review and original draft author. TZ, MJE and AM: oversight, review and editing. MJE: conceptualization. All authors confirm they had full access to all data in the review. All authors read and approved the final manuscript to be published.

Declaration of interests

The authors declare no competing interests.

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