# Glucagon-like peptide-1 receptor agonists and their effects on weight reduction

Overweight and obesity seriously damages human health. The World Health Organization estimates that 1.5 billion adults were overweight in the year of 2011. Of this overweight population, over 200 million men and nearly 300 million women were obese. At least 2.8 million adults die each year as a result of being overweight or obese. A total of 44% of the diabetes burden and 23% of the ischemic heart disease burden are attributable to overweight and obesity[1]. More than 70% of diabetic patients will experience macrovascular disease that is strongly associated with overweight and obesity[2]. Type 2 diabetes is continuing to be the leading cause of cardiovascular disorders, end-stage renal disease, blindness and amputations. Therefore, effective interventions designed to achieve weight reduction are a critical part of type 2 diabetes management to prevent the development of microvascular and macrovascular complications. However, the majority of diabetic patients gain rather than lose weight, particularly during intensifying glycemic control.

Many antidiabetic agents are currently available for glycemic control, but less than 50% of type 2 diabetic patients can reach their therapeutic goal. This problem might be related to the side-effects of antidiabetic agents, including hypoglycemia (insulin, sulfonylureas and repaglinides) and bodyweight increase (insulin, thiazolidinediones, sulfonylureas and lifestyle). Action to Control Cardiovascular Risk in Diabetes (ACCORD) initially aimed to investigate the effects of intensive glycemic control on cardiovascular endpoints in type 2 diabetes patients at high risk of cardiovascular events, but a 22% increase in total mortality was observed in

this group, mainly driven by cardiovascular mortality. The explanation for higher cardiovascular (CV) mortality remains unclear, but hypoglycemia and weight gain were responsible for the adverse outcomes[3]. These results make a great impact on the concept of hyperglycemic management in type 2 diabetes, and patients should receive treatment that enables them to safely achieve an ideal glycemic control without a risk of hypoglycemia or higher gain in bodyweight.

Hyperglycemia in type 2 diabetes has been well investigated and can be attributed to increased hepatic glucose production, defective insulin-stimulated glucose disposal in target tissues, abnormal islet cell function and hypersecretion of glucagon. Antihyperglycemic agents are directed to one or more of the aforementioned defects of type 2 diabetes, or to modify physiological processes relating to appetite or to nutrient absorption or excretion. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are secreted from the intestines, and can enhance the endogenous secretion of insulin induced by meal ingestion and inhibit glucagon secretion, thereby improving glucose homoeostasis. Notably, GLP-1 also suppresses food intake and appetite. Abnormalities in this incretin system were found in type 2 diabetes. GLP-1 receptor (GLP-1R) agonists were recently introduced as a new treatment for patients with type 2 diabetes. Several clinical trials have shown that GLP-1R agonists can effectively and safely lower hyperglycemic parameters by dependently stimulating insulin secretion and inhibiting glucagon secretion. They have a rather low risk of hypoglycemia because of their mode of action. GLP-1 can slow down gastric emptying after a meal. Additionally, GLP-1 binds to its receptor on hypothalamic neurons and stimulates satiety by directly acting on its receptor. All clinical

trials of GLP-1R agonists have shown that agonists could lead to weight reduction in type 2 diabetes.

Recently, Vilsbøll et al.[4] carried out a systematic review with meta-analyses to determine whether treatment with GLP-1R agonist resulted in weight reduction in overweight or obese patients with type 2 diabetes. Adult participants with a body mass index of 25 or higher were included in these randomized controlled trials. They received exenatide twice daily, exenatide once weekly or liraglutide once daily for at least 20 weeks. Control interventions were placebo, oral antidiabetic drugs or insulin. Vilsbøll et al. carried out a random effects meta-analysis of 3,395 participants randomly assigned to GLP-1R agonists and 3,016 assigned to control groups for the change of bodyweight from 21 trials. They found that the mean change in bodyweight was larger for patients with GLP-1R agonist treatment than those in the control groups (weighted mean difference −2.9 kg; 95% confidence interval −3.6 to −2.2; Table 1). In the overall analysis, GLP-1R agonists improved glycemic control, with an increase in patients who achieved the therapeutic glycated hemoglobin ($HbA_{1c}$) goals. Additionally, GLP-1R agonists had beneficial effects on systolic and diastolic blood pressure, and plasma concentrations of cholesterol. Importantly, they also found that GLP-1R agonists were not associated with hypoglycemia, despite the side-effects of nausea, diarrhea and vomiting. The present meta-analysis provides convincing evidence that GLP-1R agonists should be considered in patients with diabetes who are obese or overweight[4]. Several once-weekly GLP-1R agonists have been found to decrease $HbA_{1c}$, and fasting and postprandial hyperglycemia. They can also greatly reduce bodyweight.

More recently, the position statement of the American Diabetes Association

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**Table 1** | Meta-analysis of change in bodyweight (kg) from 21 trials after at least 20 weeks of treatment

| Trial | No. patients | | Mean change (standard deviation) | | Weight (%) | Weighted mean difference (95% CI) |
|---|---|---|---|---|---|---|
| | GLP-1R agonist group | Control group | GLP-1R agonist group | Control group | | |
| Bergenstal (2010) | 160 | 166 | −2.3 (3.0) | −0.8 (0.3) | 4.98 | −1.50 (−1.97 to −1.03) |
| Buse (2004) | 129 | 123 | −1.6 (3.4) | −0.6 (3.3) | 4.74 | −1.00 (−1.83 to −0.17) |
| Kendall (2005) | 241 | 247 | −1.6 (3.1) | −0.9 (3.1) | 4.93 | −0.70 (−1.26 to −0.14) |
| Pratley (2010) | 221 | 219 | −3.4 (3.0) | −1.0 (1.8) | 4.98 | −2.42 (−2.88 to −1.96) |
| Moretto (2008) | 78 | 78 | −3.1 (2.7) | −1.4 (2.7) | 4.74 | −1.70 (−2.53 to −0.87) |
| Nauck (2009) | 242 | 122 | −2.8 (0.2) | −1.5 (0.3) | 5.09 | −1.30 (−1.36 to −1.24) |
| Garber (2009) | 246 | 248 | −2.5 (7.8) | 1.0 (7.9) | 4.21 | −3.50 (−4.89 to −2.11) |
| Diamant (2010) | 233 | 223 | −2.6 (3.1) | 1.4 (3.0) | 4.93 | −4.00 (−4.55 to −3.45) |
| DeFronzo (2010) | 45 | 45 | −2.8 (3.4) | 1.5 (3.4) | 4.21 | −4.30 (−5.69 to −2.91) |
| Russell-Jones (2009) | 230 | 114 | −1.8 (5.0) | −0.4 (4.1) | 4.59 | −1.38 (−2.38 to −0.38) |
| Heine (2005) | 282 | 267 | −2.3 (3.9) | 1.8 (4.0) | 4.86 | −4.10 (−4.76 to −3.44) |
| Astrup (2009) | 93 | 98 | −7.2 (0.5) | −2.8 (0.5) | 5.08 | −4.40 (−4.54 to −4.26) |
| Elkin (2010) | 20 | 20 | −3.2 (0.5) | −1.6 (0.9) | 4.99 | −1.60 (−2.04 to −1.16) |
| Davies (2009) | 118 | 117 | −2.7 (3.4) | 3.0 (3.4) | 4.72 | −5.71 (−6.57 to −4.85) |
| Rosenstock (2010) | 73 | 70 | −5.1 (0.5) | −1.6 (0.5) | 5.08 | −3.50 (−3.66 to −3.34) |
| Zinman (2009) | 178 | 177 | −2.0 (4.0) | 0.6 (4.0) | 4.74 | −2.60 (−3.43 to −1.77) |
| Apovian (2010) | 96 | 98 | −6.2 (0.5) | −4.0 (0.5) | 5.08 | −2.19 (−2.34 to −2.04) |
| Bergenstal (2009) | 124 | 124 | −1.9 (3.8) | 4.1 (5.4) | 4.44 | −6.00 (−7.16 to −4.84) |
| Bunck (2009) | 36 | 33 | −3.6 (3.6) | 1.0 (4.6) | 3.59 | −4.60 (−6.56 to −2.64) |
| Marre (2009) | 234 | 114 | −0.2 (0.0) | −0.1 (0.6) | 5.08 | −0.10 (−0.22 to 0.02) |
| Nauck (2007) | 253 | 248 | −2.5 (3.2) | 2.9 (3.0) | 4.94 | −5.40 (−5.94 to −4.86) |

Data are modified from Vilsbøll et al.[4] CI, confidence interval; GLP-1R, glucagon-like peptide-1 receptor.

(ADA) and the European Association for the Study of Diabetes (EASD) for the management of hyperglycemia in type 2 diabetes was published. In this statement, metformin is the preferred first agent if it is not contraindicated or if tolerated. If metformin alone does not achieve or maintain a $HbA_{1c}$ target over 3 months, a second oral agent, GLP-1R agonist or basal insulin, would be added. When a two-drug combination is not yet or no longer achieving the glycemic target, this statement suggests adding a third non-insulin agent, including GLP-1R agonist[5]. Some studies have shown advantages from the addition of GLP-1R to a combination therapy. Over 80% of individuals with type 2 diabetes are overweight or obese. GLP-1R agonists show their beneficial effects on weight loss and safety without hypoglycemia in type 2 diabetes. The systematic review with meta-analysis carried out by

Vilsbøll et al. convincingly confirms the place of GLP-1R agonists in guidelines for management of hyperglycemia in type 2 diabetes.

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