Glycemic Control Impact on Body Weight Potential to Reduce Cardiovascular Risk

Glucagon-like peptide 1 agonists

GIORGIO SESTI, MD

The prevalence and incidence of type 2 diabetes are progressively increasing because of a concomitant rise in the prevalence of obesity. Intentional weight loss in patients with type 2 diabetes has been associated with a 25% reduction in total mortality and a 28% reduction in cardiovascular disease and diabetes mortality (1).

Weight gain is not only a risk factor for development of type 2 diabetes, but it is also the undesirable feature of several current antidiabetic treatments such as thiazolidinediones, sulfonylureas, and insulin, with an estimated 2-kg weight gain for every 1% decrease in HbA_{1c} (2,3). Reasons for this include defensive snacking to treat or prevent hypoglycemia, decreased glucosuria, decreased basal metabolic rate, and expansion in adipose tissue and fluid retention.

Recently, novel therapeutic agents were developed for the treatment of type 2 diabetes. Among these are the incretin-based therapies, which include glucagon-like peptide (GLP)-1 receptor agonists and inhibitors of the protease dipeptidyl peptidase (DPP)-4. Both classes of drugs use the antidiabetic properties of GLP-1, an incretin hormone that potentiates insulin secretion in a glucose-dependent manner (4). In addition, GLP-1 exerts many beneficial effects on pancreatic islet function, including stimulation of (pro)-insulin biosynthesis, reduction in β-cell apoptosis induced by toxic agents, and suppression of glucagon release from the α-cells, resulting in reduced hepatic glucose output (5). GLP-1 also decreases the rate of gastric emptying, which slows the entry of nutrients into the circulation after meals, reduces appetite, and promotes satiety, leading to weight loss upon chronic exposure (6). However, GLP-1 has a short half-life (~1–2 min), since it is rapidly degraded through NH_2-terminal cleavage by the protease DPP-4; therefore, a continuous infusion would be required to achieve a clinical effect in diabetic patients (7). Two approaches were used to overcome these limitations: *1*) GLP-1 receptor agonists ("incretin mimetics") with longer half-life and *2*) DPP-4 inhibitors ("incretin enhancers") blocking GLP-1 degradation and thus preserving the endogenous secreted hormone. Among these, sitagliptin and saxagliptin were already approved for treatment by the U.S. Food and Drug Administration and European Medicines Agency (EMEA), and vildagliptin was approved for treatment by EMEA.

At variance with DPP-4 inhibitors, GLP-1 receptor agonists provide a pharmacological dose of a GLP-1 mimetic, designed to resist degradation. Among these, exenatide and liraglutide have been approved for treatment by the U.S. Food and Drug Administration and EMEA. Although GLP-1 receptor agonists and DPP-4 inhibitors are both related to antidiabetic properties of incretins, they represent different approaches to type 2 diabetes therapy. In this article, we will discuss their clinical value, with special focus on their effect on body weight and cardiovascular risk factors.

GLP-1 AGONISTS

Exenatide

Exenatide was the first GLP-1 receptor agonist approved by regulatory agencies for human clinical use. Exenatide is a synthetic form of the naturally occurring peptide found in the saliva of the Gila monster (*Heloderma suspectum*). It has 53% amino acid homology to human GLP-1 and is a potent agonist of human GLP-1 receptor. Because exenatide contains a glycine residue at position 2, it is less susceptible to DPP-4 degradation than the native molecule and is suitable for twice-daily dosing.

In a 24-week study carried out in 232 antidiabetic drug-naive patients with type 2 diabetes, twice-daily exenatide monotherapy was associated with a significant reduction in glycosylated hemoglobin (HbA_{1c}) (8). At the end of the study, the changes from baseline HbA_{1c} were −0.7% in the exenatide 5-μg group ($P = 0.003$) and −0.9% (0.1%) in the exenatide 10-μg group ($P < 0.001$), compared with −0.2% with placebo. The improvement in HbA_{1c} was associated with a significant decrease in body weight in both groups treated with exenatide. Weight changes from baseline were −2.8 kg in the exenatide 5-μg group ($P = 0.004$) and −3.1 kg in the exenatide 10-μg group ($P < 0.001$) compared with −1.4 kg with placebo. Mean systolic blood pressure (SBP) decreased from baseline by −3.7 mmHg in both 5- and 10-μg exenatide groups (both $P = 0.037$) compared with −0.3 mmHg with placebo. Mean diastolic blood pressure (DBP) decreased from baseline by −0.8 mmHg in the exenatide 5-μg group (P = NS) and −2.3 mmHg in the exenatide 10-μg group ($P = 0.046$) compared with −0.3 mmHg with placebo. Changes in fasting total cholesterol, HDL cholesterol, and LDL cholesterol from baseline were not significantly different between the exenatide 5- and 10-μg groups and the placebo group.

Three phase III clinical trials, each of 30 weeks' duration, have examined the

From the Department of Experimental and Clinical Medicine, University of Catanzaro Magna Greacia, Catanzaro, Italy.
Corresponding author: Giorgio Sesti, sesti@unicz.it.
This publication is based on the presentations at the 3rd World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this supplement were made possible in part by unrestricted educational grants from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, Ethicon Endo-Surgery, Generex Biotechnology, F. Hoffmann-La Roche, Janssen-Cilag, Johnson & Johnson, Novo Nordisk, Medtronic, and Pfizer.
DOI: 10.2337/dc11-s228

effect of exenatide on glycemic control in patients inadequately controlled with maximally effective doses of sulfonylurea monotherapy, metformin monotherapy, or sulfonylurea + metformin combination therapy (9–11). In patients on background metformin monotherapy, the reduction in HbA_{1c} from baseline was −0.78, −0.40, and −0.08% for patients treated with 10 μg exenatide, 5 μg exenatide, and placebo, respectively ($P < 0.002$) (9). During the study, patients treated with exenatide exhibited progressive weight loss regardless of baseline BMI. The reduction in body weight from baseline was −2.8 kg ($P < 0.001$ vs. placebo), −1.6 kg ($P < 0.05$ vs. placebo), and −0.3 kg for patients treated with 10 μg exenatide, 5 μg exenatide, and placebo, respectively. No changes in plasma lipids, heart rate, blood pressure, or electrocardiogram variables were observed between treatment groups. In patients on background sulfonylurea monotherapy, the reduction in HbA_{1c} from baseline was −0.86, −0.46, and −0.12% for patients treated with 10 μg exenatide, 5 μg exenatide, and placebo, respectively ($P < 0.001$) (10). Patients treated with 10 μg exenatide showed a progressive weight reduction with an end-of-study loss of −1.6 kg from baseline ($P < 0.05$ vs. placebo), whereas subjects treated with 5 μg exenatide had an end-of-study weight loss of −0.9 kg from baseline (NS vs. placebo), and subjects in the placebo arm had an end-of-study weight loss of −0.6 kg from baseline. There were small reductions in LDL ($P < 0.05$ for pair-wise comparisons) and apolipoprotein B ($P < 0.05$ for pair-wise comparisons) concentrations in the exenatide groups compared with placebo. However, other lipid parameters (total cholesterol, triglycerides, and LDL-to-HDL ratios) did not differ significantly among treatment groups. In patients on background sulfonylurea + metformin combination therapy, the reduction in HbA_{1c} from baseline was −0.80, −0.60, and 0.2% for patients treated with 10 μg exenatide, 5 μg exenatide, and placebo, respectively ($P < 0.001$ vs. placebo) (11). Subjects treated with exenatide exhibited progressive weight reduction over the entire 30-week treatment period, with end-of-study weight loss of −1.6 kg from baseline in each exenatide group compared with end-of-study weight loss of −0.9 kg from baseline in the placebo group ($P < 0.01$ vs. placebo).

Patients from three placebo-controlled trials and their open-label extensions were enrolled into one open-ended, open-label clinical trial (12). Patients ($n = 217$) completing 3 years of twice-daily 10 μg exenatide treatment had a mean HbA_{1c} reduction of –1.0% from baseline ($P < 0.0001$). A progressive weight loss was observed with a net loss of 5.3 kg at the end of 3 years ($P < 0.0001$). In a subgroup of 151 patients with serum lipid measurements at the time of study closure, exenatide therapy for 3.5 years also significantly improved a number of cardiovascular risk factors. Total cholesterol was reduced from baseline by −10.8 mg/dL ($P = 0.0007$), triglyceride by −44.4 mg/dL ($P = 0.0003$), and LDL cholesterol by −11.8 mg/dL ($P < 0.0001$), whereas HDL cholesterol increased from baseline by 8.5 mg/dL ($P < 0.0001$). Additionally, SBP was reduced from baseline by −3.5 mmHg ($P = 0.0063$) and DBP by −3.3 mmHg ($P < 0.0001$). The greatest improvements in cardiovascular risk factors were observed in patients who had the greatest weight reductions. The 25% of subjects who lost the most weight (weight reduction of –12.8 kg) exhibited the largest mean changes in SBP (–8.1 mmHg), DBP (–5.6 mmHg), HDL cholesterol (10.6 mg/dL), and triglycerides (–104.2 mg/dL) (12). In an interim analysis of 314 overweight patients treated for 82 weeks with exenatide, weight loss was strongly influenced by baseline BMI: patients with baseline BMI <25 kg/m^2 had a mean weight reduction of 2 kg, whereas patients with baseline BMI ≥ 40 kg/m^2 had a mean reduction of >7 kg (13). Another factor influencing weight loss was the background oral antidiabetic agent. Patients taking metformin alone had a mean weight reduction of 5.3 kg compared with 3.9 kg for patients taking a sulfonylurea and 4.1 kg for patients taking a sulfonylurea in combination with metformin (13).

The efficacy of exenatide (10 μg twice daily) added to rosiglitazone alone or pioglitazone alone, or in combination with metformin, was examined in a 16-week trial (14). Addition of exenatide to thiazolidinediones in the presence or absence of metformin resulted in a reduction of HbA_{1c} by 0.89% compared with a 0.09% increase in the placebo group. Mean body weight changes at week 16 were −1.75 kg for exenatide recipients and −0.24 kg for placebo recipients ($P < 0.001$). No clinically significant changes occurred in fasting serum lipid levels or blood pressure in either group over the 16 weeks of study.

Exenatide therapy was also compared with insulin therapy as add-on to oral hypoglycemic agents. In a 26-week trial, patients with type 2 diabetes who could not achieve adequate glycemic control with combination metformin and sulfonylurea therapy at maximally effective doses were randomized to either adding exenatide 10 μg twice daily or insulin glargine daily (15). At the end of the study, both groups achieved similar improvements in glycemic control (1.11% reduction in HbA_{1c} from baseline). Patients receiving insulin glargine gained weight throughout the trial, whereas those receiving exenatide exhibited progressive reductions in body weight: body weight decreased by 2.3 kg with exenatide and increased by 1.8 kg with insulin glargine. Exenatide was also compared with biphasic insulin aspart (30% rapid-acting insulin aspart) in addition to metformin and sulfonylurea in a 52-week trial (16). Patients treated with exenatide achieved similar improvement in glycemic control as individuals treated with biphasic insulin aspart (1.04 vs. 0.89% reduction in HbA_{1c} from baseline for exenatide- and insulin-treated patients, respectively) (16). The exenatide group had a weight reduction of 2.5 kg, whereas the biphasic insulin group had a weight increase of 2.9 kg. HDL cholesterol increased to a greater extent in the biphasic insulin group (exenatide minus insulin, −1.55 mg/dL; $P = 0.003$), whereas no additional significant changes occurred in fasting lipid levels in either group over the 52 weeks of study. A statistically significant mean reduction in both SBP (−5 mmHg, $P < 0.001$) and DBP (−2 mmHg, $P = 0.03$) was observed in the exenatide group, whereas blood pressure did not change significantly with biphasic insulin.

Data from these trials suggest that exenatide induces a sustained reduction in HbA_{1c}, which is significantly greater than that with placebo and similar to what is achieved with insulin preparations. Furthermore, patients treated with exenatide exhibit a consistent weight loss, which becomes more evident when compared with the weight increase associated with insulin use. An additional finding is that treatment with exenatide is associated with a reduction in blood pressure and with positive changes in lipids, which may contribute improved cardiovascular risk profile.

Liraglutide

Liraglutide is a human acylated analog of GLP-1 with 97% amino acid sequence homology to the endogenous gut hormone that binds noncovalently to albumin. The

half-life of liraglutide was estimated to be 13 h in patients with type 2 diabetes, which makes it suitable for once-daily administration.

The Liraglutide Effect and Action in Diabetes (LEAD) trials, including >4,000 patients, were designed to investigate liraglutide as monotherapy or in combination with various oral antidiabetic drugs and to compare liraglutide with other antidiabetic therapies commonly used in the treatment of type 2 diabetes (17–25). The 52-week LEAD-3 trial compared liraglutide monotherapy with glimepiride monotherapy in patients suboptimally controlled with diet and exercise or oral antidiabetic drug monotherapy (18). Liraglutide (1.2 or 1.8 mg daily) was more effective than glimepiride in reducing HbA_{1c} level (by 0.84 and 1.14 vs. 0.51%, respectively). Moreover, a sustained weight reduction of 2.1 and 2.5 kg was observed with liraglutide monotherapy (1.2 and 1.8 mg once daily, respectively) compared with a weight gain of 1.1 kg with glimepiride ($P = 0.0001$ for both). Weight loss with liraglutide monotherapy occurred primarily in the first 16 weeks but was then sustained throughout the 52 weeks of the study. SBP was reduced by 3.6 mmHg in the 1.8 mg liraglutide group ($P < 0.01$ vs. glimepiride), by 2.1 mmHg in the 1.2 mg liraglutide group ($P = 0.29$ vs. glimepiride), and by 0.7 mmHg in the glimepiride group.

In the 26-week LEAD-2 trial, the addition of liraglutide was compared with that of glimepiride in patients not adequately controlled with oral antidiabetic therapy (19). Liraglutide (1.2 or 1.8 mg daily) was as effective as glimepiride in reducing HbA_{1c} level (by 0.97 and 1.0 vs. 0.98%, respectively). A weight reduction of 2.6 and 2.8 kg was observed with liraglutide therapy (1.2 and 1.8 mg once daily, respectively) compared with a weight gain of 1.0 kg with glimepiride ($P = 0.0001$ for both). In addition, the 1.2 and 1.8 mg liraglutide groups exhibited significant reductions in SBP of 3.2 mmHg ($P = 0.01$) and 2.7 mmHg ($P = 0.04$), respectively, compared with an increase of 0.4 mmHg observed in the glimepiride group. Dual-energy X-ray absorptiometry and computerized tomography substudies performed within LEAD-2 and LEAD-3 trials demonstrated that reductions in body weight with liraglutide were mainly due to a decrease in fat tissue and that both abdominal subcutaneous and visceral adipose tissues were reduced (20).

In the 26-week LEAD-1 trial, the addition of liraglutide (1.2 or 1.8 mg daily) to glimepiride reduced HbA_{1c} to a greater extent (by −1.1% for both doses) than rosiglitazone (−0.4%, $P < 0.0001$) (21). Mean reductions in weight from baseline were −0.2 kg with 1.8 mg liraglutide, whereas increases occurred with either 1.2 mg liraglutide (0.3 kg) or rosiglitazone (2.1 kg, $P < 0.0001$, vs. 1.8 mg liraglutide). Although decreases in SBP occurred with either 1.2 or 1.8 mg liraglutide (2.6–2.8 mmHg), they were not significantly different from rosiglitazone (2.3 mmHg).

In the 26-week LEAD-5 trial, liraglutide produced a greater reduction in HbA_{1c} level and body weight than insulin glargine on a background therapy of metformin and glimepiride. Moreover, patients treated with liraglutide had a reduction in waist circumference and lost ~1.8 kg in weight, whereas insulin glargine treatment was associated with weight gain of 1.6 kg. In the 26-week LEAD-5 trial, the efficacy of liraglutide was compared with that of insulin glargine, both in combination with metformin and glimepiride. Patients treated with liraglutide exhibited a greater reduction in HbA_{1c} (−1.33% from baseline) than individuals treated with insulin glargine (−1.09% from baseline) ($P = 0.001$) (23). Liraglutide treatment resulted in significant weight loss (−1.8 kg) compared with an increase (+1.6 kg) in the insulin glargine group ($P = 0.0001$). Waist circumference was reduced by 1.5 cm in the liraglutide group compared with a 0.89-cm increase in the insulin glargine group ($P < 0.0001$). A significant reduction in SBP (−4.0 mmHg) was observed with liraglutide compared with an increase (0.54 mmHg) with insulin glargine ($P = 0.0001$).

In the 26-week LEAD-6 trial, the efficacy of liraglutide (1.8 mg once daily) was assessed in a head-to-head comparison with exenatide (10 μg twice daily) both in combination with metformin and/or sulfonylurea (24). Liraglutide reduced HbA_{1c} significantly more than exenatide (–1.12 vs. 0.79%, $P < 0.0001$). Both drugs promoted similar weight losses (liraglutide –3.24 kg vs. exenatide –2.87 kg). Reductions of triglycerides (liraglutide –36 mg/dL vs. exenatide –20 mg/dL; $P = 0.04$) and free fatty acid (liraglutide –0.17 mmol/L vs. exenatide –0.10 mmol/L; $P = 0.001$) values were greater in the liraglutide group than in the exenatide group.

Overall, the LEAD trials demonstrated that liraglutide provides sustained HbA_{1c} reductions in monotherapy and in combination with other antidiabetic therapies. Treatment with liraglutide is associated with weight loss and reduction in fat tissue, both abdominal subcutaneous and visceral adipose tissues. In addition, liraglutide was found to be associated with a reduction in SBP.

CONCLUSIONS—Incretin-based therapies, which comprise GLP-1 receptor agonists and DPP-4 inhibitors, are new options for treatment of subjects with type 2 diabetes. These agents hold promise in overcoming some limitations of current antidiabetic treatments, including weight gain and risk of hypoglycemia. This treatment is as efficient as the other known oral antidiabetic drugs and is safer than sulfonylurea when comparing the incidence of hypoglycemic events and therefore can be considered as monotherapy and/or as a combination therapy with metformin. Both classes of drugs exert a beneficial effect on glycemic control and positive effects on β-cell function, making them a good therapeutic option early in the disease, when patients with type 2 diabetes still maintain some degree of β-cell function.

The characteristics of GLP-1 receptor agonists and DPP-4 inhibitors help facilitate therapy intensification and may help patients attain glycemic goals. Nevertheless, there are some differences between GLP-1 receptor agonists and DPP-4 inhibitors, ranging from their mode of administration to their effects on body weight. When considering what type of drug to choose between the GLP-1 receptor agonists and the GPP-4 inhibitors, the clinician has to consider parameters such as the patient's age, time from initial diabetes diagnosis, body weight, compliance, and financial means. In a head-to-head comparison with sitagliptin, the GLP-1 receptor agonist liraglutide was superior for reduction of HbA_{1c} as well as for improvements in homoeostasis model assessment of β-cell function, C-peptide concentration, and proinsulin-to-insulin ratio (25). In addition, weight loss and reductions in waist circumference were significantly greater with liraglutide than with sitagliptin. These differences will inevitably lead to a differentiation of patient groups in whom one treatment is favored over the other. In the older population, it might be wise to consider DPP-4 inhibitors because of their confined effect on lowering blood glucose and neutral effect on caloric intake and therefore less negative effect on muscle and total body

protein mass. In a younger patient recently diagnosed with type 2 diabetes, abdominal obesity, and abnormal metabolic profile, one should consider treatment with GLP-1 receptor agonists with the beneficial effect on weight loss and improved metabolic profile.

Therapies that promote weight loss can also improve insulin sensitivity and are an important addition to the treatment armamentarium for type 2 diabetes. No nausea is associated with DPP-4 inhibitors, whereas in treatment with GLP-1 receptor agonists, nausea (and vomiting) is observed in 5–35% of patients. Significant improvements in biomarkers of cardiovascular risk have been observed during GLP-1 receptor agonist treatment in clinical trials. Whether treatment with GLP-1 receptor agonists or DPP-4 inhibitors provide cardiovascular benefit remains to be investigated in trials of sufficient size and duration. This group of new drugs is another step in our progress toward personalized medicine and tailoring the specific incretin prescribed to patients based on personal criteria.

Acknowledgments—No potential conflicts of interest relevant to this article were reported.

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