Weight Loss, Glycemic Control, and Changes in Cardiovascular Biomarkers in Patients With Type 2 Diabetes Receiving Incretin Therapies or Insulin in a Large Cohort Database

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OBJECTIVE — Weight loss in patients with type 2 diabetes can improve glycemic control, lower blood pressure, and improve dyslipidemia. Glucagon-like peptide (GLP-1) receptor agonists are associated with weight loss and have potentially beneficial effects on cardiovascular risk biomarkers; however, there is limited information to indicate whether these effects remain outside of clinical trials.

RESEARCH DESIGN AND METHODS — Medical records from the General Electric Centricity research database were analyzed retrospectively to evaluate the relationship between weight loss and glycemic control and changes in blood pressure and lipids in patients with type 2 diabetes initiating therapy with exenatide, sitagliptin, or insulin. Baseline and follow-up (90–365 days after the index date) for weight, A1C, fasting blood glucose (FBG), blood pressure, triglycerides, and LDL, HDL, and total cholesterol were assessed.

RESULTS — A total of 6,280, 5,861, and 32,398 patients receiving exenatide, sitagliptin, or insulin, respectively, were included in the analysis. Exenatide-treated patients lost a mean ± SD of 3.0 ± 7.33 kg, sitagliptin-treated patients lost 1.1 ± 5.39 kg, and insulin-treated patients gained 0.6 ± 9.49 kg. There was a significant association between weight loss and a reduction in A1C and FBG with exenatide only and a reduction in blood pressure for all therapies. Weight loss was associated with some improvements in lipids, primarily in the GLP-1 receptor agonist group, with little association in the insulin group.

CONCLUSIONS — Weight reduction with GLP-1 receptor agonists was associated with a shift toward a more favorable cardiovascular risk profile. Outcome trials are needed to determine whether improvement in biomarkers translates into a reduction in cardiovascular events in patients with type 2 diabetes.

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The prevalence of type 2 diabetes continues to increase as does the number of obese individuals in the U.S. (1). There is a strong correlation between the two, with 80–95% of patients with type 2 diabetes being overweight or obese. In fact, studies have shown that the risk of developing diabetes increases in proportion to BMI (2). In addition, obesity exacerbates the metabolic abnormalities of type 2 diabetes, in particular, hyperglycemia, dyslipidemia, and hyper-tension (3). Obese individuals are at higher risk of developing cardiovascular disease, and the risk is even higher in those with type 2 diabetes who are obese (4).

In overweight and obese individuals with type 2 diabetes, weight loss is associated with improvements in risk factors. In fact, small amounts of weight loss (~5%) can improve glycemic control in type 2 diabetes (5,6). Longitudinal cohort studies indicate that changes in BMI in patients with type 2 diabetes are significant predictors of changes in A1C and blood pressure (7), and patients who lose weight are more likely to achieve goal A1C and blood pressure values than those who show stable weight or weight gain (8). Similarly, lifestyle intervention trials in patients with type 2 diabetes have shown that weight loss improves glycemic control, reduces blood pressure, and improves lipid levels (9), and even a modest weight loss can result in an improved cardiovascular risk profile (10). In patients with type 2 diabetes, intentional weight loss has been associated with a 28% reduction in cardiovascular disease and diabetes-related mortality (6). In addition, weight loss is associated with reduced diabetes-related health care costs (11).

Proper diet and exercise is the first-line therapy to promote weight loss and improve glycemia in new-onset diabetes, but most patients will require oral antidiabetes drugs (OADs) for glycemic control and many will eventually require insulin therapy. Although these therapies are effective in lowering A1C, most therapies lead to weight gain. Sulfonylureas, thiazolidinediones, and insulin result in weight gain of ~2 kg for every 1% decrease in A1C (12,13). Metformin, unlike other standard OADs, is often associated with slight weight loss.

Incretin-based therapies, including glucagon-like peptide (GLP-1) receptor agonists and dipetidyl peptidase-4 (DPP-4) inhibitors, have recently become treatment options for type 2 diabetes management, and unlike many other therapies, they do not induce weight gain (14). Therapy with GLP-1 receptor agonists results in weight loss in most patients. In controlled clinical trials, the...
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average weight loss was \( \sim 2 \) kg, which is generally sustained or progressive with long-term therapy (15). These agents have a physiological effect similar to that of native GLP-1, including enhancement of glucose-dependent insulin secretion and suppression of inappropriately high glucagon secretion. At high concentrations they also slow gastric emptying and reduce food intake (16).

By blocking DPP-4, an enzyme that breaks down GLP-1, DPP-4 inhibitors have actions similar to that of GLP-1 receptor agonists; they also enhance glucose-dependent insulin secretion and suppress glucagon, but they do not delay gastric emptying or reduce food intake. In controlled clinical trials the effect of sitagliptin on weight was neutral (17,18).

Data from clinical trials with exenatide, a GLP-1 receptor agonist, suggest that it has potentially beneficial effects on biomarkers of cardiovascular risk in patients with type 2 diabetes, including lowering blood pressure and improving dyslipidemia (19). However, there is limited information as to whether these effects remain outside of the setting of controlled clinical trials. In addition, it is not clear whether the effects on blood pressure and lipids are due to the weight loss that occurs with GLP-1 receptor agonists. Therefore, we evaluated patients with type 2 diabetes who initiated a incretin-based (GLP-1 receptor agonist or DPP-4 inhibitor) or insulin-based regimen to analyze the relationship between weight change and glycemic control and improvement in cardiovascular risk biomarkers in a real-world setting.

**RESEARCH DESIGN AND METHODS** — A retrospective analysis of outpatient electronic medical records (EMR) obtained from the General Electric Centricity research database was conducted. This research database contains information on \( > 540,000 \) patients with type 2 diabetes from 49 states between January 1996 and January 2008.

Included in the analysis were adult patients (\( > 18 \) years) with a diagnosis of type 2 diabetes (based on ICD-9 codes), who received prescription orders for exenatide, sitagliptin, or insulin on or after 1 January 2009. The first observed prescription defined the index date. Patients were to have a treatment duration of \( \geq 60 \) days and no use of a comparator regimen within 3 months before and 12 months after the index date. Patients were included if they had \( \geq 90 \) days of activity in the EMR database before and after the index date.

**Outcome measures**

Patient records were examined for body weight and at least one of the following outcomes: A1C, fasting blood glucose (FBG), systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides, LDL cholesterol, HDL cholesterol, and total cholesterol. The baseline measurement was observed within 60 days before to 30 days after the index date. The follow-up measurement was observed between 90 and 365 days after the index date. Patients without a baseline and follow-up measurement for at least one of the noted outcome measures were excluded from the study.

**Statistical methods**

For each treatment group, outcomes were stratified by various levels of weight change observed from baseline to follow-up. Analyses were performed only for patients with both baseline and follow-up values for a specific outcome parameter of interest. The statistical significance of descriptive differences in outcomes between weight change groups was measured using ANOVA for continuous measures and \( \chi^2 \) tests for categorical measures. Multivariate regressions were estimated to control for confounders among patients in various weight change categories. Linear regression was implemented to assess the effect of weight change on continuous outcomes. Logistic regression models were estimated to evaluate the effect of each level of weight change on dichotomous outcomes and are reported as odds ratios, which show the increased or decreased likelihood of the dichotomous outcome being true for patients in each weight change category relative to individuals with no weight loss (i.e., no weight change or weight gain). In addition to the weight loss categories, covariates included age, sex, baseline weight, geographic region, payer type, Charlson Comorbidity Index, number of days between baseline and follow-up observation, baseline use of other OADs, and baseline value of the outcome variable modeled. Analyses were conducted using SAS (version 9; SAS Institute, Cary, NC).

**RESULTS** — A total of 6,280, 5,861, and 32,398 patients receiving exenatide, sitagliptin, or, insulin, respectively, met...
the inclusion criteria. Baseline demographics of these patients are shown in Table 1. Baseline and follow-up values of the cardiovascular risk biomarkers assessed are shown in Table 2. Patients in the insulin group had substantially higher A1C and FBG at baseline than those receiving exenatide or sitagliptin.

**Weight change**

Exenatide-treated patients lost a mean ± SD of 3.0 ± 7.33 kg (P < 0.0001), sitagliptin-treated patients lost 1.1 ± 5.39 kg (P = 0.009), and patients receiving insulin gained 0.6 ± 9.49 kg (P = 0.002) during the follow-up period. More exenatide-treated patients lost ≥5% of their body weight, and more insulin-treated patients gained ≥5% of their body weight (Table 3, supplementary Fig. 1, available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc09-2062/DC1). The number of days from the baseline to the follow-up weight assessment was 270 ± 85.7 in the exenatide group, 216 ± 83.7 in the sitagliptin group, and 266 ± 87.6 in the insulin group.

**Glycemic control**

Glycemic control improved in all treatment groups, with reductions in A1C of 0.5 ± 1.4, 0.6 ± 1.4, and 1 ± 2.2% and in FBG of 9.9 ± 58.7, 13.5 ± 63.8, and 25.3 ± 102.8 mg/dl in the exenatide, sitagliptin, and insulin groups, respectively. Changes in body weight were significantly associated with reductions in A1C (P < 0.0001 for all treatment groups) and reductions in FBG (P = 0.002, P = 0.008, and P < 0.0001 for exenatide, sitagliptin, and insulin, respectively) (Table 3). However, for exenatide, a greater change in A1C and FBG occurred in those with weight loss and for sitagliptin and insulin, greater reductions occurred in those with weight gain.

**Blood pressure**

Both SBP and DBP were reduced from baseline at follow-up, with reductions of 2.3 ± 17.6 and 1.2 ± 10.8 mm Hg, respectively, for exenatide, 1.1 ± 18.2 and 0.6 ± 10.8 mm Hg for sitagliptin, and 1.8 ± 21.3 and 1.3 ± 12.5 mm Hg for insulin. Weight loss was significantly associated with reductions in both SBP and DBP in all treatment groups (P < 0.0001 for each) (Table 3).

**Lipid parameters**

In all three treatment groups, there was a trend toward improvement in lipid parameters from baseline to follow-up, with the exception of HDL, which remained essentially unchanged. Reductions in lipid parameters in the exenatide, sitagliptin, and insulin groups, respectively, were as follows: triglycerides, 27 ± 149.9, 20 ± 128.9, and 45 ± 225.8 mg/dl; LDL cholesterol, 4 ± 33.4, 6 ± 32.0, and 8 ± 37.7 mg/dl; HDL cholesterol, 0.5 ± 7.0, 0.7 ± 7.4, and 0.2 ± 9.9 mg/dl; and total cholesterol, 11 ± 40.3, 10 ± 40.0, and 14 ± 48.5 mg/dl. In patients initiating exenatide, change in weight was significantly associated with improvements in triglycerides (P = 0.007), LDL cholesterol (P = 0.005), and total cholesterol (P < 0.001). In patients initiating sitagliptin, change in weight was significantly associated with improvements in triglycerides (P = 0.001) and total cholesterol (P < 0.001). In patients initiating insulin, change in weight was significantly associated only with improvements in total cholesterol (P = 0.02) (Table 3).
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Table 3—Percentage of patients with weight change by category and mean change in glycemic and lipid parameters based on the specified weight change category*

| Parameter                             | Lost ≥5% | Lost 3–4% | Lost 1–2% | No change | Gained 1–2% | Gained 3–4% | Gained ≥5% | P value† |
|---------------------------------------|----------|-----------|-----------|-----------|-------------|-------------|------------|---------|
| Body weight change (%)                |          |           |           |           |             |             |            |         |
| Exenatide                             | 32.7     | 15.1      | 17.3      | 9.0       | 12.4        | 6.6         | 6.8        | NA      |
| Sitagliptin                           | 18.7     | 14.0      | 20.4      | 10.9      | 18.0        | 9.0         | 9.0        | NA      |
| Insulin                               | 17.0     | 9.0       | 13.5      | 8.0       | 15.9        | 12.4        | 24.2       | NA      |
| A1C (%)                               |          |           |           |           |             |             |            |         |
| Exenatide                             | −0.7     | −0.5      | −0.3      | −0.3      | −0.3        | −0.3        | −0.7       | <0.0001 |
| Sitagliptin                           | −0.7     | −0.5      | −0.4      | −0.5      | −0.6        | −0.6        | −0.6       | <0.0001 |
| Insulin                               | −0.8     | −0.5      | −0.6      | −0.6      | −0.7        | −0.9        | −1.7       | <0.0001 |
| FBG (mg/dL)                           |          |           |           |           |             |             |            |         |
| Exenatide                             | −16.6    | −10.3     | −5.9      | −1.9      | −2.4        | −8.7        | −11.0      | 0.002   |
| Sitagliptin                           | −19.6    | −8.3      | −8.3      | −8.4      | −13.1       | −15.1       | −23.7      | 0.008   |
| Insulin                               | −18.2    | −12.7     | −15.0     | −18.8     | −23.7       | −25.7       | −43.0      | <0.0001 |
| SBP (mmHg)                            |          |           |           |           |             |             |            |         |
| Exenatide                             | −5.0     | −3.0      | −0.9      | 0.1       | 0.0         | −0.4        | −0.3       | <0.0001 |
| Sitagliptin                           | −3.9     | −2.2      | −1.1      | −1.2      | 0.9         | −0.9        | 2.3        | <0.0001 |
| Insulin                               | −5.6     | −3.3      | −2.1      | −1.5      | −1.6        | −0.2        | 0.6        | <0.0001 |
| DBP (mmHg)                            |          |           |           |           |             |             |            |         |
| Exenatide                             | −2.4     | −1.1      | −0.5      | −0.8      | −0.3        | −0.9        | −0.4       | <0.0001 |
| Sitagliptin                           | −1.8     | −0.6      | −0.6      | −0.5      | 0.2         | −0.6        | 0.3        | 0.004   |
| Insulin                               | −2.7     | −1.9      | −1.2      | −1.0      | −1.2        | −0.8        | −0.5       | <0.0001 |
| Triglycerides (mg/dL)                 |          |           |           |           |             |             |            |         |
| Exenatide                             | −43.4    | −25.2     | −11.6     | −6.4      | −28.0       | −29.6       | 3.5        | 0.07    |
| Sitagliptin                           | −45.6    | −35.2     | −17.5     | −8.1      | −1.7        | −7.8        | −11.8      | 0.01    |
| Insulin                               | −51.4    | −37.2     | −36.8     | −44.4     | −34.8       | −49.5       | −50.3      | 0.49    |
| Total cholesterol (mg/dL)             |          |           |           |           |             |             |            |         |
| Exenatide                             | −16.4    | −9.2      | −8.8      | −9.0      | −8.0        | −6.6        | −4.7       | 0.003   |
| Sitagliptin                           | −14.5    | −14.8     | −6.0      | −5.6      | −4.7        | −12.9       | −13.5      | 0.0005  |
| Insulin                               | −14.2    | −17.8     | −12.4     | −12.5     | −12.7       | −11.7       | −16.6      | 0.02    |
| LDL-cholesterol (mg/dL)               |          |           |           |           |             |             |            |         |
| Exenatide                             | −8.1     | −0.2      | −1.4      | −3.1      | −1.4        | −2.7        | −4.0       | 0.005   |
| Sitagliptin                           | −7.3     | −9.8      | −4.7      | −2.2      | −4.1        | −8.4        | −7.9       | 0.24    |
| Insulin                               | −7.7     | −10.7     | −8.9      | −6.7      | −7.3        | −6.5        | −9.5       | 0.30    |
| HDL-cholesterol (mg/dL)               |          |           |           |           |             |             |            |         |
| Exenatide                             | −0.9     | −0.6      | −0.3      | −0.3      | −0.5        | −0.7        | 1.1        | 0.06    |
| Sitagliptin                           | −0.3     | −1.1      | −0.6      | −1.4      | −0.7        | −0.4        | −0.9       | 0.63    |
| Insulin                               | 0.1      | −0.4      | 0.2       | 0.4       | −0.8        | −0.1        | −0.3       | 0.09    |

*Percentages were rounded to whole numbers. Actual ranges were ≥0.5–<0.5% of listed ranges. †Cross-category ANOVA. NA, not applicable.

Regression analysis

Results of the multivariate regression analyses evaluating the effect of weight loss on the change in outcome variables relative to patients who did not lose weight or those who gained weight are shown in Fig. 1. After we controlled for baseline confounding factors including baseline weight, there was a clear benefit on A1C and FBG from any weight loss in exenatide-treated patients, but the benefit on A1C in sitagliptin- or insulin-treated patients was seen only in patients losing ≥8% body weight (Fig. 1A and B). Patients with weight loss of at least 3–5% were more likely to have reductions in SBP and DBP in all treatment groups (Fig. 1C and D). Patients with weight loss of ≥5% while receiving incretin-based therapies were more likely to have reductions in triglycerides, total cholesterol, and LDL cholesterol levels (Fig. 1E–G). There appeared to be minimal association of weight loss and an increase in HDL cholesterol levels in all treatment groups (Fig. 1H).

CONCLUSIONS — We evaluated the impact of weight loss on glycemic control and improvements in biomarkers of cardiovascular risk in patients with type 2 diabetes initiating treatment with a GLP-1 receptor agonist, a DPP-4 inhibitor, or insulin, three classes of drugs with different effects on weight (weight loss, weight neutral, and weight gain, respectively), in a real-world setting using a large cohort database. Patients initiating a GLP-1 receptor agonist and a DPP-4 inhibitor had significant weight loss from baseline and patients initiating insulin had significant weight gain. Significant incremental benefits in glycemic control were associated with weight loss in patients receiving a GLP-1 receptor agonist, but this association was only seen with weight loss of ≥8% with a DPP-4 inhibitor or insulin. Small amounts of weight loss were associated with reduction in SBP in all treatment groups, and larger amounts of weight loss were associated with reductions in DBP. Weight loss in patients initiating incretin-based therapies was associated with some improvements in...
lipid profiles relative to those of patients not losing weight: a reduction in triglycerides, LDL cholesterol, and total cholesterol with the GLP-1 receptor agonist and a reduction in triglycerides and total cholesterol with the DPP-4 inhibitor. There was no clear association between weight loss and improvement in lipid profiles with insulin.

The benefit of the weight loss with GLP-1 receptor agonists has been shown in other studies. In a 2-year open extension trial of exenatide in 283 patients stratified by weight change quartile, those with the greatest weight loss had the greatest improvement in A1C (15). In an 82-week, open-label extension trial of exenatide in 314 patients, significant improvements in HDL cholesterol, triglycerides, and DBP were seen with trends for improvement in total cholesterol, LDL cholesterol, and SBP. When assessed by weight change quartile, those losing the most weight had the greatest improvements in SBP, DBP, HDL cholesterol, and triglycerides (20). In 151 patients followed in open-label extension trials of exenatide for 3.5 years and stratified by weight change quartile, those losing the most weight had the greatest improvements in triglycerides, HDL cholesterol, and blood pressure. However, overall there was minimal correlation between weight loss and changes in lipid levels (19). Recently, in a 1-year extension trial of exenatide once weekly, weight change was shown to be significantly correlated with reductions in DBP, LDL cholesterol, and total cholesterol but not with triglycerides and SBP (21).

It is clear from these various studies that the weight loss associated with a GLP-1 receptor agonist provides beneficial effects on glycemic control and biomarkers of cardiovascular risk. The reasons for the differences in the biomarkers that improved in the various studies are speculative, but the differences may be due to the size of the population evaluated and the type of analysis. The present study was a retrospective analysis of data obtained from EMR; therefore, although the known variables were adjusted for in the regression analyses, unidentified factors may have confounded outcome measures. Only patients with baseline and follow-up levels of the various outcome parameters were included in each analysis, which may have included patients who inherently required more monitoring and were not necessarily representative of the entire pa-

![Figure 1](image-url)
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tient population. Nevertheless, this analysis provides insight into outcomes that occur in the clinical setting with a large number of patients and provides valuable “real-world” information.

Of the three therapies evaluated in this analysis, exenatide exhibited the strongest weight benefit, followed by sitagliptin. To further evaluate the contributions of weight loss, a regression analysis of the impact of weight loss for each outcome parameter combining all three treatment groups was performed post hoc (data not shown). There remained a significant weight effect for most of the outcome parameters independent of the treatment, suggesting the important benefits of weight loss in patients with type 2 diabetes. Furthermore, because the weight loss associated with GLP-1 agonists provided more improvement in cardiovascular biomarkers than a DPP-4 inhibitor, this may provide some insight into the amount of weight loss needed to achieve clinical benefit. In addition, pharmacological GLP-1 levels may have a weight-independent beneficial effect.

Retrospective analyses from large EMR databases provide insight into the effectiveness of drugs when used in clinical practice encompassing all types of patients. In addition, data from a large number of patients can be obtained, sample sizes that cannot be easily obtained for prospective clinical trials. However, the retrospective nature of database analyses does have limitations. To capture a large patient sample, baseline values could be obtained 60 days before or 30 days after the index date, and follow-up values could range from 90 to 365 days after the index date. Therefore, there is a potential for inadequate follow-up times to assess outcomes, particularly change in weight, the key parameter on which the analyses were based. However, the mean number of days of follow-up for weight in each group (270, 216, and 266 for exenatide, sitagliptin, and insulin, respectively) was adequate for assessment of outcomes. Similarly, the interval between baseline and follow-up assessments of other outcome parameters was ~8 months. Another limitation to the use of EMR databases is the inability to assess adherence to and persistence with the prescribed therapy as well as changes in adherence to and persistence with concomitant OADs. Because some patients were receiving sulfonylureas and thiazolidinediones, which can cause weight gain, stopping them during the follow-up period could have affected change in weight. Large database analyses are also subject to the variability induced by glycemic and lipid values measured at different laboratories.

Treatment of type 2 diabetes is multifactorial, including not only glycemic control but also control of cardiovascular risk factors. Ideal therapies may be those that achieve more than one target, including blood pressure and lipids, as well as A1C, without gain in body weight. Weight reductions with incretin-based therapies, and, in particular, GLP-1 receptor agonists for which greater weight loss was seen, were associated with shifts toward a more favorable cardiovascular risk profile. Further research is needed to determine whether these changes translate into a reduction in cardiovascular events.

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