Dapagliflozin Enhances Fat Oxidation and Ketone Production in Patients With Type 2 Diabetes

OBJECTIVE

Insulin resistance is associated with mitochondrial dysfunction and decreased ATP synthesis. Treatment of individuals with type 2 diabetes mellitus (T2DM) with sodium–glucose transporter 2 inhibitors (SGLT2i) improves insulin sensitivity. However, recent reports have demonstrated development of ketoacidosis in subjects with T2DM treated with SGLT2i. The current study examined the effect of improved insulin sensitivity with dapagliflozin on 1) mitochondrial ATP synthesis and 2) substrate oxidation rates and ketone production.

RESEARCH DESIGN AND METHODS

The study randomized 18 individuals with T2DM to dapagliflozin (n = 9) or placebo (n = 9). Before and after 2 weeks, subjects received an insulin clamp with tritiated glucose, indirect calorimetry, and muscle biopsies.

RESULTS

Dapagliflozin reduced fasting plasma glucose (167 ± 13 to 128 ± 6 mg/dL) and increased insulin-stimulated glucose disposal by 36% (P < 0.01). Glucose oxidation decreased (1.06 to 0.80 mg/kg · min, P < 0.05), whereas nonoxidative glucose disposal (glycogen synthesis) increased (2.74 to 4.74 mg/kg · min, P = 0.03). Dapagliflozin decreased basal glucose oxidation and increased lipid oxidation and plasma ketone concentration (0.05 to 0.19 mmol/L, P < 0.01) in association with an increase in fasting plasma glucagon (77 ± 8 to 94 ± 13, P < 0.01). Dapagliflozin reduced the ATP synthesis rate, which correlated with an increase in plasma ketone concentration.

CONCLUSIONS

Dapagliflozin improved insulin sensitivity and caused a shift from glucose to lipid oxidation, which, together with an increase in glucagon-to-insulin ratio, provide the metabolic basis for increased ketone production.

Sodium–glucose transporter 2 inhibitors (SGLT2i) are a novel class of antihyperglycemic drugs recently approved for treatment of type 2 diabetes mellitus (T2DM). SGLT2i lower plasma glucose by inhibiting renal sodium glucose cotransport and increasing urinary glucose excretion (1,2).

Although the mechanism of action of SGLT2i is independent of insulin action and insulin secretion, we and others have demonstrated that SGLT2i have important effects on glucose metabolism and plasma hormone concentrations (3–5). They increase insulin-mediated glucose disposal, measured with the insulin clamp technique, and improve β-cell function (3–5). Because skeletal muscle does not express SGLT2
and there are no known direct effects of SGLT2i on skeletal muscle (1,6), amelioration of glucotoxicity is the most likely mechanism via which SGLT2i improve insulin-mediated glucose uptake and β-cell function. In these studies (3), we also observed that inhibition of SGLT2 in the kidney produced a paradoxical increase in the basal rate of endogenous glucose production (EGP).

Insulin resistance has been associated with mitochondrial dysfunction and a decreased rate of mitochondrial ATP synthesis (7–9). Although the association between the mitochondrial defect and insulin resistance has been demonstrated in vivo and ex vivo, the cause-and-effect relationship between the two is still debated (10). We have demonstrated that improved insulin sensitivity, brought about by a reduction in plasma free fatty acid (FFA) concentration with acipimox, caused 45% increase in the mitochondrial ATP synthesis rate in muscle of individuals with T2DM (11), suggesting that chronically elevated plasma FFA levels (i.e., lipotoxicity), exert a detrimental effect on mitochondrial ATP synthesis. One aim of the current study was to examine the effect of improving insulin sensitivity in patients with T2DM by lowering plasma glucose concentration with dapagliflozin on mitochondrial ATP synthesis rate. Recent reports have demonstrated the development of ketoacidosis in patients with diabetes treated with SGLT2i (12–14). Therefore, a second aim was to examine the effect of SGLT2 inhibition with dapagliflozin on rates of substrate oxidation and ketone body production in patients with T2DM.

RESEARCH DESIGN AND METHODS

Subjects

Eighteen subjects with T2DM participated in the study. Subjects were in general good health as determined by medical history, physical examination, or results of routine screening blood chemistry tests; and 6) medications known to affect glucose metabolism, other than metformin and sulfonylureas. The University of Texas Health Science Center at San Antonio Institutional Review Board approved the protocol, and informed written consent was obtained from all subjects before participation.

Study Design

At 0700 h, after an −10-h overnight fast, subjects received 4-h euglycemic insulin clamp (15) with indirect calorimetry, vastus lateralis muscle biopsies, and [3-3H]glucose to quantitate whole-body insulin-stimulated glucose disposal, EGP, and substrate oxidation rates. After completing the insulin clamp, subjects were randomized to receive in double-blind fashion dapagliflozin (10 mg/day) or matching placebo for 14 days. On day 14, the last dose of treatment was administered, and the euglycemic insulin clamp, indirect calorimetry, and vastus lateralis muscle biopsies were repeated.

Euglycemic Insulin Clamp

Before the insulin clamp was started (−180 min), a prime (25 µCi × FPG/100) continuous (0.25 µCi/min) [3-3H]glucose infusion was started via a catheter placed into the antecubital vein and continued throughout study. A second catheter was placed retrogradely into a vein on dorsum of hand, which was placed in a heated box (60°C). Baseline arterialized venous blood samples for determination of plasma [3-3H]glucose radioactivity and plasma glucose, insulin, FFA, and ketone concentrations were drawn at −30, −20, −10, −5, and 0 min. Vastus lateralis muscle specimens were obtained by needle biopsy under local anesthesia before the start (−60 min) and at the end (+240 min) of the insulin clamp. At time 0, insulin was infused at 80 µU/kg · min, and the plasma glucose concentration was allowed to decrease to 100 mg/dL, at which level it was maintained by variable infusion of a 20% glucose solution. During the insulin clamp, blood samples were drawn every 5–15 min for determination of plasma insulin, glucose, and FFA concentrations and [3-3H]glucose-specific activity. Continuous indirect calorimetry using a Deltrac II ventilated hood system (Sensor Medics, Yorba Linda, CA) was performed during the last 30 min of the baseline period and during the last 30 min of the insulin clamp. Urine was collected during the baseline period and during the 240-min insulin clamp for determination of the renal glucose excretion rate. Before dapagliflozin and placebo were started and after 14 days of treatment, a 24-h urine collection was obtained for measurement of glucose excretion.

Mitochondrial ATP Synthesis

Mitochondrial ATP synthesis rate was measured ex vivo with the chemiluminescence technique, as previously described (7). Briefly, mitochondria were isolated from fresh muscle tissue by differential centrifugation, with 4 µg of mitochondrial protein aliquoted to each reaction well. Substrates were added as follows: 2.5 mmol/L pyruvate, 2.5 mmol/L glutamate, 5 mmol/L succinate plus 0.001 mmol/L rotenone, and palmitoyl-l-carnitine (PC). Malate (2.5 mmol/L) was added to complex I substrates. Luciferine/luciferase was added to monitor ATP production. Substrates were added after 5 min of incubation at 37°C, and the reaction was started by the addition of ADP.

Analytical Determinations

Plasma glucose was measured by the glucose oxidase method (Beckman Instruments, Fullerton, CA). Plasma insulin was measured by radioimmunoassay (Diagnostic Products Corp., Los Angeles, CA). Tritiated glucose-specific activity was determined on deproteinized barium/zinc plasma samples. Plasma FFA was determined by the enzymatic colorimetric quantification method (Wako Chemicals, Neuss, Germany). Plasma ketone concentration (β-hydroxybutyrate and acetoacetate) was measured by a commercially available kit (Cayman Chemical, Ann Arbor, MI).

Measurements

Under steady-state postabsorptive conditions, the rate of EGP was calculated as [3-3H]glucose infusion rate (DPM/min) divided by steady-state plasma [3-3H]glucose-specific activity (DPM/mg). During the euglycemic insulin clamp, non-steady-state conditions prevail, and the rate of glucose appearance (Ra) was calculated with the Steele equation, using a distribution volume of 250 mL/kg. EGP, which primarily reflects hepatic glucose production, was calculated by subtracting the exogenous glucose infusion rate from Ra.
The rate of insulin-mediated total-body glucose disposal (Rd) was determined by adding the rate of residual EGP to the exogenous glucose infusion rate.

The ATP synthesis rate was calculated as nanomoles per milligram of protein per minute. Rates of glucose and lipid oxidation were calculated as previously described (16). Nonoxidative glucose disposal, which primarily reflects glyco-gen synthesis (17), was calculated by subtracting the rate of glucose disposal from the total-body Rd. Insulin-stimulated whole-body tissue glucose disposal (TGD) was calculated by subtracting the rate of urinary glucose excretion from the total-body Rd.

**Statistical Analyses**

Values are expressed as mean ± SEM. The difference between means of dapaglipinsulin-treated and placebo-treated groups was compared with the unpaired t test. Rates of TGD and EGP after dapaglipin were compared with those before the start of dapaglipin with paired t test. Statistical significance was set at *α* < 0.05.

**RESULTS**

The study randomized 10 subjects to dapaglipin (age, 51.9 ± 2.3 years; weight, 95.8 ± 6.1 kg; BMI, 30.9 ± 1.8 kg/m²; A1C, 8.5 ± 0.4% [67 ± 4.4 mmol/mol]; diabetes duration, 7.6 ± 2.0 years; estimated glomerular filtration rate, 97 ± 6 mL/min/1.73 m²; background therapy, 7 metformin and 2 metformin/sulfonylurea) and 8 subjects to placebo (age, 55.4 ± 2.1 years; weight, 96.1 ± 5.4 kg; BMI, 32.6 ± 1.5 kg/m²; A1C, 8.7 ± 0.4% [72 ± 4.4 mmol/mol]; diabetes duration, 7.6 ± 2.4; estimated glomerular filtration rate, 88 ± 8 mL/min/1.73 m²; background therapy, 7 metformin and 2 metformin/sulfonylurea). Subjects were matched in age, sex, weight, and BMI. A small decrease in body weight occurred at 2 weeks, which was similar in both groups. The two groups had similar plasma lipid profiles and fasting plasma FFA concentrations.

**Effect of Dapaglipin on Insulin Sensitivity**

Consistent with previous studies, dapaglipin caused a significant 36% increase (3.85 ± 0.71 to 5.22 ± 0.56 mg/kg · min [*P* < 0.01] vs. baseline and vs. placebo) (Table 1) in whole-body insulin-stimulated TGD. There was no significant change in TGD in placebo-treated subjects (3.18 ± 0.51 to 3.57 ± 0.51, *P* = NS). Despite the significant increase in TGD, glucose oxidation during the insulin clamp decreased significantly after dapaglipin (1.36 ± 0.16 to 0.62 ± 0.17 mg/kg · min, *P* < 0.001) (Table 2). Dapaglipin caused a marked increase in insulin-stimulated nonoxidative glucose disposal (2.74 ± 0.59 to 4.74 ± 0.51 mg/kg · min vs. baseline, *P* = 0.001 and *P* < 0.01 vs. placebo) (Fig. 1).

Although 2 weeks of dapaglipin treatment had no effect on the fasting plasma FFA concentration, the basal rate of lipid oxidation, 2.48 ± 0.34 mg/kg · min, increased to 2.82 ± 0.12 while it slightly decreased in placebo-treated subjects (2.06 ± 0.15 to 1.89 ± 0.10 mg/kg · min). Thus, compared with placebo, dapaglipin caused a significant increase in the basal rate of lipid oxidation (*P* < 0.05) (Table 2).

The fasting plasma ketone concentration was 0.05 ± 0.015 and 0.11 ± 0.02 mmol/L in dapaglipin-treated and placebo-treated subjects, respectively. Dapaglipin caused a fourfold increase in fasting plasma ketone concentration (to 0.20 ± 0.05 mmol/L [*P* < 0.01] vs. baseline and vs. placebo), but no significant change occurred in placebo-treated subjects (0.09 ± 0.02 mmol/L).

**Effect of Dapaglipin on EGP and Plasma Insulin and Glucagon Concentrations**

Consistent with previous studies, dapaglipin caused a significant increase in the basal rate of EGP (1.97 ± 0.14 to 2.43 ± 0.13 mg/kg · min [*P* < 0.01] vs. baseline and vs. placebo); there was no change in the basal EGP rate in placebo-treated subjects (Table 1). The increase in the basal rate of EGP was associated with a significant decrease in fasting plasma insulin (12 ± 3 to 6 ± 2 μU/mL, *P* < 0.05) and a 22% increase in fasting plasma glucagon (77 ± 8 to 94 ± 13 pg/mL, *P* < 0.05). The ratio of fasting plasma glucagon to fasting plasma insulin concentration increased from 14 ± 5 to 35 ± 11 after dapaglipin treatment (*P* < 0.01 vs. baseline and vs. placebo). No significant change occurred in the plasma glucagon-to-insulin ratio in placebo-treated patients.

### Mitochondrial ATP Synthesis

At baseline, complex I (pyruvate, glutamate/malate, and PC)– and complex II

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**Table 1—Fasting plasma substrate and hormone concentrations and rates of TGD and EGP during the euglycemic insulin clamp**

|                          | Baseline | Placebo treatment | *P* value | Baseline | Dapaglipin treatment | *P* value |
|--------------------------|----------|------------------|-----------|----------|----------------------|-----------|
| **Fasting plasma**       |          |                  |           |          |                      |           |
| Glucose (mg/dL)          | 172 ± 8  | 160 ± 9          | NS        | 167 ± 13 | 128 ± 6              | <0.01     |
| Insulin (μU/mL)          | 14 ± 9   | 13 ± 5           | NS        | 12 ± 3   | 6 ± 2                | <0.01     |
| Glucagon (pg/mL)         | 72 ± 17  | 79 ± 11          | NS        | 77 ± 8   | 94 ± 13              | <0.05     |
| Glucagon-to-insulin ratio| 10 ± 2   | 12 ± 3           | NS        | 14 ± 5   | 35 ± 11              | <0.01     |
| FFA (μmol/L)             | 0.46 ± 0.04 | 0.42 ± 0.04 | NS        | 0.50 ± 0.04 | 0.46 ± 0.04 | NS       |
| **Ketones (mmol/L)**     |          |                  |           |          |                      |           |
| Fasting                  | 0.11 ± 0.02 | 0.09 ± 0.02 | NS        | 0.05 ± 0.01 | 0.20 ± 0.05 | <0.001   |
| Clamp                    | 0.08 ± 0.02 | 0.05 ± 0.01 | NS        | 0.06 ± 0.01 | 0.05 ± 0.01 | NS       |
| **TGD/SSPI (mg/kg · min) per μU/mL** | 3.18 ± 0.51 | 3.57 ± 0.51 | NS        | 3.85 ± 0.71 | 5.22 ± 0.56 | <0.01     |
| **EGP (mg/kg · min)**    |          |                  |           |          |                      |           |
| Fasting                  | 2.02 ± 0.08 | 1.99 ± 0.09 | NS        | 1.97 ± 0.13 | 2.43 ± 0.13 | <0.01     |
| Clamp                    | 0.48 ± 0.16 | 0.29 ± 0.12 | NS        | 0.22 ± 0.08 | 0.34 ± 0.13 | NS       |
| Urinary glucose excretion (g/24 h) | 1.38 ± 0.74 | 1.90 ± 0.78 | NS        | 1.95 ± 0.58 | 82.5 ± 10.5 | <0.001    |

SSPI, steady-state plasma insulin concentration.
(succinate)—supported ATP synthesis rates were similar in placebo-treated and dapagliozin-treated groups. After dapagliozin, the ATP synthesis rate decreased markedly with complex I substrates (pyruvate, −49%; glutamate/malate, −55%; PC (0.5 μmol/L) = −41%; and PC (1.0 μmol/L) = −55%; all P < 0.05) and complex II substrate (succinate/rotenone, −55%; P = 0.001) (Fig. 1, top panel). In the placebo-treated group, there was no significant change in the ATP synthesis rate with any substrate. The mitochondrial ATP synthesis rate correlated strongly and inversely with the plasma ketone concentration (Fig. 2).

**CONCLUSIONS**

The first major novel observation of the current study is that dapagliozin shifted energy metabolism in patients with T2DM from glucose to fat oxidation. Compared with placebo, dapagliozin caused a 16% decline in glucose oxidation and a 14% increase in lipid oxidation (Table 2). As we previously demonstrated (1), dapagliozin significantly increased insulin-stimulated whole-body glucose disposal, which was accounted for entirely by an increase in nonoxidative glucose disposal (glycogen synthesis). More striking, whole-body glucose oxidation declined by 53% during the insulin clamp, whereas lipid oxidation rose by 15% in dapagliozin-treated subjects. Consistent with these changes in substrate oxidation rates, the basal respiratory quotient (RQ) in dapagliozin-treated subjects decreased from 0.79 to 0.76 (P < 0.05 vs. change in placebo). Similarly, the RQ declined during the insulin clamp from 0.82 to 0.76 (P < 0.05). Because dapagliozin did not alter the plasma FFA concentration, it is unlikely that the increase in fat oxidation caused by dapagliozin was due to oversupply of FFA to lean tissues. These results are consistent with a recent study which demonstrated that 4 weeks of treatment with empagliozin caused an increase in fat oxidation accompanied by a decrease in glucose oxidation (18). We speculate that the increase in fat oxidation in skeletal muscle would lead to depletion of toxic intramyocellular lipids (fatty acyl-CoAs, diacylglycerol, ceramides) (18) and could contribute to the improvement in whole-body insulin-stimulated glucose disposal observed in the current study.

We interpret the changes in substrate oxidation after dapagliozin treatment as follows: muscle tissue in individuals with T2DM is severely resistant to insulin (19); consequently, plasma glucose concentration rises to a level that is sufficient to augment glucose entry into the cell by the mass action effect of hyperglycemia (20). Dapagliozin treatment induces glucosuria, causing an acute reduction in plasma glucose concentration and decreased glucose entry into muscle both in the postabsorptive and insulin-stimulated states. To meet the energy demand of the cell, the myocyte switches to fat as an alternate source of energy. Under fasting conditions, the decline in the plasma insulin concentration after dapagliozin treatment (Table 1) also could contribute to the decline in glucose oxidation (21).

The apparent paradox between the effect of dapagliozin on insulin sensitivity (increased) and glucose oxidation (decreased) could be related to a differential effect of dapagliozin on intramyocellular pathways affected by dapagliozin. Thus, all of the improvement in whole-body insulin sensitivity was secondary to an increase in nonoxidative glucose disposal (glycogen synthesis). This could be explained by amelioration of glucotoxicity and increased muscle glycogen synthase activity (22). Simultaneously, and independently, dapagliozin treatment resulted in reduced glucose oxidation secondary to the decline in the plasma glucose concentration. Because the increase in nonoxidative glucose disposal quantitatively was

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**Table 2—Effect of dapagliozin and placebo treatment on glucose and lipid oxidation and energy expenditure following an overnight fast and during the insulin clamp**

| Substrate oxidation rate | Baseline | Placebo treatment | P value | Dapagliozin treatment | P value |
|--------------------------|----------|-------------------|---------|-----------------------|---------|
| Fasting state            |          |                   |         |                       |         |
| Fasting GOx (mg/min · kg) | 0.81 ± 0.10 | 0.89 ± 0.08       | NS      | 0.80 ± 0.19           | 0.03    |
| Fasting LOx (mg/min · kg) | 2.06 ± 0.15 | 1.89 ± 0.10       | NS      | 2.82 ± 0.24           | 0.05    |
| RQ                       | 0.78 ± 0.01 | 0.80 ± 0.01       | NS      | 0.76 ± 0.01           | 0.03    |
| Energy expenditure (cal/min · kg) | 1.06 ± 0.1 | 1.0 ± 0.1        | NS      | 1.34 ± 0.1           | NS      |
| Insulin infusion         |          |                   |         |                       |         |
| Clamp GOx (mg/min · kg)  | 1.11 ± 0.29 | 1.46 ± 0.31       | NS      | 0.62 ± 0.16           | <0.001  |
| Clamp LOx (mg/min · kg)  | 1.89 ± 0.08 | 1.81 ± 0.12       | NS      | 2.39 ± 0.15           | <0.01   |
| NOGD (mg/min · kg)       | 1.95 ± 0.58 | 1.78 ± 1.00       | NS      | 2.74 ± 0.59           | <0.001  |
| RQ                       | 0.82 ± 0.01 | 0.85 ± 0.01       | NS      | 0.76 ± 0.01           | 0.02    |

GOx, glucose oxidation; LOx, lipid oxidation; NOGD, nonoxidative glucose disposal.
far greater than the inhibition of glucose oxidation, the net result was an increase in insulin-stimulated whole-body glucose disposal.

A second major novel observation of the current study was the increase in the plasma ketone concentration in dapagliflozin-treated subjects. This has important clinical implications because recent publications (12) have reported the development of ketoacidosis in patients with diabetes treated with SGLT2i. Although the increase in fasting plasma ketone concentration was small in absolute terms, the fourfold increase is consistent with the observed shift in oxidative pathways from glucose to fat (discussed above). Increased β-oxidation in dapagliflozin-treated subjects would be anticipated to result in increased production of acetyl-CoA, which either can be oxidized in the tricarboxylic acid (TCA) cycle or converted to ketones (Fig. 3). The plasma glucagon-to-insulin ratio perfusing the liver is a key determinant of the fate of acetyl-CoA (23,24). Glucagon stimulates the expression of hydroxymethylglutaryl-CoA (HMG-CoA) synthase, the rate-limiting step for the conversion of acetyl-CoA to ketones, whereas insulin suppresses its expression. The increase in the fasting plasma glucagon concentration and accompanying decrease in the plasma insulin concentration would be expected to increase HMG-CoA synthase activity, which together with the increase in mitochondrial acetyl-CoA could explain the increase in ketone production in dapagliflozin-treated subjects. Further, the global decrease in the mitochondrial ATP synthesis rate would favor a shift in acetyl-CoA metabolism from oxidation in the TCA cycle to ketone formation. Importantly, the plasma ketone level strongly and inversely correlated with the mitochondrial ATP synthesis rate (Fig. 2).

The clinical significance of the increase in ketone production after dapagliflozin treatment is not clear. However, it is noteworthy that recent clinical reports have demonstrated the development of clinically significant ketoacidosis after treatment with SGLT2i in patients with type 1 and type 2 diabetes (12–14). These reports share a number of features in common. Many cases involved patients with type 1 diabetes in whom the daily insulin dose was reduced when therapy with SGLT2i was initiated. Because SGLT2i increase glucagon secretion (3,5), it is not surprising that a reduction in the insulin dose might result in ketoacidosis. Another common feature in many cases was an associated medical or surgical condition resulting in moderate-to-severe stress. Release of catecholamines predisposes to the development of ketoacidosis both by inhibiting insulin secretion and stimulating ketone production (24). Lastly, it has been hypothesized that the increase in the plasma ketone concentration (25–27) after SGLT2i therapy could provide a readily oxidizable fuel that is preferentially taken up by the myocardium (28,29) and partly explain the beneficial cardiovascular effects observed in the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study (30). The present results are entirely consistent with this hypothesis and provide a metabolic explanation for the increase in plasma ketone concentration after treatment with an SGLT2i.

Consistent with previous studies, dapagliflozin treatment was associated
with an increase in basal rate of EGP, which is partly explained by the increase in the plasma glucagon-to-insulin ratio. Further, if the increased basal rate of EGP results from increased gluconeogenesis, this would direct mitochondrial oxaloacetate to phosphoenolpyruvate, resulting in depletion of TCA cycle intermediates and diversion of acetyl-CoA to ketone body production (Fig. 3). This also could explain the global reduction in the mitochondrial ATP synthesis rate measured ex vivo. Measurements of TCA cycle intermediates (e.g., citrate, α-ketoglutarate, and succinyl-CoA) could provide information about the contribution of decreased TCA flux to the global reduction in the mitochondrial ATP synthesis rate caused by dapagliflozin.

Inhibition of citrate synthase activity or a decrease in its gene expression or protein level caused by dapagliflozin is a third possibility that could explain the metabolic effects of dapagliflozin. Although such an effect of dapagliflozin has not previously been reported, such an effect would result in redirecting acetyl-CoA toward ketone production and oxaloacetate toward glucose production.

In summary, 2 weeks of dapagliflozin treatment caused 1) an increase in EGP, fat oxidation, and ketone production in association with increased plasma glucose and decreased plasma insulin concentration, and 2) increased total-body glucose disposal resulting from increased nonoxidative glucose disposal (glycogen synthesis).

Acknowledgments. The authors thank Lorrie Albarado and Shannon Balmer, from the University of Texas Health Science Center, for their expert secretarial assistance in the preparation of the manuscript.

Funding. The present work was supported by National Institutes of Health grant R01-DK-24092. R.A.D.’s salary is supported in part by the South Texas Veterans Health Care System.

Duality of Interest. R.A.D. is on the advisory boards of AstraZeneca, Novo Nordisk, Janssen, Boehringer Ingelheim, and Intarcia; has received research support from Boehringer Ingelheim, Takeda, AstraZeneca, and Janssen; and is on the speaker’s bureau of Novo Nordisk and AstraZeneca. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. G.D., J.X., C.S.-H., A.M., R.E., D.T., R.A.D., L.N., and M.A.-G. contributed to performing the study. G.D. and M.A.-G. developed the initial draft of the manuscript. G.D., J.X., C.S.-H., A.M., R.E., D.T., R.A.D., L.N., and M.A.-G. contributed comments to the initial version of the manuscript. R.A.D. revised the initial draft of the manuscript. R.A.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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