Journal of Diabetes Science and Technology
Volume 4, Issue 2, March 2010

ORIGINAL ARTICLES

Glucose Supply and Insulin Demand Dynamics of Antidiabetic Agents

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Abstract

Background:

For microvascular outcomes, there is compelling historical and contemporary evidence for intensive blood glucose reduction in patients with either type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM). There is also strong evidence to support macrovascular benefit with intensive blood glucose reduction in T1DM. Similar evidence remains elusive for T2DM. Because cardiovascular outcome trials utilizing conventional algorithms to attain intensive blood glucose reduction have not demonstrated superiority to less aggressive blood glucose reduction (Action to Control Cardiovascular Risk in Diabetes; Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; and Veterans Affairs Diabetes Trial), it should be considered that the means by which the blood glucose is reduced may be as important as the actual blood glucose.

Methods:

By identifying quantitative differences between antidiabetic agents on carbohydrate exposure (CE), hepatic glucose uptake (HGU), hepatic gluconeogenesis (GNG), insulin resistance (IR), peripheral glucose uptake (PGU), and peripheral insulin exposure (PIE), we created a pharmacokinetic/pharmacodynamic model to characterize the effect of the agents on the glucose supply and insulin demand dynamic. Glucose supply was defined as the cumulative percentage decrease in CE, increase in HGU, decrease in GNG, and decrease in IR, while insulin demand was defined as the cumulative percentage increase in PIE and PGU. With the glucose supply and insulin demand effects of each antidiabetic agent summated, the glucose supply (numerator) was divided by the insulin demand (denominator) to create a value representative of the glucose supply and insulin demand dynamic (SD ratio).

continued →

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Abbreviations: ([^{18}F]FDG) [^{18}F]2-fluoro-2-deoxyglucose, (ACCORD) Action to Control Cardiovascular Risk in Diabetes, (ADVANCE) Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation, (BMI) body mass index, (CE) carbohydrate exposure, (DCCT) Diabetes Control and Complications Trial, (FPG) fasting plasma glucose, (FPI) fasting plasma insulin, (GNG) gluconeogenesis, (SD) glucose supply:insulin demand ratio, (HbA1c) hemoglobin A1c, (HGU) hepatic glucose uptake, (HOMAIR) homeostasis model assessment of insulin resistance, (IL-6) interleukin-6, (IR) insulin resistance, (OGTT) oral glucose tolerance test, (PAI-1) plasminogen activator inhibitor-1, (PET) positron-emission tomography, (PGU) peripheral glucose uptake, (PIE) peripheral insulin exposure, (T1DM) type 1 diabetes mellitus, (T2DM) type 2 diabetes mellitus, (TNF-α) tumor necrosis factor-α, (TZD) thiazolidinedione, (UKPDS) United Kingdom Prospective Diabetes Study, (VADT) Veterans Affairs Diabetes Trial

Keywords: cardiovascular outcomes, glucose, insulin, pharmacodynamics, pharmacokinetics

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Abstract cont.

Results:

Alpha-glucosidase inhibitors (1.25), metformin (2.20), and thiazolidinediones (TZDs; 1.25–1.32) demonstrate a greater effect on glucose supply (SD ratio >1), while secretagogues (0.69–0.81), basal insulins (0.77–0.79), and bolus insulins (0.62–0.67) demonstrate a greater effect on insulin demand (SD ratio <1).

Conclusion:

Alpha-glucosidase inhibitors, metformin, and TZDs demonstrate a greater effect on glucose supply, while secretagogues, basal insulin, and bolus insulin demonstrate a greater effect on insulin demand. Because T2DM cardiovascular outcome trials have not demonstrated macrovascular benefit with more aggressive blood glucose reduction when using conventional algorithms that predominantly focus on insulin demand, it would appear logical to consider a model that incorporates both the extent of blood glucose lowering (hemoglobin A1c) and the means by which the blood glucose was reduced (SD ratio) when considering macrovascular outcomes.

J Diabetes Sci Technol 2010;4(2):365-381

Background

Historically, diabetes management has been guided by the positive microvascular outcomes demonstrated in the Diabetes Control and Complications Trial (DCCT)[1] and United Kingdom Prospective Diabetes Study (UKPDS).[2] In the DCCT, comparing intensive (hemoglobin A1c [HbA1c] = 7.0%) and conventional (HbA1c = 9.0%) management of patients with type 1 diabetes mellitus (T1DM), intensive therapy reduced all diabetes-specific complications evaluated (retinopathy, nephropathy, and neuropathy) by as much as 76%. Similarly, the UKPDS compared intensive (HbA1c = 7.0%) and conventional (HbA1c = 7.9%) management in patients with type 2 diabetes mellitus (T2DM); again, intensive therapy was observed to significantly reduce risk for microvascular outcomes. In 2005, long-term follow-up data from the DCCT demonstrated that, after a mean of 17 years, intensive treatment significantly reduced the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease by 57%.[3] In 2008, the UKPDS 10-year post-trial follow-up study revealed that, despite the loss of glycemic differences between intensive and conventional cohorts, there was continued microvascular benefit and an emergent reduction in myocardial infarction and all-cause mortality.[4]

With respect to microvascular outcomes, there appears to be compelling historical and contemporary evidence for intensive blood glucose reduction in patients with both T1DM and T2DM. There is also strong evidence to support a beneficial impact on macrovascular outcomes with intensive blood glucose reduction in patients with T1DM. Similar evidence remains elusive in T2DM.[5] The nonsignificant reductions in macrovascular outcomes (myocardial infarction, stroke, heart failure, angina) observed in the UKPDS intervention trial and the more recent Action to Control Cardiovascular Risk in Diabetes (ACCORD),[6] Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE),[7] and Veterans Affairs Diabetes Trial (VADT)[8] have collectively created uncertainty toward the extent of blood glucose reduction and also the optimal therapeutic choice to attain the reduction.

In this situation, where long-term, randomized controlled trials have resulted in counterintuitive outcomes, it is imperative that the methodology of therapeutic intervention be rigorously evaluated. The common theme of the aforementioned historical and contemporary cardiovascular outcome trials has been a focus on the intensive reduction of the primary biomarker HbA1c in a manner consistent with the consensus algorithm issued by the American Diabetes Association and European Association for the Study of Diabetes. Predominantly, this algorithm advocated the initial use of metformin with subsequent addition and intensification of sulfonylurea and/or insulin therapies. Inherent to this pharmacotherapeutic

approach, as well as those utilized prior to the guidelines, is an imbalance toward increased insulin exposure and increased peripheral glucose disposal. While this approach is effective at reducing HbA1c, it must be considered that both excessive insulin exposure and excessive peripheral glucose disposal have potentially deleterious effects on the vasculature.[9–12] Moreover, a potential explanation for the observed neutral or negative cardiovascular outcomes despite more intensive blood glucose reduction when using therapies that principally impact peripheral insulin exposure (PIE) and peripheral glucose disposal is that the means by which the blood glucose is reduced may be as important as the actual blood glucose. Therefore, we developed a pharmacokinetic/pharmacodynamic model to characterize the effect of conventional antidiabetic therapies on the glucose supply [carbohydrate intake and intestinal absorption (carbohydrate exposure [CE]), hepatic glucose uptake (HGU), hepatic gluconeogenesis (GNG), and insulin resistance (IR)] and insulin demand [PIE and peripheral glucose uptake (PGU)] dynamic in order to identify agents and/or pharmacotherapeutic strategies that may have benefits extending beyond the reduction of HbA1c.

Methods

Therapeutic targets of the glucose supply (CE, 1 + 2; HGU, 3; GNG, 4; IR, 5) and insulin demand (PGU, 6; PIE, 7) model are presented in **Figure 1**. To identify quantitative differences between antidiabetic agents on CE, HGU, GNG, IR, PGU, and PIE, multidatabase searches (Cochrane Central Register of Controlled Trials and Cochrane Register of Systematic Reviews, Embase, OVID Healthstar, OVID Journals, and PubMed) were conducted, cross-referencing title and keywords for all selected antidiabetic therapies and their respective targets.

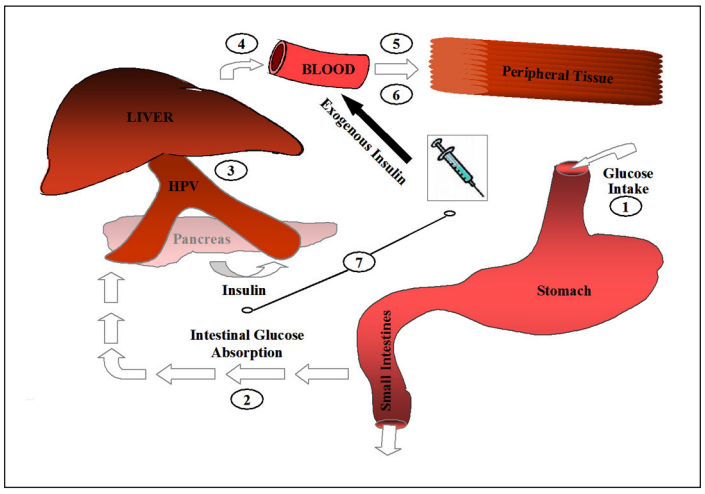

Figure 1. Glucose supply and insulin demand model. CE, 1+2; HGU, 3; GNG, 4; IR, 5; PGU, 6; PIE, 7. HPV, hepatic portal vein.

Alpha-glucosidase, biguanide, and thiazolidinedione (TZD) studies with long-term, pre–post design at maximal therapeutic doses were identified to simulate chronic administration. To maintain consistency with cardiovascular trials and accommodate known influences of hyperglycemia and hyperinsulinemia on the respective targets,[13–16] studies including patients with HbA1c in the range of 6–8% and body mass index (BMI) ≥30 kg/m^2 were preferentially selected. In the event multiple studies were available to identify the effect of an agent on a therapeutic target, the mean percent change was used. Conversely, if there was evidence that an agent would elicit a response on a given target but no mathematical representation of the difference was provided, conservative estimates consistent with the scale of other agents and the degree of glucose regulation were instituted to best represent the expected effect. Individual agents were then characterized for the 24 h percent change from baseline for CE, HGU, GNG, IR, PGU, and PIE. Carbohydrate exposure was determined as the combined effect of caloric intake and intestinal carbohydrate absorption. Hepatic glucose uptake was defined as the reported value obtained immediately following oral glucose loading. Because GNG is known to be enhanced in the fasting state and persistent throughout the prandial phase,[17,18] effect was determined during the fasting state and considered equivalent throughout the prandial phase. For studies evaluating fasting glucose and insulin concentrations, an index of IR was determined by homeostasis model assessment of insulin resistance (HOMAIR) using the following formula: Insulin (mU/liter) x Glucose (mmol)/22.5.[19] To account for known differences in secretory and uptake dynamics during the fasting and prandial phases, studies identifying the impact of therapies during the fasting state (or simulated hyperinsulinemic euglycemic clamp) and prandial phase (or oral glucose load insulin clamp) were specifically identified for changes in PGU (glucose infusion rate) and PIE (insulin concentrations) according to **Equation (1)**:

$$\text{PIE24/PGU24} = \frac{(\text{Fasting Change})(12) + (\text{Prandial Change})(12)}{24} \quad (1)$$

For sulfonylurea and insulin-based therapies, insulin concentration time profiles were obtained and super-

imposed on the baseline 24 h insulin concentration time profile of T2DM patients (**Figure 2**) to calculate the increase in PIE (trapezoidal rule).[20] Calculated increases in incremental and cumulative insulin exposure were correlated to known insulin dose-response effects on HGU, GNG, and PGU (**Figure 3**),[18,21] according to the equation $y = mx + b$. Twenty-four-hour increases in HGU, PGU, and PIE and decreases in GNG were compared to baseline values and percent change calculated.

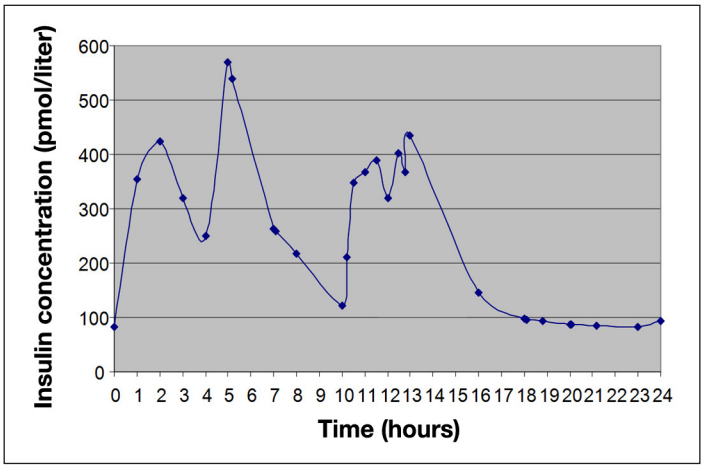

Figure 2. Standard insulin concentration time profile (T2DM).

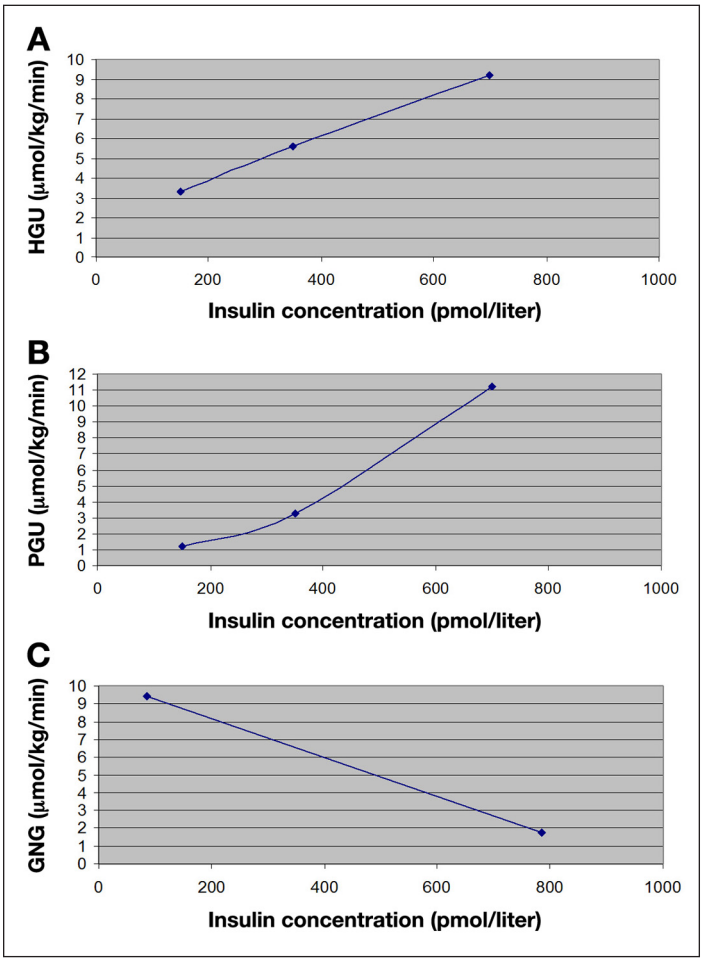

Figure 3. (A) HGU insulin-dose response relationship. **(B)** PGU insulin-dose response relationship. **(C)** GNG insulin-dose response relationship.

With alpha-glucosidase, biguanide, TZD, secretagogue, and insulin therapies characterized for their respective impacts on CE, HGU, GNG, IR, PIE, and PGU, identification of their effect on the glucose supply (decrease in CE, increase in HGU, decrease in GNG, decrease in IR) and insulin demand (increase in PIE, increase in PGU) dynamic was assessed according to **Equation (2)**:

$$\text{Glucose Supply (S)/Insulin Demand (D)} = \frac{1 + ((\text{CE}) + (\text{HGU}) + (\text{GNG}) + (\text{IR}))}{1 + (\text{PIE} + \text{PGU})} \quad (2)$$

Results

Alpha-Glucosidase Inhibitors (Acarbose and Miglitol)

The alpha-glucosidase inhibitors (1) have no significant effect on total caloric intake,[22] (2) delay and decrease carbohydrate absorption,[23–27] (3) have not been directly evaluated for HGU, (4) have negligible effect on hepatic glucose output,[28,29] (5) reduce IR,[22,30–33] (6) have variable effects on PGU,[22,28,30,34–38] and (7) reduce plasma insulin concentrations.[22,39–45] Studies meeting the review criteria for the target effects of the alpha-glucosidase inhibitors on the respective targets are summarized here. Estimates for the effect of alpha-glucosidase inhibitors on the respective targets are presented in **Table 1**.

Caloric Intake and Intestinal Carbohydrate Absorption

Meneilly and associates evaluated the effects of acarbose on total caloric intake by means of 3-day food recall and dietician interview.[22] Acarbose was administered at an initial dose of 50–100 mg three times daily. At the conclusion of 52 weeks of acarbose therapy, there was no significant change in proportion of calories as carbohydrate (-0.7 ± 0.8%), fat (0.9 ± 0.8%), or protein (-0.5 ± 0.5%), nor was there a significant change in total caloric intake (90 ± 50 kcal). Radziuk and coworkers evaluated the effect of 0, 50, and 100 mg of acarbose on the absorption of the glucose moiety of sucrose in overnight-fasted subjects receiving labeled 100 g oral sucrose load ([1-^{14}C]glucose) and simultaneous intravenous infusion of [3-^{3}H]glucose.[24] Acarbose increased malabsorption in a dose-dependent

manner; at 50 mg, there was a modest effect (6%), whereas at 100 mg, it was approximately 30%, and at the highest 150 mg dose, it was approximately 66%. These findings are supported by Sobajima *et al.*, where carbohydrate malabsorption, measured by hydrogen excretion following 2-month acarbose administration (50–100 mg three times daily) was estimated to be 31.6% of baseline.[25]

Hepatic Glucose Uptake and Hepatic Gluconeogenesis

No studies directly evaluate the impact of alpha-glucosidase inhibitors on HGU. However, evidence does suggest acarbose delays carbohydrate absorption[26,27] and increases glucagon-like peptide-1 secretion.[46,47] Therefore, it would be anticipated that alpha-glucosidase inhibitors would exhibit modest effects on retaining carbohydrate in the splanchnic area. Likewise, there is limited data regarding the impact of alpha-glucosidase inhibitors on hepatic GNG. Schnack and associates evaluated the effect of long-term miglitol therapy on hepatic glucose output in poorly controlled T2DM patients (HbA1c = 9.9%). After eight weeks of therapy (300 mg/day), miglitol had no significant effect on hepatic glucose output versus placebo (0.37 ± 0.15 versus 0.35 ± 0.17 $mg/kg^{-1}/min^{-1}$) under euglycemic clamp conditions.[28] Sels and coworkers evaluated the effects of miglitol on fasting plasma glucose (FPG) in T2DM patients. Finding similar results, 200 mg of miglitol at bedtime for 1 week was not associated with a change in hepatic glucose production.[29]

Table 1.
Glucose Supply : Insulin Demand Ratio for Antidiabetic Therapies at Maximal Therapeutic Dose

Antidiabetic agent	CE	HGU	GNG	IR	PIE	PGU	Therapeutic dose	SD ratio[a]
Miglitol	0.30	0.15	0.05	0.15	0.05	0.25	300 mg	1.25
Acarbose	0.30	0.15	0.05	0.15	0.05	0.25	300 mg	1.25
Metformin	0.15	0.40	0.35	0.38	-0.10	0.14	2000 mg	2.20
Acetohexamide	0.00	0.14	0.07	0.00	0.21	0.36	1500 mg	0.77
Chlorpropamide	0.00	0.14	0.07	0.00	0.21	0.36	500 mg	0.77
Tolazamide	0.00	0.14	0.07	0.00	0.21	0.36	1000 mg	0.77
Tolbutamide	0.00	0.14	0.07	0.00	0.21	0.36	2000 mg	0.77
Glimepiride	0.00	0.18	0.08	0.00	0.24	0.39	8 mg	0.77
Glipizide	0.00	0.18	0.08	0.00	0.24	0.39	10 mg	0.77
Glyburide	0.00	0.14	0.07	0.00	0.21	0.36	10 mg	0.77
Nateglinide	0.00	0.21	0.11	0.00	0.34	0.60	360 mg	0.69
Repaglinide	0.00	0.16	0.07	0.00	0.20	0.31	12 mg	0.81
Pioglitazone	0.00	0.40	0.21	0.35	-0.10	0.59	45 mg	1.32
Rosiglitazone	0.00	0.40	0.23	0.39	-0.10	0.70	8 mg	1.27
Troglitazone	0.00	0.40	0.22	0.35	-0.10	0.67	600 mg	1.25
Insulin aspart	0.00	0.23	0.14	0.00	0.42	0.80	0.5 U/kg	0.62
Insulin lispro	0.00	0.23	0.14	0.00	0.42	0.80	0.5 U/kg	0.62
Insulin regular	0.00	0.21	0.11	0.00	0.33	0.64	0.5 U/kg	0.67
Insulin isophane	0.00	0.23	0.10	0.00	0.28	0.40	0.5 U/kg	0.79
Insulin aspart protamine	0.00	0.23	0.10	0.00	0.28	0.40	0.5 U/kg	0.79
Insulin lispro protamine	0.00	0.23	0.10	0.00	0.28	0.40	0.5 U/kg	0.79
Insulin lente	0.00	0.23	0.10	0.00	0.28	0.40	0.5 U/kg	0.79
Insulin ultralente	0.00	0.17	0.08	0.00	0.24	0.38	0.5 U/kg	0.77
Insulin glargine	0.00	0.24	0.10	0.00	0.30	0.42	0.5 U/kg	0.78

[a] Estimates of effect for oral medications on CE, HGU, GNG, IR, PIE, and PGU were calculated for maximal therapeutic dose and linearly extrapolated for decreasing doses. Insulin, having no maximal therapeutic dose, was linearly extrapolated for increasing or decreasing dose. All combination effects on CE, HGU, GNG, IR, PIE, and PGU were considered additive.

Insulin Resistance

In the study by Meneilly and colleagues, IR was assessed at baseline and after 12 months of acarbose (HOMAIR). Insulin resistance was significantly improved following acarbose treatment (6.1 ± 0.5 versus 5.0 ± 0.5).[22] At the same acarbose dose, Calle-Pascual and associates observed reductions in FPG and fasting plasma insulin (FPI) and a slightly greater reduction in IR (~27%), as calculated by HOMAIR, after 16 weeks of therapy.[30] Concurrent with these results, Delgado *et al.* observed an approximate 15% reduction in IR after 16 weeks of therapy at a lower therapeutic dose of acarbose (100 mg daily).[33] Contradicting the findings of the previous authors, Hanefeld and colleagues as well as Fischer and associates found no significant alterations in IR.[38,41]

Peripheral Glucose Uptake

Kinoshita and group evaluated the effect of acarbose 300 mg daily on glucose utilization rate (*M* value) ($mg/kg^{-1}/min^{-1}$) under euglycemic hyperinsulinemic conditions.[37,48] After allowing the HbA1c to fall to ≤8%, baseline clamp study was performed, with follow-up study at 6 months. At the conclusion of therapy, glucose utilization rate was increased (8.00 ± 1.96 versus 9.94 ± 2.35 $mg/kg^{-1}/min^{-1}$). At the same daily dose for 16 weeks, Fischer *et al.* observed a nonsignificant increase in glucose disposal rate during euglycemic hyperinsulinemic clamp (3.2 versus 2.3 $mg/kg^{-1}/min^{-1}$).[38] In the study by Meneilly and associates, glucose infusion rate during the final 20 min of the 2 h hyperglycemic clamp (5.4 mM above basal) was assessed at baseline and after 12 months of therapy. Glucose infusion rate increased significantly after acarbose therapy (1.68 ± 0.19 versus 2.69 ± 0.19 $mg/kg^{-1}/min^{-1}$).[22] Despite this evidence, multiple studies under similar experimental conditions do not confirm the observed increases in peripheral glucose disposal after sustained alpha-glucosidase therapy.[28,35,36,49]

Peripheral Insulin Exposure

Numerous studies have identified a reduced postprandial insulin response following acarbose administration to T2DM patients.[42–45] Meneilly and associates as well as Hanefeld and coworkers have evaluated the combined fasting and postprandial effects of long-term acarbose administration.[22,41] Meneilly and associates assessed fasting and postprandial insulin secretion at baseline and 12 months of acarbose therapy (100 mg three times daily), observing significant decreases in both increments (-13 ± 4 and -271 ± 159 pmol/liter, respectively).[22] Hanefeld and coworkers evaluated the effect of acarbose therapy (100 mg three times daily) on the 24 h insulin concentration time profile. After 16 weeks of therapy, acarbose was not found to change the 24 h area under the curve of insulin from baseline.[41]

Biguanides (Metformin)

Metformin has been shown to (1) reduce caloric intake,[50–52] (2) have variable effects on intestinal carbohydrate absorption,[53–70] (3) increase HGU,[71] (4) diminish hepatic GNG,[72,73] (5) reduce IR,[71,72,74–77] (6) increase PGU,[74,78] and (7) reduce insulin exposure.[71,72,76,78] Studies meeting review criteria for the target effects of metformin are presented here. Estimates for the effect of metformin on the respective targets are presented in **Table 1**.

Caloric Intake and Intestinal Carbohydrate Absorption

Anorexia is occasionally reported following the introduction of metformin therapy to T2DM patients.[51] Lee and Morley evaluated the effect of metformin on caloric intake in patients with T2DM. Patients were randomly given placebo, 850, or 1700 mg of metformin for three days and subsequently evaluated for caloric intake during three consecutive 10 min intake periods. Caloric intake was reduced during each eating interval in a dose-dependent manner. Total caloric intake during the 30 min period was reduced 30% and 50% at 850 and 1700 mg, respectively.[52] Despite the substantial reductions in caloric intake observed at the respective doses, it should be considered that the impact is thought to be sustained with only extremely high doses (>2 $g/kg^{-1}/day^{-1}$).[60,79]

Animal and human studies to determine the impact of biguanides on intestinal carbohydrate absorption have yielded conflicting results.[53–59] Bailey reviewed the effects of metformin on intestinal glucose handling (absorption and metabolism) in animal and human models.[60] *In vitro* animal studies have demonstrated metformin to cause a concentration-dependent decrease in glucose transport at concentrations in the millimolar range.[61–64] *In vivo*, Wilcock and Bailey observed net glucose transfer in the serosal fluid was reduced 12% in mice at a dosage of 50 mg/kg (slightly greater than the maximum 3 g dose).[65] In a preparation of brush border vesicles isolated from rabbit intestine (5 mM metformin), Kessler and colleagues observed a nominal decrease in glucose uptake.[66] In clinical studies of noninsulin-dependent diabetes mellitus patients, there is evidence to suggest that biguanides may delay the rate, but not the extent of glucose absorption.[58,67] During a 75 g oral glucose load challenge with labeled [1-^{14}C] glucose, Jackson *et al.* observed the absorption of glucose to be slightly delayed but ultimately unaltered over the 3 h study period.[67]

Metformin has also been noted to increase intestinal glucose utilization.[68,69] Pénicaud *et al.* administered 350 mg/kg^{-1}/day^{-1} to obese fa/fa rats for eight days, observing an increased glucose utilization by 39% in the jejunum.[68] During intravenous glucose tolerance test, Bailey and colleagues administered metformin 250 mg/kg^{-1} to normal rats, observing an increased glucose utilization by 30–60% in mucosa from different regions of the intestine.[69] Despite substantial increases in intestinal glucose utilization induced by metformin, it must be considered that evidence suggests an increased lactate exposure in the hepatic portal vein.[70] The increased exposure to lactate may yield increased glucose–lactate cycling between the splanchnic tissues and diminish the impact of intestinal metabolism on overall glycemia.[60]

Hepatic Glucose Uptake

Iozzo *et al.* evaluated the impact of metformin (2000 mg daily) and rosiglitazone (8 mg daily) therapy on HGU.[71] Positron-emission tomography (PET) studies in combination with [^{18}F]2-fluoro-2-deoxyglucose ([^{18}F]FDG) and the insulin clamp technique[48] were performed before treatment and at 26 weeks to assess HGU. At 90 min of the 150 min normoglycemic hyperinsulinemic period, patients were intravenously administered [^{18}F]FDG, and consecutive scans of the liver were obtained at 20 min. Although baseline HGU was not presented, metformin and rosiglitazone similarly and significantly increased HGU (placebo-subtracted value = +0.008 ± 0.004 and +0.007 ± 0.004 μmol/kg^{-1}/min^{-1}, respectively). Despite the failure of this study to define a specific increase versus baseline in HGU following an oral glucose load, the relationship identified between metformin and TZD would infer a similar impact.

Hepatic Gluconeogenesis

Stumvoll and associates evaluated the metabolic effects of metformin in T2DM patients receiving metformin 2550 mg daily.[72] Prior to and at the conclusion of the 16-week treatment period, patients were fasted and assessed for the rate of plasma lactate to plasma glucose conversion (GNG). Metformin was found to reduce the rate of conversion by 37% (7.3 ± 0.7 versus 4.6 ± 0.6 μmol/kg^{-1}/min^{-1}). Hundal and coworkers also evaluated the mechanism by which metformin reduces glucose production in patients with T2DM.[73] To address known methodological limitations used in previous studies assessing GNG, two independent and complimentary methods (nuclear magnetic resonance spectroscopy and ^2H_2O method) were employed to assess the impact of metformin therapy (2550 mg daily). Supporting the findings of Stumvoll and associates, the rate of hepatic GNG was reduced 36% as evaluated by the nuclear magnetic resonance method (0.59 ± 0.03 versus 0.18 ± 0.03 mmol/m^{-2}/min^{-1}) and 33% by the ^2H_2O method (0.42 ± 0.04 versus 0.28 ± 0.03 mmol/m^{-2}/min^{-1}) after three months of treatment.

Insulin Resistance

In a meta-analysis of randomized controlled trials in people at risk for T2DM, metformin reduced calculated IR (HOMAIR) by 22.6%. In studies of patients with T2DM and maximal therapeutic doses of metformin,[71,72,74,75] calculated IR was reduced 38–44%.

Peripheral Glucose Uptake

In the aforementioned analysis by Stumvoll *et al.*, it was noted that the rate of plasma glucose turnover (hepatic glucose output and systemic glucose disposal) was reduced with metformin from 2.8 ± 0.2 to 2.0 ± 0.2 mg/kg^{-1}/min^{-1}.[72] Importantly, the reduction in plasma glucose turnover was attributed to the reduction in hepatic glucose output; systemic glucose disposal did not change.[72] Corroborating evidence that metformin does not substantially increase PGU, Tiikkainen *et al.* and Inzucchi and associates observed nominal increases with long-term administration of metformin at therapeutic doses. Tiikkainen and colleagues clamped patients at 144 mg/dl before and after 16 weeks of metformin 2000 mg daily. The glucose rate of disappearance remained unchanged (0.09 ± 0.01 versus 0.10 ± 0.01 mg/kg^{-1}/min^{-1}).[74] Inzucchi and associates clamped patients at 100 mg/dl before and after 12 weeks of metformin 2000 mg daily. During the euglycemic hyperinsulinemic clamp period, glucose infusion rate was increased 13% (240 versus 272 mg/m^{-2}/min^{-1}).[78]

Peripheral Insulin Exposure

Metformin was consistently found to reduce FPI concentrations (range: 10–30%). In the aforementioned studies by Iozzo and group and Stumvoll and colleagues, FPI was reduced ~30% (63 ± 12 to 43.0 ± 5.0 pmol/liter) and 17% (12 ± 5 to 10 ± μU/ml), respectively.[71,72] Tiikkainen and associates observed an ~30% reduction in FPI (13 versus 9 mU/liter), and Sharma *et al.* found an ~10% reduction (76.0 ± 54.5 to 69.0 ± 45.0 pmol/liter) following administration of metformin 2000 mg daily for 16 weeks.[74,75] Evaluating both the fasting and mealtime effects of metformin, Inzucchi and colleagues found mean fasting and postprandial plasma insulin concentrations to be slightly, but not significantly, reduced with metformin 2000 mg daily for 12 weeks.[78]

Thiazolidinediones (Pioglitazone, Rosiglitazone, and Troglitazone)

The TZD agents (1) have no significant effect on total caloric intake,[80–82] (2) have no evidence for diminished intestinal absorption, (3) increase HGU,[71,83,84] (4) diminish hepatic GNG,[17,78,85] (5) reduce IR,[86–89] (6) increase PGU,[74,78,83] and (7) reduce insulin exposure.[17,89–91] Studies meeting review criteria for the target effects of the TZDs are presented here. Estimates for the effect of TZDs on the respective targets are presented in **Table 1**.

Caloric Intake and Intestinal Carbohydrate Absorption

The effect of TZDs on caloric intake has been evaluated in T2DM patients treated with pioglitazone and rosiglitazone. Smith and associates estimated subjective measures of hunger (visual analog scale) and satiety in patients treated with pioglitazone 45 mg/day.[80] At the conclusion of 24 weeks, pioglitazone demonstrated no effect on hunger and satiety. Strowig and Raskin assessed caloric intake via food records in patients administered rosiglitazone 4 mg twice daily.[81] At the conclusion of 32 weeks, mean caloric intake did not differ between treatment groups (rosiglitazone 2066.4 ± 589.2 and 1994.9 ± 726.5 calories/day for baseline and week 32, respectively). The effect of troglitazone on caloric intake in patients with diabetes has not been directly evaluated. However, in healthy volunteers, Cominancini and coworkers evaluated the effects of troglitazone 400 mg daily.[82] Troglitazone was not associated with changes in carbohydrate or total caloric intake after 2 weeks of therapy.

Hepatic Glucose Uptake

Bajaj and colleagues and Kawamori and associates have evaluated the effect of pioglitazone on HGU.[83,84] Kawamori and associates administered pioglitazone 30 mg daily to patients treated with either diet alone or sulfonylurea therapy. Following 12 weeks of therapy, the rate of splanchnic glucose uptake increased from 28.5 ± 19.4% to 59.4 ± 27.1% (p = .010).[84] Bajaj *et al.* administered pioglitazone 45 mg once daily after a 48 h medication washout period. At 16 weeks, splanchnic glucose uptake increased from 33.0 ± 2.8% to 46.2 ± 5.1%.[83] As previously mentioned, Iozzo and coworkers evaluated the effects of rosiglitazone on HGU, utilizing the insulin clamp technique and PET studies.[71] After 26 weeks, rosiglitazone 4 mg twice daily significantly increased HGU versus placebo (+0.007 μmol/min^{-1}/kg^{-1}). Since the study did not present baseline data to allow for percent change calculation, rosiglitazone was considered to have similar characteristics to pioglitazone for HGU. Troglitazone has not been directly evaluated for impact on HGU and was considered comparable to pioglitazone and rosiglitazone.

Hepatic Gluconeogenesis

Gastaldelli *et al.* evaluated the fasting and mixed-meal effects of pioglitazone and rosiglitazone on hepatic GNG.[17,85] Pioglitazone 45 mg daily for 16 weeks reduced fasting endogenous glucose production (13.1 ± 0.3 versus 12.0 ± 0.6 7 μmol/min^{-1}/kg^{-1}) and GNG contribution (73.1 ± 2.4% versus 64.4 ± 3.1%). During the mixed meal, endogenous glucose production was again reduced (6.5 ± 0.7 versus 5.4 ± 0.7 μmol/min^{-1}/kg^{-1}) as was the contribution of GNG to the total rate of appearance (45.6 ± 1.7% versus 41.3 ± 2.6%).[17] In the second study, rosiglitazone 8 mg daily for 12 weeks reduced fasting endogenous glucose production (18.6 ± 0.9 versus 16.3 ± 0.6 μmol/min^{-1}/kg^{-1}) and GNG contribution (67 ± 4% versus 59 ± 3%).[85] The direct effect of troglitazone on hepatic GNG has not been evaluated. However, Inzucchi and associates evaluated the effect of troglitazone on endogenous glucose production and found no significant difference after administration of troglitazone 400 mg daily for 12 weeks.[78]

Insulin Resistance

Langenfield *et al.* evaluated the effect of pioglitazone on IR as determined by HOMAIR.[86] Pioglitazone at a dose of 45 mg daily for 24 weeks in T2DM patients resulted in a decrease in IR from 6.15 ± 4.05 to 3.85 ± 1.92. Comparative analyses have identified similar effects of pioglitazone and rosiglitazone on IR. In a 12-week trial of pioglitazone 45 mg daily and rosiglitazone 4 mg twice daily, Goldberg and colleagues reported a reduction from 8.2 ± 0.3 to 5.4 ± 0.2 and 7.8 ± 0.4 to 4.8 ± 0.2, respectively.[87] Under the same experimental design, Deeg and colleagues observed similar reductions in IR for pioglitazone and rosiglitazone (8.3 versus 5.4 and 7.9 versus 4.7, respectively).[88] Yatagai *et al.* evaluated the effects of troglitazone 400 mg daily on IR (HOMAIR). After 12 weeks, IR was reduced from 5.7 ± 0.7 to 4.5 ± 0.8.[89]

Peripheral Glucose Uptake

Pioglitazone, rosiglitazone, and troglitazone have been shown to increase basal and incremental PGU. Bajaj *et al.* observed the glucose infusion rate to be significantly greater during euglycemic insulin clamp (5.6 mmol/liter) after treatment with pioglitazone 45 mg daily for 16 weeks (6.9 ± 0.5 versus 5.0 ± 0.5 mg/kg^{-1}/min^{-1}).[83] Glucose infusion rate was also significantly increased during the 180–420 min period of the 75 g oral glucose load-insulin clamp (5.3 ± 0.5

versus 2.9 ± 0.5 mg/kg^{-1}/min^{-1}). Tiikkainen and associates demonstrated that rosiglitazone 4 mg twice daily for 16 weeks increased glucose disposal rate (0.10 ± 0.02 versus 0.17 mg/kg^{-1}/min^{-1}) with glycemic maintenance at ~8 mmol/liter.[74] Inzucchi and coworkers found administration of troglitazone 400 mg daily for 12 weeks significantly increased glucose disposal rate (172 versus 265 mg/m^{-2}/min^{-1}) during the final hour of hyperinsulinemic–euglycemic clamp study (5.6 mmol/liter).[78]

Peripheral Insulin Exposure

Gastaldelli and colleagues evaluated the effect of pioglitazone 45 mg daily for 16 weeks on the metabolic and hormonal response to a mixed meal in T2DM patients.[17] Fasting plasma insulin and plasma insulin during the mixed meal challenge (0–6 h) were similarly reduced versus baseline (88 versus 81 pmol/liter and 268 versus 248 pmol/liter, respectively). Miyazaki and associates evaluated the dose-response effect of 7.5–45 mg of pioglitazone on fasting insulin secretion after 26 weeks. Fasting plasma insulin concentrations were similarly reduced (15–25%) at the respective pioglitazone doses.[90]

Miyazaki and DeFronzo have reported that rosiglitazone demonstrates similar effects to pioglitazone on insulin secretion.[91] After three months of therapy with rosiglitazone 8 mg daily, FPI was reduced (18 ± 1 versus 13 ± 1 μU/ml) without change in the mean insulin concentration (37 ± 4 versus 36 ± 4 μU/ml) during a 2 h oral glucose tolerance test (OGTT). Pioglitazone similarly reduced FPI (15 ± 1 versus 13 ± 2 μU/ml) and also demonstrated no change in mean insulin concentration during a 2 h OGTT.

Yatagai and coworkers evaluated the effects of troglitazone 400 mg daily on FPI concentration in T2DM patients.[89] After 12 weeks of therapy, FPI concentration was found to be slightly reduced (14.3 ± 2.1 to 12.9 ± 2.6 μU/ml). Similarly, Inzucchi and colleagues evaluated the effects of troglitazone 400 mg daily for 12 weeks.[78] At the conclusion of the study, fasting and postprandial plasma insulin concentrations were reported to be slightly, but not significantly, reduced.

Secretagogues and Exogenous Insulin

Secretagogues and exogenous insulin (1) have variable effects on caloric intake,[92–104] (2) have no evidence for diminished intestinal carbohydrate absorption, (3) increase HGU,[21] (4) diminish GNG,[18,21] (5) have variable effects on IR,[38,103,105–112] (6) increase PGU,[21] and (7) increase PIE.[113–122]

Caloric Intake and Intestinal Carbohydrate Absorption

It has been hypothesized that increased plasma insulin concentrations increase appetite and cause undesirable weight gain.[92–95] The UKPDS and other studies in T2DM patients have demonstrated that initiation of insulin is often accompanied by duration- and intensity-dependent weight gain (5–10%).[96–100] The potential cause of increased weight gain has been attributed to increased caloric intake secondary to hyperinsulinemia or hypoglycemic fear and also a reduction in the basal metabolic rate.[97,101,102] However, it must be considered that weight gain is not a universal finding and that modest reductions in daily caloric intake have been observed.[103,104] Moreover, insulin therapy is commonly, but not unequivocally, associated with increased caloric intake and subsequent weight gain.

Standard and Insulin Concentration Time Profiles

Gannon and Nuttall identified the 24 h insulin secretion profile in patients with T2DM prior to initiating dietary control measures (**Figure 2**). On average, patients were aged 63 years (range 51–82), with a 4-year duration of diabetes (range 1–15), BMI of 31 kg/m^2 (range 27–36), and a total glycosylated hemoglobin of 9.6% (range 8.6–11.2).[20]

Hepatic Glucose Uptake, Hepatic Gluconeogenesis, and Peripheral Glucose Uptake

Basu and associates evaluated the insulin dose-response curves for stimulation of splanchnic (hepatic) glucose uptake, suppression of endogenous glucose production, and PGU.[21] Patients were fed a standard 10 cal/kg meal (55% carbohydrate, 30% fat, 15% protein) and stabilized overnight at a glucose level of ~5 mmol/liter (90 mg/dl). On the subsequent morning, insulin was infused at variable rates from 0 to 180 min (~0.5 mU/kg^{-1}/min^{-1}), 181 to 300 min (~1.0 mU/kg^{-1}/min^{-1}), and 301 to 420 min (~2.0 mU/kg^{-1}/min^{-1}). The insulin dose-response relationship for splanchnic glucose uptake and PGU during the final 30 min of the low- (~150 pmol/liter), medium- (~350 pmol/liter), and high- (~700 pmol/liter) dose insulin infusions are presented in **Figure 3**. To most accurately quantify the hepatic contribution to glucose supply, the insulin dose-response relationship to hepatic GNG was utilized in place of total endogenous glucose production. Gastaldelli and coworkers evaluated the effect of physiological hyperinsulinemia on GNG in T2DM.[18] Under euglycemic clamp conditions, total rates of glucose appearance were calculated from a previously established two-compartmental model.[123] Endogenous glucose output was subsequently calculated as the difference between the rate of glucose appearance and the exogenous glucose rate. Percent contribution of

GNG to the plasma glucose was calculated as the ratio of C5:^2H_2O enrichments. Under basal conditions, mean plasma insulin concentration was 12.2 ± 1.2 μU/ml (~85 pmol/liter) and increased to 113 ± 6 μU/ml (~780 pmol/liter) during euglycemic hyperinsulinemic clamp. Endogenous glucose output reduced from 15.2 ± 0.4 to 7.1 ± 0.9 and plasma C5:^2H_2O ratio declined from 0.60 ± 0.02 to 0.25 ± 0.02. The insulin dose-response relationship for suppression of hepatic GNG is presented in **Figure 3**.

Insulin and Sulfonylurea Concentration Time Profiles

Twenty-four-hour insulin concentration time curves were obtained for sulfonylurea, meglitinide, and exogenously administered insulin products.[113–122] Due to a lack of available evidence characterizing the 24 h insulin concentration profile of first generation sulfonylurea agents, comparable dose relationships were drawn with the profile for glyburide. Twenty-four -hour steady state insulin concentration time curves were superimposed on the baseline secretion profile of the standard T2DM patient. As an example, the concentration time profile of insulin glargine at a dose of 0.5 U/kg is presented in **Figure 4**. Using the trapezoidal rule, glargine increased PIE 30% versus baseline (5765 versus 7495 pmol/h^{-1}/liter^{-1}, respectively). Applying the superimposed 24 h insulin concentration time curve to the insulin dose-response relationships for HGU, GNG, and PGU, glargine was observed to increase HGU and PGU (24% and 42%, respectively), while decreasing GNG by 10%. Hepatic glucose uptake, GNG, PGU, and PIE values for the remaining exogenously administered insulin products and sulfonylurea agents are presented in **Table 1**.

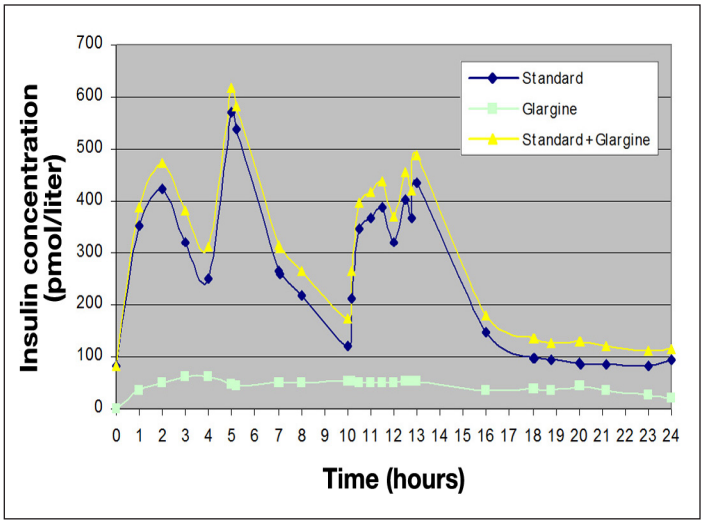

Figure 4. Standard + insulin glargine concentration time profile (T2DM).

Insulin Resistance

In 1993, Hotamisligil and colleagues identified the relationship between inflammation and metabolic conditions, such as obesity and IR, by demonstrating adipocyte expression of the proinflammatory cytokine tumor necrosis factor-α (TNF-α) and that expression in the adipocytes of obese animals is markedly increased.[124] Further efforts in the area of obesity have identified obesity to be a state of chronic inflammation, as indicated by increased plasma concentrations of C-reactive protein, interleukin-6 (IL-6), and plasminogen activator inhibitor-1 (PAI-1).[125–127] Dandona *et al.* have characterized the anti-inflammatory effect of insulin (reduction of reactive oxygen species generation by mononuclear cells, nicotinamide adenine dinucleotide phosphate oxidase suppression, reduced intranuclear NF-κB, suppressed plasma intercellular adhesion molecule-1 and monocyte chemotactic protein-1, reduced intranuclear Egr-1, monocyte chemotactic protein-1, and PAI-1) as well as the link between IR, obesity, and diabetes.[128–130] Crook *et al.* and Pickup *et al.* first proposed T2DM to be a chronic inflammatory condition characterized by increased concentrations of acute phase reactants (sialic acid, IL-6).[131,132] Indeed, several studies have confirmed the presence of inflammatory mediators predicts T2DM.[133–139] It has been noted that the increased concentration of proinflammatory cytokines (i.e., TNF-α, IL-6) associated with obesity and T2DM may interfere with insulin action by suppressing signal transduction. Therefore, the anti-inflammatory effects of insulin may be blunted, which, in turn, may promote inflammation.[130]

The extensive characterization of obesity and T2DM as inflammatory conditions with blunted anti-inflammatory (and possibly proinflammatory) effects of insulin creates inconsistency when characterizing insulin's effect on IR. It has been argued that, by increasing weight gain, insulin therapy would exacerbate IR.[112] So too, there is conflicting evidence that insulin and sulfonylurea agents have no significant effect, or alternatively a beneficial effect, on IR as assessed by HOMAIR.[38,103,105–111] Contradictory evidence in combination with known pathophysiologic evidence would indicate a net neutral effect of insulin on IR.

Discussion

The administration of therapies that increase exposure to insulin and increase peripheral glucose disposal may not be without consequence. It has been extensively documented that hyperinsulinemia, hyperglycemia, IR, and inflammation are central to the development of atherosclerosis.[9–12,130,140,141] Hence, it may not be altogether

unsurprising that there is difficulty in drawing direct relationships between blood glucose reduction and macrovascular outcomes when the strategies employed to rigorously reduce blood glucose do so by preferentially increasing the burden of insulin exposure and peripheral glucose disposal.

After reviewing the available literature for the impact on the respective targets, alpha-glucosidase inhibitors (1.25), TZDs (1.27–1.35), and metformin (2.20) were associated with the highest ratios, while insulin (0.62–0.79) and secretagogues (0.69–0.81) were associated with the lowest ratios. Keeping with the hypothesis that preferentially increasing insulin exposure and peripheral glucose disposal versus more selectively modifying CE, HGU, GNG, and IR may be detrimental, our glucose supply and insulin demand characterization is consistent with evaluations of oral antidiabetic therapies on cardiovascular outcomes wherein alpha-glucosidase inhibitors, metformin, and TZDs appear to be associated with cardiovascular benefit, and sulfonylureas appear to be associated with possible negative effects.[111,142–153]

To test the hypothesis that the means by which the blood glucose is reduced is as important as the actual blood glucose, it is necessary to construct a longitudinal model that incorporates macrovascular outcomes, the extent of blood glucose reduction (HbA1c), and the manner by which it was reduced (glucose supply:insulin demand [SD] ratio). This hypothesis should be tested in a longitudinal dataset that includes validated macrovascular outcomes, continuous laboratory follow-up, and an accurate representation of the antidiabetic agents and doses throughout the assessment period. Intuitively, the optimal dataset would be from the recent long-term cardiovascular outcome trials (ACCORD, ADVANCE, VADT); however, it must be considered that our model is heavily dependent on accurate quantification of medication exposure that would be assumed without detailed adherence documentation or pharmacy claims history. Alternatively, the construction of a retrospective dataset from an electronic data source may serve to quantify medication exposure more accurately but would also be complicated by small patient yield due to complexities of validating macrovascular outcomes and identifying patients with continuous laboratory and medication follow-up.

Model Assumptions and Limitations

The construction of the glucose supply and insulin demand model required multiple assumptions. The 24 h effect profile for all antidiabetic therapies has not been comprehensively assessed. This imposed limitations on our ability to more accurately quantify hepatic GNG throughout the prandial phase. With respect to insulin's effect on hepatic GNG, there was insufficient evidence to determine the nonlinear dose-response relationship. Therefore, because hepatic glucose production is very sensitive to suppression by low concentrations of insulin,[21,74,154] it is possible that we may have underestimated insulin's impact on GNG inhibition.

Second, the standard 24 h insulin concentration time profile was identified in patients who were not subjected to dietary control measures, were relatively early in the disease course, and had a large HbA1c range. Despite evidence that decreased insulin secretion over time is not inevitable in the course of diabetes,[155] it is generally accepted that T2DM patients have a progressive loss of insulin secretion over time.[156–161] Therefore, it may be necessary to account for progressive decreases in insulin secretion over time in subsequent analyses. Concordantly, it is also possible that there may be variable effects with differing degrees of insulinemia and glycemia.

Third, insulin concentrations were considered additive on the standard 24-insulin concentration time profile. Under euglycemic conditions in normal subjects, it has been suggested that endogenous insulin secretion may be diminished with exogenous insulin administration.[162–164] The effect of exogenous insulin to suppress endogenous insulin secretion would suggest an overestimation of the effect on HGU, hepatic GNG, PIE, and PGU.

Lastly, estimates of effect for oral medications on CE, HGU, GNG, IR, PIE, and PGU were calculated for maximal therapeutic dose and linearly extrapolated for decreasing doses, while insulin, having no maximal therapeutic dose, was linearly extrapolated for increasing or decreasing dose. It is possible that the effects of therapies on the respective targets are not linear or completely synergistic. It is also likely that the respective targets may have differing impacts on disease progression and require multiple coefficients to optimize the model.

Conclusions

Alpha-glucosidase inhibitors, metformin, and TZDs demonstrate a greater effect on glucose supply (CE, HGU, GNG, IR), while secretagogues, basal insulin, and bolus insulin demonstrate a greater effect on insulin demand (PIE, PGU). Because T2DM cardiovascular outcome trials have not demonstrated a macrovascular benefit with more aggressive blood glucose reduction when

using conventional algorithms that predominantly focus on insulin demand (secretagogues and basal and bolus insulins), it would appear logical to consider a model that incorporates both the extent of blood glucose lowering (HbA1c) and the means by which the blood glucose was reduced (SD ratio) when considering macrovascular outcomes.

Acknowledgment:

To Steve Feuerstein for data extraction and formatting.

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