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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).

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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.

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