Impact of Sitagliptin on Markers of β-cell Function: A Meta-Analysis

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Abstract: *Background:* Progressive β-cell dysfunction and β-cell failure are fundamental pathogenic consequences of type 2 diabetes. Dipeptidyl peptidase-IV inhibitors may exhibit improvement on preclinical measures of both β-cell function, homeostasis model assessment of β-cell (HOMA-β) index, and β-cell dysfunction, proinsulin/insulin ratio (PI/IR), correlating to β-cell survival. *Research Design and Methods:* A systematic literature search through July 2008 was conducted to extract a consensus of randomized, controlled trials of sitagliptin therapy on measures of β-cell function. A random-effects model meta-analysis evaluated effects on HOMA-β and PI/IR versus placebo. Several subgroup analyses, including active control, were conducted. Studies were included if they met the following criteria: (1) randomized trials on sitagliptin; (2) placebo or active control; and (3) data reported on HOMA-β or PI/IR. *Results:* A total of 11 trials (n = 3039) reported effects on HOMA-β and 8 trials (n = 2325) on PI/IR versus placebo. Four trials (n = 1425) were included in the active control subgroup analysis. Sitagliptin significantly improved HOMA-β index by 12.03% [95% confidence interval (CI), 9.45–14.60] versus placebo. Sitagliptin also significantly decreased PI/IR −0.06 (95% CI, −0.08 to −0.04). Sitagliptin was inferior to active control for HOMA-β index [5.64% (95% CI, 0.38–10.90)], but not different in terms of PI/IR [0.01 (95% CI, −0.04 to 0.06)]. *Conclusions:* Despite significant improvement in HOMA-β index and PI/IR from placebo, there does not seem to be a benefit of dipeptidyl peptidase-IV inhibitors over other agents with respect to β-cell function/activity. Long-term prevention of β-cell dysfunction cannot be ruled out.

Key Indexing Terms: DPP-IV inhibitor; Diabetes; Sitagliptin; HOMA-β; Proinsulin; β-Cell function; Meta-analysis. **[Am J Med Sci 2009;337(5):321–328.]**

Progressive β-cell dysfunction and β-cell failure are fundamental pathogenic consequences of type 2 diabetes, as indicated by the United Kingdom Prospective Diabetes Study.[1,2] The inadequacy of treatment allocation (including diet, insulin, chlorpropamide, glibenclamide, and metformin) on β-cell salvation, diminished β-cell function on diagnosis, and sustained decline in β-cell mass and function in type 2 diabetes have prompted emerging medical therapies that target pathogenic β-cell deterioration.[3,4]

Considering the historic insufficiency of hypoglycemic agents on β-cell salvation, simple increases in insulin [eg, sulfonylureas (SFU) or insulin] or reductions in insulin resistance [eg, thiazolidinediones (TZDs)] seem to be only minor pieces in the complex mechanism of β-cell destruction (Table 1).[5] In fact, Saisho et al[6] suggest that not only hyperglycemia, but also glycation is involved in β-cell dysfunction. On autopsy evaluation of human pancreatic tissue, a significant reduction in β-cell mass is observed in both impaired glucose tolerance (40%) and type 2 diabetes (60%) compared with nondiabetic controls.[7] Although islet cell formation and β-cell replication remained normal, an increase in β-cell apoptosis was observed, signifying a possible mechanism in β-cell destruction.[7] Logically, the inhibition of this increased apoptosis, in light of normal islet neogenesis, may lead to the restoration of β-cell mass.[4] The reduction in β-cell mass because of apoptosis may be accelerated by glucotoxicity and lipotoxicity, complicated by increased lipolysis inducing elevations in free fatty acids causing prolonged exposure and, ultimately, β-cell injury (Table 1).[8,9] These histologic changes are mirrored by functional changes in the body; however, considering the infeasibility of islet evaluation of β-cell mass, growth, and death, surrogate markers are commonly used to estimate β-cell function.

Both β-cell function, via homeostasis model assessment of β-cell (HOMA-β) index, and β-cell dysfunction, via proinsulin/insulin ratio (PI/IR), can be estimated in type 2 diabetes.[10,11] Increases in HOMA-β indicate the preservation of β-cell function and/or activity, whereas decreases in PI/IR driven by proinsulin indicate the improvement in the secretory and, possibly, resistance profile of the β cell.[5,12,13] Worsening of these surrogate measures may correlate to β-cell failure.[10,14] Reductions in HOMA-β have historically been a measurement of β-cell deterioration associated with both hemoglobin A1C (A1C) elevations and additional therapy to maintain glycemic goals, whereas increases in HOMA-β are considered beneficial.[4] PI/IR is negatively correlated with insulin secretion in both healthy and diabetic subjects, implying that PI/IR may be a strong predictor of β-cell dysfunction.[6] In fact, PI/IR is independently correlated with glycation endproducts, which has been insinuated as an independent etiology of β-cell failure.[6]

Recently, the discovery of the mechanism behind incretin hormones in glucose regulation has evoked considerable research in the area of β-cell function. Incretin hormones, specifically glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), account for the majority of the postprandial incretin response, regulating blood glucose through several distinct mechanisms, including enhancement of insulin release, suppression of glucagon, decrease in appetite, and delayed gastric emptying.[15,16] GLP-1 receptor signaling directly modifies the susceptibility to apoptotic injury, and provides a new potential mechanism for preservation or enhancement of β-cell mass.[17] GLP-1 analogs have demonstrated both neogenesis and prolonged β-cell survival, by means of reduction in cytokine-induced apoptosis, in preclinical studies.[5,17,18] Dipeptidyl peptidase-IV (DPP-IV) inhibitors, such as sitagliptin, are a novel approach to the treat-

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TABLE 1. Potential mechanisms of β-cell destruction

Mechanism	Characteristic
Glucotoxicity	↑ Apoptosis
	↓ Insulin synthesis
	Insulin store depletion
	Metabolic stress
	Chronic oxidative stress
Lipotoxicity	↓ Insulin synthesis
	Metabolic stress
	Loss of insulin response
	Free fatty acid esterification/cellular deposition
Amyloid deposition	Impaired insulin secretion and absorption
	↑ Apoptosis
↑ Secretory demand	Endoplasmic reticulum stress
	Aberrant protein folding
Inflammation	Altered cytokine/adipokine secretion from dysfunctional adipocytes
	Innate/autoimmune processes
	Glucose induced

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ment of type 2 diabetes, acting as incretin enhancers. By inhibiting the primary enzyme in incretin degradation, DPP-IV inhibitors allow endogenous GLP-1 and GIP to be maximized. Consequently, it has been hypothesized that DPP-IV inhibitors exhibit improvement on preclinical measures of both β-cell function and dysfunction, thereby eliciting benefits in preventing or delaying the decline in β-cell mass/function.[4]

In preclinical studies, DPP-IV inhibitors have been shown to augment β-cell mass by enhancing endogenous incretin action, increasing the number of replicating islet cells, and reducing the number of apoptotic islet cells.[19] Additionally, there is a significant increase in measures of β-cell function and β-cell mass, even weeks after discontinuation of treatment, suggesting a disease-modifying effect.[19,20]

Sitagliptin (Januvia, Merck & Co., Whitehouse Station, NJ) is a once-daily Food and Drug Administration–approved highly selective DPP-IV inhibitor that has demonstrated benefit to glycemic control, increasing active GLP-1 and improving indices of β-cell function in type 2 diabetes.[21] Preclinical studies are consistent with the theory of β-cell restoration and preservation with sitagliptin, specifically.[4] It has been suggested that sitagliptin improves β-cell function in a glucose-dependent manner without detriment to body weight.[4]

Considering the lack of concurrence among randomized trial results, we conducted a meta-analysis of randomized controlled trials published through July 2008 to evaluate the effect of sitagliptin on HOMA-β and PI/IR.

RESEARCH DESIGN AND METHODS

Study Selection

A systematic literature search of MEDLINE from 1966 through July 2008; EMBASE from 1990 through July 2008; and the Cochrane Database to identify randomized clinical trials of sitagliptin utilization with a primary or secondary endpoint of HOMA-β or PI/IR was conducted. A search strategy using the MeSH and text keywords *MK-431* and *sitagliptin* was utilized. A manual search of abstracts presented between 2003 and 2007 at the American Diabetes Association Scientific Sessions was conducted. In addition, a manual review of references from primary or review articles was performed to identify any additional relevant studies. All potentially relevant articles were reviewed independently by all three investigators with disagreements decided by consensus. To be included in this meta-analysis, studies had to (1) be randomized trials of sitagliptin ≥12 weeks in duration; (2) be placebo or active controlled; and (3) report data on HOMA-β and/or PI/IR in patients with diabetes.

Validity Assessment

The following methodologic features most relevant to the control of bias were assessed: randomization, random allocation concealment, masking of treatment allocation, blinding, and withdrawals. All studies were evaluated by 3 independent reviewers with disagreements decided by consensus.

Data Abstraction

All data were independently abstracted through the use of a standardized data abstraction tool. The following information was sought from each article: author identification, year of publication, type of study design, concomitant medication, sample size, duration of patient follow-up, age, gender, race, body mass index, baseline A1C, duration of diabetes, HOMA-β, and PI/IR. In cases in which there was more than 1 published report on the same population or group of patients, the most recent article was selected for analysis, although previous articles could be reviewed to supplement for missing data where applicable. An attempt was made to contact corresponding authors for numerical values not provided in the text or abstract.

Statistical Analysis

HOMA-β and PI/IR were treated as continuous variables. Effect sizes were reported as weighted mean differences with 95% confidence intervals (CI) calculated using StatsDirect statistical software version 2.4.5 (available at http://www.statsdirect.com) using a random-effects model (DerSimonian-Laird).[22] Statistical heterogeneity was measured using the Q statistic ($P < 0.1$ was considered representative of significant statistical heterogeneity), as well as through an I^2 test.[23]

The selection of a random-effect versus fixed-effect model in meta-analyses is controversial. The use of a random-effect model in the calculation of CI results in wider intervals and, thus, a more conservative estimate of treatment effect when compared with a fixed-effect model. To reconcile this issue, sensitivity analysis was conducted whereby the meta-analysis was reanalyzed using a fixed-effects model (Mulrow-Oxman methodology).

Several methods were used to assess the potential for publication bias. Visual inspection of funnel plots for both the HOMA-β and PI/IR endpoints was conducted. The Egger weighted regression method was also used to statistically assess publication bias for primary and subgroup analyses ($P < 0.05$ was considered representative of significant statistical publication bias).

RESULTS

Study selection process is described in Figure 1. Of 201 screened articles and abstracts, 150 relevant articles and abstracts were identified, 43 were retrieved for detailed evaluation, and 12 met inclusion criteria. Eleven studies[24–34] (n = 3039) for HOMA-β and 8 studies[26–33] (n = 2325) for PI/IR provided data adequate for meta-analysis in the primary cohort (Table 2). Four studies (n = 1425) were included in the sitagliptin