The Disposition Index Does Not Reflect Beta Cell Function in IGT Subjects Treated with Pioglitazone

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Aims/Hypothesis: The insulin secretion/insulin resistance (disposition) index ($\Delta I/\Delta G \div IR$) commonly is used as a measure of beta cell function (Δ=change from baseline). This relationship is curvilinear and becomes linear when log transformed. ΔI is determined by two variables: insulin secretory rate (ISR) and metabolic clearance of insulin (MCR_I). We postulated that the characteristic curvilinear relationship would be lost if Δ plasma C-peptide (instead of Δ plasma insulin) was plotted against insulin sensitivity.

Methods: 441 IGT individuals from ACT NOW received an OGTT and were randomized to pioglitazone or placebo for 2.4 years.

Results: Pioglitazone reduced IGT conversion to diabetes by 72% ($p<0.0001$). $\Delta I/\Delta G$ vs Matsuda Index (MI) of insulin sensitivity showed the characteristic curvilinear relationship. However, when $\Delta CP/\Delta G$ or $\Delta ISR/\Delta G$ was plotted against MI, the curvilinear relationship was completely lost. This discordance was explained by two distinct physiologic effects that altered plasma insulin response in opposite directions: (i) increased ISR and (ii) augmented MCR_I. The net result was a decline in plasma insulin response to hyperglycemia during OGTT. These findings demonstrate a physiologic control mechanism wherein the increase in ISR ensures adequate insulin delivery into portal circulation to suppress HGP while delivering reduced but sufficient amount of insulin to peripheral tissues to maintain the pioglitazone-mediated improvement in insulin sensitivity without excessive hyperinsulinemia.

Conclusions: These results demonstrate the validity of disposition index when relating plasma insulin response to insulin sensitivity, but underscore the pitfall of this index when drawing conclusions about beta cell function, since insulin secretion declined despite an increase in plasma insulin response.

Considerable controversy exists concerning the most appropriate methodology to evaluate beta cell function in glucose intolerant states and in response to a therapeutic intervention in patients with impaired glucose tolerance/type 2 diabetes mellitus (T2DM) (1–3). Although the plasma insulin concentration is the ultimate determinant of insulin-mediated glucose disposal, approximately half of all insulin secreted into the portal vein is removed by the liver (4) and insulin degradation is markedly reduced in insulin resistant states such as obesity and T2DM (5, 6). Measurement of the plasma C-peptide concentration with deconvolution analysis and validation of a standard plasma C-peptide disappearance function have made it possible to quantitate the insulin secretory rate (7), independent of the insulin clearance. The insulin secretion/insulin resistance, or so called disposition, index widely has been used as a measure of beta cell function (Δ=change from baseline) (8–10). Previous studies have demonstrated that plot of insulin resistance vs the ratio of the increment in plasma insulin (ΔI)/increment in plasma

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.
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Received February 20, 2014. Accepted June 9, 2014.

Abbreviations:

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glucose (ΔG) following oral and intravenous (IV) glucose is curvilinear and becomes linear on log transformation (8, 9). However, recent studies have questioned the validity of the disposition index as a measure of beta cell function (1–3). Beta cell sensitivity to glucose, as well as the beta cell response to the rate of change in plasma glucose concentration, also have been shown to be important determinants of beta cell function (1–3).

In ACT NOW (11, 12), 602 IGT individuals were randomized to pioglitazone or placebo for 2.4 years. 45 placebo-treated vs 15 pioglitazone-treated subjects developed diabetes (HR = 0.28, $P < .0001$) (11). Physiologic factors associated with high final glucose tolerance status have been published (13). Herein, we examine the relationship between the plasma insulin response, insulin secretion (plasma C-peptide deconvolution) and metabolic clearance rate of insulin before and after pioglitazone in subjects with IGT.

Materials and Methods

Subjects. 602 high risk IGT subjects participated in ACT NOW (11). Demographic, anthropometric, and metabolic characteristics at baseline were similar in pioglitazone- and placebo-treated groups (11). Here, we report on 441 subjects who completed the study (Table 1). Subjects lost to follow-up or who dropped-out and did not have study end OGTT were not included. During screening, 120 subjects with normal OGTT were identified and are included as the control group.

Study Design. (11, 12) and results have been published (11). Eight centers participated in the study which was approved by each site's IRB. 441 IGT subjects in the present report were randomized to pioglitazone (n = 213) or placebo (n = 228) and followed for 2.4 years.

At baseline subjects received a 2-hour 75 g OGTT with plasma glucose, insulin, C-peptide measured at –30, –15, 0 and every 15 minutes thereafter (11, 12). Additional baseline assessments included medical history, physical examination, BMI, waist circumference, HbA1c, lipids, screening blood tests, urinalysis, and electrocardiogram (ECG).

Table 1. Baseline characteristics of the 441 IGT subjects who had a baseline and end of study OGTT

Characteristic	Pioglitazone	Placebo	
	(*n* = 213)	(*n* = 228)	P-value
Isolated IGT (number)	64	73	
IGT/IFG (number)	149	155	
Ratio of women to men (%)	56/44	58/42	
Race or ethnic group (number)			
Hispanic	55	54	
White	114	137	
Black	37	30	
Other	7	7	
Family history of diabetes--number, (%)	115, (54%)	126, (55%)	
Mean age (years)	53.9 ± 0.7	52.5 ± 0.8	0.16
Mean BMI (kg/m^2)	33.4 ± 0.4	34.4 ± 0.4	0.09
Waist circumference -- cm			
Men	109 ± 1	112 ± 1	0.12
Women	102 ± 1	103 ± 1	0.41
HbA1c (%)	5.52 ± 0.03	5.60 ± 0.03	0.22
Fasting plasma glucose (mg/dl)	105 ± 0.5	105 ± 0.5	0.67
2-hr plasma glucose (mg/dl)	169 ± 1	169 ± 1	0.90
Fasting plasma insulin (mU/liter)	10.2 ± 0.6	10.2 ± 0.6	0.72
Lipid levels (mg/dl)			
Total cholesterol	170 ± 2	171 ± 2	0.80
LDL cholesterol	105 ± 2	106 ± 2	0.66
HDL cholesterol	40 ± 1	41 ± 1	0.64
Triglycerides	123 ± 4	118 ± 4	0.35
Fasting Free fatty acids (umol/liter)	550 ± 14	547 ± 13	0.85
Blood pressure (mmHg)			
Systolic	127 ± 1	127 ± 1	0.87
Diastolic	74 ± 1	73 ± 1	0.46

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Participants were randomized to pioglitazone (PIO), 30 mg, or placebo (PLAC). After one month, pioglitazone was increased to 45 mg. Participants returned at 2, 4, 6, 8, 10, 12 months during year one and every 3 months thereafter. Subjects were followed until they reached the primary end point of diabetes or reached study end (2 years after last subject was enrolled). The OGTT was repeated at study end or time of conversion to diabetes. Primary outcome was the development of diabetes (FPG $\geq$ 126 mg/dl or 2-hour glucose $\geq$ 200 mg/dl), confirmed by a repeat OGTT.

Data Analysis. Matsuda Index (MI) of insulin sensitivity was calculated from plasma glucose and insulin concentrations during OGTT and has been shown to correlate closely with insulin-mediated glucose disposal during euglycemic insulin clamp in subjects with NGT, in subjects with IGT, and in subjects with T2DM (14). The OGIS index of insulin sensitivity (15) also was calculated and the results for each physiologic parameter were superimposable with those obtained using the Matsuda Index (data not shown). The incremental area under the plasma glucose, insulin, C-peptide curves during OGTT was determined using the trapezoidal rule. Insulin secretion rate (ISR) was calculated from plasma C-peptide deconvolution with standard C-peptide clearances (7). Beta cell function was calculated as the insulin secretion/insulin resistance (disposition) index using: $\Delta I_{0-120}/\Delta G_{0-120}$ x MI; $\Delta CP_{0-120}/\Delta G_{0-120}$ x MI: $\Delta ISR_{0-120}/\Delta G_{0-120}$x MI (3, 16, 17). MCR_I was estimated as ISR (pmol/min) divided by the plasma insulin concentration (pmol/ml) during OGTT. Beta cell sensitivity to glucose and beta cell rate sensitivity were calculated using the slope of dose response curve of ISR vs plasma glucose concentration during the rising part of OGTT (3, 17).

Statistical analyses addressed the following question: Change in which parameters of beta cell function were associated with the salutatory effect of pioglitazone on OGTT. Metabolic/physiologic/anthropometric changes associated with protection against diabetes were reported previously (13) and are not addressed herein. Intention to treat analyses were conducted using all follow-up data. Continuous variables were compared between treatment groups by t-tests if normally distributed. Baseline plasma insulin/C-peptide concentrations, insulin/C-peptide AUCs, Matsuda Index of insulin sensitivity, and disposition index were natural log transformed before comparisons. Changes from baseline to follow-up were compared between groups by *t* test when variables were normally distributied and Wilcoxon's test for variables non-normally distributed. Statistical significance was accepted for 2-sided alpha < 0.05. Data are presented as mean $\pm$SE. Statistical analysis was performed using Statview and JMP from SAS. Insulin secretion rates and beta cell glucose sensitivity were calculated using the software MLAB (Civilized Software Inc., Silverspring, MD).

Results

Study Cohort

Characteristics of the study population are shown in Table 1. There were no significant differences in any clinical, anthropometric, laboratory parameters between placebo and pioglitazone groups.

Follow-up Results

45 (19.7%) of 228 individuals in placebo and 15 (7.0%) of 213 in pioglitazone groups developed diabetes during follow-up of 2.4 years. The annual incidence diabetes rates, after adjusting for age, gender, center and calculated using person-years, were 8.2% and 3.1%, respectively ($P < .001$).

Effect of Pioglitazone on HbA1c, Plasma Glucose, BMI

HbA_{1c} differed between groups ($P < .003$) throughout study, increasing by 0.28% (1.9 mmol/mol) in PLAC and 0.07% (0.5 mmol/mol) in PIO ($P < .0001$). At study end, the decrements in FPG (-10.7 $\pm$ 0.9 vs –4.0 $\pm$ 0.09 mg/dl) and 2-hour PG (-28.7 $\pm$ 2.6 vs –5.9 $\pm$ 2.6 mg/dl) were greater in PIO vs PLAC ($P < .0001$). BMI increased in PLAC (0.5$\pm$0.2 kg/m^2, $P < .006$) and PIO (1.6$\pm$0.2 kg/m^2, $P < .0001$), but the increment was greater with PIO ($P < .0001$).

Effect of Pioglitazone on Insulin Sensitivity, Insulin Secretion, Beta Cell Function

Matsuda Index (MI) of insulin sensitivity (and OGIS; data not shown) increased by 92% in PIO (3.9 $\pm$ 0.2 to 7.5 $\pm$ 0.3, $P < .0001$) and 17% in PLAC (4.0 $\pm$ 0.2 to 4.7 $\pm$ 0.3, $P = .002$) ($P < .0001$, PIO vs PLAC). Fasting insulin secretory rate (plasma C-peptide deconvolution) increased in PLAC (420 $\pm$ 14 to 558 $\pm$ 21 pmol/min, $P < .0001$ vs baseline) and did not change in PIO (411 $\pm$ 14 to 446 $\pm$ 19) ($P < .0001$, PIO vs PLAC). Total insulin secreted during OGTT (0–120 minutes) increased modestly in both groups (PIO, 165 $\pm$ 3 to 189 $\pm$ 5 nmol; PLAC, 167 $\pm$ 3 to 202 $\pm$ 6 nmol; $P < .0001$ vs. baseline for both groups; p=ns, PIO vs PLAC). Disposition index calculated as $\Delta I_{0-120}/\Delta G_{0-120}$ x MI increased by 65% with PIO (3.2 $\pm$ 0.1 to 5.3 $\pm$ 0.3, $P < .0001$) and did not change significantly with PLAC (3.2 $\pm$ 0.1 to 3.7 $\pm$ 0.2, p=NS) ($P < .0001$, PIO vs. PLAC). When the disposition index was calculated as $\Delta ISR_{0-120}/\Delta G_{0-120}$ x MI, the increase in beta cell function with PIO (64 $\pm$ 3 to 198 $\pm$ 17, $P < .0001$) also was significantly greater than PLAC (66 $\pm$ 4 to 107 $\pm$ 8, $P < .0001$) ($P < .0001$, PIO vs PLAC).

Relationship Between Plasma Insulin & C-peptide Responses to Hyperglycemia and Insulin Sensitivity

At baseline, plot of the Matsuda Index of insulin sensitivity (as well as OGIS, data not shown) vs plasma insulin response to hyperglycemia ($\Delta I_{0-120}/\Delta G_{0-120}$) during OGTT was curvilinear with no separation between PIO and PLAC groups (Figure 1A). At study end or time of diabetes diagnosis, the curve was leftward shifted in IGT

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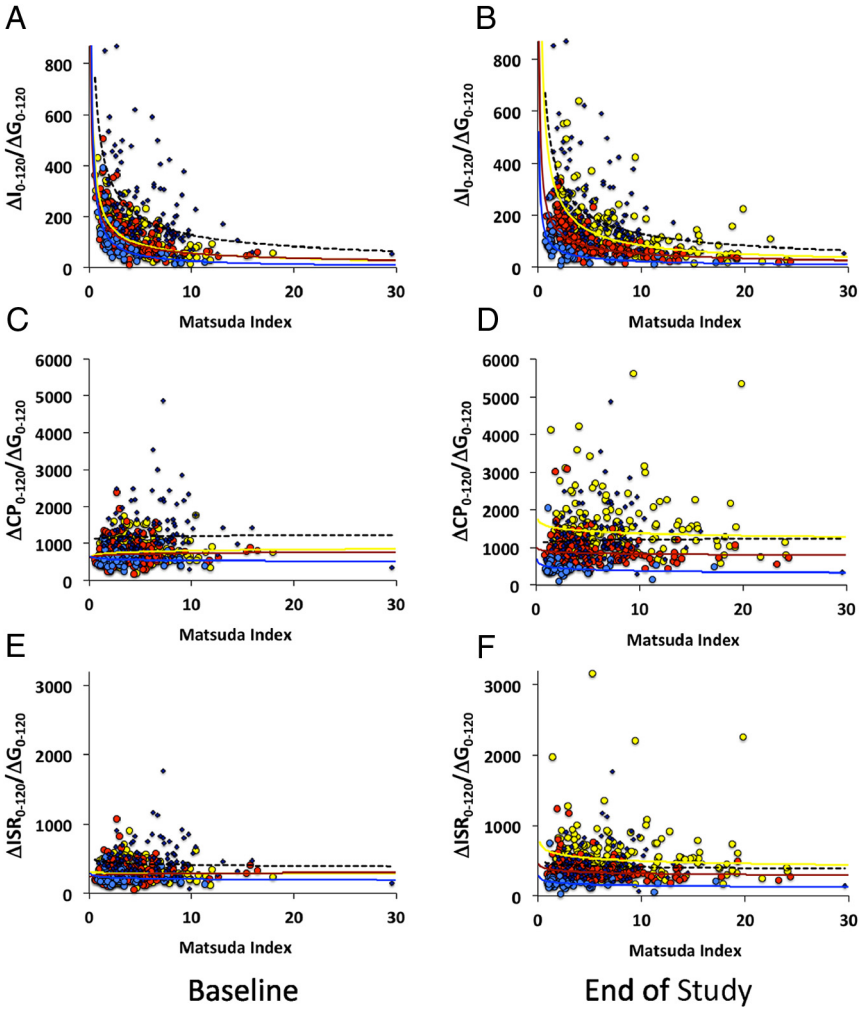

Figure 1. *Top Panels*: Relationship between insulin secretion ($\Delta I_{0-120}/\Delta G_{0-120}$) and Matsuda Index of insulin sensitivity at baseline (A) and end of study (B) for NGT controls (blue diamonds); IGT subjects who converted to NGT (yellow circles); IGT subjects who remained IGT (red circles); IGT subjects who converted to T2DM (light blue circles) (all subjects, n = 441). *Middle Panels*: Relationship between plasma C-peptide response ($\Delta CP_{0-120}/\Delta G_{0-120}$) and Matsuda Index of insulin sensitivity at baseline (C) and study end (D). See legend for Figure 1. *Bottom Panels*: Relationship between insulin secretory rate ($\Delta ISR_{0-120}/\Delta G_{0-120}$) and Matsuda Index of insulin sensitivity at baseline (E) and study end (F). See legend for Figure 1.

subjects who converted to diabetes, unchanged in subjects who remained as IGT, and rightward shifted in subjects who reverted to NGT (Figure 1B). For any level of insulin resistance, the plasma insulin response in subjects who developed T2DM was less than in subjects who remained IGT which, in turn, was less than in subjects who reverted to NGT. However, pioglitazone-treated IGT subjects who reverted to NGT still fell below the "control NGT" group (Figure 1B).

At baseline (Figure 1C and 1E) and study end (Figure 1D and 1F), plot of $\Delta CP_{0-120}/\Delta G_{0-120}$ vs Matsuda Index (and OGIS) and plot of $\Delta ISR_{0-120}/\Delta G_{0-120}$ vs Matsuda Index (and OGIS) failed to demonstrate the characteristic curvilinear relationship observed when $\Delta I_{0-120}/\Delta G_{0-120}$ was related to insulin sensitivity (Figure 1A and 1B). Rather, the curves for all groups (NGT controls, IGT → NGT, IGT → T2DM, IGT → IGT) were flat and horizontal to the X-axis. When ln $\Delta I_{0-120}/\Delta G_{0-120}$ (Figure 2A and 2B) was plotted against the ln Matsuda Index, a strong inverse linear correlation was observed in PIO (r=-0.649 and −0.542 at baseline and at end of study, respectively, $P < .001$) and PLAC (r=-0.674, and r=-0.481 at baseline and at end of study, respectively, $P < .001$) groups. However, when ln $\Delta CP_{0-120}/\Delta G_{0-120}$ (Figure 2C and 2D) and ln $\Delta ISR_{0-120}/\Delta G_{0-120}$ (Figure 2E and 2F) were plotted against ln Matsuda Index, no correlation was observed.

Plasma Glucose & Insulin Concentrations, ISR, and MCR_I in PIO and PLAC (Figure 3)

Pioglitazone significantly reduced the incremental AUC (0–120 minutes) for plasma glucose ($P < .001$) during OGTT and significantly increased the incremental AUC for CP_{0-120} and ISR_{0-120} (both $P < .005$) (Figure 3A and 3D). Nonetheless, the plasma insulin response decreased markedly ($P < .0001$) (Figure 3B). Although not directly measured, this finding only can be explained by a pronounced increase in MCR_I in response to pioglitazone ($P < .001$) (Figure 3C). These results demonstrate that pioglitazone exerts independent effects on insulin secretion and MCR_I, and that the balance between these two effects determines the plasma insulin response.

PLAC treatment had no significant effect on ΔAUC (0–120 minutes) for plasma glucose, insulin, and C-peptide concentrations, ISR or MCRI during OGTT (Figure 3).

Effect of Pioglitazone on Beta Cell Sensitivity to Glucose and Rate Sensitivity

Following pioglitazone, beta cell sensitivity to glucose increased by 63% (173 ± 6 to 271 ± 10 pmol/min ÷ mM, $P < .0001$ vs baseline and $P < .001$ vs placebo), while rate sensitivity increased modestly (1543 ± 135 to 2020 ± 204 pmol/min ÷ mM, $P = .07$ vs baseline and p=ns vs placebo). There was no relationship between ln beta cell glucose

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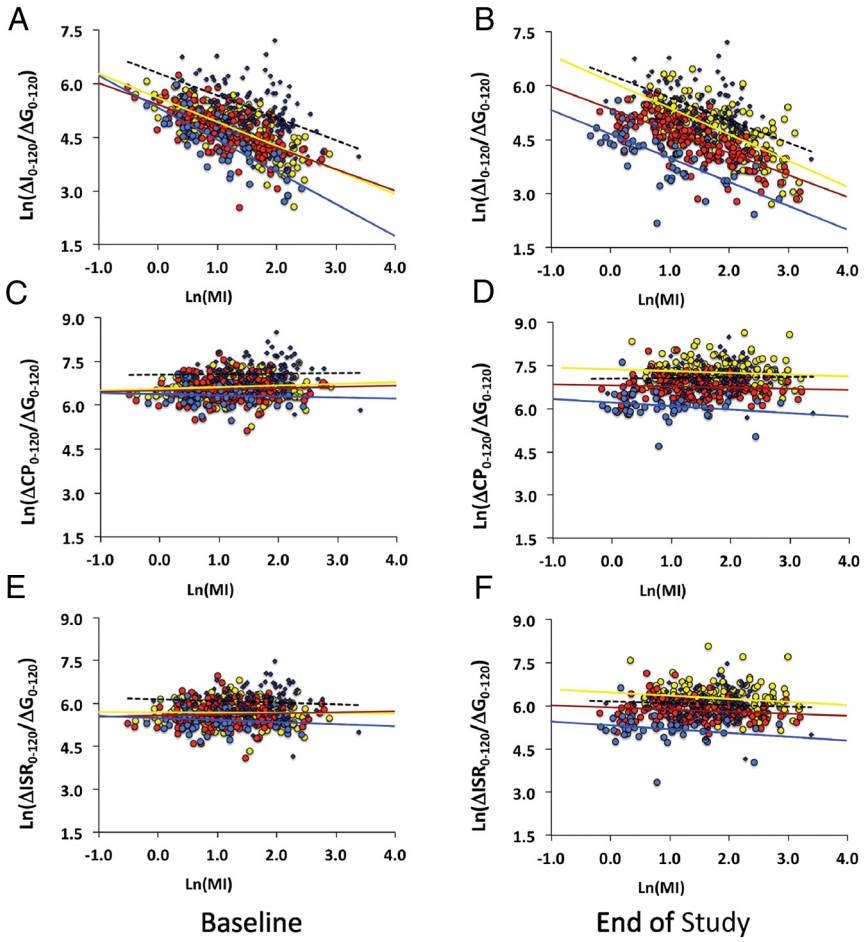

Figure 2. *Top Panels*. Relationship between ln ($\Delta I_{0-120}/\Delta G_{0-120}$) vs ln Matsuda Index at baseline (A) and end of study (B). See Figure 1 legend for color coding. *Middle Panels*. Relationship between ln ($\Delta CP_{0-120}/\Delta G_{0-120}$) vs ln Matsuda Index at baseline (C) and end of study (D). See Figure 1 legend for color coding. *Bottom Panels*. Relationship between ln ($\Delta ISR_{0-120}/\Delta G_{0-120}$) vs ln Matsuda Index at baseline (E) and end of study (F). See Figure 1 legend for color coding.

sensitivity and ln insulin sensitivity (Matsuda Index) at baseline (r = 0.20, P=NS) or following pioglitazone (r = 0.01, P=NS) (Figure 4). Ln of beta cell glucose sensitivity was inversely related to ln mean G_{0-120} both at baseline (r=-0.298, $P < .0001$) and following pioglitazone (r=-0.33, $P < .399$) (Figure 4). Similar relationships were observed in the placebo group (Figure 4).

Factors Associated with Improved Beta Cell Function Following Pioglitazone

The disposition index ($\Delta ISR_{0-120}/\Delta G_{0-120}$ x Matsuda Index [MI]) is determined by: (i) beta cell insulin secretory response (ΔISR_{0-120}), (ii) increment in plasma glucose (ΔG_{0-120}) ie, stimulus for insulin secretion, (iii) insulin resistance (1/MI). In PIO-treated subjects insulin secretory rate increased by ~21% (Figure 3) and ISR related to the increment in plasma glucose rose by 83%, while the Matsuda Index of insulin sensitivity improved by 160%. Thus, all three factors contributed to the improvement in beta cell function ([$\Delta ISR_{0-120}/\Delta G_{0-120}$] x [MI]). Beta cell function did not change significantly in the placebo group.

Plasma insulin concentration is the result of balance between ISR and MCR_I. In PIO subjects the plasma insulin response declined (Figure 3B), yet ISR increased (Figure 3D). This is explained by the marked increase in MCR_I (Figure 3C).

Discussion

The present results demonstrate that the insulin secretion/insulin resistance (disposition) index, beta cell sensitivity to glucose, and, to a lesser extent, rate sensitivity all are important determinants of beta cell function.

The disposition index is a widely used measure of beta cell function (8–10). When the incremental plasma insulin concentration/incremental in plasma glucose concentration following oral (10) and IV (8, 9) glucose administration is plotted against insulin resistance, a curvilinear relationship is observed. Natural log transformation of this plot yields a linear relationship, suggesting that beta cells can read the severity of insulin resistance and appropriately adjust insulin secretion to maintain normal glucose tolerance. However, this curvilinear relationship was developed using the plasma insulin response to a glucose challenge. Because ~50% of secreted insulin is removed by liver (18), use of plasma insulin response to draw inferences about the beta cell function may result in erroneous conclusions. Further, it is well established that the MCR_I is prolonged in insulin resistant states (5, 6, 19, 20), further clouding interpretation of the disposition index.

The plasma insulin response to a glucose challenge, beit oral or IV, represents the sum of the amount of insulin secreted and insulin degraded by all tissues in the body. Thus, the curvilinear relationship between $\Delta I/\Delta G$ vs insulin sensitivity (that becomes linear on ln transformation) indicates that, from the whole body standpoint, the composite of beta cell secretion of insulin plus the MCR_I will

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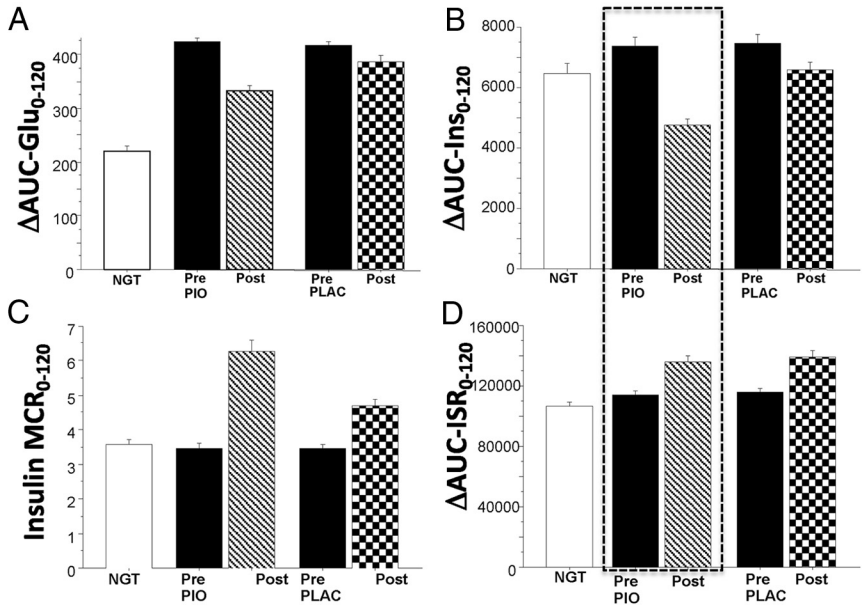

Figure 3. Change (Δ) in plasma glucose (0–120 minutes) AUC (upper left) (A), change (Δ) in plasma insulin (0–120 minutes) AUC (upper right) (B), change (Δ) in MCR of insulin (0–120 minutes) (bottom left) (C), and change (Δ) in insulin secretory rate (ISR) (0–120 minutes) AUC (D) in: (i) normal glucose tolerant (NGT) control subjects, (ii) pioglitazone-treated IGT subjects pre- and postpioglitazone (PIO) treatment, and (iii) placebo-treated subjects pre- and postplacebo (PLAC). The dashed rectangle highlights the opposite changes in plasma insulin response and insulin secretory rate following pioglitazone treatment.

be regulated coordinately to generate a plasma insulin concentration that maintains normal glucose homeostasis. The importance of taking into account the separate effects of insulin secretion and MCR_I when interpreting the disposition index are dramatically illustrated by the present results. Thus, at baseline and study end, plot of insulin sensitivity vs the plasma insulin response to hyperglycemia ($\Delta I_{0-120}/\Delta G_{0-120}$) yielded the typical curvilinear relationship (Figure 1A and 1B). At study end or time of diagnosis of diabetes, the curve was shifted leftward for subjects who converted to diabetes, rightward in subjects who converted to NGT, and unchanged in subjects who remained IGT (Figure 1B), but shape of the curve remained intact. Natural logarithmic transformation yielded a linear relationship with strong correlation between ΔI/ΔG vs insulin sensitivity (Figure 2A and 2B). However, whether at baseline or study end, plot of $\Delta CP_{0-120}/\Delta G_{0-120}$ (Figure 1C and 1D) and $\Delta ISR_{0-120}/\Delta G_{0-120}$ (Figure 1E and 1F) vs insulin sensitivity resulted in complete loss of the curvilinear relationship, and logarithmic transformation yielded a horizontal line parallel to the x-axis (Figure 2). Insulin resistance per se (5, 6), as well as elevated plasma FFA levels, have been shown to inhibit the MCR_I (21). With respect to this, the improvement in insulin sensitivity (Matsuda Index) following pioglitazone was correlated with the increase in MCR_I ($r = 0.63$, $P < .0001$). There was no correlation between the change in plasma FFA concentration and MCR_I was weak ($r = 0.132$, $P + .01$).

These results demonstrate that, at whole body level, there is a reciprocal mechanism that integrates the beta cell response (insulin secretion) with degradation of insulin (MCR_I) to produce a plasma insulin profile that maintains glucose tolerance. Thus, following pioglitazone, insulin secretion is enhanced and the resultant portal hyperinsulinemia leads to more effective suppression of hepatic glucose production (HGP) (22). However, chronic physiologic hyperinsulinemia induces insulin resistance in muscle (23), the tissue responsible for removal of majority of ingested or infused glucose. Further, pioglitazone is a potent insulin sensitizer in muscle (24, 25) and less insulin is required to stimulate muscle glucose uptake. The liver, by enhancing its degradation of insulin, shields peripheral tissues from excessive exposure to hyperinsulinemia, while increased insulin secretion into the portal circulation ensures normal suppression of HGP. Lastly, calculation of the ISR (plasma C-peptide deconvolution) demonstrates the stimulatory effect of pioglitazone on insulin secretion (Figure 3) and is consistent with previous results in T2DM subjects (26).

With pioglitazone treatment, plasma glucose during the OGTT declined and ISR increased, demonstrating increased beta cell glucose sensitivity (Figure 3). An inverse correlation between plasma glucose concentration and beta cell glucose sensitivity has been demonstrated in NGT, IGT, and T2DM subjects (1–3). The present results (Figure 4) are in agreement with these previous results (1–3). Further, these observations are consistent with the glucotoxicity hypothesis, ie, that chronically elevated plasma glucose levels lead to a decline in beta cell sensitivity to glucose (27). Lastly, we failed to observe any relationship between insulin sensitivity and beta cell glucose sensitivity before or after pioglitazone (Figure 4).

There are several limitations of the present study. First, since, following pioglitazone, MCR_I was not measured directly, precise quantitation of change in MCR_I cannot be determined. However, the decrease in plasma insulin response with an increase in plasma C-peptide concentration (and ISR), ie, opposite directional changes, is difficult to explain except by a major change in the MCR_I. Second, it is possible that pioglitazone alters MCR_{CP}. Since direct MCR_{CP} measurement before and after pioglitazone in in-

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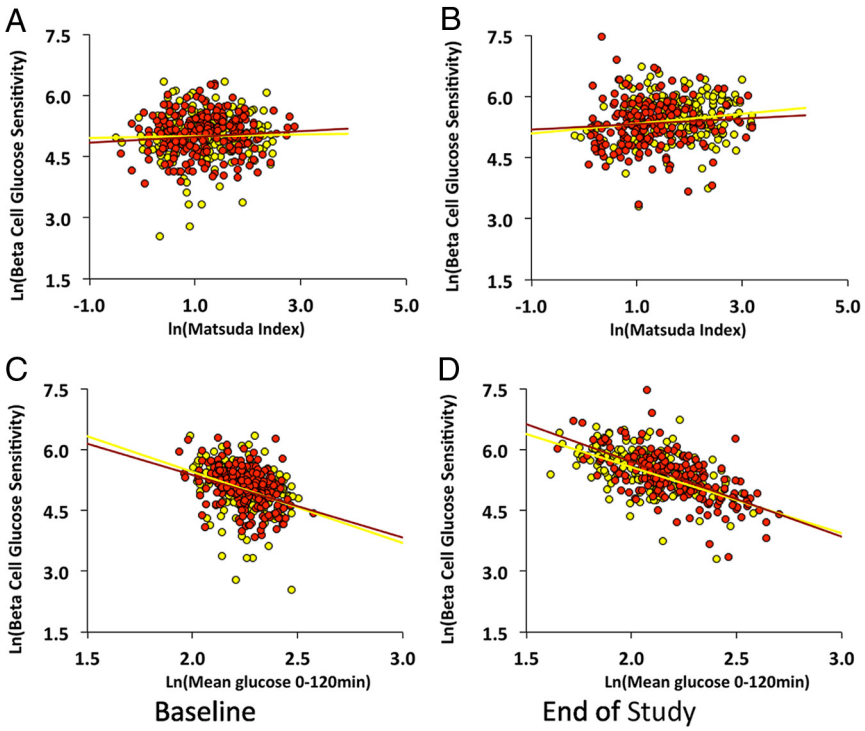

Figure 4. *Top Panels*: Beta cell glucose sensitivity vs Matsuda Index of insulin sensitivity in pioglitazone-treated and placebo-treated subjects at baseline (left) and at end of study (right). No relationship between beta cell glucose sensitivity and insulin sensitivity was observed. Pioglitazone-treated subjects (yellow circles and yellow line); placebo-treated subjects (red circles and red line). *Bottom Panels*: Beta cell glucose sensitivity vs plasma glucose concentration (0–120 minutes) during OGTT in pioglitazone-treated and placebo treated subjects at baseline (left) and end of study (right). Pioglitazone-treated subjects (yellow circles and yellow line); placebo-treated subjects (red circles and red line).

dividual subjects was beyond the scope of present study, this possibility cannot be excluded, although we are unaware of published data to support such an effect. Third, it is possible that failure to observe the characteristic curvilinear relationship between insulin sensitivity and insulin secretion, using plasma C-peptide as opposed to plasma insulin concentration, is unique to intervention with pioglitazone. However, at baseline (prior to pioglitazone therapy) the curvilinear relationship between ISR during OGTT and insulin sensitivity is lost when plasma C-peptide is substituted for plasma insulin (Figure 1C-D). This suggests that the disposition index only displays the characteristic curvilinear relationship when insulin sensitivity is plotted against change in the plasma insulin response, which represents the composite of changes in ISR and MCR_I. Fourth, it could be argued that some of the correlations in the present study are related to the redundancy of glucose and/or insulin in the numerator (insulin secretion/beta cell function) and denominator (Matsuda Index). However, we previously have shown that substitution of insulin-mediated glucose disposal (measured with euglycemic insulin clamp) for Matsuda Index yields identical results (16). Further, substitution of OGIS, which minimizes the redundancy is plasma insulin concentration, yielded identical results to the Matsuda Index.

In summary, our results disclose a novel physiologic control mechanism via which the increase in insulin secretion is opposed by an increase in MCR_I. This results in a plasma insulin concentration that enhances/maintains glucose tolerance in IGT subjects without creating peripheral hyperinsulinemia following treatment with the insulin sensitizing agent pioglitazone. The increase in insulin secretion, in concert with the increase in MCR_I, produces a plasma insulin response which, when related to the underlying severity of insulin resistance, generates the characteristic curvilinear curve described by the disposition index. However, if one replaces the plasma insulin response by ISR or C-peptide, the curvilinear relationship is lost (Figure 1). Therefore, the disposition index should not be construed to reflect the relationship between beta cell function and insulin sensitivity, but rather the integrated response between insulin secretion plus MCR_I vs insulin sensitivity. Lastly, improved beta cell sensitivity to glucose represents an important mechanism via which thiazolidinediones improve beta cell function and is unrelated to changes in insulin sensitivity.

Acknowledgments

We appreciate the enormous and expert help of our nurses and other technical staff without whom this study would not have been possible. We also are indebted to the 602 individuals with impaired glucose tolerance who participated in this study. Dr. DeFronzo's salary is supported by the STVHCS-AMD. The study was supported by an investigator initiated and unrestricted research grant from Takeda Pharmaceuticals North America. Takeda played no role in the study design, data collection/analysis, or manuscript preparation/review. Dr. Ralph DeFronzo is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Ralph DeFronzo wrote the first draft of the manuscript, which then was reviewed and revised by all contributing authors prior to sub-

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mission (DT, AG, MAG). AG performed all of the statistical analyses.

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This work was supported by Dr. DeFronzo reports receiving grants from Amylin, Bristol Myers Squibb, Boehringer-Ingelheim and Takeda, and he serves on the advisory board for Amylin, Takeda, Bristol-Myers Squibb, Astra Zeneca, Novo Nordisk, Janssen, Lexicon, and Boehringer Ingelheim and is a member of the Speakers Bureau for Novo Nordisk, Bristol Myers Squibb, Astra Zeneca, and Janssen. Dr. Tripathy reports receiving consultant fees from HDL Diagnostics Inc. Dr. Gastaldelli reports receiving grant support from Amylin and Roche, and is a consultant for Roche. Dr. Abdul-Ghani reports no conflict of interest.

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