Significant correlation between BMI/BW with insulin resistance by McAuley, HOMA and QUICKI indices after 3 months of pioglitazone in diabetic population

Lukshmy M. Hettihewa*^ , Lalith P. Dharmasiri*, Chamil D. Ariyaratne*, Sudheera S. Jayasinghe*,
Thilak P. Weerarathna#, Imendra G. Kotapola§

*Department of Pharmacology, Faculty of Medicine, University of Ruhuna, #Department of Medicine, Faculty of Medicine, University of Ruhuna, ^ Molecular Science and Biomedical Unit, University of Ruhuna, §Department of Physiology, Faculty of Medicine, University of Ruhuna, Matara, Sri Lanka

We investigated the kinetic effect of pioglitazone (PIO) on changes of body mass index (BMI), body weight (BW), lipids and Insulin Resistance (IR) in patients with type 2 diabetes mellitus. **MATERIALS AND METHODS:** Twenty-four patients of type 2 diabetes with fasting blood glucose (FBG) > 7 mmol/l (126 mg/dl) were randomly selected on one (if the patient is symptomatic) or two occasions (if the patient is asymptomatic). Patients were treated with 15 mg of PIO daily and investigated for BW, BMI, FBG, fasting insulin (FI) and triglycerides (TG). IR was calculated by McAuley (McA), homeostasis model assessment (HOMA) and QUICKI indices at baseline and repeated after 3 months. **RESULTS:** Mean age was 45.83 ± 1.82. There was no significant change in BMI (23.95 ± 0.82 to 24.08 ± 0.85 kg/m²), BW (58.78 ± 2.00 to 59.08 ± 2.00 kg) and TG (1.82 ± 0.08 to 1.7 ± 0.05 mmol/l) after 3 months of therapy (mean ± SE, $P > 0.05$). There was a significant reduction in FI (37.58 ± 6.09 to 15.37 ± 3.28 mu/l) and IR by McA (4.68 ± 0.25 to 6.18 ± 0.31) with PIO treatment ($P < 0.001$). Reduction of IR by HOMA and QUICKI indices was also significant (17.51 ± 3.36 to 5.41 ± 1.57 and 0.27 ± 0.0 to 0.34 ± 0.01, $P > 0.001$, respectively) after therapy. There was a reduction of TG levels in our participants, but it is not statistically significant. No significant correlation was observed between BMI or BW with any of the IR indices before the therapy, but significant correlation developed later between BMI with FI ($r = 0.4$, $P > 0.05$) and McA ($r = 0.48$, $P = 0.02$) after 3 months. The reduction of hepatic insulin sensitivity index (hepatic ISI) was significant and found a substantial positive association between hepatic ISI with BMI after the PIO therapy. Correlation between hepatic ISI with HOMA, QUICKI and McA was also significant but no significant correlation was detected between TG, HOMA or QUICKI with BMI or BW before or after therapy in our study cohort. There was an improvement of both hepatic and peripheral insulin sensitivity with 3 months of PIO. In addition, significant correlations between BMI vs. McA and FI but not with HOMA or QUICKI. **CONCLUSIONS:** We propose that reduction of IR is related to the TG metabolic pathway possibly by clearance of VLDL TGs and activation of lipoprotein lipase in plasma by PIO.

KEY WORDS: Fasting insulin and type 2 diabetes, HOMA, insulin resistance, McAuley, QUICKI

Correspondence to Dr. L.M. Hettihewa, Senior Lecturer, Head, Molecular science and Biomedical Unit and Department of Pharmacology, Faculty of Medicine, University of Ruhuna, Matara, Sri Lanka. E-mail: lukshmy@yahoo.com or menik@med.ruh.ac.lk

Introduction

Incidence of type 2 diabetes is reaching epidemic proportions globally, particularly in south Asian region. Type 2 diabetes is characterized by insulin resistance (IR) and relative insulin deficiency, hence early identification is important for the management strategies of DM.[1-3] The euglycemic insulin clamp and the intravenous glucose tolerance tests are gold standard methods for

measurement of insulin resistance in research, but they are cumbersome in clinical practice and are difficult to perform in population-based research studies. Therefore, indirect indices: McAuley (McA), homeostasis model assessment (HOMA) and QUICKI were used for the assessment of IR in our study.[3-5]

The accumulation of visceral fat is particularly assumed to play an important role in the etiology of IR notably by the overexposure of the liver to free fatty acids,[6] which results in insulin resistance and hyperinsulinemia.[1,2,7] Peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists, improve insulin sensitivity and lipemia partly through enhancing adipose tissue proliferation and capacity for lipid retention.[7,8]

Objectives

Our objective was to determine the effect of pioglitazone (PIO) therapy on kinetic changes of IR and obesity in adult type 2 diabetic population and correlate of IR with obesity, body mass index (BMI), body weight (BW) and triglycerides (TGs).

Materials and Methods

The protocol for the present study was approved by ethical committee of Faculty of medicine, University of Ruhuna. Twenty-four patients of type 2 diabetes with fasting blood glucose (FBG) > 7 mmol/l (126 mg/dl) were selected if they were symptomatic or on two occasions when they were asymptomatic. All patients were given verbal and written information about the study prior to providing written consent and invited for verbal and written feedback of individual results at the end of the study. Clinical history including age, sex, drugs, smoking, alcohol consumption level of physical exercise, previous history and family history of diabetes, dyslipidemia, coronary artery disease and peripheral vascular disease were obtained. Exclusion criteria were: age outside the range of 30-65 years, hypothyroidism, liver, kidney or heart failure and neoplasm. Patients were given 15 mg of PIO daily and investigations were repeated at monthly intervals for 3 months. Height and weight were determined with the subjects wearing light clothing without shoes. Each participant's weight and height were recorded and BMI was calculated using height (m) and weight (kg). After 12 h of overnight fasting, blood samples were collected and deposited in dry tubes. The plasma was separated immediately using centrifugation at 4,000 rpm for a period of 10 min. FBG was assessed by absorbance method (diagnostica - Merck). Fasting insulin (FI) was

measured by ELISA (diagnostic - automation). TG levels were measured enzymatically by colorimetric tests (LABKIT). McA described a method for measurement of insulin resistance, which correlates with estimates of IR measured by the euglycemic clamp technique.[4] It was calculated as follows.

McA = exp [2.63 − 0.28 (insulin in mu/l) − 0.31 (TGs in mmol/l)]

HOMA = insulin (mU/m)×[glucose (mmol/l)/22.5]

$$QUICKI = \frac{1}{(\log \text{insulin} + \log \text{glycaemia mg/dL})}$$

Subjects with McA ≤ 5.8[4] and FI ≥ 12 mu/l[4,9-11] have been considered as insulin resistant in diabetic population. Patients were considered as insulin resistant when McA ≤ 5.8, HOMA ≥ 2.6 and QUICKI ≤ 0.33.[4] Hepatic insulin sensitivity index (hepatic ISI) was calculated from the estimated FPG and FPI as follows.[7]

$$\frac{k}{FPG \times FPI}$$

This equation[7] is mathematically equivalent to the reduced formula of the HOMA, where $k = 22.5 \times 18$ and the hepatic ISI correlates closely with that measured directly with tritiated glucose.[7,12] The product of basal hepatic glucose production (measured with tritiated glucose) and the FI concentration provides a direct measure of hepatic IR under postabsorptive conditions, whereas the inverse provides a measure of hepatic insulin sensitivity.[7,12]

Statistical analysis

For the descriptive statistics after having checked the normality of the variables using the Kolmogorov-Smirnov test, the usual central and dispersion methods were used: average, SD and 95% CI. Power and sample size calculations were carried out based on the results of the current study, comparing changes in FI, IR, BW and BMI in 3 months of PIO, allowing declaration of a difference before and after in same treatment group, at a significance level $\alpha = 0.05$, with power of 80%. The statistical significance of differences between the mean values were evaluated using the paired Student's *t*-test in the case of normal distribution of data sets and using the Kolmogorov-Smirnov test when at least in one of the data sets, the normal distribution was excluded. Correlation between two variables was studied with the Spearman rank-order. All statistical analyses were performed using Microcal origin 4.1(2005) and Microsoft Excel whenever applicable.

Results

Baseline characteristics and changes in insulin resistance in our study group

The study cohort included 24 patients with mean age of 45.83 ± 1.82. Female to male ratio was 7:5. Table 1 shows the significant difference in mean values of FI, McA, HOMA and QUICKI indices after 3 months of PIO. Though there was a reduction of TG, it was not statistically significant. Overall, these data support the

Table 1: Indices of insulin resistance

Basic characteristics	Baseline (mean ± SEM)	Three months (mean ± SEM)	P value (baseline Vs. 3 months)
Age	45.83 ± 1.82	-	-
BW (kg)	58.78 ± 2	59.08 ± 2	$P = 0.42$
BMI (kg/m²)	23.95 ± 0.82	24.08 ± 0.85	$P = 0.37$
TG (mmol/l)	1.82 ± 0.08	1.70 ± 0.05	$P < 0.001*$
FI (mu/l)	37.58 ± 6.09	16.58 ± 3.62	$P < 0.001*$
McAuley	4.84 ± 0.27	6.26 ± 0.28	$P < 0.001*$
HOMA	17.50 ± 3.36	5.40 ± 1.57	$P < 0.001*$
QUICKI	0.27 ± 0.00	0.34 ± 0.01	$P < 0.001*$

Characteristics and biochemical parameters after 3 months of PIO therapy. Values are given M±SE

conclusion that PIO treatment significantly increased insulin sensitivity in these patients.

Statistically significant correlation between BMI with McA and FI after 3 months of PIO therapy; Our results show that there is no significant difference in changes of BMI, TG and BW after 3 months of PIO therapy [Table 1]. In contrast, there was a significant reduction in FI, IR by McA, HOMA and QUICKI indices at the end of treatment [$P < 0.001$, Table 1]. There was no significant correlation between BMI and BW with McA, HOMA, QUICKI or FI before the therapy ($P > 0.05$). But there was significant correlation between BMI with FI ($r = 0.4$, $P > 0.05$) and McA ($r = 0.48$, $P = 0.02$) after 3 months of PIO therapy [Figure 1]. There was no significant correlation of BW with McA, HOMA and QUICKI. There was no significant correlation of FI after PIO therapy (data not shown).

Correlation of BMI with HOMA and QUICKI after 3 months of PIO

On observing significant correlation of BMI with McA or FI, we extended our study to evaluate correlation with others indirect indices as well. We found that the difference in IR by HOMA and QUICKI after PIO therapy
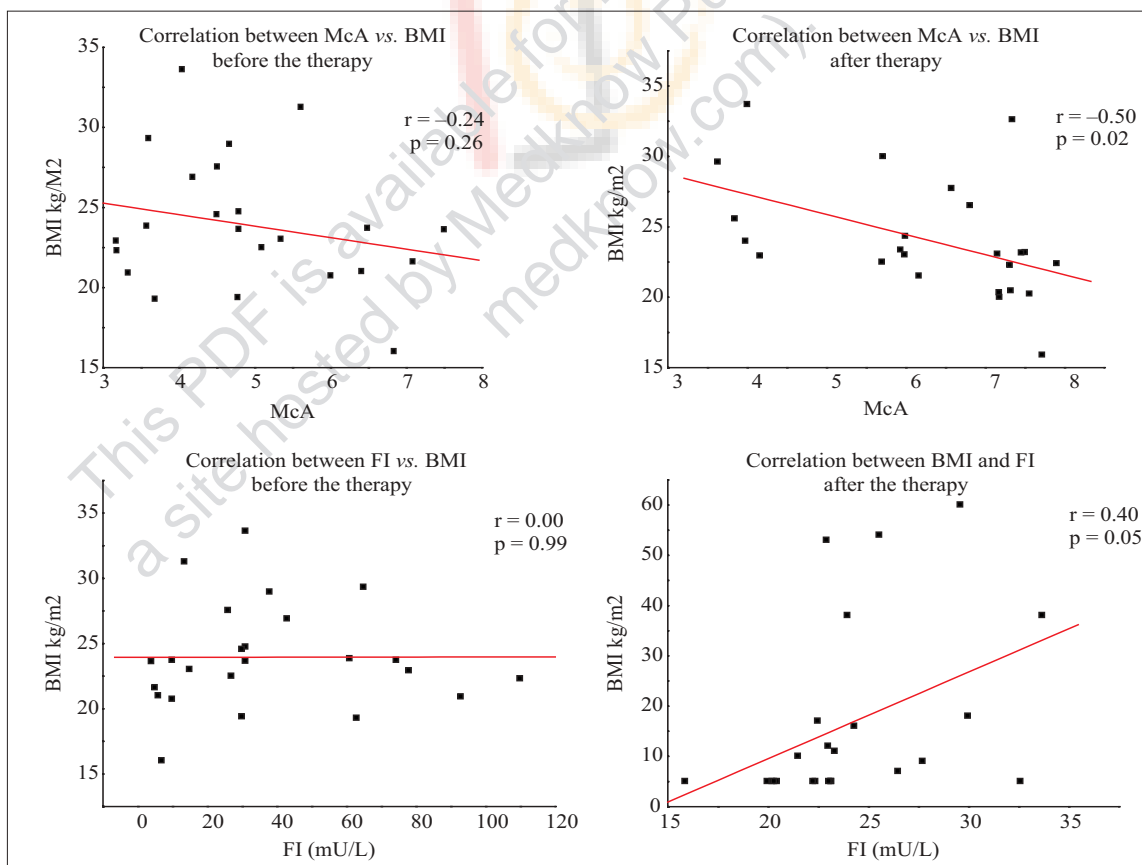

Figure 1: Correlation between changes in BW, BMI with mean FI and McA with the 15 mg of PIO treatment in patients with type 2 diabetes. The Pearson's correlation coefficient and associated *P*-value are shown

was also statistically significant; this further confirmed the finding of reduction in IR in our participants with PIO therapy. We also investigated to see any correlation between HOMA, QUICKI with BMI or BW. Although there was an improvement of correlation between HOMA and QUIKI with either BMI or BW, it was not statistically significant [Table 2].

Considering significant correlation of BMI with McA but not with HOMA or QUICKI, we considered the possibility of involvement of TG metabolism in the improvement of IR, despite increment of BMI. Therefore, we further investigated to see any correlation with TG in our study cohort.

Correlation coefficient was calculated between TG with BMI, BW, FI, McA, HOMA and QUICKI. Although there was clinical reduction (but not statistically significant) in TG levels, we could not find any significant correlation between TG with any of the above parameters in our study group.

Statistically significant correlation of BMI with hepatic ISI after 3 months of PIO therapy

We further extended our study to see any effects of PIO on hepatic ISI in our study cohort. The reduction of hepatic ISI with PIO therapy was statistically significant [Figure 2]. There was a significant reduction in mean hepatic ISI after 3 months of PIO in our patients (0.15 ± 0.03 to 0.43 ± 0.05, $P < 0.05$). Pearson's correlation coefficient was used to investigate the correlations. There was a substantial positive association between hepatic ISI with BMI [Figure 3] after the PIO therapy. Correlation between hepatic ISI with HOMA, QUICKI and McA was also significant ($P < 0.001$, data are not shown).

Discussion

In the light of well-documented relationship between obesity and IR, the treatment effects of PIO appear to be paradoxical because their insulin-sensitizing effects occur in the presence of an increase in BW and whole-body adiposity. Therefore, the goal of this study was to identify the possible mechanism of this phenomenon.

Recent studies have demonstrated that the PIO-induced weight gain is associated with an increase in subcutaneous adipose tissue and a concomitant decrease in visceral fat content.[7] Increase in BW in our study, despite the improved insulin sensitivity can be explained by this
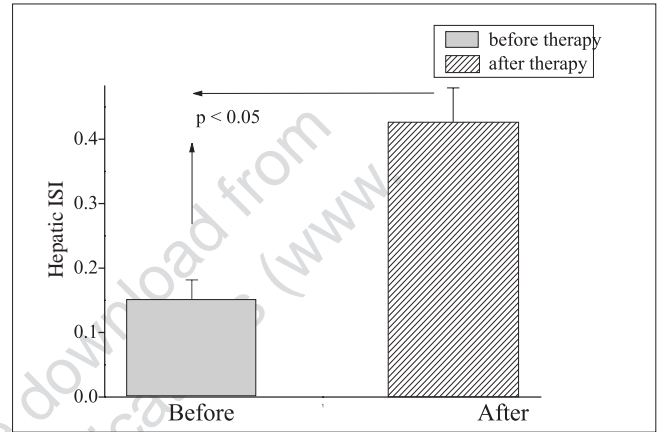

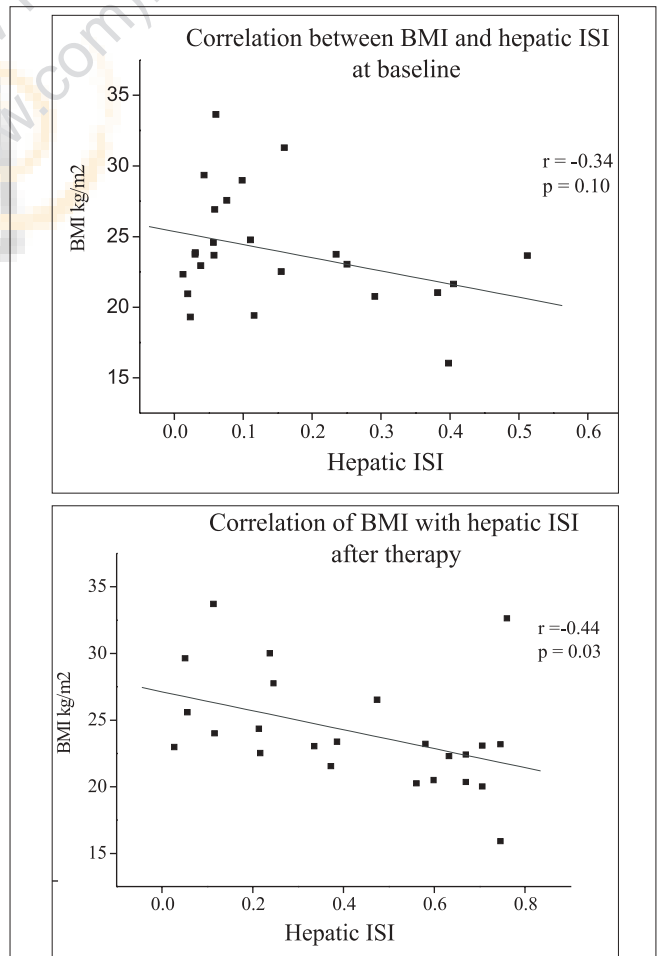**Figure 2:** Difference in mean values of hepatic ISI index in our study cohort ($P < 0.05$)

Figure 3: Correlation of BMI and hepatic insulin sensitivity index before and after PIO therapy

Table 2: Correlation of HOMA and QUICKI with BMI and body weight

Parameters	Before the therapy	After the therapy
BMI *vs.* HOMA	$r = -0.02$, $P = 0.9$	$r = 0.22$, $P = 0.3$
BMI *vs.* QUICKI	$r = -0.23$, $P = 0.28$	$r = -0.37$, $P = 0.07$
BW *vs.* HOMA	$r = -0.01$, $P = 1.0$	$r = 0.13$, $P = 0.54$
BW *vs.* QUICKI	$r = -0.17$, $P = 0.4$	$r = -0.30$, $P = 0.14$

fat redistribution due to remodeling of abdominal fat tissue.[7] Another previous study shows that there was a dose-dependent increase in BW and BMI after 24 weeks in the PIO-treated groups.[10] The seemingly paradoxical relationship between weight gain and improved glucose homeostasis/insulin sensitivity most likely is explained by the basic cellular mechanism of action of the thiazolidinediones, which exert their effects through the PPAR-γ. PPAR-γ activation also induces key enzymes involved in lipogenesis in newly formed adipocytes.[2]

Our patients, who were insulin resistant, have become insulin sensitive after 3 months of PIO. In addition, there was significant correlation of BMI with McA as well as with FI levels after PIO therapy. Significant correlations between BMI *vs.* McA and FI but not with HOMA or QUICKI indicate that the possible mechanism of IR reduction by PIO is by interference with TG metabolism. Our results are supported by previous results, showing that PPAR-γ agonists improve insulin sensitivity mainly through adipose tissue remodeling, increased capacity for lipid uptake or retention and altered adipocytokine secretion pattern.[13,14] Kazunori *et al.,* also show that PIO reduces TG by decreasing secretion of both VLDL TGs and VLDL apoB via lipoprotein lipase activation, by improving adipose tissue sensitivity to insulin and also reduction of plasma insulin and hepatic lipogenesis.[14] They did not observe any significant difference in total cholesterol and LDL levels with PIO.[14] Increased visceral fat is associated with IR [14] and reduction in visceral fat would be expected to lead to an enhancement in insulin sensitivity.[15] Because thiazolidinedione treatment consistently reduces plasma free fatty acid levels,[15] this may provide another explanation for the improvement in insulin sensitivity despite weight gain. Considering above reports, our data suggest that there may be a common metabolic pathway for both reduction of IR and plasma TG levels possible via increase of lipoprotein lipase activity.

Insignificant correlation between BMI with HOMA or QUICKI can be due to exclusion of TG levels in HOMA and QUICKI equations. Further, McA was identified as the method of detecting IR when confronted with minimal model approximation of the metabolism of glucose (MMAMG) with very high sensitivity and specificity values.[4,5] In contrast, another study shows evidence in all participants (black and white adolescent girls), during 10 years, changes in BMI were positively correlated with changes in insulin ($r = 0.26$, $P < 0.0001$) as well as in HOMA insulin resistance ($r = 0.24$, $P < 0.0001$).[11] This finding concurs with our results to explain development of correlation between BMI with IR indices after the PIO therapy. Although we studied patients with 15 mg of PIO, we would not comment on the effects of high doses of 30 or 45 mg of PIO on correlation of IR WIth BMI or hepatic ISI. But Yoshinori *et al.,* says that PIO improves glycemic control through the dose-dependent enhancement of β-cell function and improved whole-body and hepatic insulin sensitivity.[14] We also found that PIO treatment causes significant increment of hepatic ISI in diabetic patients and it has significant correlations with BMI, McA, HOMA and QUICKI indices. Our results are compatible with Yoshinori Miyazaki *et al.,* showing that hepatic ISI increased in the 15-, 30- and 45-mg/day PIO groups[13] ($P < 0.05$-0.01). Because basal hepatic glucose production is closely correlated with FBS, the inverse of the product of FBS and FI provides an index of hepatic insulin sensitivity.[16] It can be concluded that PIO decreases FBS levels through improvements in hepatic/whole-body insulin sensitivity and in β-cell function in type 2 diabetic patients.

Acknowledgments

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