Pioglitazone and metformin are equally effective in reduction of chemerin in patients with type 2 diabetes

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Keywords
Chemerin, Metformin, Pioglitazone

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J Diabetes Invest 2014; 5: 327–332
doi: 10.1111/jdi.12157

ABSTRACT
Aims/Introduction: Chemerin, a novel member of the family of adipocytokines, has been shown to be associated with insulin resistance, as well as micro- and macrovascular complications of diabetes. We investigated the effects of pioglitazone and metformin, two commonly prescribed antidiabetic agents, on the reduction of serum chemerin concentrations.

Materials and Methods: In an open-labeled randomized clinical trial, 81 patients with newly diagnosed type 2 diabetes who were not taking antidiabetic medications were recruited. Patients were randomly assigned to either pioglitazone 30 mg daily or metformin 1,000 mg daily. Serum chemerin concentrations, indices of glycemic control, serum lipids concentrations, and anthropometric parameters were measured at baseline and after 3 months.

Results: Pioglitazone and metformin did not alter waist circumference, weight or body mass index after 3 months. In contrast, all indices of glycemia and insulin resistance improved substantially after 3 months' treatment with both medications ($P<0.01$ in all analyses). There was a significant decrease in chemerin concentrations after 3 months in the pioglitazone group ($P=0.008$). Similarly, metformin caused a significant drop in chemerin concentrations at week 12 ($P=0.015$). When compared, metformin and pioglitazone proved to be equally effective in the alleviation of chemerin concentrations ($P=0.895$, effect size: 0.1%).

Conclusions: The present findings show that pioglitazone and metformin have comparable efficacy on serum chemerin concentrations, albeit through different mechanisms. Future studies need to focus on the clinical implications of lowered chemerin concentration on improvement of diabetes complications. This trial was registered with ClinicalTrials.gov (no. NCT01593371).

INTRODUCTION
A large body of evidence that has accumulated over the past decade has shown beyond doubt that adipose tissue plays a key role in inflammatory status related to overnutrition, sedentary lifestyle, overweight, and obesity through secretion of a wide range of hormones and adipokines1–3. Besides the production of numerous adipokines that act at both a local and systemic level, adipose tissue is involved in expression of a variety of receptors allowing a dynamic interrelationship between adipocytes and the neurohormonal system. By this and other proposed mechanisms, adipocytes and their products, adipokines; contribute to the development and progression of metabolic abnormalities associated with obesity, insulin resistance, hypertension, and atherosclerosis4–3.

Chemerin is a recently discovered adipokine that acts as a ligand for G protein-coupled receptors4. Chemerin through its own receptor, CMKLR1, regulates adipocyte differentiation and adipogenesis5. Recent studies have found a link between

Received 13 May 2013; revised 24 July 2013; accepted 8 August 2013

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elevated concentrations of circulating chemerin and insulin resistance in both type 1 and type 2 diabetic patients.6,7 More importantly, chemerin has also been linked to long-term micro- and macrovascular complications of diabetes, including diabetic nephropathy, coronary and carotid artery disease.8–10

In this regard, some studies have suggested that antidiabetic agents, including pioglitazone and metformin, might exert their beneficial effects on insulin sensitivity partly through alleviation of chemerin messenger ribonucleic acid expression and protein production.11–13 Our current knowledge regarding the efficacy of these widely used antidiabetic medications is largely confined to experimental models involving rat models; studies comprising of human populations with diabetes are currently lacking. Therefore, in a randomized clinical trial setting, we aimed to examine the impact of treatment with pioglitazone and metformin on the regulation of serum chemerin concentrations in a sample of newly diagnosed, medication naïve, type 2 diabetes patients.

METHODS

Recruitment of Participants and Design Overview

In this single center, open label, randomized, parallel group clinical trial, patients with newly diagnosed type 2 diabetes not currently receiving antihyperglycemic medications were recruited. Between July and October 2011, a total of 98 patients from the diabetes clinic of Vali-Asr Hospital (Tehran, Iran) were enrolled. Participants were considered eligible if they: (i) met the recent American Diabetes Association (ADA) criteria for diagnosis of type 2 diabetes mellitus;14 (ii) had not been taking oral antihyperglycemic medications for treatment of diabetes or other hyperglycemia-associated conditions (e.g., polycystic ovary syndrome); (iii) did not have a history or symptoms suggestive of coronary artery disease, cerebrovascular disease, liver or renal disease; (iv) had not been taking corticosteroids; and (v) had not been consuming alcoholic beverages regularly. By using software for random numbers generation, participants were allocated to either pioglitazone or metformin arms of the trial. Initially, 98 patients were recruited (55 and 43 patients in the pioglitazone and metformin groups, respectively). The metformin group received 500 mg metformin tablets two times daily; whereas 15 mg pioglitazone tablets twice daily were prescribed for the participants in the pioglitazone arm. Participants were informed regarding the possible side-effects of the medications prescribed, and were instructed to return if they experienced any significant discomfort. A follow-up visit was scheduled 12 weeks after the initiation of antihyperglycemic medication. The trial was carried out in accordance with the guidelines laid down in the Declaration of Helsinki. The protocol of the study was approved by the Tehran University of Medical Sciences board of ethics. Written informed consent was obtained from all participants before enrolment, and was formally recorded by the interviewing physician. The present trial is registered with ClinicalTrials.gov (registration number: NCT01593371); additional information regarding the trial protocol can be found on the website.

Assessment

At the beginning of the study, patients were interviewed using a predesigned questionnaire. After detailed history taking, a physical examination was carried out by the same physician, and the following clinical and anthropometric measurements were carried out: two readings of systolic and diastolic blood pressure 5 min apart were obtained using a standard mercury sphygmomanometer (Big Ben adults; Riester, Jungingen, Germany), and the average was recorded. Using a digital scale (GS49; Beurer, Ulm, Germany) weight was determined and recorded to the nearest 0.1 kg. Height was measured on a standard height board, and was recorded to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Using an inflexible tape, waist circumference was measured at the mid-way between the costal margin and pelvic brim, and was recorded with 0.1-cm precision. Hip circumference was measured at the point where the hip is the widest, and was recorded with an accuracy of 0.1 cm. Similar measurements were repeated at the follow-up visit.

Laboratory Evaluations

At baseline and follow-up visits, 10 mL of venous blood was obtained after 12 h of fasting. Fasting plasma glucose (FPG) was measured using the glucose oxidize method. The percentage of glycated hemoglobin (HbA1c) was determined using high-performance liquid chromatography (HPLC). Fasting serum insulin concentrations were assessed by chemiluminescent immunoassay technique (Immunootech, Prague, Czech Republic). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin (IU) multiplied by FPG (mg/dL), divided by 405 according to the formula provided by Matthews et al.15 Serum concentrations of total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c) and triglycerides were measured by enzymatic colorimetric assays (Pars Azmun, Karaj, Iran). Serum chemerin concentrations were determined using the enzyme-linked immunosorbent assay method (Merck Millipore, Billerica, MA, USA) with an inter- and intra-assay coefficient of variation (CV) of 4–6 and 5%, respectively.

Statistical Analysis

For statistical analyses carried out herein, statistical package for social sciences (SPSS) version 19.0 for windows (IBM Corporation, New York, NY, USA) was used. In all statistical tests, a P-value of <0.05 was considered significant. The sex of the participants within each trial arm is presented as female-to-male ratio. Sex distribution between the two groups was compared using the chi-squared-test. Continuous variables are shown as mean ± standard deviation. Baseline clinical and demographic characteristics of trial participants were compared using inde-
pended t-test. Mean changes in indices of obesity and glycemia, along with changes in chemerin concentrations within each trial arm were calculated and assessed using paired t-test. The efficacy of two interventions on chemerin concentrations were compared using analysis of covariance (ANCOVA). In baseline univariate ANCOVA, chemerin levels at week 12 entered the model as the dependent variable, whereas baseline values were treated as covariates. Additionally, a multivariate model was computed to account for the effect of possible confounding variables. For baseline and multivariate models, effect size was also determined using. Based on Cohen’s recommendations regarding effect size, an eta squared of approximately 1% indicates a small effect, whereas values of approximately 6 and 13.8% represent medium and large effect sizes, respectively.

RESULTS
In the current study, data from the clinical trial ‘Comparison of Metformin and Pioglitazone Effects on Adipokines Concentrations in Newly Diagnosed Type 2 Diabetes Patients: NCT01593371’ was used. This trial originally included 98 participants (55 participants in the pioglitazone arm and 43 patients in the metformin arm). Four patients from the pioglitazone arm and two from the metformin arm did not return for the week 12 visit, and were not included. Another patient receiving pioglitazone did not agree to a second blood draw, and was also excluded. After centrifugation, all serum samples were transferred to a hospital laboratory, and were kept in a −70°C freezer until required. At the time of measurement of serum chemerin concentrations, all 91 frozen specimens underwent quality assessment by the laboratory coordinator, and inadequate samples (n = 10) were not used for further evaluation. A total of 81 samples (42 from pioglitazone patients and 39 from metformin patients) passed the quality check, and thereby were included in the analysis.

Baseline characteristics of 81 patients enrolled in the present trial are shown in Table 1. Women comprised 67 and 49% of the trial participants in the pioglitazone and metformin groups, respectively. The age of the participants ranged from 40 to 69 years, and was comparable between the two groups. Obesity indices including waist circumference, hip circumference, weight and BMI did not differ significantly between trial arms. Systolic blood pressure of the pioglitazone group patients was slightly higher; however, this difference did not reach statistical significance (mean difference 5.12 mmHg, 95% confidence interval −10.35 to 0.10). Diastolic blood pressure was similar between groups. Indices of glycemia including FPG, fasting insulin, HOMA-IR and HbA1c were also comparable in both groups (Table 1). Except for triglycerides, serum lipids concentrations were not significantly different between the two groups. Participants in the metformin arm tended to have higher concentrations of serum triglycerides (P = 0.045). Finally, similar concentrations of baseline chemerin were observed in the pioglitazone and metformin groups. Furthermore, baseline chemerin concentrations did not differ significantly between the two sexes (106.92 ± 23.05 in females and 98.46 ± 18.99 in males, P = 0.110).

Within group changes in baseline variables and in chemerin concentrations are presented in Table 2. Pioglitazone did not alter waist circumference, weight or BMI after 3 months. In contrast, all indices of glycemia (including FPG, fasting insulin, HOMA-IR, HbA1c) improved substantially after 3 months’ treatment with pioglitazone (P < 0.01 in all cases). There was a significant decrease in chemerin concentrations after 3 months in the pioglitazone group (P = 0.008). Regarding metformin, although no significant changes in obesity indices were detectable, all glycemic indices improved significantly (P < 0.001 in all cases). Similar to pioglitazone, metformin caused a significant drop in chemerin concentrations at week 12 (P = 0.015).

Comparative efficacy of each treatment in reducing chemerin concentrations was tested using uni- and multivariate ANCOVA models (Table 3). The univariate model showed that both medications are equally effective in reducing chemerin concentrations (P = 0.895, F = 0.064; effect size: 0.1%). A similar finding was replicated after controlling for the confounding variables of age, systolic blood pressure, HOMA-IR, HbA1c, total choles-

### Table 1 | Baseline characteristics of the study participants

|                     | Pioglitazone (n = 42) | Metformin (n = 39) | P-value |
|---------------------|-----------------------|--------------------|---------|
| Sex (female/male)   | 28/14                 | 19/20              | 0.11    |
| Age (years)         | 51.25 ± 7.84          | 50.03 ± 9.13       | 0.891   |
| Waist circumference (cm) | 97.39 ± 10.19        | 94.12 ± 10.51      | 0.163   |
| Hip circumference (cm) | 107.37 ± 8.69        | 106.92 ± 11.19     | 0.841   |
| Weight (kg)         | 77.01 ± 13.61         | 74.34 ± 12.81      | 0.368   |
| BMI (kg/m²)         | 30.12 ± 4.47          | 28.81 ± 4.45       | 0.193   |
| Systolic blood pressure (mmHg) | 121.5 ± 9.5      | 116.3 ± 13.6       | 0.055   |
| Diastolic blood pressure (mmHg) | 77.6 ± 7.2        | 76.6 ± 6.2         | 0.508   |
| Fasting plasma glucose (mmol/L) | 9.40 ± 2.09       | 9.92 ± 2.94        | 0.366   |
| Serum insulin (pmol/L) | 76.33 ± 34.52        | 84.94 ± 35.91      | 0.275   |
| HOMA-IR             | 4.42 ± 2.04           | 5.37 ± 2.84        | 0.091   |
| HbA1c (mmol/mol)    | 65 ± 16.5             | 66 ± 12.8          | 0.641   |
| Total cholesterol (mmol/L) | 5.09 ± 0.99       | 5.06 ± 1.00        | 0.890   |
| LDL-c (mmol/L)      | 3.03 ± 0.81           | 3.11 ± 0.75        | 0.662   |
| HDL-c (mmol/L)      | 1.30 ± 0.35           | 1.20 ± 0.25        | 0.697   |
| Triglycerides (mmol/L) | 1.72 ± 1.00         | 2.20 ± 1.11        | 0.045   |
| Chemerin (ng/mL)    | 107.04 ± 21.01        | 101.30 ± 22.96     | 0.247   |

HbA1c, glycated hemoglobin; LDL-c, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; HDL-c, high-density lipoprotein cholesterol.
terol, HDL-C, triglycerides and waist circumference ($P = 0.870, F = 0.040; \text{effect size: } 0.1\%$).

**DISCUSSION**

Chemerin, a novel member of the adipokine family, is an important modulator of human immune defense against exogenous pathogens, inflammation, and glucose and lipid metabolism\textsuperscript{16,17}. Also known as ‘retinoic acid receptor responder protein 2’ (RARRES2), ‘tazarotene-induced gene 2 protein’ (TIG2) or ‘RAR-responsive protein TIG2’, chemerin is an 18-kDa preprotein activated through proteolytic cleavage of its C-terminal portion; the final product is the 16 kDa bioactive form\textsuperscript{18}. Chemerin and its cognate receptor ‘CMKLR1’ are ubiquitously expressed in white adipose tissue, although abundant levels of chemerin have also been identified in multiple organs, including the liver, ovaries, pituitary gland and lungs, as well as in dendritic cells\textsuperscript{18,19}. Results from both animal models and human studies have found a significant link between chemerin and components of metabolic syndrome\textsuperscript{5,20}. Bozaoğlu \textit{et al.}\textsuperscript{20} in a sample of 1,431 Mexican–American patients participating in San Antonio Family Heart Study observed that chemerin was significantly correlated with BMI, total body fat, TG, HDL-c, total serum cholesterol, fasting insulin, fasting glucose and HOMA-IR in the non-diabetic subset of the population, independent of age and sex.

In the present study, the effects of pioglitazone and metformin on serum concentrations of chemerin were investigated. We herein showed that pioglitazone significantly decreased chemerin concentrations in diabetes patients after 3 months. Pioglitazone, a member of the thiazolidinedione (TZD) family, improves blood glucose control through alleviation of insulin resistance. This aim is achieved through binding the peroxisome proliferator-activated receptor gamma (PPAR-\textgamma\textsuperscript{21}). PPAR-\textgamma is an essential mediator, not only in regulation of adipose tissue differentiation, but also in functions of adipose tissue that involve lipid storage and secreting various adipokine-

| Table 2 | Changes in baseline and outcome variables in pioglitazone and metformin groups after 3 months |
|---------|------------------------------------------------------------------------------------------------|
|         | Baseline | 3 months | Difference \textsuperscript{†} (95\% CI) | P-value\textsuperscript{†} |
| **Pioglitazone** | | | | |
| Waist circumference (cm) | 97.39 ± 10.19 | 97.20 ± 10.37 | −0.19 (−0.67, 1.04) | 0.659 |
| Weight (kg) | 77.01 ± 13.61 | 77.74 ± 14.73 | +0.73 (−0.84, 1.21) | 0.258 |
| BMI (kg/m\textsuperscript{2}) | 30.12 ± 20.7 | 30.17 ± 47.1 | +0.25 (−0.23, 0.30) | 0.305 |
| Fasting plasma glucose (mmol/L) | 9.40 ± 2.09 | 7.64 ± 1.68 | −1.76 (−2.49, −1.03) | <0.001 |
| Serum insulin (pmol/L) | 76.33 ± 34.52 | 50.07 ± 20.56 | −26.25 (−37.02, −5.42) | <0.001 |
| HOMA-IR | 4.42 ± 2.04 | 2.42 ± 1.07 | −2.00 (−2.60, −1.40) | <0.001 |
| HbA1c (mmol/mol) | 65 ± 16.5 | 57 ± 17.7 | −7.9 (−12.2, −3.5) | 0.001 |
| Chemerin (ng/mL) | 107.04 ± 21.01 | 99.07 ± 21.32 | −7.96 (−13.70, −2.22) | 0.008 |
| **Metformin** | | | | |
| Waist circumference (cm) | 94.12 ± 10.51 | 94.17 ± 10.51 | +0.05 (−0.43, 0.33) | 0.793 |
| Weight (kg) | 74.34 ± 12.81 | 74.49 ± 12.31 | +0.15 (−0.86, 0.56) | 0.672 |
| BMI (kg/m\textsuperscript{2}) | 28.81 ± 4.45 | 28.88 ± 4.36 | +0.07 (−0.35, 0.20) | 0.590 |
| Fasting plasma glucose (mmol/L) | 9.29 ± 2.94 | 7.78 ± 1.33 | −1.42 (−2.98, −1.30) | <0.001 |
| Serum insulin (pmol/L) | 84.94 ± 35.91 | 51.32 ± 25.84 | −33.54 (−38.89, −28.27) | <0.001 |
| HOMA-IR | 5.37 ± 2.84 | 2.54 ± 1.34 | −2.83 (−3.50, −2.15) | <0.001 |
| HbA1c (mmol/mol) | 66 ± 12.8 | 57 ± 15.5 | −9.1 (−12.6, −5.6) | <0.001 |
| Chemerin (ng/mL) | 101.30 ± 22.96 | 95.47 ± 21.76 | −5.82 (−10.44, −1.21) | 0.015 |

\textsuperscript{†}Comparing baseline and 3 month measurements within each group. HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance.

| Table 3 | Comparing the effects of pioglitazone and metformin on chemerin concentrations |
|---------|--------------------------------------------------------------------------------|
| Chemerin | Baseline mean \textsuperscript{†} | 3-month mean (95\% CI) | Effect size, \% | F | P-value |
| | Metformin | Pioglitazone | | | |
| Baseline model | 104.17 | 97.50 (97.74, 102.25) | 97.05 (92.30, 101.81) | 0.1 | 0.064 | 0.895 |
| Adjusted model | 103.14 | 97.36 (92.45, 102.26) | 96.67 (90.57, 102.77) | 0.1 | 0.040 | 0.870 |

\textsuperscript{†}Adjusted for the effects of covariates in the model. \#Adjusted for age, systolic blood pressure, homeostasis model assessment of insulin resistance, glycated hemoglobin, total cholesterol, high-density lipoprotein cholesterol, triglycerides and waist circumference.
It is postulated that TZDs, when bound to PPAR-γ, decrease the release of free fatty acids and tumor necrosis factor-α from adipose tissue, which ultimately leads to ameliorated insulin sensitivity in insulin target tissues.

Accumulating evidence from animal and cellular models have clearly shown that exposure to PPAR-γ agonists promote changes in the white adipose tissue that are characteristic of brown fat cells. More recently, Vernochet et al. showed that PPAR-γ agonists suppressed the expression of select white adipose tissue genes, including chemerin and resistin. Collectively, these observations provide a conceptual framework that helps us understand the exact molecular underpinnings of how TZDs eventually cause a significant reduction in chemerin concentrations in human sera, as shown in the present study. In concert with the experimental evidence mentioned, here we showed that a decrease in chemerin concentrations is paralleled by a significant improvement in all indices of glycemia, including FPG, insulin, HOMA-IR and HbA1c.

In the current study, 3 months’ monotherapy with metformin was associated with a significant reduction in chemerin. Along the same lines, Tan et al. in a group of 21 women with polycystic ovary syndrome (PCOS) reported that 6 months’ therapy with metformin significantly decrements chemerin concentrations. In the same study, ex vivo experiments on adipose tissue explants replicated similar findings.

Pei et al. reported that in high-fat fed insulin resistance rats that exert high serum concentrations of chemerin, metformin use was associated with a diminished messenger ribonucleic acid expression of chemerin in white adipose tissue. Altered expression of chemerin by metformin might be a result of attenuated endoplasmic reticulum stress in adipose tissue, mediated through decreased inositol-requiring kinase-1 (IRE-1) phosphorylation. IRE-1α is involved in activation of nuclear factor kappa B, which is known to induce expression of chemerin.

In the present study, chemerin reduction was accompanied by a concomitant amelioration of insulin resistance and hyperglycemia; no significant changes in the surrogate markers of obesity (i.e., waist circumference, weight and BMI) were detected, however. It is possible, therefore, that short-term effects of metformin on chemerin are largely mediated through insulin-dependent pathways, with quantitative changes in obesity indices having a small role in this regard. Complementary evidence was provided by Kloting et al. showing that insulin-resistant subjects have significantly higher chemerin concentrations compared with their insulin-sensitive counterparts matched for body fat mass and BMI. Furthermore, Tan et al. in their assessment of women with PCOS found that adipocytes’ production and secretion of chemerin is increased with insulin.

Here, we showed that both classes of antidiabetic medications were equally effective with respect to chemerin reduction. Although a number of studies have previously examined the effects of metformin and pioglitazone in both experimental and human models, clinical data comparing the impact of biguanides and TZD on chemerin concentrations is human sera are currently lacking. The present study provides preliminary evidence regarding comparable efficacy of metformin and pioglitazone in decreasing chemerin, albeit through different pathways. These findings add to our current knowledge of how the complex of adipose tissue responds to, and is regulated by, the available antidiabetic medications. Future studies are paramount to elucidate how these metabolic alterations contribute to the development (or prevention) of common micro- and macrovascular complications of diabetes.

ACKNOWLEDGEMENTS
This study was funded by Tehran University of Medical Sciences. The authors declare that there is no conflict of interests associated with the results presented in this study.

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