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# Both slow-release and regular-form metformin improve glycemic control without altering plasma visfatin level in patients with type 2 diabetes mellitus

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**Abstract**

Both slow-release (SR) and regular-release (RR) metformin were effective in the treatment of type 2 diabetes mellitus. We compare the efficacy, safety, and effects on serum adipocytokines and inflammatory markers of both regimens in patients with type 2 diabetes mellitus. A prospective, randomized, double-blind study enrolled 55 patients with type 2 diabetes mellitus, which were randomly assigned to receive either metformin SR or RR (at a maximal dosage of 2000 mg/d for 12 weeks). Glycosylated hemoglobin $A_{1c}$ ($HbA_{1c}$), fasting plasma glucose, adipocytokines, C-reactive protein, and insulin resistance and pancreatic beta-cell function were measured before and after treatment. Significant decreases ($P < .001$) in mean $HbA_{1c}$ and fasting plasma glucose levels were observed in each group. However, the mean changes in $HbA_{1c}$ from baseline to end point in the 2 groups were not significantly different. Changes in metabolic parameters were similar except that a decreased total cholesterol level was observed in the metformin RR group. Neither regimen treatment had any influence on insulin resistance, but metformin RR improved beta-cell function. Neither regimen had an effect on serum adipocytokines or inflammatory markers. Once-daily metformin SR was as safe and effective as metformin RR in type 2 diabetic patients. Neither dosage form affected serum adipocytokines and inflammatory markers.


## 1. Introduction

Metformin hydrochloride is one of the most frequently prescribed oral antidiabetic drugs for the treatment of type 2 diabetes mellitus [1]. Metformin reduces hyperglycemia by reducing hepatic glucose output and ameliorating insulin resistance. It is recommended as the first-line choice in overweight type 2 diabetic patients who have failed diet control. It has been shown to reduce the risk of diabetes-related end points and has favorable side effects, such as lesser weight gain and fewer hypoglycemia attacks [2].

Adipose tissue is one of the major target tissues modulating insulin resistance. The adipocyte secretes a number of polypeptides, such as leptin, adiponectin, tumor necrosis factor α (TNF-α), and interleukin 6 (IL-6), which may be associated with the development of obesity, insulin resistance, and diabetes [3]. Visfatin is a recently discovered adipocytokine that is predominantly produced by visceral adipose tissue and has insulin-mimetic actions. A recent study reported that plasma visfatin levels are correlated with body mass index (BMI) and body fat content [4]. Plasma C-reactive protein (CRP) is a marker of low-grade inflammation. It is also elevated in obesity and is largely regulated by pro-inflammatory adipocytokines such as IL-6 [5]. Levels of CRP often correlate with severity of insulin resistance [6].

Metformin has an insulin-sensitizing action through an adenosine monophosphate–activated protein kinase pathway [7]. This action is thought to provide an extra benefit in addition to its action in increasing insulin-mediated suppression of hepatic glucose production. Recently, the Food and Drug Administration has approved a slow-release (SR) formulation of metformin, which provides once-daily administration for the treatment of type 2 diabetes mellitus. One recent study reported that metformin SR had comparable efficacy and fewer side effects than the metformin regular-release (RR) formulation [8]. Previous studies have provided evidence that metformin has actions in addition to

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its effects on glucose metabolism, including the reduction of thrombotic factor and inflammatory markers [9,10]. The concentrations of all of the above adipocytokines and CRP are positively correlated to insulin resistance, type 2 diabetes mellitus, and the presence of chronic inflammation except for adiponectin level, which is negatively correlated [3,11,12]. Elevated plasma concentrations of visfatin [13], CRP [14,15], IL-6 [16,17], and TNF-α [18] and reduced concentrations of adiponectin [19] are not only observed in type 2 diabetes mellitus, but also have predictive power for the development of this syndrome.

In the treatment of type 2 diabetes mellitus, metformin lessens insulin resistance and acts as an insulin sensitizer. However, few data exist on the effect of metformin on adipocytokines and/or CRP in type 2 diabetes mellitus. According to previous studies, metformin has no effect on TNF-α [20] or adiponectin [21,22] concentrations, but has an effect to lower CRP [23] in type 2 diabetes mellitus. However, there are no available data on the effect of metformin on visfatin, a novel adipocytokine involved in insulin resistance. Although the metabolism and pharcokinetics were similar in both regimens of metformin, there were limited data to evaluate the metabolic characteristics and their effects on the adipocytokines.

There are 2 major purposes of this study. First, we want to look for differences between the 2 metformin formulations on the levels of adipocytokines and the inflammatory marker, CRP. To address this issue, we measured concentrations of 3 adipocytokines and CRP before and after a 14-week treatment period with both metformin regimen. Second, we compared the efficacy, tolerability, and safety of metformin SR and metformin RR in the same treatment protocol.

## 2. Research design and methods

### 2.1. Subjects and study design

A randomized, double-blind, parallel, active-control study was conducted. The study protocol was approved by institutional review boards. All subjects gave written informed consent to participate in the study before enrollment.

The study enrolled subjects 30 to 75 years of age with type 2 diabetes mellitus that had been first diagnosed with this disease after 30 years of age. Other inclusion criteria were the following: glycosylated hemoglobin $A_{1c}$ ($HbA_{1c}$) levels between 7.0% and 12.0% and fasting plasma glucose (FPG) concentrations between 126 and 300 mg/dL with diet and exercise alone for at least 1 month, or attainment of this degree of glucose control with a stable dose of sulfonylurea or repaglinide for at least 3 months before the study, and the same degree of glycemic control at both the screening and randomization visits. Subjects were excluded from the study if they have type 1 diabetes mellitus, were pregnant, or have childbearing potential; had a history of lactic acidosis, allergy to metformin, unstable cardiovascular disease, chronic obstructive pulmonary disease, or gastric or duodenal ulcers; had serum creatinine level of more than 1.5 mg/dL (male patients) or more than 1.4 mg/dL (female patients); had impaired liver function (aspartate aminotransferase and/or alanine aminotransferase >2 times the upper limit of reference range); or had any uncontrolled or untreated systemic disease considered by the investigator to make them unfit to enter the study. Fifty-five subjects were randomized into the study, and all randomized subjects were included in the intention-to-treat population.

After a 2-week washout of previous oral antidiabetic drugs, eligible patients were randomly assigned in a 1:1 ratio into 2 groups to receive initially either 1000 mg metformin SR once daily (28 subjects, Met-SR group) or 500 mg metformin RR (27 subjects, Met-RR group) twice daily. The dosage was then increased up to a maximal dosage of 2000 mg/d within 1 month during a 2-week titration interval to find the correct dose to keep FPG levels less than 140 mg/dL. The dosage arrived at during the titration period was then continued for 12 weeks. All study drugs were taken after meals.

Patients were evaluated every week during the screening and washout periods, the 2-week period during dosage titration, and then every 4 weeks until the end of study. The primary efficacy end point was the net change in 12-week $HbA_{1c}$ compared with baseline $HbA_{1c}$ in the 2 groups. The secondary efficacy parameters were changes in FPG and lipid profile concentrations over the period from baseline to the end of the study. Changes in plasma adiponectin, TNF-α, IL-6, visfatin, and CRP were also measured. In addition, insulin resistance and pancreatic beta-cell function were evaluated before and after the 12-week treatment in both groups. Finally, the net change in these parameters was compared between the 2 groups. The criteria for withdrawal from the study included patients who decided to withdraw consent, patients in whom the trial dose of metformin lacked efficacy (ie, those who had FPG levels >300 mg/dL at any visit during the trial), those who were either lost to follow-up or died, and those about whom the investigators had safety concerns. Safety was evaluated through the following measurements: adverse events, changes upon physical examination, and clinical laboratory test results.

### 2.2. Laboratory measurements

After a 10-hour fasted state, blood samples were obtained for determining plasma glucose, insulin, creatinine, alanine aminotransferase, and lipid profiles. Plasma circulating visfatin, adiponectin, CRP, TNF-α, and IL-6 levels were also measured. Serum concentrations of biochemistry and total cholesterol (TC) were measured using a dry multilayer analytic slide method in a Fuji Dri-Chem 3000 analyzer (Fuji Photo Film, Minato-Ku, Tokyo, Japan). The determination of serum triglyceride after enzymatic splitting with lipoprotein lipase was assayed by a colorimetric enzymatic test on a Hitachi 717 analyzer (Biomedilines, San Diego, CA). Plasma glucose concentration was determined by the glucose

oxidase method on a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Plasma insulin was measured with a commercial radioimmunoassay kit (Coat-A-Count Insulin Kit, Diagnostic Products, Los Angeles, CA). The intra- and interassay coefficients of variance (CVs) for insulin measurement on this assay are 3.3% and 2.5%, respectively. Hemoglobin $A_{1c}$ was measured using a Bio-Rad Variant II automatic analyzer (Bio-Rad Diagnostic Group, Los Angeles, CA). The intra- and interassay CVs for $HbA_{1c}$ were 1.9% and 3.7%, respectively. Plasma CRP levels were measured using the Tina-quant (Latex) high-sensitivity assay (Roche Diagnostics, Mannheim, Germany). Serum adiponectin concentrations were assayed with a radioimmunoassay established by Linco Research (St Charles, MO). This assay has a sensitivity of 1 ng/mL and intra- and interassay CV of less than 8%. Serum IL-6 concentrations were determined by a human high-sensitivity enzyme-linked immunosorbent assay established by Diaclone Research (Besancon Cedex, France). The intra- and interassay CVs for IL-6 were 5.5% and 1.4%, respectively. Serum TNF-$\alpha$ was measured with the Biotrak high-sensitivity human enzyme-linked immunosorbent assay kit from Amersham Biosciences (Buckinghamshire, UK). The within- and between-assay CV for TNF-$\alpha$ has been determined to be less than 10%. Serum visfatin was determined by a commercial enzyme immunoassay kit (Phoenix Pharmaceuticals, Burlingame, CA). All of the concentrations of the above adipocytokines and CRP were determined in duplicate and the values of the 2 samples were averaged. Insulin resistance and pancreatic beta-cell function were assessed using the homeostasis model assessment (HOMA) originally described by Matthews et al [24], in which HOMA for insulin resistance (HOMA-IR) = FPG (mmol/L) × fasting plasma insulin (FPI) ($\mu$IU/mL)/22.5. The HOMA-IR correlates closely with the insulin sensitivity index as measured by the gold standard euglycemic hyperinsulinemic clamp. In this model, pancreatic beta-cell secretory function (HOMA-$\beta$) = 20 × FPI ($\mu$IU/mL)/[FPG (mmol/L) − 3.5].

### 2.3. Statistical analysis

All statistical analyses were performed using SAS 8.2 software (SAS Institute, Cary, NC). Efficacy and safety analyses were performed using an intent-to-treat population, defined as all randomly assigned patients who received a study drug and had available efficacy data.

The primary end point, net change in $HbA_{1c}$, was analyzed using the method of confidence intervals calculated by *t* test. Descriptive statistics are also presented. For secondary efficacy end points, data of continuous type were analyzed using *t* test or Wilcoxon rank sum test. Categorical secondary efficacy end points were analyzed by means of the Mantel-Haenszel test or Fisher exact test. Descriptive statistics including estimates of mean and 2-sided 95% confidence intervals are presented for variables of continuous type, and frequency tables are provided for categorical data. Statistical significance was defined as $P < .05$.

Adverse event analyses included all patients who received at least one dose of the study drug. Fisher exact test was used to compare the incidence of adverse events between treatment groups.

## 3. Results

A total of 55 patients were enrolled and randomly assigned to a treatment group. Four from the Met-SR group and 4 from the Met-RR group were withdrawn from the trial mainly because of gastrointestinal side effects. There were no significant differences between the treatment groups in demographic and baseline characteristics. Fasting plasma insulin and triglyceride levels were higher in the Met-RR group (Table 1), but this difference did not attain statistical

Table 1
Clinical characteristics and metabolic variables in patients with type 2 diabetes mellitus before and after metformin RR and metformin SR treatment

| | Metformin RR (n = 23) | | | Metformin SR (n = 24) | | |
|---|---|---|---|---|---|---|
| | Before | After | *P* | Before | After | *P* |
| Age (y) | 57.6 ± 1.7 | | | 58.0 ± 1.4 | | |
| Sex (M/F) | 13/10 | | | 10/14 | | |
| Body weight (kg) | 67.7 ± 2.3 | 67.5 ± 2.4 | NS | 65.3 ± 2.6 | 65.0 ± 2.7 | NS |
| BMI ($kg/m^2$) | 25.6 ± 0.7 | 25.5 ± 0.7 | NS | 25.3 ± 0.8 | 25.0 ± 0.8 | NS |
| Systolic blood pressure (mm Hg) | 129.1 ± 3.0 | 132.6 ± 2.5 | NS | 124.2 ± 2.0 | 127.7 ± 2.2 | NS |
| Diastolic blood pressure (mm Hg) | 83.3 ± 2.2 | 82.0 ± 1.5 | NS | 81.1 ± 1.9 | 81.2 ± 1.9 | NS |
| FPG (mmol/L) | 10.45 ± 0.56 | 8.95 ± 0.45 | <.001 | 10.19 ± 0.44 | 8.17 ± 0.50 | <.001 |
| Fasting plasma insulin (pmol/L) | 55.6 ± 10.3 | 53.8 ± 8.7 | NS | 31.1 ± 4.3 | 38.6 ± 9.7 | NS |
| $HbA_{1c}$ (%) | 9.3 ± 0.3 | 7.9 ± 0.3 | <.001 | 9.1 ± 0.3 | 7.8 ± 0.2 | <.001 |
| Creatinine (mg/dL) | 0.92 ± 0.04 | 0.90 ± 0.04 | NS | 0.90 ± 0.04 | 0.86 ± 0.05 | NS |
| Alanine aminotransferase (U/L) | 33.0 ± 3.4 | 30.0 ± 3.3 | NS | 28.3 ± 3.2 | 27.5 ± 3.4 | NS |
| HOMA-IR | 3.8 ± 0.9 | 3.0 ± 0.5 | NS | 2.0 ± 0.4 | 2.0 ± 0.5 | NS |
| HOMA-$\beta$ | 25.0 ± 4.1 | 35.0 ± 7.2 | <.05 | 20.1 ± 2.0 | 29.5 ± 8.7 | NS |
| TC (mmol/L) | 5.00 ± 0.17 | 4.67 ± 0.18 | <.05 | 4.98 ± 0.23 | 5.00 ± 0.25 | NS |
| Triglyceride (mmol/L) | 2.82 ± 0.39 | 2.74 ± 0.45 | NS | 2.11 ± 0.24 | 2.33 ± 0.36 | NS |

Data are expressed as mean ± SEM. Baseline characteristics in both groups were not significantly different. NS indicates not significant.

Table 2
The effects of adipocytokines and pro-inflammatory cytokines in patients with type 2 diabetes mellitus before and after metformin RR and metformin SR treatment

| | Metformin RR | | | Metformin SR | | |
|---|---|---|---|---|---|---|
| | Before | After | *P* | Before | After | *P* |
| Adiponectin (μg/mL) | 11.5 ± 1.5 | 10.1 ± 1.2 | NS | 11.9 ± 1.7 | 11.7 ± 1.1 | NS |
| CRP (mg/L) | 0.28 ± 0.08 | 0.32 ± 0.10 | NS | 0.18 ± 0.05 | 0.15 ± 0.04 | NS |
| Visfatin (ng/mL) | 22.6 ± 2.3 | 24.6 ± 1.1 | NS | 17.9 ± 2.2 | 16.4 ± 1.5 | NS |
| IL-6 (pg/mL) | 2.29 ± 0.27 | 2.29 ± 0.23 | NS | 1.69 ± 0.19 | 1.92 ± 0.13 | NS |
| TNF-α (pg/mL) | 0.15 ± 0.05 | 0.17 ± 0.08 | NS | 0.13 ± 0.02 | 0.15 ± 0.03 | NS |

Data are expressed as mean ± SEM.

significance. Significant reductions in FPG and mean $HbA_{1c}$ concentrations were seen after treatment in both groups ($P < .001$). The Met-RR group had improved HOMA-β and TC levels significantly ($P < .05$), but such improvement was not seen in the Met-SR group (Table 1). None of the adipocytokine levels were significantly changed after treatment in either group (Table 2). In addition, when changes (ie, 14-week value − baseline value) in the various parameters measured in this study were compared, no significant differences between the 2 groups were seen in these changes (Table 3).

## 4. Discussion

Our data showed that both metformin RR and metformin SR regimens produced significant and similar decreases in $HbA_{1c}$ but no difference in the reduction of FPG levels. A beneficial effect of metformin on the lipid profile in type 2 diabetes mellitus has been observed in previous studies, but with various results in both dosage forms of metformin [25-28]. In the current study, a decrease in TC was noted in the Met-RR group, but not in the Met-SR group, a result similar to some previous studies [27,28]. The possible reason for the difference is that immediate-release metformin is taken with meals and may therefore affect postprandial triglyceride and fatty acid flux, and this effect is not seen with SR formulations. The decreased insulin resistance seen (although not a statistically significant degree) in the Met-RR group but not in the Met-SR group may also have contributed to the difference in the lipid profiles of the 2 formulations.

An improvement of insulin sensitivity with metformin therapy in type 2 diabetes mellitus has been noted in the past. One proposed mechanism is through stimulation of adenosine monophosphate–activated protein kinase pathway [7]. Our results did not show any efficacy on insulin resistance in either dosing regimen. One possible reason is that neither regimen reduced the FPI level, a major determining factor in evaluation of insulin resistance by the HOMA method.

The effects of different kinds of oral antidiabetic drugs on serum CRP levels have been evaluated in previous trials but with some discrepancies in the results. Decreased CRP levels have been seen in type 2 diabetes mellitus after treatment with thiazolidinedione (TZD) [23,28], sulfonylurea [29], and metformin [14,23,30-32]. However, one study reported that metformin did not reduce CRP levels [29]. In our study, neither dosage formulation of metformin had any effect on serum CRP levels. Several possible mechanisms might explain the lack of effect of metformin on CRP levels in our study. First, metformin might have an impact on CRP secretion and/or synthesis, which is independent of insulin sensitivity [32]. Second, decreased CRP level correlates with the degree of improvement of insulin sensitivity instead of the degree of glycemic control achieved [23], and this could explain why our study did not show any effect of metformin on CRP changes. Third, in contrast to the above report, another report showed that decreased CRP is associated with glycemic control [31]. Our report showed change of CRP to be correlated to change in $HbA_{1c}$ ($r = 0.34$, $P < .05$; data was not shown) but showed no effect of metformin itself on CRP levels.

Adiponectin has been postulated to play an important role in the modulation of glucose and lipid metabolism in insulin-sensitive tissues in humans. Adiponectin is inversely related to insulin resistance and obesity, and levels are decreased in type 2 diabetes mellitus [19]. Most previous studies show that metformin therapy does not increase serum levels of

Table 3
Changes in characteristics, adipocytokines, and pro-inflammatory cytokines from baseline to 12 weeks after metformin RR and metformin SR treatment

| | Metformin RR | Metformin SR | *P* |
|---|---|---|---|
| Body weight (kg) | −0.11 ± 0.45 | −0.22 ± 0.35 | NS |
| BMI (kg/m$^2$) | −0.14 ± 0.21 | −0.37 ± 0.50 | NS |
| Systolic blood pressure (mm Hg) | +3.44 ± 2.88 | +3.54 ± 2.45 | NS |
| Diastolic blood pressure (mm Hg) | −1.35 ± 1.89 | +0.08 ± 1.94 | NS |
| FPG (mmol/L) | −27.04 ± 6.96 | −36.38 ± 9.98 | NS |
| Fasting plasma insulin (pmol/L) | −0.2 ± 6.77 | +2.45 ± 8.17 | NS |
| $HbA_{1c}$ (%) | −1.35 ± 0.25 | −1.26 ± 0.21 | NS |
| TC (mmol/L) | −12.56 ± 4.80 | +0.75 ± 5.81 | NS |
| Triglyceride (mmol/L) | −5.00 ± 17.71 | +14.35 ± 17.23 | NS |
| HOMA-IR | −0.87 ± 0.65 | −0.22 ± 0.51 | NS |
| HOMA-β | +9.98 ± 4.68 | +8.49 ± 7.13 | NS |
| Adiponectin (μg/mL) | −1.35 ± 1.48 | −0.23 ± 1.10 | NS |
| CRP (mg/L) | +0.04 ± 0.08 | −0.02 ± 0.05 | NS |
| Visfatin (ng/mL) | +2.03 ± 2.32 | −1.46 ± 2.15 | NS |
| IL-6 (pg/mL) | −0.004 ± 0.238 | −0.228 ± 0.137 | NS |
| TNF-α (pg/mL) | +0.06 ± 0.04 | +0.05 ± 0.02 | NS |

Data are expressed as mean ± SEM.

adiponectin [21,22,29]. In contrast, levels are elevated with treatment with TZD [22,14,33]. In a report by Phillips et al [21], TZD therapy increased adiponectin levels but metformin therapy did not, a result partly because TZD caused greater improvement in insulin sensitivity than metformin at similar levels of glycemic control. Our data did not show any benefit of metformin on adiponectin levels. One possible reason is that there was no improvement in insulin sensitivity in either metformin treatment group in our study.

Tumor necrosis factor α, an adipocytokine associated with visceral adiposity and type 2 diabetes mellitus, is considered to be a mediator of insulin resistance because it induces serine phosphorylation of the insulin receptor and thus inhibits insulin signaling [34]. There are limited data on the TNF-α level with metformin therapy in type 2 diabetes mellitus. The improvement in insulin resistance seen after metformin therapy was not seen to be modulated by TNF-α in 2 studies of subjects from high-risk populations, prediabetic individuals [20], and patients with coronary artery disease [35]. In addition, no effect on TNF-α of metformin treatment was seen in another study with similar glycemic control [36]. These data suggest that TNF-α may modulate insulin action in muscle and adipose tissue through a different pathway than through phosphorylating the insulin receptor. Also, TNF-α may down-regulate adiponectin production [37], and because adiponectin reduces the production and activity of TNF-α [38] and IL-6 [39], more TNF-α and IL-6 would be present than without this negative feedback. This TNF-α–mediated down-regulation of adiponectin would also explain why IL-6 levels were not changed after metformin therapy.

Elevated plasma levels of visfatin have been noted in type 2 diabetes mellitus [13]. However, this association disappeared after the data were adjusted to take into account waist-to-hip ratio and the BMI. This result was similar to that of a recent report that showed a reduced plasma visfatin level in obesity but no correlation between visfatin and insulin resistance [40]. A recent trial reports that visfatin activates the intracellular signaling cascade of insulin action pathway and mimics the effects of insulin [41]. Another recent report suggests that secretion of visfatin is influenced by insulin and glucose through a pathway involving phosphatidylinositol 3-kinase and protein kinase B [42]. There has been no report evaluating the effect of metformin on plasma visfatin levels in type 2 diabetes mellitus. Our study is the first one to evaluate the influence of metformin on this novel adipocytokine. Unfortunately, there was no obvious effect of short-term metformin treatment on visfatin levels.

There are several limitations in our study. Firstly, no placebo group was enrolled because of ethical consideration. It might reduce the power of the effect of metformin on these markers or parameters. Secondly, the sample size of 2 groups maybe too small to demonstrate the efficacy and the safety concern about the treatment. In summary, the present study suggests metformin SR to be as highly effective, safe, and well tolerated as metformin RR in short-term therapy in type 2 diabetes mellitus. However, neither regimen of metformin had any effect on insulin sensitivity, serum CRP, or adipocytokine concentrations. A large-scale, placebo-controlled study should be conducted to ascertain exactly what effects of metformin in addition to glycemic control exist.

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