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The effects of pioglitazone and metformin on plasma visfatin levels in patients with treatment naive type 2 diabetes mellitus

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ABSTRACT

Aims: Circulating visfatin levels are altered in insulin resistant states. We evaluated the effects of two insulin-sensitizing hypoglycemic agents on plasma visfatin and adiponectin levels in patients with newly diagnosed and untreated type 2 diabetes mellitus (T2DM).
Methods: Forty-four patients with T2DM were randomized to treatment either with pioglitazone (15–45 mg/day) or metformin (1000–2000 mg/day). Plasma visfatin and adiponectin levels and homeostasis model assessment of insulin resistance (HOMA-IR) scores were determined at baseline and at 12th week of treatment.
Results: By the end of the 12th week, fasting plasma glucose, HbA1c, HOMA-IR scores and waist circumferences improved equally in both treatment arms. HDL cholesterol and adiponectin levels increased only in the pioglitazone group ($p = 0.01$ and $p = 0.003$, respectively). On the other hand, metformin treatment had additional regulatory effects on BMI, blood pressure and total and LDL-cholesterol levels ($p = 0.002$, $p = 0.01$, $p = 0.004$, $p = 0.001$ and $p < 0.001$, respectively). Neither pioglitazone nor metformin displayed a significant effect on circulating visfatin concentration.
Conclusions: Despite improvements in insulin sensitivity and glycemic regulation, either pioglitazone or metformin treatment did not result in any effect on blood visfatin levels in patients with treatment naïve T2DM.

1. Introduction

Adipose tissue has been recognized as an active endocrine organ contributing to metabolic homeostasis by secreting adipokines such as leptin, adiponectin, tumor necrosis factor-α, interleukin-6, plasminogen activator inhibitor-1, visfatin and resistin [1]. Visfatin which was previously described as a pre-B cell colony-enhancing factor is abundantly expressed in visceral adipose tissue. Its synthesis and secretion was shown to be up regulated in several animal models of obesity as well as in humans with abdominal obesity and/or type 2 diabetes mellitus (T2DM) [2–4]. It was also shown that visfatin binds to the insulin receptor at a different site, and exerts hypoglycemic effect by reducing

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Abbreviations: T2DM, type 2 diabetes mellitus; HOMA-IR, homeostasis model assessment of insulin resistance; BMI, body mass index; WC, waist circumference; FPG, fasting plasma glucose; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride.

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Table 1 – The comparison of the results at baseline and after a 12-week treatment with pioglitazone or metformin

	Pioglitazone (n = 21)		Metformin (n = 23)		p1	p2	p3
	BT	AT	BT	AT			
BMI (kg/m^2)	30.41 ± 4.2	30.33 ± 4.4	31.41 ± 3.8	29.41 ± 3.05	0.41	0.45	**0.002**
Age (years)	54.9 ± 7.8		55.09 ± 9.9		0.94		
Gender (M/F)	8/13		9/12		0.75†		
Waist (cm)	103.57 ± 8.2	100.76 ± 7.1	103.6 ± 7.0	98.45 ± 8.9	0.91	**<0.001**	**<0.001**
SBP (mmHg)	130.95 ± 9.4	129.04 ± 9.4	130.23 ± 9.7	124.25 ± 12.49	0.81	0.46	**0.01**
DBP (mmHg)	82.61 ± 4.4	81.1 ± 6.3	82.14 ± 6.4	77.50 ± 6.2	0.78	0.16	**0.004**
FPG (mg/dl)	128.2 ± 23.5	112.6 ± 15.4	133.6 ± 36.5	111.0 ± 16.2	0.57	**0.01**	**0.001**
TC (mg/dl)	217.52 ± 49.62	217.52 ± 49.6	207.8 ± 29.4	189.25 ± 23.7	0.45	0.44	**0.001**
TG (mg/dl)	183.95 ± 105.04	162.23 ± 84.6	166.05 ± 81.8	150.05 ± 67.3	0.54	0.29	0.32
HDL (mg/dl)	48.04 ± 9.4	53.25 ± 10.7	48.31 ± 13.1	49.37 ± 11.8	0.94	**0.01**	0.39
LDL (mg/dl)	132.66 ± 35.6	128.62 ± 30.51	132.42 ± 30.9	112.57 ± 27.9	0.98	0.76	**<0.001**
HbA1c	6.34 ± 1.2	5.6 ± 0.7	6.74 ± 1.3	6.15 ± 0.53	0.31	**0.01**	0.02
Insulin (mU/ml)	8.4 ± 4.8	7.0 ± 2.9	10.36 ± 2.96	9.7 ± 3.7	0.12	0.14	0.56
HOMA-IR	2.79 ± 1.9	1.94 ± 0.83	3.42 ± 1.3	2.7 ± 1.2	0.22	**0.03**	**0.009**
Adiponectin (μg/ml)	6.86 ± 3.3	11.02 ± 6.5	5.33 ± 2.6	5.86 ± 4.4	0.11	**0.003**	0.78
Visfatin (ng/ml)	5.86 ± 4.60 (5.30)	9.97 ± 19.61 (3.31)	5.81 ± 2.5 (1.79)	4.0 ± 6.3 (2.35)	0.83‡	0.49‡	0.95‡

The data is presented as the mean ± S.D. (median). †Chi-square test; ‡Mann–Whitney U-test; p1: pio vs. metformin before treatment (BT). Student's t-test; p2: pioglitazone BT vs. after treatment (AT). Paired samples t-test; p3: metformin BT vs. AT. Paired samples t-test.

glucose release from hepatocytes and stimulating glucose utilization in peripheral tissues [5].

Pioglitazone and metformin are insulin-sensitizing agents which have different mechanisms of action and main target tissues. Pioglitazone acts primarily on adipocytes and its main mechanism of antidiabetic effect is to increase the glucose disposal rate in muscle and adipose tissue as well as decreasing endogenous glucose production [6]. Metformin, a biguanide derivative, decreases hepatic glucose production [7] through adenosine monophosphate-activated protein kinase activation [8].

The importance of elevated visfatin levels in people with T2DM is not known. In addition, there are limited and conflicting reports regarding the effect of hypoglycemic treatment on visfatin levels. Pioglitazone therapy has recently been reported to have no effect on plasma visfatin concentration in subjects with T2DM [9]. This was also true for metformin in a study with different formulations of the drug [10]. However, those studies enrolled patients with long time disease who were already under antidiabetic treatment. As in the case of most other adipokines, blood visfatin concentration may easily be affected by the hypoglycemic treatment and stable metabolic status [11,12]. Therefore, in the present study, to see whether an improvement in insulin sensitivity modulates circulating visfatin levels, we evaluated the effects of two different insulin sensitizers, pioglitazone and metformin, on plasma visfatin concentrations in patients with newly diagnosed and previously untreated T2DM who had no confounding factors for insulin sensitivity.

2. Patients and methods

2.1. Subjects

Fifty-three patients with T2DM were recruited from the outpatient clinic of the Department of Internal Medicine, Gulhane School of Medicine. The characteristics of the subjects are summarized in Table 1. The enrollment criteria were as follows: age between 30 and 70 years, body mass index (BMI) less than 35 kg/m^2, no other illnesses including liver failure, renal failure, heart failure or other chronic disease as determined by history, physical examination, and screening tests. The patients were randomized to pioglitazone (15 mg/day; 26 subjects) or metformin (1000 mg/day; 27 subjects) treatment groups. All subjects gave signed, voluntary, informed consent before participation. The study protocol was approved by the local ethical committee of the Gulhane School of Medicine.

The baseline and endpoint anthropometric parameters were height, weight, waist circumference (WC) and BMI. Height and weight were measured with subjects in light clothing but no shoes. BMI was calculated and expressed in kilograms per meter square. WC was measured with a soft tape on standing subjects midway between the lowest rib and the iliac crest. The laboratory studies included fasting plasma glucose (FPG), HbA1c, insulin, total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride (TG), visfatin and adiponectin levels. These tests were performed in the morning at 8 am after a 10-h overnight fast.

2.2. Treatment procedure and follow-up

Twelve weeks follow-up and six visits were applied to patients treated either with pioglitazone or metformin. Pioglitazone treatment was initiated with a dose of 15 mg/day and could be increased up to 45 mg/day in increments of 15 mg. Metformin therapy was started with a dose of 1000 mg/day and could be increased up to 2000 mg in increments of 500 mg. The dose of medication was titrated during on-therapy visits, based on failure to achieve a glycemic target of mean daily glucose less than or equal to 110 mg/dl. The mean daily glucose was calculated from daily (before meals and at bedtime) patient-measured glucose levels for 3 days prior to on-therapy visits. The dose of study medication was increased to the maximum