Journal of Cardiology (2009) **54**, 52—58

ELSEVIER

JOURNAL of CARDIOLOGY
Official Journal of the Japanese College of Cardiology
www.elsevier.com/locate/jjcc

ORIGINAL ARTICLE

Effect of pioglitazone on left ventricular diastolic function and fibrosis of type III collagen in type 2 diabetic patients

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Received 31 October 2008; received in revised form 26 February 2009; accepted 16 March 2009
Available online 29 April 2009

KEYWORDS
Left ventricular diastolic function;
Diabetes mellitus;
Pioglitazone;
Type III collagen

Summary
Background: Myocardial fibrosis is the major factor that regulates left ventricular (LV) diastolic function. Pioglitazone, an anti-diabetic drug, is reported to improve the LV diastolic function in diabetic patients, but its influence on myocardial fibrosis has not been clarified. We evaluated the effect of pioglitazone on LV diastolic function and myocardial fibrosis in type 2 diabetic (T2DM) patients.
Methods and results: Fifteen T2DM patients were enrolled in the ON group, and the parameters were examined before and after pioglitazone administration (15—30 mg/day) for 6 months. Twenty-four T2DM patients were assigned to the OFF group, and the parameters were examined before and 6 months after cessation of pioglitazone. We measured echocardiographic parameters such as early diastolic mitral annular velocity (E') and plasma concentration of aminoterminal propeptide of procollagen type III (PIIIP), a marker of myocardial fibrosis. In the ON group, pioglitazone significantly increased E' (6.04 ± 1.70 cm/s vs. 6.51 ± 1.64 cm/s, $p < 0.01$) and decreased PIIIP (0.553 ± 0.056 U/ml vs. 0.517 ± 0.072 U/ml, $p < 0.05$). There was a significant negative correlation between the change in PIIIP and the change in E' ($r = -0.424$, $p = 0.046$). On the other hand, E' was significantly decreased (5.69 ± 1.34 cm/s vs. 4.97 ± 1.20 cm/s, $p < 0.01$) in the OFF group. PIIIP was not significantly changed in the OFF group, but there was a significant negative correlation between the change in PIIIP and the change in E' ($r = -0.374$, $p = 0.035$).

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doi:10.1016/j.jjcc.2009.03.004

Conclusion: Six months of pioglitazone administration suppressed the synthesis of type III collagen, and this was associated with improved LV diastolic function in T2DM patients. Cessation of pioglitazone weakened the suppression of the synthesis of type III collagen, which in turn seemed to be associated with worse LV diastolic function.

Introduction

The thiazolidine derivative pioglitazone, a peroxisome proliferator-activated receptor (PPAR)-γ agonist, is currently used as an anti-diabetic drug. It is reported to have a variety of actions in addition to a hypoglycemic action and an ameliorating effect on insulin resistance. Improvement of abnormal lipid metabolism, an anti-inflammatory effect, an anti-atherogenic action, and an inhibitory effect on oxidative stress have been reported. With respect to the heart, it was reported to inhibit myocardial cell hypertrophy in rats [1], inhibit myocardial fibrosis in a rat model of diabetes [2], inhibit progression of human coronary artery atherosclerosis [3], and inhibit recurrence of cardiovascular events [4]. We previously reported that pioglitazone improved left ventricular diastolic function in type 2 diabetic patients [5]. Myocardial fibrosis is the major factor that regulates left ventricular diastolic function. Moreover, it has been reported that a relationship was observed between aminoterminal propeptide of procollagen type III (PIIIP), a marker of myocardial fibrosis, and heart failure in humans [6—9]. The purpose of the present study is to investigate how left ventricular diastolic function and PIIIP change as a result of initiation of oral administration of pioglitazone and discontinuation of oral administration in type 2 diabetic patients.

Methods

Subjects and study protocol

We studied 15 patients with type 2 diabetes in the ON group (8 men and 7 women; mean age, 67.8 years) and 24 patients with type 2 diabetes in the OFF group (12 men and 12 women; mean age, 67.2 years). Patients were excluded if they had heart failure, left ventricular systolic failure, moderate-to-severe valvular disease, atrial fibrillation, liver dysfunction, collagen disease, renal failure, pulmonary fibrosis, or osteoporosis. During this study, the doses of neither antihypertensive drugs nor anti-diabetic drugs were changed. Informed consent was obtained from all patients before participation in the study, and the protocol was approved by the Human Investigations Committee of our institution. Parameters were examined before and after pioglitazone administration (15—30 mg/day) for 6 months in the ON group, and they were examined before and 6 months after cessation of pioglitazone in the OFF group.

Echocardiography

M-mode echocardiography and two-dimensional imaging were performed using a cardiac ultrasound unit (SONOS 5500; Hewlett Packard, Andover, MA, USA) in a blinded fashion before and after treatment. Each patient was examined in the left lateral decubitus position. Measurements included left ventricular ejection fraction (LVEF) calculated using Teichholtz's formula, left ventricular Tei index (LVTEI) [10], and left ventricular mass index (LVMI) [11]. Assessment of early diastolic mitral annular velocity (E') was performed by pulsed wave tissue Doppler imaging of the septal wall in apical 4-chamber view. Doppler echocardiogram was recorded at a sweep of 50 mm/s and the mean value of three cardiac cycles was obtained. After measurement of cardiac parameters, blood pressure at the brachial artery and body weight were measured.

Plasma sample measurements

Blood samples were collected from an antecubital vein in the supine position before and after 6 months of treatment. Plasma PIIIP level was measured with a specific immunoradiometric assay using a commercial kit (CIS Bio International, Nagoya, Japan).

Statistical analysis

Data are expressed as mean ± standard deviation (S.D.). Paired *t*-test was used for comparison of intragroup data. Linear regression analysis was used