Pioglitazone Rapidly Increases Serum Adiponectin Levels in Men With Normal Glucose Tolerance

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The thiazolidinedione (TZD) class of antidiabetic drugs has various pleiotropic effects on cardiovascular diseases and lipid metabolism (1). TZDs including pioglitazone have been shown to increase circulating adiponectin in diabetic subjects, although the mechanism is not well understood (2,3). Since, in previous studies, adiponectin levels in diabetic patients were evaluated after 3 weeks, or more, of pioglitazone treatment, elevated adiponectin may be, in part, secondary to improved lipid and glucose handling in these studies. In this study, we examined short-term effects of pioglitazone on serum adiponectin in non-diabetic subjects to assess the effect of pioglitazone independently of glycolipid metabolism.

The study comprised 10 men aged 28–42 years (34 ± 2 [mean ± SE]) with normal glucose tolerance, which was confirmed by 75-g oral glucose tolerance test. Subjects gave written informed consent, and the study was approved by the institutional review board of the University of Kochi Medical School. Study participants were treated with pioglitazone 30 mg/day for 14 days, and fasting blood samples were obtained at baseline, and at days 3, 7, 10 and 14 of pioglitazone treatment. The serum levels of total and high-molecular weight (HMW) adiponectin were measured using commercially available enzyme-linked immunosorbent assay kits (Otsuka Pharmaceuticals, Tokyo, Japan and Fujirebio, Tokyo, Japan, respectively).

Both total and HMW adiponectin levels rapidly increased within 3 days of pioglitazone treatment in all subjects, and continued to increase throughout the study (total adiponectin: 6.6 ± 1.0, 7.9 ± 1.2, 9.9 ± 1.6, 11.8 ± 1.9, and 13.7 ± 2.2 μg/ml [$P < 0.05$, repeated measures ANOVA] and HMW adiponectin: 4.3 ± 0.8, 5.2 ± 1.0, 7.0 ± 1.3, 8.4 ± 1.5, and 10.4 ± 1.9 μg/ml [$P < 0.05$] at days 0, 3, 7, 10, and 14, respectively). In addition, the HMW to total adiponectin ratio, which may be a useful predictor of insulin

resistance and metabolic syndrome (4), was significantly increased after 14 days (0.59 ± 0.06 to 0.72 ± 0.04, $P < 0.01$). On the other hand, pioglitazone treatment for 14 days did not change fasting plasma glucose (5.4 ± 0.1 to 5.4 ± 0.1 mmol/l), C-reactive protein (0.31 ± 0.07 to 0.30 ± 0.07 mg/l) or lipid profile (data not shown). Small decreases in fasting plasma insulin (7.0 ± 0.7 to 6.3 ± 0.8 μU/ml), homeostasis model assessment (HOMA) of insulin resistance (1.7 ± 0.2 to 1.5 ± 0.2), and leptin levels (4.2 ± 0.5 to 3.4 ± 0.3 ng/ml) were detected after 14 days, but they were not statistically significant. We cannot overlook the possibility that the combination of these minor metabolic effects may contribute to the increased adiponectin; however, these parameters had not changed after 7 days of pioglitazone treatment, when adiponectin levels were already elevated (data not shown).

Thus, pioglitazone rapidly increases serum adiponectin levels, which precedes changes in the status of glycolipid metabolism or inflammation. Our data strongly support the primary effect of pioglitazone on the regulation of circulating adiponectin.

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