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Does pioglitazone improve depression through insulin-sensitization? Results of a randomized double-blind metformin-controlled trial in patients with polycystic ovarian syndrome and comorbid depression

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Summary Thiazolidinediones have shown beneficial effects in short-term treatment of depression. However, it is unclear whether the antidepressant efficacy of these agents is related to their insulin-sensitizing action. We conducted the present study to compare the antidepressant efficacy of pioglitazone with another insulin-sensitizer, metformin, in obese patients with concomitant polycystic ovarian syndrome (PCOS) and major depressive disorder (MDD). In a six-week double-blind study, 50 patients with PCOS and MDD (DSM-IV-TR criteria) with Hamilton depression rating scale (HDRS) score of <20, randomly received pioglitazone (15 mg twice daily; PO) or metformin (750 mg twice daily; PO). Assessment was done using HDRS (weeks 0, 3, 6) together with fasting Insulin, glucose, and lipid profile, liver enzymes, homeostatic model assessment of insulin resistance (HOMA-IR), anthropometric measures, and serum androgens (weeks 0 and 6). Pioglitazone was superior to metformin in reducing HDRS scores at the end of the study [38.3% versus 8.3% reduction from baseline scores, $F(1, 37) = 73.513$, $P < 0.001$]. Changes from baseline in HOMA-IR values at week 6 were not significantly different between the two

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groups ($P = 0.888$). Baseline (but not follow-up) HDRS and HOMA-IR values were significantly correlated ($r = 0.393$, $P = 0.012$). In multiple regression analysis, treatment with pioglitazone independent of HOMA-IR values predicted greater score reduction on HDRS at week 6 (standardized beta = 0.801, $P < 0.001$). Biochemical and hormonal profile did not differ between the two groups at week 6. Metformin was associated with higher frequency of gastrointestinal side effects ($P = 0.014$). In summary, we showed that pioglitazone improved depression with mechanisms largely unrelated to its insulin-sensitizing action (registration number: IRCT201106081556N23).

1. Introduction

Pioglitazone, a thiazolidinedione (TZD), is an insulin sensitizer which is currently approved for treatment of diabetes mellitus type 2. This drug exerts its effect through activation of peroxisome proliferator-activated receptor (PPAR)-gamma, a mechanism which seems to account not only for its insulin-sensitizing action but also probably for its several other unique properties (Spiegelman, 1998). PPAR-gamma agonists, including pioglitazone, have beneficial effect on lipid metabolism, exert potent central and peripheral anti-neuroinflammatory actions, and show significant neuroprotective properties (Garcia-Bueno et al., 2010; Heneka and Landreth, 2007). Several animal and human studies have demonstrated advantageous effects of TZDs on neurological and psychiatric conditions including autism (Boris et al., 2007), Alzheimer's disease (d'Abramo et al., 2006; Miller et al., 2011), multiple sclerosis (Kaiser et al., 2009), and major depressive disorder (MDD) (Rosa et al., 2008; Eissa Ahmed and Al-Rasheed, 2009; Kemp et al., 2009, 2012; Salehi-Sadaghiani et al., 2012; Sepanjnia et al., 2012). Several small studies in human with MDD and concomitant metabolic syndrome or insulin resistance have shown significant antidepressant effect for TZDs (Rasgon et al., 2010; Kemp et al., 2012). A recent trial by our group has provided evidence for adjunctive effect of pioglitazone in treatment of patients with MDD who did not have metabolic syndrome (Sepanjnia et al., 2012).

Patients with polycystic ovarian syndrome (PCOS) frequently experience mild to moderate mood disturbances, which might be partly explained by insulin resistance, higher BMI, and lower androgen levels in these patients (Barry et al., 2011; Jedel et al., 2011). However, not all studies have provided evidence for these explanations (Jedel et al., 2010). On the other hand, TZDs have demonstrated significant efficacy for treatment of metabolic problems in these patients (Aroda et al., 2009; Kim et al., 2010, 2011; Du et al., 2012). TZDs reduce insulin resistance and fasting glucose (Aroda et al., 2009; Du et al., 2012), treat menstrual irregularities (Yilmaz et al., 2005), improve ovulation rates (Legro et al., 2007), and decrease concentration of inflammatory cytokines (Kim et al., 2011) in patients with PCOS. These effects are despite the fact that TZDs are associated with an increase in BMI.

Insulin resistance and impaired glucose tolerance is associated with higher frequency of depression (Koponen et al., 2008; Almeida et al., 2009). There seems to be a bidirectional relation between mood and metabolic disturbances including PCOS (Koponen et al., 2008; Barry et al., 2011). In some cases, treatment of insulin resistance seems to be associated with improvement in depression as well (Rasgon et al., 2002). Therefore, an important question regarding pioglitazone is whether the antidepressant effect of this drug is exerted through insulin sensitization or is related to other actions of PPAR-gamma agonists. All previous human studies except one (Sepanjnia et al., 2012) have provided evidence for antidepressant properties of pioglitazone in patients with concomitant metabolic disturbances although some also showed that the antidepressant effect of pioglitazone is minimally related to its insulin-sensitizing action. Even though excluding patients with significant metabolic disturbances, a recent study by our group could not firmly answer the above mentioned question about the mechanism of depression improvement by pioglitazone, primarily due to lack of follow-up metabolic data (Sepanjnia et al., 2012).

We conducted the present study to answer the question: Are the antidepressant properties of pioglitazone independent of its insulin-sensitization properties?

Our aim was to evaluate the short-term antidepressant efficacy of pioglitazone compared with another insulin-sensitizer, metformin, in patients with concomitant PCOS and MDD. We selected the metformin because it is nearly similar to its degree of insulin sensitization to pioglitazone whereas, the mechanisms of action of the two drugs differ. Both drugs improved insulin sensitivity as shown by HOMA-IR whereas only pioglitazone have been shown that improves depression (Sepanjnia et al., 2012). Regarding mechanisms of action, metformin similar to TZDs do not influence insulin concentrations and therefore is not associated with hypoglycemia (Phielix et al., 2011). Both metformin and TZDs effectively enhance insulin sensitivity in the liver and the brain, improve homeostatic model assessment of insulin resistance (HOMA-IR) values, increase hepatic glucose uptake, and decreases hepatic gluconeogenesis (Monte et al., 2010; Gupta et al., 2011; Pipatpiboon et al., 2012).

2. Methods

2.1. Trial setting and design

This was a six-week, randomized, controlled, double-blind, and parallel-group study conducted in outpatient clinics of two tertiary referral gynecology centers (Arash Hospital, and Vali-Asr Hospital) affiliated with Tehran University of Medical Sciences, Tehran, Iran from July 2011 to May 2012.

2.2. Changes to trial design

In the original protocol, the trial design was based on three visits at baseline, weeks 4, and 8. To decrease the time of follow-up and therefore the loss-to-follow-up rates we changed the visit schedule to baseline, weeks 3, and 6. The changes were considered at the beginning of the study.

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