COMMENTARY

Changes in bone biological markers after treatment of Iranian diabetic patients with pioglitazone: No relation to polymorphism of PPAR-γ (Pro12Ala)

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Sir

The article "Changes in bone biological markers after treatment of Iranian diabetic patients with pioglitazone: No relation to polymorphism of PPAR-γ (Pro12Ala) that published in recent issue encourage us to think about changes of bone mineral density with commonly used drugs to control hyperglycemia in type 2 diabetic patients.

Thiazolidinediones including pioglitazone are agents that lower blood glucose by improving target cell response to insulin.[1] Pioglitazone is a selective agonist for peroxisome proliferator-activated receptor-gamma (PPAR-γ). Activation of nuclear PPAR-γ receptors influences the production of a number of gene products involved in glucose metabolism.[2] There are also evidences that these drugs could affect the process of bone remodeling. In animal studies, PPAR-γ agonist treatment was followed by increased bone loss and impaired osteoblast function.[3] Few human studies evaluated the effects of treatment with PPAR agonist on BMD and measures of bone turnover. Activation of PPAR-γ pathway by an endogenous PPAR-γ ligand inhibited the formation and activation of osteoclasts in human mesenchymal stem cells.[4]

In a randomized study of healthy postmenopausal woman by Gray *et al*., to evaluating the effect of PPAR agonist treatment on BMD levels, treatment with rosiglitazone, a thiazolidinedione, was associated with decreased markers of bone formation and significantly decreased BMD after 14 weeks of regular use compare to placebo.[5]

In the ADOPT study, including women from 30-60 years of age with type 2 diabetes, increased numbers of peripheral fractures were reported in patients treated with the thiazolidinedione rosiglitazone.[6] A Previous study in humans on the effects of PPAR-γ agonist treatment on fracture risk and BMD in patients with diabetes showed that adverse effects were seen in women only.[7]

The human genome is highly polymorphic for common variation that confers susceptibility to common, complex diseases. These variants typically confer much weaker effects than variants associated with monogenic diseases, and must interact with other genes and environmental triggers to establish disease. This polymorphism may be responsible for variable cellular response to therapeutic or side effects of a drug.[8]

It is known that pro12Ala polymorphism of PPAR-γ reduces the transcriptional activity of PPAR and is involved in the pathogenesis of insulin resistance, and Osteoporosis.[9] There is also some evidence that varied effect of thiazolidinediones in bone markers may be due to polymorphism of PPAR-γ genes. Rhee *et al*., have reported the Pro12Ala polymorphism is significantly associated with lower serum OPG level as a key inhibitor of osteoclastogenesis, thus in favor of decrease bone density,[9] but this sample of Iranian population have shown that the Pro12Ala polymorphism is not associated with low BMD at the lumbar spine and femoral neck. Currently, there are few data available on the skeletal actions of Pro12Ala in humans.

According to available data, in both pre and postmenopausal diabetic women, long term follow-up studies are need to determine subgroup of patients, who are high risk for bone loss with thiazolidinediones use.

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