Dear Sirs,

The article by Kapoor et al. reports that rosiglitazone increases testosterone (bioavailable, free and total) levels in hypogonadal men with type 2 diabetes. These findings are important because they support the view that in men, both the evolution and some of the manifestations of type 2 diabetes are partially the result of testosterone deficiency rather than due to insulin resistance alone. This can be viewed as the hypogonadal-metabolic-atherogenic disease and aging connection.

In their discussion, the authors hypothesise that the effect of rosiglitazone on testosterone is the result of a hypogonadal-obesity-adipocytokine cycle. They propose that this occurs because of a reduction in visceral fat mass which then results in decreased aromatase activity and therefore a diminished conversion of testosterone to oestradiol.

Although these explanations are reasonable and adequate, there are other issues to be considered as well. First, peroxisome proliferator-activated receptor (PPAR) gamma agonists such as rosiglitazone promote adipocyte differentiation, which may be associated with decreased aromatase activity. Second, rosiglitazone inhibits 11beta-hydroxysteroid dehydrogenase-1 (11beta-HSD-1) activity thereby improving insulin sensitivity by decreasing the activation of cortisol as well as its effect on adipocyte proliferation and fat cell mass. Finally, hypotestosteronemia might reduce the androgenic inhibitory effects that usually limit adipogenesis and which ordinarily interfere with the expansion of adipose tissue mass.

Visceral adiposity, along with an expanded total body fat mass, is associated with greater aromatase and 11beta-HSD-1 activity. The increased aromatase activity results in the reduction of testosterone and increased production of oestradiol, both of which allow for continued adipogenesis and the ongoing cycle of cooperation between enzymes. The results of this clinical study suggest that the beneficial effects of rosiglitazone may in part be due to interruption of this cycle.

Conflict of interest statement
None declared.

References