Carruthers M, Trinick TR, Jankowska E, Traish AM. Are the adverse effects of glitazones linked to induced testosterone deficiency? Cardiovasc Diabetol 2008; 7: 30.(23063) BACKGROUND: Adverse side-effects of the glitazones have been frequently reported in both clinical and animal studies, especially with rosiglitazone (RGZ) and pioglitazone (PGZ), including congestive heart failure, osteoporosis, weight gain, oedema and anaemia. These led to consideration of an evidence-based hypothesis which would explain these diverse effects, and further suggested novel approaches by which this hypothesis could be tested. PRESENTATION OF HYPOTHESIS: The literature on the clinical, metabolic and endocrine effects of glitazones in relation to the reported actions of testosterone in diabetes, metabolic syndrome, and cardiovascular disease is reviewed, and the following unifying hypothesis advanced: "Glitazones induce androgen deficiency in patients with Type 2 Diabetes Mellitus resulting in pathophysiological changes in multiple tissues and organs which may explain their observed clinical adverse effects." This also provides further evidence for the lipocentric concept of diabetes and its clinical implications. TESTING OF THE HYPOTHESIS: Clinical studies to investigate the endocrine profiles, including measurements of TT, DHT, SHBG, FT and estradiol, together with LH and FSH, in both men and women with T2DM before and after RGZ and PGZ treatment in placebo controlled groups, are necessary to provide data to substantiate this hypothesis. Also, studies on T treatment in diabetic men would further establish if the adverse effects of glitazones could be reversed or ameliorated by androgen therapy. Basic sciences investigations on the inhibition of androgen biosynthesis by glitazones are also warranted. IMPLICATIONS OF THE HYPOTHESIS: Glitazones reduce androgen biosynthesis, increase their binding to SHBG, and attenuate androgen receptor activation, thus reducing the physiological actions of testosterone, causing relative and absolute androgen deficiency. This hypothesis explains the adverse effects of glitazones on the heart and other organs resulting from reversal of the action of androgens in directing the maturation of stem cells towards muscle, vascular endothelium, erythroid stem cells and osteoblasts, and away from adipocyte differentiation. The higher incidence of side-effects with RGZ than PGZ, may be explained by a detailed study of the mechanism by which glitazones down-regulate androgen biosynthesis and action, resulting in a state of androgen deficiency.