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EDITORIAL COMMENT

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The effects of the peroxisome proliferator-activated receptor agonists pioglitazone and rosiglitazone on serum lipids are well recognized. It appears that the two commonly used glitazones differ in their effects on lipid metabolism, and these differences may be significant in light of the suggestion that rosiglitazone treatment is associated with an increase in cardiovascular risk, which is not seen to the same extent (if at all) with pioglitazone. Several studies have confirmed that, when compared with placebo, rosiglitazone increases total cholesterol, LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C), but has little effect on triglycerides. Pioglitazone has somewhat different effects, with a greater increase in HDL-C, a less consistent increase in total cholesterol and LDL-C and a reduction in triglycerides. One direct comparison of rosiglitazone and pioglitazone in over 800 patients confirmed these trends, despite no difference in effect on glycaemic control [1].

As yet, there is no clear explanation for the differential effects of the two glitazones on lipoprotein metabolism, and Brackenridge *et al.* [2•] sought to explore this in a study that investigated secretion and catabolism of VLDL, IDL and LDL following an infusion of ^{13}C-labelled leucine. The study was carefully conducted in 24 patients with type 2 diabetes, but found only modest changes in lipid-related parameters with either drug. Many previous studies looking at the effects of glitazones on lipid metabolism have been conducted in patients with relatively poorly controlled lipids; in the study by Brackenridge *et al.* [2•], base line lipid control was closer to current standards, with baseline LDL-C less than 3.0 mmol/l, HDL-C more than 1.0 mmol/l and triglycerides less than 2.0 mmol/l. They observed some trends towards differences between the two drugs, in particular, pioglitazone produced a modest decrease in LDL-C from 2.8 to 2.4 mmol/l, whereas with rosiglitazone, there was an increase in LDL-C from 2.4 to 2.6 mmol/l. This was accompanied by a shift in the distribution of LDL subfractions towards a larger and more buoyant distribution, which would be anticipated to somewhat ameliorate the effect of an increase in LDL-C concentration. However, overall the increase in LDL-C is likely to be harmful. With both glitazones, there was a reduction in VLDL triglyceride/apolipoprotein B, indicating a decrease in large VLDL particles. The study was powered to detect a 45% difference in VLDL production rate at a 5% level of significance, and, therefore, could have missed quite substantial differences between the glitazones in effects on lipid metabolism. Therefore, the explanation for the differences consistently observed in other studies remains unclear.

Another class of drugs with harmful effects on lipid metabolism are the second-generation antipsychotics. These effects are secondary in part to weight gain, and are associated with an increase in insulin resistance [3]. Lifestyle measures to prevent weight gain following the initiation of treatment can be effective [4], but there has also been interest in the role of insulin sensitizers, including the glitazones. Henderson *et al.* [5•] have reported a small, randomized trial of rosiglitazone vs. placebo in patients starting on clozapine. There was no significant weight gain, perhaps reflecting effective lifestyle support, and, consequently, there was no evidence of deterioration in metabolic parameters in the placebo group following the initiation of clozapine. The combination of rosiglitazone with clozapine was associated with trends towards improving insulin sensitivity and glucose utilization, and a reduction in small, dense LDL particles and a trend towards increased LDL size. One small previous study [6] has similarly investigated the effects of coadministration of rosiglitazone with olanzepine, showing an improvement in insulin sensitivity but no improvement in the lipid profile. Metformin represents an alternative [7], and perhaps has a stronger evidence base in its favour if lifestyle measures are ineffective, but it is clear that further work is required to understand the mechanisms underlying the adverse effects of antipsychotics on lipid metabolism.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1 Goldberg RB, Kendall DM, Deeg MA, *et al.* A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. Diabetes Care 2005; 28:1547–1554.

2 • Brackenridge AL, Jackson N, Jefferson W, *et al.* Effects of rosiglitazone and pioglitazone on lipoprotein metabolism in patients with type 2 diabetes and normal lipids. Diabet Med 2009; 26:532–539.
Rosiglitazone and pioglitazone have differential effects on lipid metabolism, and the mechanisms behind this observation remain poorly understood. This study uses ^{13}C-labelled leucine infusion to study lipoprotein kinetics, but fails to find any clear difference between the two drugs.

3 Olfson M, Marcus SC, Corey-Lisle P, *et al.* Hyperlipidemia following treatment with antipsychotic medications. Am J Psychiatry 2006; 163:1821–1825.

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4 Wu RR, Zhao JP, Jin H, *et al.* Lifestyle intervention and metformin for treatment of antipsychotic-induced weight gain: a randomized controlled trial. JAMA 2008; 299:185–193.

5 • Henderson DC, Fan X, Sharma B, *et al.* A double-blind, placebo-controlled trial of rosiglitazone for clozapine-induced glucose metabolism impairment in patients with schizophrenia. Acta Psychiatr Scand 2009; 119:457–465.

Weight gain in patients receiving antipsychotic treatment is a significant clinical problem leading to increased cardiovascular risk. This study suggests that a glitazone modestly improves some of the metabolic consequences, but larger and longer term clinical studies are clearly required.

6 Baptista T, Rangel N, El Fakih Y, *et al.* Rosiglitazone in the assistance of metabolic control during olanzapine administration in schizophrenia: a pilot double-blind, placebo-controlled, 12-week trial. Pharmacopsychiatry 2009; 42:14–19.

7 Bushe CJ, Bradley AJ, Doshi S, Karagianis J. Changes in weight and metabolic parameters during treatment with antipsychotics and metformin: do the data inform as to potential guideline development? A systematic review of clinical studies. Int J Clin Pract 2009; 63:1743–1761.

Further recommended reading

Laatsch A, Merkel M, Talmud PJ, *et al.* Insulin stimulates hepatic low density •• lipoprotein receptor related protein 1 (LRP1) to increase postprandial lipoprotein clearance. Atherosclerosis 2009; 204:105–111.

Insulin improves clearance of postprandial lipoproteins, and there is a strong association between insulin resistance and postprandial dyslipidaemia. This study shows that one of the mechanisms involved is stimulation by insulin of translocation of hepatic lipoprotein receptor-related protein 1 (LRP-1) from storage vesicles to the plasma membrane, where uptake of LRP-1 ligands is increased.

Leung WC, Hessel S, Meplan C, *et al.* Two common single nucleotide polymorph- •• isms in the gene encoding beta-carotene 15,15'-monoxygenase alter betacarotene metabolism in female volunteers. FASEB J 2009; 23:1041–1053.

Beta-carotene is a provitamin A carotenoid, and it has long been recognized that there is considerable interindividual variation in conversion to retinol. This study reports two single-nucleotide polymorphisms in female volunteers, which begin to explain this phenomenon.

Kastarinen H, Horkko S, Kauma H, *et al.* Low-density lipoprotein clearance in • patients with chronic renal failure. Nephrol Dial Transplant 2009; 24:2131–2135.

Impairment of LDL clearance in dialysis patients is well established. This study extends the observation of reduced clearance to patients with reduced renal function not requiring dialysis. The clearance of LDL is related to the severity of renal impairment, but a substantial reduction is only observed in advanced renal failure.