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# Pioglitazone

## A Viewpoint by John R. Petrie

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As β-cell dysfunction progresses, many patients with type 2 diabetes eventually require combinations of oral therapies and subsequently insulin. The rather disappointing effect sizes for prevention of end-points (microvascular and macrovascular) in the UK Prospective Diabetes Study have been seen by some as an indictment of the overall strategy of lowering blood glucose levels. However, this may have been a reflection of the inability of currently available glucose lowering therapies to maintain glycaemic targets in the intensive treatment group. Thiazolidinediones were hailed at their introduction in 1997 as the first 'insulin sensitisers': antihyperglycaemic drugs with a mechanism of action relevant to the pathophysiology of type 2 diabetes mellitus. They have now been used in more than a million patients.

Thiazolidinediones lower blood glucose levels, partially correct dyslipidaemia associated with type 2 diabetes mellitus and may alleviate associated hypertension. Like troglitazone and rosiglitazone before it, pioglitazone acts as an agonist at a nuclear receptor known as PPAR-γ, which controls a variety of key genes involved in regulating lipid metabolism. These receptors have been characterised extensively from a molecular point of view over the last 5 years, but the physiological basis of the 'insulin sensitising' effect of the thiazolidinediones remains controversial. The prevailing view is that they primarily promote differentiation of adipocytes, with indirect 'insulin sensitising' effects secondary to the removal of triglycerides from skeletal muscle. However, the known expression of PPAR-γ at lower levels in other tissues, together with the observation that thiazolidinediones efficiently lower blood glucose levels in aP2/DTA mice (which have no adipose tissue), suggest a more direct interface between PPAR-γ and insulin signalling.

For the clinician, the central issue with thiazolidinediones is safety. With troglitazone, serious hepatic adverse events were too rare (1 in 15 000) to be encountered in premarketing studies (usually fewer than 10 000 patients), but were severe enough to require eventual withdrawal from clinical use worldwide. At the time of writing there have been at least 2 case reports of hepatic failure with rosiglitazone (10 months post-launch), which suggests a better safety profile than that of troglitazone. Safety data for the newcomer, pioglitazone, are available from premarketing studies similar in size to those that were available before marketing of the other 2 drugs.

It is hoped that extremely rare but potentially serious adverse events with the remaining thiazolidinediones can be prevented via awareness of the need for careful monitoring of liver function and prompt withdrawal of therapy. If this is the case, thiazolidinediones will become an increasingly important part of the therapeutic armamentarium as confidence increases. However, with increasing knowledge of the complex downstream mechanisms of PPAR-γ action, future agents may be designed as modulators rather than direct agonists of this receptor. ▲