Thiazolidenediones and the metabolic syndrome

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Insulin resistance is defined as an impaired biological response to insulin and is a primary defect in type 2 diabetes (T2DM). To describe the metabolic syndrome as a combination of glucose intolerance, hyperlipidaemia and hypertension in association with central obesity is simplistic, but it remains a good clinical description of this cardiovascular disease which we are seeing in ever increasing numbers worldwide. However, it is a complex disorder with not only the metabolic disturbances already described, but also abnormalities of clotting, vascular reactivity and endothelial dysfunction, leading to premature, generalised vascular disease. In non-diabetic individuals, insulin resistance in combination with hyperinsulinaemia has a strong predictive value for the future development of T2DM.

The fact that most available treatments for T2DM have focussed largely on lowering blood sugar simply reflects the delayed realisation that diabetes is a progressive metabolic disorder, of which hyperglycaemia is but one component. The traditional treatments (sulphonylureas, insulin and metformin) have limited efficacy and, in the majority of people with T2DM, glycaemic control deteriorates relentlessly due to worsening insulin resistance and declining insulin secretory reserve.[1]

The metabolic syndrome is characterised by:

- Central obesity
- Hypertension
- Raised triglycerides
- Low HDL
- Glucose intolerance
- Insulin resistance

The metabolic syndrome seems to be a polygenic disorder appearing when genetically susceptible individuals experience a significant environmental change. For example, the Pima Indians of North America were once a subject of scientific interest when, at the beginning of the 20th century, they were investigated because of the apparent lack of diabetes. In less than a hundred years, a change in environment from hunter-gatherer to urban consumer, has resulted in a population with almost the highest prevalence of diabetes in the world.

The person with the metabolic syndrome is a heterogeneous individual: some manifest specific components of the syndrome such as hypertension and glucose intolerance whilst in others severe hyperlipidaemia accompanies relatively minor abnormalities of glucose tolerance. Microalbuminuria, another manifestation of the disorder, appears to be a surrogate marker of a generalised vasculopathy and indicates increased risk of death from a cardiovascular cause. Although it does not predict progression to frank nephropathy in the same way as it does in type 1 diabetes (mainly because death occurs from a cardiovascular cause before end-stage renal failure is reached), some groups are much more likely to develop renal failure secondary to their diabetes. The New Zealand Maori, for example, have an eightfold incidence of death from renal failure compared to New Zealand Europeans with T2DM.

So what are the environmental triggers that precipitate the metabolic syndrome? We are uncertain, although the association obesity and a sedentary lifestyle seem to be likely triggers, as their changing prevalence closely mirrors the epidemic of T2DM. Others have suggested that it is not just genes and environment but the foetal environment which is to blame, citing retrospective studies of low birth weight babies and demonstrating their future predisposition to develop coronary heart disease and T2DM particularly if they become obese in later life.[2] Whilst this association exists, it seems unlikely to be the sole explanation for the current

increased incidence of T2DM worldwide.

Can the progression to diabetes be halted? The answer is uncertain, but several studies have shown that weight reduction and increased physical activity can slow the progression from impaired glucose tolerance to frank diabetes. Patients with established diabetes show improvements in all aspects of the syndrome with these interventions, but normalisation of the metabolic environment has not been shown. Intuitively, it appears that the later the diagnosis is made, the less effective are any of the interventions, and the UKPDS study demonstrated this for the first time (Figure 1) in a large cohort of patients with apparently newly presenting T2DM. These patients had a high prevalence of complications at presentation and evidence from studies of the progression of retinopathy suggests that most people who present with symptomatic T2DM (as opposed to asymptomatic individuals screened with glucose tolerance tests) are thought to have had frank diabetes for between eight and 12 years and impaired glucose tolerance for many years before this.

Although ethnic differences exist, the main determinates of insulin resistance are the degree of central obesity, age and physical activity. Other factors include pregnancy and drugs such as steroids and beta-blockers.

Figure 1. Glycaemic control in Conventional and Intensive groups of UKPDS over duration of the study

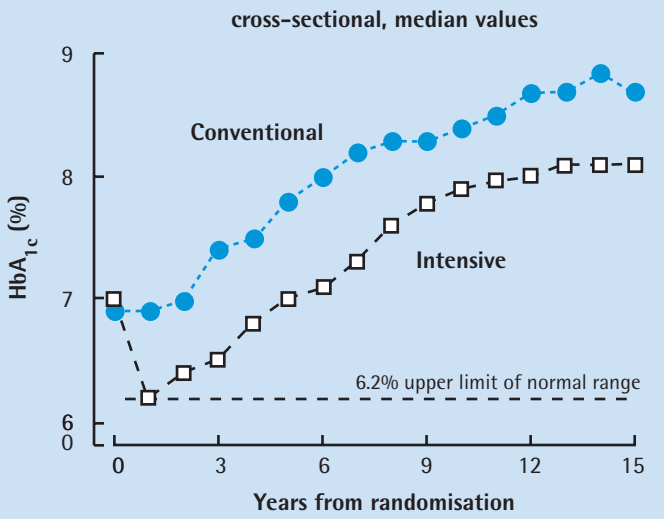


Diagram: UKPDS

How should we judge new therapies for type 2 diabetes?

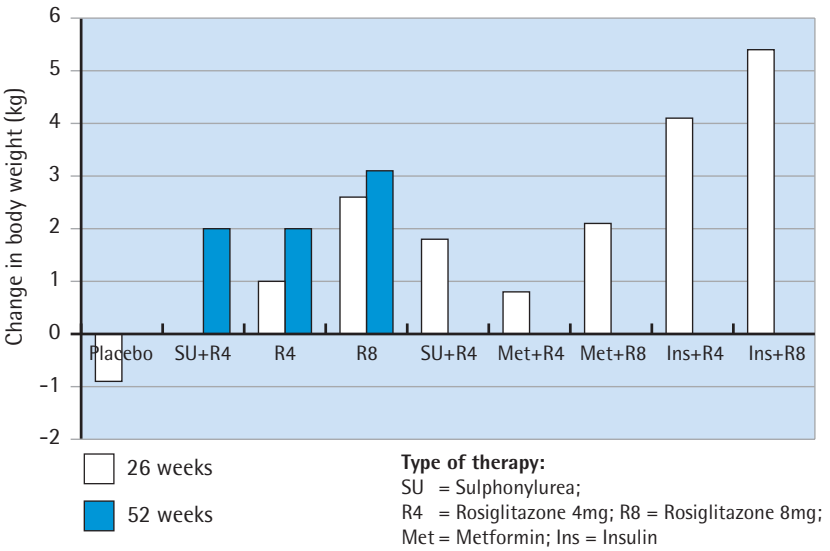
This article will focus on new approaches to dealing with the issue of insulin resistance, using the new insulin sensitisers: the thiazolidenediones.

With a trial as formidable as the UK Prospective Diabetes Study to refer to, we need to be quite clear about what we are hoping to achieve when using new drugs for T2DM outside the context of a trial. The clinician might look for the following features in a new drug:

- Superior glycaemic control to currently available treatments – either alone or in combination, OR
- Novel properties that result in, for example, preservation of ß-cell function, OR
- Long-term safety data, similar improvements in glycaemia and reduction in complications as with existing therapies, OR
- Long-term weight reduction, OR
- Improvement in other aspects of the metabolic syndrome.

In the following section I have tried to evaluate how well the glitazones meet these criteria.

Figure 2. Effect of Rosiglitazone on body weight from a range of trials where Rosiglitazone used alone or in combination with other therapies



Effects of thiazolidenediones on the metabolic syndrome

Thiazolidenediones (TDZ) are a relatively new group of drugs including rosiglitazone and pioglitazone. The first molecule to be marketed was troglitazone, which was withdrawn due to hepatic toxicity. TDZ act through the perioxisome proliferator-activated receptor γ (PPAR γ) and lower glucose by acting as an insulin sensitiser, improving glucose uptake by liver

muscle and fat and reducing hepatic glucose output. Thus, both glucose and insulin levels fall, which may 'rest' the beta cells. Studies using these agents have been relatively short-term but fasting blood sugars have shown no deterioration over 2.5 years, either as monotherapy or in combination with sulphonylurea or metformin. It must be remembered however that the UKPDS study lasted 12–15 years and it is premature to claim that glitazones 'preserve pancreatic function'. There are at least two long-term studies in progress which, if confirmed, will have a major impact on the early treatment of patients with the metabolic syndrome. One of these is looking at the effects of rosiglitazone in patients with established T2DM (A Diabetes Outcome Progression Trial – ADOPT). In this study, time to failure of monotherapy as the primary outcome measure will compare rosiglitazone 8mg daily with metformin 2g/day or glibenclamide 15mg. DREAM (Diabetes Reduction Approaches with ramipril and rosiglitazone Medications) is a four-year study observing the effect of medication on patients with IGT.

In general, TDZ are relatively weak hypoglycaemic agents resulting in mean falls in HbA1c of up to 1% either alone or in combination with sulphonylureas, metformin or repaglinide. As monotherapy they do not cause hypoglycaemia and are well tolerated. The licensing authorities around the world have granted use for differing indications, but in Europe this has been limited to combination treatment with either a sulphonylurea or metformin. Monotherapy and combination therapy with insulin have not been permitted, although logically this is perhaps where most benefit may be seen. The problem has been the lack of good head-to-head studies with current therapies. Consequently, use has been mainly in patients who are approaching secondary failure where the results are predictably disappointing. If the patient is already on combination therapy with a sulphonylurea and metformin, and one of them is discontinued (the licence did not encourage triple therapy for which there was even less data) there is initially a worsening of control as it can take several weeks for the effects of TDZ to kick in.

How should we judge new therapies for type 2 diabetes?

- Achieves superior glycaemic control to currently available treatments – either alone or in combination?
- OR novel properties that result in preservation of ß-cell function
- OR long-term safety data demonstrating similar improvements in glycaemia and reduction in complications as with existing therapies
- OR induce significant long-term weight reduction
- OR improvement of other aspects of metabolic syndrome

Monotherapy is approved in the US and other countries, but elsewhere worries about cost and long-term safety (compared to established therapies) remain issues. Studies with troglitazone showed that some of the maximum falls in blood glucose were achieved in combination with insulin, but pre-licensing studies with rosiglitazone and pioglitazone found an increased number of patients with Congestive Heart Failure (CHF) in the insulin and glitazone group. This could be due to fluid retention, which is known to occur (average weight gain approximately two to three kilograms) – Figure 2 – or increased vascular permeability which has been demonstrated in vitro in isolated pulmonary arteries. Many patients experience mild peripheral oedema with these drugs. Outcome studies are needed before TDZ are used in patients with known CHF or routinely with insulin. However, there are situations where, with informed consent, their combined use could be justified, e.g. poorly controlled symptomatic patients already on large doses of insulin with metformin or a sulphonylurea. In this situation some sort of assessment of left ventricular function should be undertaken, but even then, combination therapy should be reserved for patients where other efforts have been made to 'rescue' the patient with either a Very Low Calorie Diet (VLCD) or insulin doses up to 3u/kg.

Effects of thiazolidenediones on the metabolic syndrome

- Beneficial effects on BP, insulin resistance
- Lowers triglycerides
- Increases HDL
- Increase in LDL (but increase in LDL-particle size)
- Fat redistribution from central to peripheral

Other effects of thiazolidenediones

TDZ have a number of effects apart from lowering blood glucose, most of them beneficial. Hypertension is extremely common in people with T2DM and, as with blood glucose, this tends to worsen with time. Patients taking TDZ experience a small fall in systolic and diastolic BP compared to patients on sulphonylureas who sustained a rise in systolic BP. These effects were sustained for one year.

Fibrinolysis is abnormal in T2DM and this may relate to high levels of plasminogen-activator inhibitor-1 (PAI-1) compared to non-diabetics. In a comparative study of placebo or rosiglitazone 4mg bd with glibenclamide 10mg daily for 26 weeks, PAI-1 antigen levels fell by 34%.

Endothelial dysfunction, as assessed by falling levels of nitric oxide synthetase, and asymetric dimethylarginine, improved and cardiovascular risk factors such as C-Reactive protein fall.

Small studies of the effects of rosiglitazone on patients with

microalbuminurua demonstrated a reduction in the albumin/ratio of 54% compared to only 23% in patients on glibenclamide. Whether this relates to improvements in glycaemic control, a reduction in BP or other mechanisms is uncertain.

The typical lipid profile of someone with the metabolic syndrome is a raised LDL-cholesterol, low HDL-C and elevated triglycerides (TG). The LDL particles are particularly small, dense and more atherogenic than LDL sub-fractions in non-diabetics. Rosiglitazone causes a small rise in LDL-C, which gradually falls back to pre-treatment levels with time. The claim that the LDL is of a less atherogenic quality (lighter and larger) remains to be seen but any negative effects are offset by a rise in HDL and a fall in TG. The overall effect is somewhat neutral but only outcome studies will determine whether these effects are neutral, beneficial or harmful.

The other universal effect of the TDZ class of drugs, are the effects on fat distribution, organ weight and fluid retention.

Animal and some human studies have suggested that there is a redistribution of body fat from central to peripheral. Hepatic fat is reduced, visceral fat unaffected or decreased. This could be beneficial except that peripheral fat hyperplasia occurs offering the potential of future fat deposition should further weight gain occur. Whether it is relevant to clinical practice has yet to be determined.

Who is suitable for a thiazolidenedione ?

- Obese patients intolerant of metformin who have sub-optimal control on adequate doses of a sulphonylurea.
- Patients with a raised creatinine (>0.15mmol/l) in whom metformin is contraindicated with sub-optimal control on maximum doses of gliclazide or glipizide (glibenclamide is contraindicated in renal impairment).
- Patients with sub-optimal control despite maximum doses of a sulphonylurea and metformin when insulin therapy may need to be deferred e.g. employment such as a lorry driver, severe needle phobia.

Who is unsuitable for a thiazolidenedione?

- Patients with a history of cardiac failure.
- Patients on insulin.
- Patients with active liver disease or ALT > 2.5x normal.

Haemodilution occurs due to fluid retention and an expansion of plasma volume. Haematocrit falls and in all animal species studied, heart muscle mass increases – an effect thought to be due to the increase in pre-load (from plasma volume expansion).

None of the hepatic toxicity problems seen with troglitazone have been documented with either rosiglitazone or pioglitazone, but treatment should not be initiated in patients with active liver disease or where ALT >2.5x the upper limit of normal. Minor abnormalities of liver function are very common in patients with T2DM – usually due to fatty deposition. There is no requirement for dose reduction with increasing age or renal impairment.

The lack of long-term studies precludes them from replacing our traditional first line agents but they may be a very useful addition when glycaemic control fails to stay within target despite maximum doses of a sulphonylurea or metformin

In summary, therefore, this is an exciting new class of drugs offering potential benefits to patients at all ends of the spectrum of the metabolic syndrome. The lack of long-term studies precludes them from replacing our traditional first line agents but they may be a very useful addition when glycaemic control fails to stay within target (HbA1c 7% or better) despite maximum doses of a sulphonylurea or metformin. Patients should be warned that they will not see an immediate fall in blood sugar, but a slow steady improvement over many weeks. Patients already on dual therapy with a sulphonylurea and metformin should probably have a month or so of triple therapy (particularly if symptomatic) before withdrawing one of the initial agents. In my experience I have been surprised how many patients want to try triple therapy before considering insulin. Provided goals and time limits are set, this seems to be a reasonable alternative to insulin plus metformin which also has its drawbacks, not least of which is a mean weight gain of 6kg. Unfortunately, T2DM remains a very difficult condition to treat, but TDZ are a useful addition to our armamentarium. No double blind comparative studies of pioglitazone or rosiglitazone yet have been completed.

References

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