

Metformin and The United Kingdom Prospective Diabetes Study: A Commentary

revisão

INTRODUCTION TO UKPDS

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The United Kingdom Prospective Diabetes Study (UKPDS) was the largest and longest trial ever conducted into diabetes mellitus. This landmark study was set up in 1977, recruited 5,012 patients with type 2 diabetes mellitus (DM) from 23 centres in the UK, and finished at the end of 1997, with the initial final results published in two papers in the *Lancet* and in a further three papers in the *British Medical Journal* in September 1998 (1-5), at the same time as the results were first presented publically at the European Association for the Study of Diabetes (EASD) meeting in Barcelona.

The study was co-ordinated by the late Professor Robert Turner and his colleagues in Oxford, UK.

The UKPDS asked *two* principle questions:

1. Can the risk of complications in type 2 DM be reduced by *intensive* blood glucose control?
2. In type 2 DM subjects with hypertension, can the risk of complications be reduced by *tight* blood pressure control?

The two principal positive conclusions from the UKPDS were:

1. *Intensive blood glucose reduction is worthwhile.*
2. *Tight blood pressure control will show clear benefits.*

These results have been widely published and reviewed in the scientific literature (6-9), with regard to stressing the importance of both glycaemic and blood pressure control in type 2 DM. The UKPDS is the abiding legacy of Robert Turner (10).

In the UKPDS, intensive blood glucose control with sulphonylureas or insulin, compared with conventional treatment (diet alone), with a 11% difference in glycated haemoglobin maintained over 10 years (mean 7.0% compared to 7.9%) showed a 25% reduction in microvascular complications but no significant benefit was seen in macrovascular complications (1).

However, in the overweight patients where metformin was an additional option in therapy to sulphonylureas or insulin, there were definite and significant benefits in macrovascular end points observed. This short review will highlight these positive outcomes seen with metformin therapy.

METFORMIN IN TYPE 2 DIABETES MELLITUS

Metformin has been used for over 40 years as an effective glucose-lowering agent in type 2 DM. Typically it reduces both basal and post-prandial hyperglycaemia by about 25-30% on over 90% of type 2 DM patients when given either alone or in combination with other therapies, either sulphonylureas or insulin.

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In a meta-analysis of published controlled, randomised, prospective trials of metformin compared to sulphonylurea therapy between 1957 and 1994, metformin was shown to have comparative glycaemic efficacy with both first- and second-generation sulphonylureas but there was a weight benefit in favour of metformin (11). A daily dose of metformin of 2,000 mg probably gives an optimal blood glucose lowering effect (12).

Type 2 DM is part of a cluster of cardiovascular disease risk markers generally known as the metabolic syndrome or insulin resistance syndrome (Syndrome X). Cardiovascular disease accounts for about 70% of deaths in type 2 DM, with coronary artery disease, stroke and peripheral vascular disease 2-4 times more common in type 2 DM subjects. Metformin counters insulin resistance and offers benefits against many features of the insulin resistance syndrome by preventing body weight gain, reducing hyperinsulinaemia and improving the lipid profile, especially reducing raised triglyceride levels.

In addition, metformin reduces elevated plasminogen activator inhibitor 1 levels, and therefore improves fibrinolysis, and may improve peripheral blood flow. These benefits of metformin in the metabolic syndrome have recently been reviewed, both in the English (13-15) and Brazilian literature (16).

UKPDS: IMPLICATIONS FOR METFORMIN THERAPY

In the UKPDS, metformin was compared with insulin and sulphonylurea therapy to determine the nature of any specific advantages or disadvantages in a sub-set of overweight type 2 diabetic subjects. This will be considered under two major headings:

1. Metformin as an effective *glucose lowering agent*
2. Effect of metformin on *clinical outcomes*.

Effective Glucose Lowering Agent

Intensive therapy with metformin gave rise to a median HbA1c value of 7.4% compared to 8.0% in the conventional treatment group treated with diet alone. A similar outcome was observed for the other intensive therapies, sulphonylureas and insulin. Body weight was increased by intensive therapy with sulphonylureas (2.3 kg) or insulin (4.5 kg). Compared with conventional therapy, no weight change was seen in patients assigned to metformin. Insulin therapy increased plasma insulin concentrations whereas metformin therapy produced a small decrease (2.8 to 3.5 u/ml in mean fasting insulin concentration), that persisted through-

out the study. Over the 10 years of follow up, the proportion of patients per year taking the allocated treatment who had a hypoglycaemic episode were 0.9%, 12.1%, 17.5%, 34.0% and 4.2% for conventional, chlorpropamide, glibenclamide, insulin and metformin therapy respectively. No patient on metformin had a major hypoglycaemic episode.

Effect of Metformin on Clinical Outcomes

Metformin reduces the incidence of microvascular and macrovascular complications in overweight patients with type 2 DM.

In these overweight type 2 diabetic patients, metformin reduced the incidence of microvascular and macrovascular complications by 32% compared to patients on conventional therapy ($p=0.0023$). The metformin group also had significantly greater risk reduction than the group assigned to intensive therapy with a sulphonylurea or insulin ($p=0.0034$) with regard to these microangiopathic and macroangiopathic diabetic outcomes.

Metformin improves survival in type 2 DM.

Metformin was shown to improve survival in overweight type 2 diabetic subjects. Metformin as primary therapy reduced the risk of diabetes related deaths by 42% ($p=0.017$) and reduced all cause mortality by 36% ($p=0.011$). In a separate substudy, metformin and sulphonylurea combination therapy, after a median of 6.6 years had a similar morbidity compared with sulphonylurea therapy alone but there was a higher risk of diabetes related deaths in the combination therapy group (26 deaths) compared with the group assigned sulphonylurea alone (14 deaths).

A further analysis of the UKPDS cohort of patients showed that the expected number of deaths in the sulphonylureas alone was 35 deaths. The disparity between the groups was concluded to be due to "fewer than expected deaths in the sulphonylurea alone group rather than over-representation in the sulphonylurea-metformin combined group" (17).

The current opinion on combination therapy is to initiate a sulphonylurea-metformin combination if control is inadequate on monotherapy alone. In the case of type 2 DM subjects on combined therapy, the advice is to continue if glycaemic control is good but if it is poor to switch to insulin therapy but maintain metformin if the patient is overweight to avoid further weight gain.

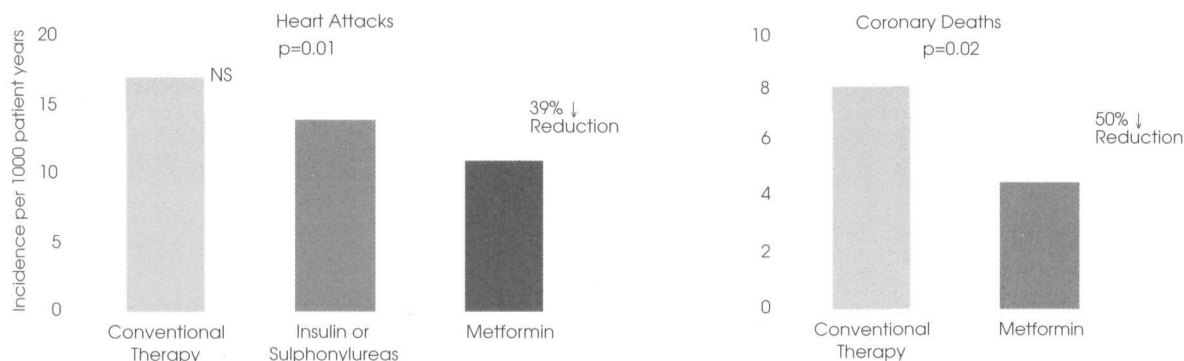


Figure 1 - Metformin prevents heart attacks and reduce coronary deaths in type 2 diabetes mellitus.

Metformin prevents heart attacks and reduces coronary deaths in type 2 DM.

Further analysis of the macrovascular benefits of metformin therapy shows that metformin treatment has a major benefit in diabetic cardiovascular complications with a 39% risk reduction in myocardial infarction ($p=0.01$) and a 50% risk reduction in coronary deaths ($p=0.02$) (Fig. 1). This is a significant outcome for the UKPDS as heart disease is a major factor in morbidity and premature death in type 2 DM.

Metformin therapy was also associated with a 41% risk reduction of stroke compared to conventional therapy (n.s.) but when compared to the outcome for intensive therapy with sulphonylureas or insulin, there was a significant difference ($p=0.032$).

The major benefits of metformin therapy in overweight patients in the UKPDS are summarised in Table 1, comparing the metformin intensive therapy group with the sulphonylurea/insulin intensively treated patients. With regard to microvascular outcomes, there was no significant risk-reduction in microvascular complications with any of the intensive therapies. With regard to metformin treatment, there was a 29% risk reduction compared with 16% for the sulphonylurea/insulin therapies. The small number of

clinical events in this arm of the study prevented these differences being significant.

CONCLUSION

Type 2 DM is **not** “mild diabetes”. It is a progressive killing disease (18). Because most patients with type 2 DM are overweight and have associated cardiovascular risk factors, drugs that improve these abnormalities are preferred (19). Since intensive glucose control with metformin appears to reduce the risk of diabetes related end points, especially myocardial infarction and fatal coronary deaths, in overweight diabetic patients and is associated with less weight gain and fewer hypoglycaemic attacks than insulin or sulphonylureas, it may be the first line pharmacology therapy of choice in these patients.

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Tabela 1 - UKPDS: Metformin study results in overweight patients (from ref. 2).

	Metformin Intensive		Sulphonylurea / Insulin Intensive	
	Change in risk*	P value	Change in risk*	P value
Any diabetes-related endpoint	↓ 32%	0.0023	↓ 7%	NS
Diabetes-related deaths	↓ 42%	0.017	↓ 20%	NS
All cause mortality	↓ 36%	0.011	↓ 8%	NS
Myocardial infarction	↓ 39%	0.01	↓ 21%	NS
Microvascular disease	↓ 29%	NS	↓ 16%	NS

* Compared with conventional therapy.

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