# Timely Addition of Insulin to Oral Therapy for Type 2 Diabetes

The U.K. Prospective Diabetes Study (UKPDS) has shaped our view of the management of type 2 diabetes more than any other trial. It proved that glycemic control limits retinopathy (and probably other microvascular complications) as much for type 2 diabetic patients as had previously been shown for type 1 diabetic patients (1). It defined the progressive natural history of type 2 diabetes, with declining β-cell function over time and a need for progressively more active treatment to maintain glycemic control (2). In addition, it has offered important insights into the effects of several forms of treatment.

For example, newly diagnosed patients entering the UKPDS who did not need immediate insulin therapy received intensive dietary therapy, but only 15% of them were able to reach target levels of glycemic control (fasting blood glucose ≤108 mg/dl) after 3 months, and the results were even worse after a year (3). This disappointing result indicates that lifestyle intervention alone will only occasionally be successful for patients presenting with overt diabetes. The UKPDS also reassured us that insulin and sulfonylureas do not increase cardiovascular mortality, as had been feared. It showed that glyburide caused more hypoglycemia than chlorpropamide and glipizide (1) and that metformin (4) was the one drug used that did not cause weight gain compared with therapy based on lifestyle. These insights have helped us deploy these treatments more effectively.

One of the main conclusions the UKPDS investigators themselves have drawn from their findings is that combinations of treatments will routinely be needed for type 2 diabetes (5). In this issue of *Diabetes Care*, they report the results of a 6-year substudy using a predefined combined regimen (Glucose Study 2) that was motivated in part by the findings described above and conducted toward the end of the overall trial (6). In eight centers, 826 patients were randomized shortly after diagnosis of type 2 diabetes to treatment with diet alone, insulin alone, or a sulfonylurea alone initially, but insulin was added when fasting blood glucose was persistently >108 mg/dl. The sulfonylureas used were glipizide or chlorpropamide, perhaps because earlier in the trial, glyburide was associated with more hypoglycemia. Insulin was given first as ultralente alone, with mealtime regular insulin added subsequently as needed. As in the main UKPDS protocol, both pharmacotherapeutic regimens outperformed diet alone. However, the regimen mandating the timely addition of insulin to a sulfonylurea proved superior to insulin alone. The median $HbA_{1c}$ over 6 years was 0.5% lower with the progressive (monotherapy to combined therapy) regimen, which was associated with similar weight gain but less hypoglycemia compared with insulin alone. The advantage in glycemic control was quantitively very like that seen in smaller and shorter studies, performed later in the course of type 2 diabetes (7,8), which also compared sulfonylurea/insulin therapy with aggressively titrated insulin-only therapy. Experience from the main UKPDS predicts that this much glycemic benefit should reduce microvascular events by 10–15%.

However, oral agent/insulin combinations are still not very widely used. Aside from previous lack of evidence from large trials reporting that combined therapy is better than insulin alone, acceptance of combinations has been hindered by lack of a clear physiologic rationale. The UKPDS investigators endorse the theory that injected long-acting insulin can improve overnight glucose control sufficiently to reduce glucose toxicity (and lipotoxicity), thereby allowing a sulfonylurea to have its full effect potentiating mealtime insulin secretion. Another possibility is that chronic use of sulfonylureas increases the contribution of endogenous insulin secretion to regulation of basal glucose production, leading to greater glycemic stability. This effect might derive partly from reducing (usually by 20–50%) the requirement for exogenous insulin, which cannot be adapted to varying needs after injection, especially during exercise, when mobilization of insulin from subcutaneous depots can inappropriately increase. Ongoing sulfonylurea treatment may also enhance the opportunity for normal downregulation of endogenous insulin when blood glucose declines. These mechanisms could lead to smaller within- and between-day variations of blood glucose as well as less risk of hypoglycemia at any mean level of glycemia, resulting in the opportunity to achieve lower $HbA_{1c}$ values without excessive hypoglycemia, as was seen in this UKPDS substudy.

In theory, these mechanisms might apply not just to sulfonylureas but also to metformin and thiazolidinediones, in slightly differing ways, when they are combined with insulin therapy. A recent physiologic study (9) of concurrent use of metformin or troglitazone with very intensive insulin therapy, delivered as continuous subcutaneous insulin infusion, showed that the insulin dosage that was needed declined ~30% with metformin and 50% with the thiazolidinedione, whereas C-peptide levels were unchanged. Under these conditions of increased tissue responsiveness to insulin, appropriate modulations of endogenous insulin secretion should be more effective in attenuating both increases and decreases of blood glucose. With metformin, which acts mainly at the liver, the clinical result should be less risk of hypoglycemia. With thiazolidinediones, which act mainly at muscle and fat, a reduction of postprandial hyperglycemia may be just as important. The ability of metformin to improve the effectiveness of multiple injections of insulin for type 2 diabetes was apparent in a small 6-month clinical study (10) in which optimized treatment achieved $HbA_{1c}$ 6.5% with metformin plus insulin but only 7.5% with placebo plus insulin. This study also confirmed another advantage of using metformin with insulin—limitation of the

weight gain usually seen with intensification of insulin treatment.

The UKPDS report may underestimate the benefits of combined oral agent/insulin therapy because the agents used in this substudy that started over a decade ago are being replaced by better versions. Chlorpropamide and conventional glipizide are now rarely used, whereas glimepiride and extended-release glipizide are gaining on glyburide, which is still the most widely used sulfonylurea in the U.S., partly because of its very low cost. Bovine ultralente insulin is gone, and human ultralente insulin is likely to be supplanted by insulin glargine, a long-acting analog that promises to supplement basal insulin more reliably. Moreover, metformin, rosiglitazone, and pioglitazone are now available in the U.S.

Using the newer products, current and future trials should expand our understanding of the effectiveness of oral agent/insulin combination regimens. For example, one study is comparing the ability of bedtime NPH insulin versus bedtime glargine to reestablish optimal glycemic control while one or two oral agents are continued. A preliminary report, which included data from >300 patients (11) and pooled data from the two randomized treatment groups, showed that remarkably good control is possible using this oral agent plus basal insulin strategy. Mean $HbA_{1c}$ was reduced from 8.6% at baseline to 6.9% after 18 weeks of forced titration of insulin dosage. Median $HbA_{1c}$ must have been lower because 66% of patients achieved $HbA_{1c}$ ≤7%. Presumably, adding rapid-acting insulin for some patients would have further improved the results.

Long-term trials with cardiovascular end points are planned to test the hypothesis, supported at present only by epidemiologic evidence that near-normal glycemic control may reduce macrovascular morbidity and mortality in type 2 diabetes. The glycemic targets in such trials will have to correspond to $HbA_{1c}$ ≤6.5%—a range that was not maintained in the UKPDS in either the main monotherapy protocol or the early combined therapy substudy discussed here. The median $HbA_{1c}$ of 6.6% that was shown with early addition of ultralente insulin to glipizide or chlorpropamide in the UKPDS sets a challenge for the newer studies to match or surpass using multiple combinations of newer agents. For clinical practice in the meantime, this latest report from the UKPDS documents the effectiveness of the timely addition of insulin to an oral regimen to defend $HbA_{1c}$ 7.0%, which is a widely accepted target based on microvascular end point trials.

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**References**

1. UK Prospective Diabetes Study Group: Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:838–853, 1998
2. UK Prospective Diabetes Study Group: UK Prospective Diabetes Study 16: overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes* 44:1249–1258, 1995
3. UK Prospective Diabetes Study Group: UK Prospective Diabetes Study 7: response of fasting plasma glucose to diet therapy in newly presenting type II diabetic patients. *Metabolism* 39:905–912, 1990
4. UK Prospective Diabetes Study Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998
5. Turner RC, Cull CA, Frighi V, Holman RR, the UK Prospective Diabetes Study Group: Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49): *J Am Med Assoc* 281:2005–2012, 1999
6. Wright A, Burden ACF, Paisey, RB, Cull, CA, Holman, RR, for the UK Prospective Diabetes Study Group: Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study. *Diabetes Care* 25:330–336, 2002
7. Riddle MC, Hart J, Bingham P, Garrison C, McDaniel P: Combined therapy for obese type 2 diabetes: suppertime mixed insulin with daytime sulfonylurea. *Am J Med Sci* 303:151–156, 1992
8. Shank ML, DelPrato S, DeFronzo RA: Bedtime insulin/daytime glipizide: effective therapy for sulfonylurea failures in NIDDM. *Diabetes* 44:165–172, 1995
9. Yu JG, Kruszynska YT, Mulford MI, Olefsky JM: A comparison of troglitazone and metformin on insulin requirements in euglycemic intensively insulin-treated type 2 diabetic patients. *Diabetes* 48:2414–2421, 1999
10. Aviles-Santa L, Sinding J, Raskin P: Effects of metformin in patients with poorly controlled insulin-treated type 2 diabetes mellitus. *Ann Intern Med* 131:182–188, 1999
11. Rosenstock J, Riddle M, Dailey G, Gerich J, Mecca T, Wilson C, Bugos C: Treatment to Target Study: feasibility of achieving control with the addition of basal bedtime insulin glargine (Lantus) or NPH insulin in insulin-naive patients with type 2 diabetes on oral agents (Abstract). *Diabetes* 50 (Suppl. 2):A129, 2001