Predicting hypos in T2D – the ups and downs matter!

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Hypoglycaemia remains a major rate-limiting step in the achievement and maintenance of tight glycaemic control in patients with type 2 diabetes, and fear of hypoglycaemia inhibits intensive glycaemic management strategies. Indeed in recent clinical trials, notably the Diabetes and Insulin Glucose infusion After Myocardial Infarction 2 (DIGAMI 2) study (results presented at the European Association for the Study of Diabetes), it proved impossible in a clinical trial setting to intensify glycaemic control with insulin to allow clear separation between the three groups of patients in the study. The message seemed to be that with the presently available glucose-lowering strategies it is possible to go so far but no further in terms of the achievement of tight glycaemic control. What is less clear is whether this was because of patients' or healthcare professionals' reluctance to move to intensive treatment regimens of four injections a day, either because of perceived inconvenience or because of real fears of hypoglycaemia, or both.

We know hypoglycaemia rates in intensively controlled type 2 patients are significantly less than in tightly controlled type 1 patients – severe hypoglycaemia was experienced by 30 % of tightly controlled type 1 patients in the Diabetes Control and Complications Trial (1987) and only 2 % of the UKPDS study (1998) – but the potential morbidity associated with hypoglycaemia in a type 2 population given their increased age and more intensive co-morbidity may be significantly greater.

Ways of predicting hypoglycaemia with confidence would help. This report from the Diabetes Outcomes in Veterans Study (DOVES) includes a mathematical model for predicting hypoglycaemia in type 2 diabetes. Although the paper is a bit hard going, especially for those of you who, like me, are not mathematical modellers, the bottom lines are accessible and important for routine practice. Self-monitoring of blood glucose is a much better predictor than HbA_{1c} measurement in predicting long-term hypoglycaemia. Hypoglycaemia is more likely if the mean blood glucose is low and its standard deviation is high. Indeed a large variation in blood glucose was an independent risk factor that can only be ascertained by frequent home blood glucose monitoring. In other words, HbA_{1c} cannot be substituted for blood glucose measurements in identifying well-controlled patients who are at risk of hypoglycaemia. In the study the risks of hypoglycaemia proved unique to each subject, stable up to one year and as much due to glucose variability as the mean glucose concentration. The risk of hypoglycaemia could be predicted with a single week of intensified blood glucose monitoring as long as readings are obtained before meals and at bedtime. The model was able to predict hypoglycaemic events in subjects on constantly varying treatment regimens suggesting the method is quite robust and minimally affected by the routine treatment changes that occur in routine clinical practice.

For all those of you out there holding the purse strings this study suggests that restricting the frequency of home blood glucose monitoring by being miserly with the 'scripts for strips' is unreasonable. If people are striving for a good control, it is important for them to know that they are not overdoing it or inappropriately increasing the hypoglycaemia risk, by running too low and allowing fluctuations that are too wide. The ups and downs of glycaemic variability as well as the average overall control do matter.

DCCT Research Group (1987) Diabetes Control and Complications Trial (DCCT): results of feasibility study. The DCCT Research Group. *Diabetes Care* **10**(1): 1–19

UK Prospective Diabetes Study (UKPDS) Group (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* **352**: 837–53

ARCHIVES OF INTERNAL MEDICINE

Weight loss with pharmacotherapy

Readability	✓ ✓
Applicability to practice	✓ ✓ ✓
WOW! factor	✓ ✓ ✓

1 Studies including pharmacotherapy as the primary weight loss strategy in adults with type 2 diabetes were included in a systematic literature review.

2 Weight loss over 26–52 weeks with fluoxetine, sibutramine and orlistat can be statistically significant but loss magnitude is modest and long-term safety and health benefits remain unclear.

Norris SL, Zhang X, Avenell A, et al (2004) Efficacy of pharmacotherapy for weight loss in adults with type 2 diabetes mellitus: a meta-analysis. *Archives of Internal Medicine* **164**: 1395–1404

ARCHIVES OF INTERNAL MEDICINE

Probabilistic model for predicting hypos in type 2

Readability	✓ ✓ ✓
Applicability to practice	✓ ✓ ✓ ✓
WOW! factor	✓ ✓

1 The prospective, observational DOVES trial aimed to develop and validate a method to evaluate the risk of hypoglycaemia in people with stable, insulin-treated diabetes.

2 Blood glucose levels were measured four times daily for eight weeks in 195 patients (95 % men) and for each patient a mean value with standard deviation (SD) calculated.

3 Patients were randomised to a validation or derivation set. A logistic function based on glucose SD and mean values was used to describe the eight-week hypoglycaemia risk in the derivation group. This was then used to assign a predicted probability of hypoglycaemia to people in the validation group. Patients were assigned risk quartiles and followed-up for up to a year.

4 Mean and SD glucose levels were highly influential hypoglycaemia determinants in 72 derivation group patients. Long-term hypoglycaemia occurrence in the validation group differed significantly across quartiles ($p<0.001$).

5 Probability function was significantly higher than HbA_{1c} area using receiver operating characteristic curve analysis as their 95 % confidence intervals did not overlap. People who developed long-term hypoglycaemia at a greater than median rate were identified by this function.

6 Prediction of long-term hypoglycaemia in type 2 diabetes is more accurate with self-monitoring of blood glucose than HbA_{1c}.

Murata GH, Hoffman RM, Shah JH, Wendel CS, Duckworth WC (2004) A probabilistic model for predicting hypoglycemia in type 2 diabetes mellitus. *Archives of Internal Medicine* **164**: 1445–50

'The CHF incidence rate in type 2 diabetes may be much greater than previously believed'

DIABETES CARE

CHF incidence in type 2 diabetes

Readability	✓ ✓ ✓ ✓
Applicability to practice	✓ ✓ ✓ ✓
WOW! factor	✓ ✓ ✓

1 Updated congestive heart failure (CHF) incidence rate estimates in patients with type 2 diabetes were compared to those without diabetes, and risk factors for CHF development in diabetes described.

2 The study followed 17 076 people without CHF (8231 patients with type 2 diabetes and 8845 age- and sex-matched people without diabetes) for up to 72 months in order to estimate CHF incidence rate.

3 Cox regression showed that people with diabetes were 2.5 times more likely to develop CHF than people without diabetes.

4 In people with and without diabetes, the difference in CHF development rates were much greater in younger age groups.

5 Greater body mass index and poorer glycaemic control were important predictors of CHF development.

6 In type 2 diabetes, CHF incidence rate may be greater than thought. Risk factor modification is important and may benefit younger patients the most.

Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB (2004) The incidence of congestive heart failure in type 2 diabetes. *Diabetes Care* **27**: 1879–84

DIABETES CARE

Lower HbA_{1c} and no weight gain with triple therapy

Readability	✓ ✓
Applicability to practice	✓ ✓ ✓ ✓
WOW! factor	✓ ✓ ✓

1 Triple therapy with insulin, metformin and a thiazolidinedione was compared to dual therapy with insulin and either metformin or a thiazolidinedione to determine safety and effectiveness in 28 patients with type 2 diabetes.

2 Patients on insulin monotherapy were randomly assigned insulin and metformin (n=14) or insulin and troglitazone, a thiazolidinedione, (n=14) for four months. They were then given triple therapy for a further four months.

3 Compared to dual therapy, total daily insulin dose and HbA_{1c} were reduced further in all patients on triple therapy. The greatest reductions were seen with troglitazone addition. When patients were treated with metformin before troglitazone was initiated, weight gain was avoided.

4 In type 2 diabetes, triple therapy with insulin, metformin and a thiazolidinedione can be safe and effective.

Strowig SM, Avilés-Santa ML, Raskin P (2004) Improved glycemic control without weight gain using triple therapy in type 2 diabetes. *Diabetes Care* **27**: 1577–83

JOURNAL OF HUMAN NUTRITION AND DIETETICS

Long-term benefits of various diets

Readability	✓ ✓
Applicability to practice	✓ ✓ ✓
WOW! factor	✓ ✓

1 This systematic review aimed to determine the best long-term diet for weight loss and cardiac risk improvement in obese adults.

2 Data from randomised controlled trials lasting at least a year were extracted from handsearched journals and 13 databases and trial quality was assessed.

3 There was significant weight loss with low fat diets up to three years. Blood pressure, fasting plasma glucose and lipids improved after a year on low fat diets.

4 Greatest weight loss over one year was with a very low calorie diet, which had beneficial effects on asthma.

5 Protein sparing modified fasts (PSMFs) were associated with greater lowering of HbA_{1c} and fasting plasma glucose than low calorie diets. Low carbohydrate PSMFs were not associated with greater long-term weight loss than low or very low calorie diets.

6 There is little evidence to support diets other than low fat diets for weight reduction.

Avenell A, Brown TJ, McGee MA, et al (2004) What are the long-term benefits of weight reducing diets in adults? A systematic review of randomized controlled trials. *Journal of Human Nutrition and Dietetics* **17**: 317–35

'These data suggest that the effects of pioglitazone are more sustained than those of glibenclamide for improving insulin sensitivity in patients with type 2 diabetes.'

DIABETIC MEDICINE

Sustained effects of pioglitazone vs glibenclamide

Readability	✓ ✓
Applicability to practice	✓ ✓ ✓
WOW! factor	✓ ✓ ✓

1 This year-long study in patients with type 2 diabetes compared glibenclamide and pioglitazone effects on glycaemic control, insulin sensitivity and lipids.

2 Patients received either pioglitazone or glibenclamide monotherapy once daily. Doses were titrated over 12 weeks to achieve glycaemic targets, then patients were maintained for 40 weeks on the titrated doses.

3 Compared to glibenclamide, insulin sensitivity was significantly increased with pioglitazone.

4 While after 12 weeks HbA_{1c} was significantly lower with glibenclamide, after 52 weeks HbA_{1c} levels with glibenclamide were significantly higher than with pioglitazone.

5 Pioglitazone significantly increased mean HDL-cholesterol, decreased mean triglycerides and mean total cholesterol/HDL-cholesterol while not significantly increasing mean LDL-cholesterol or total cholesterol levels compared to glibenclamide.

6 There was more sustained improvement in insulin sensitivity and greater glycaemic control with pioglitazone than wtih glibenclamide.

Tan MH, Johns D, Strand J, et al (2004) Sustained effects of pioglitazone vs. glibenclamide on insulin sensitivity, glycaemic control, and lipid profiles in patients with type 2 diabetes. *Diabetic Medicine* **21**: 859–66