A link between hypoglycaemia and microvascular complications?

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In science there is very little that can be taken as absolute and uncontested fact. Having said that, we are on reasonably safe ground saying that high blood glucose is associated with, and is the cause of, microvascular complications. There are a number of plausible mechanisms supported by a wealth of laboratory data.

In addition, there are well-designed clinical studies that demonstrate the relationship between blood glucose concentrations and risk of nerve, kidney or eye damage. The DCCT (Diabetes Control and Complications Trial; DCCT Research Group,1993) remains important because it demonstrated, to the satisfaction of most people, that interventions that improve glucose control reduce the risk of microvascular disease. Translating this into clinical practice, lowering HbA_{1c} is likely to reduce the risk of long-term complications but at the expense of an increased risk of day to day hypoglycaemia.

Hypoglycaemia is in itself associated with considerable morbidity and potential mortality. Kilpatrick and colleagues (2012; summarised alongside) now add to this another potential risk – hypoglycaemia might in itself increase microvascular risk. This has been suggested previously by other authors.

Although it might be argued that there are plausible mechanisms, the supporting laboratory data are much weaker. Previous epidemiological studies have suggested a link (Desouza et al, 2010), but it is difficult to tease out whether an increased risk is due to the episode of low blood glucose or possibly the high blood glucose that so often follows. The authors have used the DCCT dataset to try to address this issue.

This study compared a group of patients with type 1 diabetes who received intensive management of glucose control versus a matched group of people with diabetes who received conventional management. There was a significant difference in HbA_{1c} between the groups, but also a higher risk of hypoglycaemia in the intensive group.

> ***"The frequency of hypoglycaemia did not predict the risk of microvascular disease in either the intensive or conventional arms of the study. I doubt that this paper will entirely lay the matter to rest, but if the effect is there, it is a weak one."***

The authors have now used this data to try to relate the frequency of hypos in each group to subsequent microvascular outcomes. Their conclusion is that the frequency of hypoglycaemia did not predict the risk of microvascular disease in either the intensive or conventional arms of the study. I doubt that this paper will entirely lay the matter to rest, but if the effect is there, it is a weak one.

Desouza CV, Bolli GB, Fonseca V (2010) Hypoglycemia, diabetes, and cardiovascular events. *Diabetes Care* **33**: 1389–94

Diabetes Control and Complications Trial Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* **329**: 977–86

DIABETIC MEDICINE

Microvascular influence of hypoglycaemia

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

1 Data from the DCCT (Diabetes Control and Complication Trial) were reanalysed to determine whether the frequency of severe hypoglycaemia had an influence on the development and progression of retinopathy or nephropathy in people with T1D.

2 The DCCT was a 9-year study of T1D (n=1441) comparing the effect of intensive versus conventional blood glucose management on the development of microvascular complications.

3 HbA_{1c} at study baseline, mean HbA_{1c} throughout the study and the number of severe hypoglycaemic episodes during the trial were compared to examine the risk of development/progression of retinopathy and nephropathy.

4 Average HbA_{1c} during the study and/or HbA_{1c} at baseline were independently predictive of nephropathy and retinopathy in both the intensively and the conventionally treated patients (all $P \leq 0.001$).

5 The number of hypoglycaemic episodes did not add to HbA_{1c} in predicting retinopathy (odds ratio, 0.99 [95% confidence interval [CI], 0.96–1.01; P=0.51] in intensively treated patients; 0.94 [95% CI, 0.89–1.00; P=0.05], conventional]) or nephropathy (odds ratio, 0.98 [95% CI, 0.95–1.01; P=0.48] intensive; 1.03 [95% CI, 0.98–1.10; P=0.17] conventional).

6 The authors concluded that there was no evidence to support the role of exposure to hypoglycaemia in the worsening of microvascular complications in those with T1D.

Kilpatrick ES, Rigby AS, Atkin SL, Frier BM (2012) Does severe hypoglycaemia influence microvascular complications in Type 1 diabetes? An analysis of the Diabetes Control and Complications Trial database. *Diabetic Medicine* Feb 14 [Epub ahead of print]

DIABETOLOGIA

Serum vitamin D in pregnancy and children's T1D

Readability	✓✓
Applicability to practice	✓
WOW! factor	✓

1 The study examined the hypothesis that maternal vitamin D deficiency during pregnancy or infancy is one of the suggested environmental factors for T1D and for its increasing incidence.

2 Researchers compared serum 25-hydroxy-vitamin D (25-OH D) levels during early pregnancy in mothers of children who subsequently developed T1D (case mothers) with mothers of non-diabetic healthy children (control mothers) of the same age.

3 Children with T1D were identified from the Finnish nationwide prescription register. 25-OH D concentration was measured from serum samples collected during the first trimester of pregnancy from all Finnish women (Finnish Maternity Cohort). A total of 343 case mothers and 343 control mothers were included. Samples from case and control mothers were collected throughout the year and matched on the day of collection.

4 Mean 25-OH D levels in case mothers (43.9 nmol/L) and control mothers (43.7 nmol/L) were not different. Of all women, 481 (70.1%) were vitamin D deficient or insufficient.

5 The authors concluded that there was no difference in serum 25-OH D concentrations in the first trimester of pregnancy between mothers whose children developed T1D and mothers of children without diabetes of the same age. They added that it was difficult to detect possible effects of maternal vitamin D deficiency during early pregnancy on the development of T1D in the offspring in this population, as such a large proportion of women were vitamin D deficient or insufficient.

Miettinen ME, Reinert L, Kinnunen L et al (2012) Serum 25-hydroxyvitamin D level during early pregnancy and type 1 diabetes risk in the offspring *Diabetologia* **55**: 1291–4

DIABETES CARE

Hypoglycaemia affects QTc interval in T1D

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

1 Prolonged corrected QTc interval reflects abnormalities of ventricular myocardial repolarisation and is an independent marker of increased mortality in T1D.

2 The authors examined whether severe hypoglycaemia was associated with QTc interval abnormalities in T1D.

3 A corrected QTc interval of 0.44 seconds was considered abnormally prolonged. Severe hypoglycaemia was defined as an attack serious enough to require the help of another person.

4 The study included 3248 people with T1D. Prevalence of QTc interval prolongation was greater in those who had experienced three or more hypoglycaemic attacks. The frequency of severe hypoglycaemia was independently associated with QTc interval prolongation, even after adjustment for diabetes complications, including autonomic neuropathy (odds ratio, 1.27; 95% confidence interval, 1.02–1.58).

5 It was concluded that severe hypoglycemia is independently associated with a prolonged QTc interval.

Gruden G, Giunti S, Barutta F et al (2012) QTc interval prolongation is independently associated with severe hypoglycemic attacks in type 1 diabetes from the EURODIAB IDDM complications study. *Diabetes Care* **35**: 125–7

"Structured education is associated with an improvement in glycaemic control at 1 year, and there remains a persistent and clinically relevant reduction in HbA_{1c}"

DIABETIC MEDICINE

Structured patient education leads to HbA_{1c} improvement

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

1 The provision of structured education is increasingly important in the management of T1D, but there are few long-term follow-up data from such programmes to demonstrate their benefits and efficacy.

2 The authors analysed annual HbA_{1c} and weight data in 111 people who attended an initial series of Dose Adjustment For Normal Eating (DAFNE) courses and in a matched group of 111 patients with T1D of similar age and duration of diabetes who had not undergone structured education.

3 In the group which undertook DAFNE structured education, the mean (± standard deviation) HbA_{1c} fell from 71±12 mmol/mol (8.6±1.1%) at baseline to 65±12 mmol/mol (8.1±1.1%) at year 1, with a subsequent rise to 67±13 mmol/mol (8.3±1.2%) at year 7 (P=0.0048 vs baseline).

4 In the comparator group, the baseline HbA_{1c} level was 70±14 mmol/mol (8.5±1.3%) and remained approximately constant during 7 years of follow-up.

5 Weight increased by 2.4±6.0 kg and 2.8±6.6 kg in the DAFNE and comparator group, respectively, during follow-up (not significant).

6 The authors concluded that DAFNE structured education is associated with an improvement in glycaemic control at 1 year, and there remains a persistent and clinically relevant reduction in HbA_{1c} of 3 mmol/mol after 7 years; furthermore glycaemic control after DAFNE is achieved without excess weight gain.

Gunn D, Mansell P (2011) Glycaemic control and weight 7 years after Dose Adjustment For Normal Eating (DAFNE) structured education in type 1 diabetes. *Diabet Med* Dec 1 [Epub ahead of print]

DIABETIC MEDICINE

Co-administration of pandemic and seasonal flu jabs

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

1 The researchers evaluated the co-administration of pandemic and seasonal influenza vaccine in young subjects with T1D.

2 Patients (n=80; mean age, 16.7±5.5 years) received a single or a double dose of influenza A (H1N1) vaccine, simultaneously with a single dose of seasonal influenza vaccine.

3 One month after immunisation, no significant differences were observed between the one-dose and two-dose schedules. Seasonal vaccine induced a significant increase of both seroprotection rates and antibody levels.

4 The authors concluded that one injection of pandemic influenza vaccine is immunogenic and safe in young people with T1D.

Zuccotti GV, Pariani E, Scaramuzza A et al (2011) Long-lasting immunogenicity and safety of a 2009 pandemic influenza A(H1N1) MF59-adjuvanted vaccine when co-administered with a 2009-2010 seasonal influenza vaccine in young patients with type 1 diabetes mellitus. *Diabet Med* **28**: 1530–6

DIABETES

Risk of T1D with low maternal vitamin D

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

1 The authors tested whether lower maternal serum concentrations of 25-hydroxy-vitamin D (25-OH D) during pregnancy were associated with an increased risk of childhood-onset T1D.

2 Researchers compared 25-OH D levels from late pregnancy in 109 women delivering a child who developed T1D before 15 years of age (case subjects) and from 219 control women in Norway.

3 There was a trend towards a higher risk of T1D associated with lower levels of vitamin D during pregnancy.

4 The authors concluded that the odds of T1D were more than two-fold higher in offspring of women with the lowest levels of 25-OH D compared with those with the highest levels.

Sørensen IM, Joner G, Jenum PA et al (2012) Maternal serum levels of 25-hydroxy-vitamin D during pregnancy and risk of type 1 diabetes in the offspring. *Diabetes* **61**:175–8

DIABETOLOGIA

Glycaemia affects foetal abnormalities

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

1 This study assessed the influence of peri-conception HbA_{1c} on the risk of congenital anomaly in offspring of women with T1D and T2D.

2 Data from registers of congenital anomaly and diabetes in pregnancy were used. A total of 401 149 singleton pregnancies (1677 in women with diabetes) were included.

3 The rate of non-chromosomal major congenital anomaly in women with diabetes was 71.6 per 1000 pregnancies, a relative risk of 3.8 compared with women without diabetes.

4 Periconception HbA_{1c} (adjusted odds ratio [aOR] 1.3 [95% CI, 1.2–1.4] per 1% [11 mmol/mol] linear increase in HbA_{1c} above 6.3% [45 mmol/mol]) and pre-existing nephropathy (aOR, 2.5 [95% CI, 1.1–5.3]) were significant independent predictors of congenital anomaly.

5 Peri-conception glycaemia is the most important modifiable risk factor for congenital anomaly in women with diabetes, concluded the authors, who added that the association with nephropathy merits further study.

Bell R, Glinianaia SV, Tennant PW et al (2012) Peri-conception hyperglycaemia and nephropathy are associated with risk of congenital anomaly in women with pre-existing diabetes: a population-based cohort study. *Diabetologia* Feb 8 [Epub ahead of print]