Management & prevention of type 2 diabetes

Is cancer risk associated with glycaemic control?

Roger Gadsby, GP and Senior Lecturer, Centre for Primary Healthcare Studies, Warwick University, Coventry

Diabetes and the risk of cancer is currently a "hot" topic. Four articles (Colhoun et al; Currie et al; Hemkens et al; Jonasson et al) published in the September 2009 issue of *Diabetologia* sought to explore whether treatment with the long-acting insulin analogue insulin glargine could possibly be associated with an increased risk of cancer. These articles gave conflicting results, and the methodological quality of some of them has been debated. No alteration in prescribing was suggested following these publications, but further research was recommended. Further studies should be published later this year.

It is emerging that diabetes itself is associated with an increased risk of certain forms of cancer. Obesity is associated with an increased risk of cancer, and diabetes is associated with obesity. This could explain, at least partially, the association between cancer and diabetes.

Another way that cancer could be associated with diabetes is through hyperglycaemia. In the article by Johnson and Bowker (2011; summarised alongside), they seek to examine this possibility. The authors conducted a meta-analysis of four trials reporting cancer mortality rates for an intensively controlled versus a standard controlled glycaemic group. In these studies, 222 cancer deaths were experienced in 53 892 person-years of intensified glycaemic control compared with 155 cancer deaths during 38 743 person-years of standard control.

In a further three studies, cancer incidence was reported: 357 events in 47 974 person-years with improved glycaemic control and 380 events in 45 009 person-years in the control arm. The authors conclude that data from large, randomised, controlled trials of intensified glycaemic control suggest that cancer risk is not reduced by improving glycaemic control in people with type 2 diabetes. Therefore, this article does not support the hypothesis that hyperglycaemia is causally linked to increased cancer risk.

Colhoun HM; SDRN Epidemiology Group (2009) Use of Insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. *Diabetologia* **52**: 1755–65

Currie CJ, Poole CD, Gale EA (2009) The influence of glucose lowering therapies on cancer risk in type 2 diabetes. *Diabetologia* **52**: 1766–77

Hemkens LG, Grouven U, Bender R et al (2009) Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues – a cohort study. *Diabetologia* **52**: 1732–44

Jonasson JM, Ljung R, Talback M et al (2009) Insulin glargine and short term incidence of malignancies – a population based follow up study in Sweden. *Diabetologia* **52**:1745–54

DIABETES, OBESITY & METABOLISM

Safety and efficacy of linagliptin in people with T2D

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

1 In this study, the safety and efficacy of linagliptin (a dipeptidyl peptidase-4 inhibitor) as add-on therapy to metformin was assessed in poorly controlled people with T2D.

2 Participants (aged 18–80 years) continued on metformin and were randomised to receive linagliptin 5 mg/day (n=524) or placebo (n=177) for 24 weeks.

3 Baseline mean HbA_{1c} levels were 8.0% (64 mmol/mol) and 8.1% (65 mmol/mol) in the placebo and treatment groups, respectively; these levels were changed by 0.15% (1.6 mmol/mol) and –0.49% (–5.4 mmol/mol) at study end.

4 Neither group was associated with significant changes in mean body weight (placebo, –0.5 kg; linagliptin, –0.4 kg) and occurrences of hypoglycaemia were rare (2.8% and 0.6%, respectively).

5 The authors concluded that linagliptin add-on therapy in people with T2D showed improved glycaemic control compared with placebo.

Taskinen MR, Rosenstock J, Tamminen I et al (2011) Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Diabetes Obes Metab* **13**: 65–74

DIABETOLOGIA

Intensive glycaemic control does not reduce cancer risk

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

1 The aim of this study was to determine whether data from major randomised controlled trials would support the hypothesis that improving glycaemic control would reduce the risk of cancer or cancer mortality in T2D.

2 The authors assessed data from the UKPDS (UK Prospective Diabetes Study) 33, UKPDS 34, ACCORD (Action to Control Cardiovascular Risk in Diabetes), VADT (Veterans Affairs Diabetes Trial), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation), PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) and RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) trials.

3 The UKPDS 33, UKPDS 34, ACCORD and VADT studies reported cancer mortality rates of 222 events in 53 892 person-years with intensive control and 155 events in 38 743 person-years with standard control; the overall pooled risk ratio (RR) for cancer mortality was 1.00 (P=0.98).

4 The ADVANCE, PROactive and RECORD studies reported cancer incidence of 357 events in 47 974 person-years with improved glycaemic control and 380 events in 45 009 person-years in the control arms; the pooled RR for cancer incidence was 0.91 (P=0.20).

5 No evidence was found to support the hypothesis that hyperglycaemia is a modifiable risk factor for increased incidence of cancer or cancer mortality in T2D.

Johnson JA, Bowker SL (2011) Intensive glycaemic control and cancer risk in type 2 diabetes: a meta-analysis of major trials. *Diabetologia* **54**: 25–31

"People with T2D view once-weekly medications as a good treatment option, particularly if they are dissatisfied with their current therapy or outcomes."

DIABETES, OBESITY & METABOLISM

People with T2D's views of once-weekly injectable antidiabetes drugs

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

1 The aim of this study was to determine the beliefs, preferences and expectations surrounding once-weekly, injectable antidiabetes medications among people with T2D.

2 Data were collected on 1516 adults with T2D who anonymously completed a USA national Chronic Illness Panel online survey that assessed attitudes towards once-weekly medications.

3 Of the respondents, 161 individuals were not currently taking any antidiabetes drugs and thus were excluded from the study.

4 The final sample consisted of 1355 individuals, with 63% taking oral antidiabetes drugs and 37% taking injectable antidiabetes drugs.

5 Overall, 46.8% responded that they would be likely to take a once-weekly injectable drug if recommended by their physician; this positive response was more common among injection users than non-injection users (73.1% vs 31.5%; $P<0.001$).

6 The positive response towards taking once-weekly medications was associated with poorer diabetes quality of life (odds ratio [OR], 1.37; $P<0.01$) among injection users only and with poorer perceived glycaemic control (OR, 1.24; $P<0.05$) among non-injection users only.

7 The authors concluded that people with T2D view once-weekly medications as a good treatment option, particularly if they are dissatisfied with their current therapy or outcomes.

Polonsky WH, Fisher L, Hessler D et al (2011) Patient perspectives on once-weekly medications for diabetes. *Diabetes Obes Metab* **13**:144–9

DIABETIC MEDICINE

Linagliptin added to metformin in people with poorly controlled T2D

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

1 The current authors aimed to determine if the combination of the dipeptidyl peptidase-4 inhibitor linagliptin and metformin is safe and efficacious in people with T2D who had been poorly controlled on metformin alone.

2 Study participants had been diagnosed with T2D for ≥3 months, were aged 21–75 years and had a BMI of 25–40 kg/m^2.

3 After exclusions, 333 participants were randomised to receive linagliptin 1 mg/day ($n=65$), 5 mg/day ($n=66$), 10 mg/day ($n=66$), glimepiride 1–3 mg/day ($n=65$) or placebo ($n=71$) along with metformin therapy for 12 weeks; the primary outcome was change in HbA_{1c} level from baseline.

4 Linagliptin treatment resulted in placebo-corrected reductions in HbA_{1c} levels of 0.40% (4.4 mmol/mol) for 1 mg, 0.73% (8.0 mmol/mol) for 5 mg and 0.67% (7.3 mmol/mol) for 10 mg; the reduction seen with glimepiride was 0.90% (9.8 mmol/mol).

5 The rates of adverse events were similar among all five treatment groups; however, three individuals (5%) taking glimepiride experience hypoglycaemia compared with none in the linagliptin and placebo groups.

6 Linagliptin add-on therapy to metformin in people with T2D was concluded to be well tolerated and associated with improved glycaemic control, particularly the 5-mg dose.

Forst T, Uhlig-Laske B, Ring A et al (2010) Linagliptin (BI 1356), a potent and selective DPP-4 inhibitor, is safe and efficacious in combination with metformin in patients with inadequately controlled type 2 diabetes. *Diabet Med* **27**: 1409–19

DIABETES, OBESITY & METABOLISM

Improved glycaemic control with saxagliptin treatment

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

1 This multicentre, randomised, placebo-controlled study assessed the safety and efficacy of saxagliptin in people with T2D and renal impairment.

2 Adults with inadequately controlled diabetes (HbA_{1c} level 7–11%; 53–97 mmol/mol) and renal impairment (creatinine clearance [CrCl] rate of <50 mL/min) were included in the study.

3 The degree of renal impairment was stratified into moderate (CrCl rate ≥30 to <50 mL/min), severe (<30 mL/min and no dialysis) and end-stage renal disease (ESRD) on haemodialysis.

4 A total of 170 individuals were randomised to receive saxagliptin 2.5 mg/day ($n=85$) or placebo ($n=85$) for 12 weeks.

5 The adjusted mean change in HbA_{1c} level from baseline to week 12 was the primary efficacy endpoint; there was a significantly greater reduction seen in the saxagliptin group compared with the placebo group (between-group difference of 0.42% [4.6 mmol/mol]; $P=0.007$).

6 The reductions in HbA_{1c} level were greater with saxagliptin treatment compared with placebo in the moderate (–0.64% [–7.00 mmol/mol] vs –0.05% [–0.50 mmol/mol]) and severe (–0.95% [–10.40 mmol/mol vs –0.50% [–5.5 mmol/mol]) renal impairment subgroups, whereas no difference was seen in those with ESRD.

7 Saxagliptin was concluded to have glycaemic benefits and no increase in the incidences of adverse or hypoglycaemic events in poorly controlled people with T2D and renal impairment.

Nowicki M, Rychlik I, Haller H et al (2011) Saxagliptin improves glycaemic control and is well tolerated in patients with type 2 diabetes mellitus and renal impairment. *Diabetes Obes Metab* **13**: 523–32