Management & prevention of type 2 diabetes

Diabetes and dementia: Reasons to be worried or optimistic?

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If you ask the public to vote on health concerns, dementia comes very high on the list of diseases they worry about most. This is no surprise given the devastating effect dementia can have on the lives of both the individuals and their loved ones. The economic implications for the care of people with dementia are also very worrying. With this in mind, multiple international research initiatives are trying to determine how best to predict who is most at risk of dementia in order to put in place better preventative measures.

Diabetes, of course, is one condition linked to greater dementia risk, although the magnitude of risk is not well established and may be changing over time. With this in mind, Davis and colleagues sought to determine the excess risk of dementia in their longitudinal follow-up of the Freemantle Diabetes Study in Australia (summarised alongside). Notably, dementia is not an easy outcome to capture fully in any country, as many people will die before it is ever known that they had the condition. Thus, research in this area is much more difficult than when looking at outcomes such as myocardial infarction, which invariably result in hospitalisation. That said, the authors were able to capture data from a combination of databases available to them in Western Australia, an approach shown to improve the pick-up of people with dementia and which, therefore, makes the results more likely to be valid. The authors were also careful to account for the competing risk of death, as people with diabetes tend to die younger than those without, and thus would have less time to develop dementia.

Overall, the findings suggest that people with type 2 diabetes have a modestly higher risk of dementia, developing it around 1.7 years earlier. However, as they also died earlier, they lived with dementia for roughly the same length of time as people without diabetes.

These results parallel other studies demonstrating higher dementia rates and greater cognitive decline in people with diabetes (Biessels et al, 2014; Lyall et al, 2017). Collectively, the studies suggest more work is needed in this area to determine how best to delay dementia in people with diabetes, as well as elucidating the mechanisms behind this higher risk.

Looking beyond diabetes, there is some good news, as dementia rates appear to be lower than predicted given rising life expectancy. Indeed, in a recent US study, the prevalence of dementia in cohorts of people with average ages around 75 years were lower in 2012 than in 2000 by around 25% (Langa et al, 2017). The authors speculate that improving education could be relevant to this trend but, of course, lowering of cardiovascular risk over time via a whole host of factors (less smoking, lower cholesterol levels, better primary and secondary preventative measures) are also likely to be critical. Indeed, more and more evidence implies a link between cardiovascular disease and dementia. It is therefore hoped that, by better addressing cardiovascular risk in our patients with diabetes via multifactorial risk factor management across lifestyle, lipid, blood pressure and glycaemia domains, we are also lowering their risk of cognitive decline and dementia. ■

Biessels GJ, Strachan MW, Visseren FL et al (2014) Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions. *Lancet Diabetes Endocrinol* **2**: 246–55

Langa KM, Larson EB, Crimmins EM et al (2017) A comparison of the prevalence of dementia in the United States in 2000 and 2012. *JAMA Intern Med* **177**: 51–8

Lyall DM, Celis-Morales CA, Anderson J et al (2017) Associations between single and multiple cardiometabolic diseases and cognitive abilities in 474 129 UK Biobank participants. *Eur Heart J* **38**: 577–83

Diabetologia

Dementia risk in people with T2D

Readability	✓✓✓✓
Applicability to practice	✓✓
WOW! Factor	✓✓✓✓

1 In this study, the authors used data from the Fremantle Diabetes Study, a longitudinal, community-based cohort study of people with diabetes from Western Australia, to evaluate the risk of dementia, taking into account the competing risk of death, in people with T2D.

2 Each person with T2D (n=1291) was matched with four age-, gender- and postcode-matched controls without diabetes (n=5159) at study entry.

3 Over a mean follow-up of 13.8 years, 13.9% of the T2D cohort and 12.4% of the controls developed dementia, while 54.8% and 41.1%, respectively, died.

4 The incidence of dementia was significantly higher with T2D (incidence rate ratio [IRR], 1.28; 95% confidence interval [CI], 1.08–1.51), as was the competing risk of death (IRR, 1.50; 95% CI, 1.38–1.64).

5 Incident dementia occurred 1.7 years earlier (95% CI, 0.6–2.9 years) in the T2D cohort. People with dementia and T2D died a mean 2.3 years earlier (95% CI, 1.1–3.6 years) than those with dementia but no T2D. This suggests that dementia in T2D occurs with a younger age but has a similar duration of survival.

6 T2D was associated with an adjusted subdistribution hazard ratio (HR) of 1.18 and a cause-specific HR of 1.51 for all-cause dementia. As a consequence of the higher risk of premature mortality, the increased risk of dementia in type 2 diabetes is not as marked as would be suggested by the cause-specific HR alone.

Davis WA, Zilkens RR, Starkstein SE et al (2017) Dementia onset, incidence and risk in type 2 diabetes: a matched cohort study with the Fremantle Diabetes Study Phase I. *Diabetologia* **60**: 89–97

"The authors conclude that gout is associated with an increased risk of developing T2D, particularly in women. They recommend that people with gout undergo aggressive management of T2D risk factors."

Diabet Med

Patient-level predictors of achieving early glycaemic control

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓

1 The authors of this population-based follow-up study used data from a large medical registry in northern Denmark to explore which demographic and clinical characteristics predicted early achievement of glycaemic control in people with new-onset T2D.

2 A total of 38 418 adults with incident diabetes between 2000 and 2012 who had the appropriate HbA_{1c} data recorded were identified.

3 Of this cohort, 27 545 (72%) achieved the primary endpoint of an HbA_{1c} <53 mmol/mol (7.0%) within 3–6 months of treatment initiation.

4 HbA_{1c} at treatment initiation was the strongest predictor of achieving early control. Using those with a baseline HbA_{1c} of ≤58 mmol/mol (7.5%) as a reference, people with an HbA_{1c} of 59–75 mmol/mol (7.6–9.0%) were 37% less likely to achieve early control, while those with an HbA_{1c} >75 mmol/mol (9.0%) were 42% less likely.

5 All other predictors were only weakly associated with achievement of early control, with relative risks of ≥0.95.

6 These results present a simple method for clinicians to identify newly diagnosed people with T2D who are at risk of failing to achieve early glycaemic control. Such people may require more intensive treatment and follow-up.

7 The authors note that disparities may still exist for other factors that could not be assessed, including income, education and lifestyle.

Svensson E, Baggesen LM, Thomsen RW et al (2016) Patient-level predictors of achieving early glycaemic control in type 2 diabetes mellitus: a population-based study. *Diabet Med* **33**: 1516–23

Am J Med

Association between gout and incident T2D risk

Readability	✓✓✓✓
Applicability to practice	✓✓
WOW! Factor	✓

1 This retrospective study was conducted to assess the association between gout and incident T2D in a large population-based cohort from Taiwan.

2 In total, 29 765 people with gout (average age, 55.4 years) and 59 530 controls, matched for age, age group, gender and region, were evaluated.

3 Over a follow-up of 13 years, 3940 patients (13.24%) with gout and 6334 controls (10.64%) developed T2D (incidence rate ratio, 2.03; P<.0001).

4 The incidence of T2D was higher in women than in men, irrespective of gout status. Among people with gout, the incidence of T2D was significantly higher in women (31.3 vs 15.1 per 1000 person-years).

5 Compared to men and women without gout, the adjusted hazard ratio for T2D in the gout cohort was 1.62 (95% confidence interval [CI], 1.54–1.70) in men and 1.97 (95% CI, 1.81–2.14) in women.

6 The interaction between gender and gout on T2D incidence was significant (beta=0.18; P<0.0001).

7 The authors note that they were unable to adjust for all T2D risk factors, such as diet and lifestyle, and these findings should be validated in other populations (Taiwan has the highest prevalence of gout in the world).

8 Nonetheless, they conclude that gout is associated with an increased risk of developing T2D, particularly in women. They recommend that people with gout undergo aggressive management of T2D risk factors.

Tung YC, Lee SS, Tsai WC et al (2016) Association between gout and incident type 2 diabetes mellitus: a retrospective cohort study. *Am J Med* **129**: 1219.e17–25

Diabet Med

Stroke risk at different BP ranges in people with T2D

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓

1 Using Swedish national records, these authors conducted a large, observational case–control study to assess the risk of stroke at varying blood pressure (BP) ranges in people with T2D compared with the general population.

2 A total of 408 076 people with and 1 913 507 without T2D were analysed over a median follow-up of 4 years.

3 Overall, 19 548 people with T2D (4.8%) had a stroke, compared with 61 690 controls (3.2%). Incidence rates per 1000 person-years were higher in the T2D group for overall stroke (10.6 vs 6.8), ischaemic stroke (9.6 vs 5.9) and haemorrhagic stroke (1.0 vs 0.9).

4 After adjustment for age, gender, diabetes duration and comorbidities, the hazard ratio (HR) for any stroke in people with T2D as a whole was 1.43 (95% confidence interval, 1.41–1.46).

5 The excess risk was derived from the three highest BP categories: 130–139/80–89 mmHg (HR, 1.20), 140–159/90–99 mmHg (HR, 1.47) and ≥160/100 mmHg (HR, 1.97).

6 People with T2D and BP <130/80 mmHg had a similar risk of stroke to the general population. This was partly due to a reduced risk of haemorrhagic stroke, which offset the small increases in risk of ischaemic stroke (HRs ranging from 1.06 to 1.18) present even in people with lower BP.

7 These findings further emphasise the importance of good BP control in people with T2D.

Hedén Ståhl C, Lind M, Svensson AM et al (2016) Long-term excess risk of stroke in people with type 2 diabetes in Sweden according to blood pressure level: a population-based case-control study. *Diabet Med* **34**: 522–30

Diabetes Res Clin Pract

Continuous versus 5:2 dieting in people with T2D: Pilot study

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 This 12-week pilot study assessed the effectiveness of an intermittent fasting diet comprising 2 days' severe energy restriction and 5 days' habitual eating (a 5:2 diet), in comparison with a standard diet involving continuous moderate energy restriction, for the management of T2D.

2 On fasting days, participants in the 5:2 group ate 400–600 kcal/day, with normal eating on the other 5 days, while the continuous diet group ate 1200–1550 kcal/day throughout the week. The diets were composed of around 30% protein, 45% carbohydrate and 25% fat.

3 A total of 63 overweight or obese people with T2D were enrolled. Of these, 81% completed the study, with similar dropout rates in the two groups. Using intention-to-treat analysis did not affect the results.

4 The primary outcome, HbA_{1c}, fell significantly, with no significant difference between the 5:2 and continuous groups (mean reduction, 6.6 vs 8.7 mmol/mol [0.6% vs 0.8%]).

5 Body weight also decreased to similar extents in the two groups (6.2% vs 5.6% of body weight).

6 Measures of body composition, including total body fat, fat mass and fat-free mass, all improved significantly over time, with no significant difference between groups.

7 Although larger studies over a longer time frame are required, this pilot study suggests that intermittent fasting may be a useful alternative to continuous dieting in people with T2D.

Carter S, Clifton PM, Keogh JB et al (2016) The effects of intermittent compared to continuous energy restriction on glycaemic control in type 2 diabetes; a pragmatic pilot trial. *Diabetes Res Clin Pract* **122**: 106–12

Ann Intern Med

Pioglitazone in people with T2D and NASH

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 In this single-centre, double-blind randomised controlled trial, the efficacy of pioglitazone for the treatment of non-alcoholic steatohepatitis (NASH) was evaluated.

2 A total of 101 people with T2D or prediabetes and comorbid NASH were randomised to pioglitazone or placebo, both in addition to a hypocaloric diet, for 18 months.

3 The primary outcome, a reduction of at least 2 points in two histologic categories of the non-alcoholic fatty liver disease activity score without worsening of fibrosis, occurred in 58% of pioglitazone recipients and 17% of placebo recipients ($P<0.001$).

4 Similarly, resolution of NASH was more common in the pioglitazone group (51% vs 19%; $P<0.001$).

5 Pioglitazone was also associated with improvement in individual histologic scores, reduced hepatic triglyceride content and improved insulin sensitivity in adipose, hepatic and muscle tissue.

6 There were no severe adverse events leading to discontinuation and no cases of bladder cancer, osteoporosis or fracture. However, pioglitazone was associated with a weight gain of 2.5 kg compared with placebo.

7 Pioglitazone treatment was continued for a further 18 months in an open-label follow-up, and the histological benefit continued with no major adverse events.

8 The authors conclude that pioglitazone is safe and effective for the treatment of NASH in people with prediabetes or T2D.

Cusi K, Orsak B, Bril F et al (2016) Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. *Ann Intern Med* **165**: 305–15

Diabetologia

30 minutes' walking per day: Is timing important?

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓✓

1 Current guidelines suggest that people with T2D have at least 150 minutes of physical activity per week, which translates to 30 minutes per day, 5 days per week.

2 These authors sought to determine whether separating this activity into three 10-minute walks after meals, rather than walking for a single bout of 30 minutes, had any effect on glycaemic control.

3 In a randomised crossover study, 42 adults with T2D (mean age, 60 years; mean HbA_{1c}, 59 mmol/mol [7.5%]) were assigned to a 30-minute walk at any time of day, or three post-meal walks, both every day for 2 weeks, in a randomised order. There was a 1-month washout period between interventions.

4 Overall, postprandial glycaemia (3 hours post-meal), as measured by the incremental area under the blood glucose curve (iAUC) was 12% lower (95% confidence interval [CI], 1–22%) during the post-meal walking arm.

5 This difference was largely explained by the 22% reduction in iAUC (95% CI, 9–33%) following the evening meal, when participants tended to be most sedentary and to have eaten the most carbohydrate.

6 No significant differences in anthropometric, blood pressure or lipid measurements were observed.

7 Longer-term studies to assess whether these postprandial changes translate into improvements in overall glycaemic control would be useful.

Reynolds AN, Mann JI, Williams S, Venn BJ (2016) Advice to walk after meals is more effective for lowering postprandial glycaemia in type 2 diabetes mellitus than advice that does not specify timing: a randomised crossover study. *Diabetologia* **59**: 2572–8

> *"The authors conclude that pioglitazone is safe and effective in people with prediabetes or T2D and non-alcoholic steatohepatitis."*