Management & prevention of type 2 diabetes

NEJM

TODAY Study: Tackling glycaemic control in adolescents

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

1 The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study group compared the effects of early combined treatment with metformin alone on glycaemic control in young people with T2D.

2 Children and adolescents aged between 10 and 17 years with recently diagnosed T2D (n=699) were treated with metformin (1000 mg twice daily) until HbA_{1c} levels reached <64 mmol/mol (8%). Following this they were randomised to receive metformin monotherapy, metformin plus rosiglitazone or metformin plus a lifestyle intervention programme, and followed up for an average of 3.86 years. Time-to-treatment-failure (HbA_{1c} ≥64 mmol/mol [8%] for 6 months or persistent metabolic decompensation) was compared between treatment groups.

3 Treatment failure occurred in 45.6% of people across all treatment groups at a median time of 11.5 months. Compared with metformin alone, metformin plus rosiglitazone significantly reduced the occurance of treatment failure (P=0.006), and metformin plus lifestyle intervention did not have a superior effect on glycaemic control.

4 Compared with other racial and ethnic groups, metformin monotherapy was least effective in non-hispanic black individuals. Metformin plus rosiglitazone was more effective in girls than in boys.

5 The authors concluded that the study findings suggest that young people with T2D may benefit from combination treatment initiated early following diagnosis.

TODAY Study Group (2012) A clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med* **366:** 2247–56

T2D in Youth: A cause for present and future concern?

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As published evidence has reported, for T2D to develop at a younger age, individuals have to reach a higher BMI, and the average BMI at T2D diagnosis declines with increasing age (Hillier and Pedula, 2001; Logue et al, 2011). The occurrence of high BMIs in younger people with T2D was recently confirmed by the TODAY (Treatment Options for Type 2 Diabetes in Adolescents and Youth) study group who investigated American children aged 10–17 years (average age 14 years) with T2D and an average BMI of nearly 35 kg/m^2 (TODAY Study Group, 2012; summarised alongside).

The TODAY study compared the effects of metformin alone, metformin with rosiglitazone and metformin with lifestyle interventions on average HbA_{1c} over an average of 3.86 years' follow-up. Whilst the headline results suggest the addition of rosiglitazone to metformin rather than lifestyle intervention was superior to metformin alone in preventing glycaemic deterioration, the results present the worrying finding of a rapid deterioration in glycaemic control in adolescents, considerably more rapid that previously reported for adults with T2D (Brown et al, 2010). This is a concern given an increasing number of younger people with T2D in clinical practice, as recently reported by Harron et al (2011). The authors could not find any clear evidence for poorer compliance amongst the younger cohort to explain this observation; thus, the mechanism for this pattern can only be guessed at but are there any clues?

Looking at the TODAY study outcomes, it is noteworthy from the supplementary data that BMI increased over time in all three arms of the study and, as expected, more so in young people randomised to treatment with metformin plus rosiglitazone. The BMI increase in the other two study arms somewhat contrasts to what has been noted with metformin therapy in other studies of adults, albeit in those at risk of diabetes, in which a 2 kg weight loss was observed (Knowler et al, 2002). Of course, the children in the TODAY study must have experienced a very rapid weight gain early in life to reach such high BMIs. This weight gain is difficult to slow or reverse even with therapies known to have beneficial effects on weight in adults. Of interest, evidence from other sources suggests that rapid weight gain in children may lead to a more rapid decline in beta-cell function, perhaps double the rate of decline reported in adults (Libman and Arslanian, 2006). This is of course unlikely to be due to beta-cell death but may more likely be caused by the effects of ectopic fat in the pancreas (this suggestion requires direct study).

Reports of a growing population of young people with T2D, regardless of the mechanisms behind this, herald worrying conclusions as developed (and developing) countries will be faced with a growing patient group who may be harder to manage. So what are the management options for this group? Rosiglitazone is no longer recommended for T2D management in many countries and, rather than prescribing glitazones (due to weight gain and other well-documented safety concerns), newer therapies that promote weight loss as well as glycaemia benefits are likely to be better treatment options for younger individuals with T2D, although many of these therapies are costly.

Better still would be earlier identification of youngsters at elevated risk of diabetes, and more evidenced-based investment in helping them and their families to make key sustainable lifestyle changes. At the same time, policies targeted at helping people to lessen their calorie intake (and thus lessen their obesity risk) must be considered, and we in the diabetes community must continue to apply pressure to hasten adoption of such policies

NB: Rosiglitazone was withdrawn from clinical use in the UK in 2010.

Brown JB, Conner C, Nichols GA (2010) Secondary failure of metformin monotherapy in clinical practice. *Diabetes Care* **33**: 501–6

Harron KL, Feltbower RG, McKinney PA et al (2011) Rising rates of all types of diabetes in south Asian and non-south Asian children and young people aged 0-29 years in West Yorkshire, U.K., 1991-2006. *Diabetes Care* **34**: 652–4

Hillier TA, Pedula KL (2001) Characteristics of an adult population with newly diagnosed type 2 diabetes: the relation of obesity and age of onset. *Diabetes Care* **24**: 1522–7

Knowler WC, Barrett-Connor E, Fowler SE et al (2002) Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* **346**: 393–403

Libman IM, Arslanian SA (2007) Prevention and treatment of type 2 diabetes in youth. *Horm Res* **67**: 22–34

Logue J, Walker JJ, Colhoun HM et al (2011) Scottish Diabetes Research Network Epidemiology Group. Do men develop type 2

"Overall, treatment non-compliance was associated with increased all-cause mortality in insulin-treated people with T2D."

DIABETES RES CLIN PRACT

Glycaemic control: Predictors in T2D

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

1 In a prospective cohort study of people with sub-optimally controlled T2D (n=211), the authors investigated the impact of sociodemographic, health- and medication-related characteristics on 1-year glycaemic control (HbA_{1c} ≤58 mmol/mol [7.5%]).

2 Follow-up analysis indicated that older age, lower BMI, lower HbA_{1c} and five or fewer prescribed medications were factors predictive of adequate 1-year glycaemia.

3 Treatment adherence resulted in significantly improved 1-year HbA_{1c} (P=0.001); this effect was comparable to the outcome achieved with taking additional hypoglycamic medications.

4 The authors concluded that better glycaemic control in older people is not explained by better medication adherence but likely by lower BMI.

Nagrebetsky A, Griffin S, Kinmonth AL et al (2012) Predictors of suboptimal glycaemic control in type 2 diabetes patients. *Diabetes Res Clin Pract* **96**: 119–28

DIABETES CARE

T2D treatment: Non-compliance linked to all-cause mortality

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

1 The authors set out to determine the effect of treatment non-compliance (medication non-compliance and/or missed primary care or hospital-scheduled appointments) on all-cause mortality in people with T2D.

2 UK general practice record data from people with diagnostic codes indicative of T2D or who had received an oral antidiabetic drug prescription and were taking insulin (n=15 984) were analysed to idenitify individuals who had not complied with treatment. Mortality was assessed from the end of a 36-month period.

3 Medication non-compliance was significantly higher (P<0.05) in women, smokers, those with higher HbA_{1c}, and those with prior contacts in primary care. Overall, treatment non-compliance was associated with increased all-cause mortality in insulin-treated people, independent of mortality-related factors.

4 The authors concluded that understanding T2D patient treatment compliance may improve life expectancy.

Currie CJ, Peyrot M, Morgan CL et al (2012) The impact of treatment noncompliance on mortality in people with type 2 diabetes. *Diabetes Care* **35**: 1279–84

DIABETOLOGIA

Low-carbohydrate diets may be "a safe alternative" in T2D

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

1 The authors compared the effects of a low-carbohydrate diet (20 energy per cent [E%] from carbohydrate) with a low-fat diet (LFD; 30 E% from fat) on glycaemic control, weight loss and cardiovascular risk factors in people with T2D, over 24 months.

2 Individuals were randomised to a LCD (n=30) or LFD (n=31); both diets were based on attendance at four 1-hour nurse-led group infomation meetings at 2, 6 and 12 months.

3 Weight loss did not differ between diet groups. In the LCD group, at 6 months (when compliance was optimal) reduction in the average insulin dose was significantly higher compared with the LFD group (P=0.046).

4 It was concluded that the LCD with 20 E% from carbohydrate can be considered as a safe alternative to LFDs.

Guldbrand H, Dizdar B, Bunjaku B et al (2012) In type 2 diabetes, randomisation to advice to follow a low-carbohydrate diet transiently improves glycaemic control compared with advice to follow a low-fat diet producing a similar weight loss. *Diabetologia* **55**: 2118–27

DIABETIC MEDICINE

High-dose statin therapy significantly affects T2D glycaemic control

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

1 The CORALL study was a 24-week open-label, randomised, parallel-group, phase IIIb, multicentre study comparing the lipid-loweing effects of two statins (rosuvastatin and atorvastatin) in people with dislipidaemia and T2D. The authors also investigated the effect of high-dose statin therapy on glycaemic control over 18 weeks following initiation of rosuvastatin and atorvastatin.

2 Dutch Caucasian individuals (n=263) were randomised to receive rosuvastatin (n=131) or atorvastatin (n=132); doses were titrated up every 6 weeks reaching 40 mg and 80 mg, respectively, at 24 weeks. HbA_{1c} and mean fasting plasma glucose levels were collected at baseline, 6 and 18 weeks. Statistical analysis was performed on paired results.

3 There was no significant change in HbA_{1c} from baseline treatment of either drug at a dose of 20 mg.

4 Compared with baseline measurements, at 18 weeks, atorvastatin 80 mg and rosuvastatin 40 mg were associated with significant increases in HbA_{1c} (P=0.003 and P<0.001, respectively). Change in LDL cholesterol was not related to HbA_{1c}.

5 Mean fasting plasma glucose only increased significantly from baseline upon treatment with atorvastatin 20 mg (P=0.002).

6 The authors concluded that high-dose statin therapy is associated with a small but significant deterioration in glycaemic control in people with dislipidaemia and T2D. They recommend further studies to investigate the longer-term implications of these findings.

Simsek S, Schalkwijk CG, Wolffenbuttel BH et al (2012) Effects of rosuvastatin and atorvastatin on glycaemic control in Type 2 diabetes – the CORALL study. *Diabet Med* **29**: 628–31