Management & prevention of type 2 diabetes

Combination glucose-lowering therapy at diagnosis: Prime time or proof of concept?

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At type 2 diabetes diagnosis, current treatments emphasise the primacy of lifestyle changes with or without metformin, depending on individuals' characteristics and glycaemia levels. Rarely do doctors ever consider dual therapy, never mind triple therapy, at, or near, diagnosis unless significant hyperglycaemia and related symptoms require rapid resolution. Nevertheless, Abdul-Ghani et al (summarised alongside) hypothesised that since type 2 diabetes is a condition with several pathophysiological determinants – namely insulin resistance, beta-cell dysfunction and hyperglucagonaemia, amongst others – prescribing multiple therapies to address each of these facets may lead to better and more sustained reduction in glucose levels. They did so by comparing a combination of metformin plus pioglitazone and exenatide versus escalating doses of metformin followed by sequential addition of sulphonylurea and insulin glargine in a 2-year open-labelled trial in just over 200 drug-naïve people with type 2 diabetes. Their results are in part predictable (due to characteristics of the drugs in the two arms), but nevertheless the results are noteworthy with clear evidence of greater initial and sustained reduction (at least over 2 years) in HbA_{1c} in the triple-therapy group. Furthermore, this group also experienced far less hypoglycaemia and achieved minor weight loss compared with an average weight gain of over 4 kg in the conventional therapy group. Although more participants complained of nausea and slightly more had peripheral oedema in the triple therapy group, the majority of participants were able to stay on all three drugs. The authors did not, however, have enough power to look at end-points, cost-effectiveness or quality of life, but changes in measured parameters provide hints that such aspects could have been favourably altered.

Overall, while the strengths and, in particular, several of the limitations of the study are well considered by the authors, do the results have any potential future clinical relevance? The average age of the participants (around 46 years of age), the levels of obesity (around 36 kg/m^2), and the ethnic make-up of the cohort (mostly Mexican-Americans – a group known to be at particular high risk of diabetes [Arredondo and Reyes, 2013]), suggest the patients recruited into the study are at high risk of adverse complications of diabetes, linked in part to more rapid glycaemia progression. There is now a general recognition that younger, often more obese people and those with greater genetic drive towards diabetes (i.e. via family history or ethnic background), often have worse glycaemic control at diagnosis or more rapid deterioration in their glucose control or both, with greater risk of microvascular complications. For this group, novel approaches to lowering glucose levels are needed given our collective failure to make major gains thus far (Diabetes UK, 2009; Constantino et al, 2013). It is also now recognised that attempting to intensively lower glucose levels in people with prolonged duration of diabetes, who often have multiple complications, is potentially less favourable – and in some cases may do more harm – than lowering glucose in those with short diabetes duration and fewer complications (Sattar, 2014).

Finally, there is often clinical inertia to up-titrating glucose-lowering therapies and many individuals are being exposed to higher glycaemia levels for longer than should be the case. Collectively, these observations do suggest merit in considering a dual- or triple-therapy approach in select patients at, or near, diagnosis. The authors were quick to point out that longer trials are needed to ascertain the longer-term benefits of triple therapy; however, it is clear that their proof-of-concept study and general paradigm of early aggressive glucose-lowering therapy merits further consideration in specific groups. ■

References on next page

Diabetes Obes Metab

Initial combination therapy versus sequential add-on therapy

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

1 The aim of this study was to test whether initiating therapy with a combination of agents among people with new-onset T2D would produce greater results in HbA_{1c}, hypoglycaemia and weight loss than traditional sequential addition of glucose-lowering agents.

2 Recently diagnosed, drug-naïve adults with T2D were randomly assigned to receive triple therapy of metformin, pioglitazone and exenatide (n=106) or conventional therapy of metformin, followed by a sulphonylurea and insulin glargine (n=115) approximately 5 months after clinical diagnosis of T2D.

3 The target was to maintain HbA_{1c} at <6.5% (48 mmol/mol) for 2 years. The mean follow-up was 18 months, and the dropout rates for both treatment arms were approximately 25–30%.

4 There was a significantly greater reduction in HbA_{1c} among those on combination therapy compared to those on conventional therapy (P<0.001).

5 Those receiving combination therapy experienced a 7.5-fold lower rate of hypoglycaemia, and a mean weight loss of 1.2 kg compared to those on conventional therapy who had a mean weight gain of 4.1 kg (P<0.01).

6 This study suggests that initial combination therapy may be more effective at lowering and maintaining good glycaemic control, and avoiding weight gain, than traditional sequential drug initiation.

Abdul-Ghani MA, Puckett C, Triplitt C et al (2015) Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT). *Diabetes Obes Metab* **17**: 268–75

Diabet Med

Reversibility of T2D is dependent on extent of weight loss after surgery

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

1 The authors sought to determine the impact of diabetes duration and extent of weight loss on the reversibility of T2D after a bariatric surgical procedure.

2 In this analysis, complete data for 89 people with T2D who had undergone a bariatric surgical procedure were used. The authors then separated the cohort into three groups depending on diabetes duration prior to surgery: short duration, <4 years; medium duration, 4–8 years; and long duration, >8 years.

3 An HbA_{1c} of <43 mmol/mol (6.1%) was achieved by 62% of people in the short-duration group and 26% in the long-duration group. There was a clear relationship between greater weight loss and lower HbA_{1c} levels across the whole cohort post-surgery ($P<0.0001$).

4 Among the limitations cited by the authors, they noted that it is extremely difficult to accurately calculate the date of diabetes onset. However, if this did have an effect it would be in underestimating diabetes duration, which would increase the reversal rates in the long-duration group.

5 The study shows that weight loss is a key factor in lowering HbA_{1c} levels after bariatric surgery. Normoglycaemia can be achieved in long-duration T2D, but a greater degree of weight loss is required compared to short-duration diabetes.

Steven S, Carey PE, Small PK, Taylor R (2015) Reversal of type 2 diabetes after bariatric surgery is determined by the degree of achieved weight loss in both short- and long-duration diabetes. *Diabet Med* **32**: 47–53

Diabetes Care

Trends in T2D incidence over past decades

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

1 It is well documented that the prevalence of obesity has increased over recent years, but less is known about whether T2D incidence is continuing to rise. The authors, therefore, examined trends in diabetes incidence over the previous four decades.

2 Participants from the Framingham study that were aged 40–55 years and free from diabetes at baseline were followed for the development of diabetes in the 1970s, 1980s, 1990s and 2000s.

3 Diabetes diagnosis was defined as either a fasting glucose ≥126 mg/dL (7 mmol/L) or use of anti-diabetes medication.

4 The annualised rates of diabetes per 1000 individuals were 2.6, 3.8, 4.7 and 3.0 (for women) and 3.4, 4.5, 7.4 and 7.3 (for men) in the 1970s, 1980s, 1990s, and 2000s, respectively.

5 Compared with the 1970s, the age- and sex-adjusted relative risks of diabetes were 1.37 (95% confidence interval [CI], 0.87–2.16 [$P=0.17$]), 1.99 (95% CI, 1.30–3.03 [$P=0.001$]) and 1.81 (95% CI, 1.16–2.82 [$P=0.01$]) in the 1980s, 1990s and 2000s, respectively. Compared with the 1990s, the relative risk of diabetes in the 2000s was not significantly different.

6 The analysis showed that the risk of new-onset diabetes continued to be higher in the 2000s compared with the 1970s. Since the 1990s, diabetes incidence has remained steady, despite the ongoing trend of rising obesity prevalence.

Abraham TM, Pencina KM, Pencina MJ, Fox CS (2015) Trends in diabetes incidence: the Framingham Heart Study. *Diabetes Care* **38**: 482–7

Diabet Obes Metab

Effectiveness of lifestyle-based weight loss interventions

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

1 A systematic review and meta-analysis were carried out to investigate the effectiveness of lifestyle-based weight loss interventions for adults with T2D.

2 A comprehensive search of PubMed, Embase, CINAHL and Web of Science from January 2003 to July 2013 was conducted. The eligibility criteria for studies were randomised controlled trials evaluating weight loss interventions of ≥12 weeks' duration compared to usual care or a different intervention.

3 Ten studies were eligible for inclusion. Study cohorts ranged from 27 to 5145 participants, and the duration of the interventions ranged from 16 weeks to 9 years. Six studies, comprising 5795 people in total, compared lifestyle intervention with usual care and the pooled effect on weight was –3.33 kg and the pooled effect on HbA_{1c} was –0.29% (3.2 mmol/mol), with both attenuated in sensitivity analyses.

4 The pooled within-group effect on weight ($n=3063$) from all 10 lifestyle intervention groups was –5.33 kg (95% confidence interval, –7.33, –3.34 kg), which was also attenuated in sensitivity analyses.

5 Lifestyle-based weight loss interventions can achieve, on average, modest reductions in weight and HbA_{1c} levels, although in this meta-analysis, the observed results were heavily influenced by one particular trial – the Look AHEAD trial.

Terranova CO, Brakenridge CL, Lawler SP et al (2015) Effectiveness of lifestyle-based weight loss interventions for adults with type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab* **17**: 371–8

> *"The study suggests that initial combination therapy at diabetes diagnosis may be more effective at lowering and maintaining good glycaemic control, and avoiding weight gain, than traditional sequential drug initiation."*

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Constantino MI, Molyneaux L, Limacher-Gisler F et al (2013) Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. *Diabetes Care* **36**: 3863–9

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