Diabetes journals

Minimising weight gain from intensive glycaemic control: A multifactorial approach

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Weight gain is a well-known consequence of the intensive treatment of T2D. In an era of individualised therapy targets, the definition of intensive treatment varies, while different therapy strategies are associated with different degrees of weight gain. The determinants of weight gain in relation to intensification of glucose control in people with T2D are unclear. The objective of this analysis was to identify determinants of weight gain in people with T2D allocated to intensive versus standard glycaemic control in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Determinants of weight gain over 2 years in 8929 participants (4425 intensive arm and 4504 standard arm) with T2D were assessed using general linear models to examine the association between each baseline characteristic and weight change at the 2-year visit. A linear regression of change in weight and HbA_{1C} was used with general linear models to examine the association between each medication at baseline and weight change at the 2-year visit, stratified by glycaemia allocation.

There was significantly more weight gain in the intensive glycaemia arm of the trial compared with the standard arm (3.0 versus 0.3 kg). On multivariate analysis, younger age, male sex, Asian race, no smoking history, high HbA_{1c}, baseline BMI of 25–35 kg/m^2, high waist circumference, baseline insulin use and baseline metformin use were independently associated with weight gain over 2 years. Reduction of HbA_{1c} from baseline was consistently associated with weight gain only when baseline HbA_{1c} was elevated. Medication usage accounted for 15% of the variability of weight change, with initiation of thiazolidinedione (TZD) use the most prominent factor. Intensive participants who never took insulin or a TZD had an average weight loss of 2.9 kg during the first 2 years of the trial. In contrast, intensive participants who had never previously used insulin or TZD but began this combination after enrolling in the ACCORD trial had a weight gain of 4.6–5.3 kg at 2 years.

No single factor was strongly associated with, and potentially responsible for, the change in weight seen in each group. In both treatment arms, participants with the highest baseline HbA_{1C} gained weight with improvement in HbA_{1C}. In contrast, when HbA_{1C} was lower than 7.8% at baseline, a drop in HbA_{1C} during treatment was associated with a decrease in weight in both arms. However, the degree of both HbA_{1C} decline and weight loss in these participants was relatively small.

> ***"On multivariate analysis, younger age, male sex, Asian race, no smoking history, high HbA_{1c}, baseline BMI of 25–35 kg/m^2, high waist circumference, baseline insulin use and baseline metformin use were independently associated with weight gain over 2 years."***

Thus in clinical practice, an attempt to intensify treatment in patients with a very high HbA_{1c} is likely to lead to a significant weight gain. In such circumstances, therefore, particular attention needs to be paid the use of therapy approaches to minimise weight gain. Change in HbA_{1c} during the trial did not predict weight gain uniformly, suggesting that weight gain is not an inevitable consequence of improvements in glucose control. During the first year of treatment, variability in baseline medications and baseline HbA_{1c} accounted for almost all (88%) of the change in weight in the intensive arm but less than half of the weight change in the standard arm, while TZD use accounted for a much higher percent of variability in weight in the intensive than the standard arm.

The observations from this analysis indicate that many factors, beyond simple therapy choice and glycaemic targets, need to be considered in relation to minimising weight gain consequent upon attempts to improve glucose control. Only by taking such a holistic multifactorial approach can weight gain be attenuated in minimised in people with T2D.

DIABETES CARE

Intensive glycaemic control correlates to weight gain in T2D

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

1 Intensive treatment of T2D often results in weight gain, although the reasons for weight change in response to intensive glycaemic control are unclear.

2 The authors of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial aimed to determine the factors associated with weight gain in 8929 people with T2D over 2 years.

3 Participants were randomised to receive either intensive glycaemic control (*n*=4425) with an HbA_{1c} target of <6.0% (42 mmol/mol) or standard therapy (*n*=4504) with an HbA_{1c} target of between 7.0 and 7.9% (53 to 63 mmol/mol).

4 Significantly greater weight gain was observed in the intensive treatment arm compared with standard treatment (3.0 ± 7.0 kg versus 0.3 ± 6.3 kg). Medication use was responsible for <15% weight gain variation, particularly in thiazolidinedione (TZD) or insulin therapy.

5 Participants who had not used insulin or TZD previously, but began after enrolling into the trial, displayed a weight gain of 4.6 to 5.3 kg after 2 years. Weight gain was correlated to a decrease in baseline HbA_{1c} in participants with a high baseline HbA_{1c}.

6 The authors concluded that weight gain was greater with intensive glycaemic control compared to standard therapies, especially if TZD or insulin therapy were initiated. Weight gain was associated with reduced HbA_{1c} in participants with high baseline values.

Fonseca V, McDuffie R, Calles J et al (2013) Determinants of weight gain in the action to control cardiovascular risk in diabetes trial. *Diabetes Care* 14 Feb [Epub ahead of print]

DIABETIC MEDICINE

HbA_{1c} and CV mortality: The role of education

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

1 Previous research suggests that aspects of socioeconomic deprival, such as low education, can predict mortality in people with diabetes.

2 The authors aimed to investigate the relationship between educational level, HbA_{1c}, cardiovascular events and mortality in a cohort of 32 871 people treated with glucose-lowering agents for T2D.

3 Electronic health records from 84 primary care centres were retrospectively analysed in this observational study. Educational level was defined as "compulsory", which encompassed 9-year comprehensive school or "upper school", which included all further education.

4 The relationship between HbA_{1c} and risk of all-cause and cardiovascular mortality was J-shaped. The lowest risk for cardiovascular mortality was observed at a HbA_{1c} level of 6.8% (51 mmol/mol) for participants treated with oral agents and 7.3% (56 mmol/mol) in individuals receiving insulin therapy.

5 An elevated risk for cardiovascular death was observed in participants with low education and HbA_{1c} (hazard ratio [HR] 1.6, 95% CI, 1.2–2.1; *P*=0.0008). However, individuals with high education did not display an increased risk of cardiovascular death (HR 1.2 [0.8–1.6]; *P*=0.3873).

6 The authors concluded HbA_{1c} levels were correlated to an increased risk for all-cause and cardiovascular mortality in T2D, especially in people with a low educational background.

Ostgren CJ, Sundström J, Svennblad B et al (2013) Associations of HbA1c and educational level with risk of cardiovascular events in 32 871 drug-treated patients with Type 2 diabetes: a cohort study in primary care. *Diabet Med* 28 Jan [Epub ahead of print]

DIABETES CARE

Increased all-cause and cardiovascular mortality in T2D

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

1 The authors aimed to establish the risk of all-cause and cardiovascular mortality in a cohort of people with T2D. Health records from the General Practice Research Database (GPRD) were searched to identify 87 098 middle-aged (40 to 65 years) participants for inclusion into the study.

2 The risk of all-cause mortality was two-fold higher in people with T2D (hazard ratio [HR] 2.07 [95% CI, 1.95–2.20], adjusted for smoking) and the risk of cardiovascular mortality was three-folder higher (HR 3.25 [2.87–3.68], adjusted for smoking) compared to those without diabetes.

3 Women were found to have a greater risk than men and older people (>55 years) were more at risk than younger people (<55 years).

4 The authors concluded that middle-aged people with T2D are still have an elevated risk of mortality.

Taylor KS, Heneghan CJ, Farmer AJ et al (2013) All-cause and cardiovascular mortality in middle-aged people with type 2 diabetes compared with people without diabetes in a large U.K. primary care database. *Diabetes Care* 22 Feb [Epub ahead of print]

DIABETES RES CLIN PRACT

Cardio-metabolic risk prediction

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

1 The authors investigated the efficiency of waist to height ratio (WHtR) as a marker for diabetes and cardio-metabolic risk compared to BMI, waist circumference (WC) and waist to hip ratio (WHR), in a cohort of ethnically South Asian individuals (*n*=4485).

2 WHtR was significantly lower in males compared to females (0.477 ± 0.065 versus 0.508 ± 0.081; *P*<0.001). Area under the curve (AUC) of WHtR was higher than BMI, WC and WHR in diabetes, pre-diabetes, hypertension and hypercholesterolemia.

3 The authors concluded that WHtR is a reliable marker for metabolic risks in people from a South Asian descent.

Jayawardana R, Ranasinghe P, Sheriff MH (2013) Waist to height ratio: A better anthropometric marker of diabetes and cardio-metabolic risks in South Asian adults. *Diabetes Res Clin Pract* 5 Jan [Epub ahead of print]

DIABETES CARE

iScore predicts tPA response

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

1 The authors aimed to investigate if the iScore is predictive of therapeutic response to thrombolysis (tPA) in people with diabetes and a history of acute ischaemic stoke compared to people without diabetes.

2 The iScore was calculated for 12 686 individuals attending stroke centres which participated in the Registry of the Canadian Stroke Network (RCSN).

3 People with diabetes (*n*=1689) experienced an increased rate of adverse outcomes after tPA (24.3 versus 31.1%; relative risk 0.90 [95% CI, 0.82–0.98]). Risk of intracerebral haemorrhage was the same in both groups. The iScore was predictive of tPA response in people with and without diabetes (*P*=0.07).

4 The authors concluded that the iScore can reliably predict tPA response in people with and without diabetes.

Nikneshan D, Raptis R, Pongmoragot J et al (2013) Predicting clinical outcomes and response to thrombolysis in acute stroke patients with diabetes. *Diabetes Care* 28 Jan [Epub ahead of print]

"The authors concluded HbA_{1c} levels were correlated to an increased risk for all-cause and cardiovascular mortality in T2D, especially in people with a low educational background"