

Can obese adults with type 2 diabetes lose weight while on insulin therapy?

Billy Law

Prevalence of obesity and insulin therapy in adults with type 2 diabetes in the UK is growing rapidly. Mitigating weight gain and inducing weight loss has many health benefits, but insulin therapy, which is sometimes required for glucose control, is commonly observed to cause weight gain. Therefore, is it possible for obese adults with type 2 diabetes on insulin therapy to lose weight? This article reviews evidence related to weight outcomes in obese adults with type 2 diabetes on insulin therapy. From the available evidence, suggestions are made on mitigating weight gain, and even inducing weight loss, in this ever-growing population.

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The Australian context

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This article teases out some of the determinants and predictors of weight gain associated with insulin therapy. A few key messages from this article may provide clinicians with the confidence to predict, prevent and address any weight gain. Whilst weight gain is common with insulin therapy, it is clearly not inevitable.

Notably, higher BMI at insulin initiation is not a predictor of greater weight gain, with very obese individuals possibly gaining less weight than those with a lower BMI, so high BMI should not be seen as an impediment to starting insulin therapy. Earlier initiation of insulin is associated with less weight gain. It follows that in people in whom insulin is delayed, weight gain is more likely to be an issue. People in whom insulin initiation is delayed are likely to have a higher glycaemic load to address and hence may require more insulin to achieve glycaemic targets.

The choice of insulin has an impact too. Insulin detemir is weight-neutral and may even be associated with modest weight loss, whilst glargine U100 and its newly available stablemate, glargine U300, are associated with weight gain. Currently, only glargine U100 is reimbursed for

type 2 diabetes by the PBS. At the time of writing, glargine U300 is available to prescribing GPs on a patient familiarisation program.

The choice of agents used in combination therapy with insulin has an impact too. Metformin is generally considered to be weight-neutral, whilst sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists are not only insulin-sparing but are also associated with weight loss, even when combined with insulin. Dapagliflozin is currently the only SGLT2 inhibitor that is PBS-reimbursed for use in combination with insulin, while, as of 1 October 2015, the PBS listing of exenatide twice daily has been extended to allow triple therapy with insulin and metformin.

Lifestyle modification, in particular when accompanied by significant weight loss, is associated with improved glycaemic control and mitigation of insulin dose escalation. However, persistence of lifestyle modification remains a significant challenge in the “free-living” person with type 2 diabetes. Weight loss, by whatever means, has beneficial effects. This is a dose-dependent effect and is most notable when associated with bariatric surgery.

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Article points

1. Studies investigating weight management in obese adults with type 2 diabetes on insulin therapy are limited.
2. Limiting weight gain or inducing weight loss may improve insulin sensitivity, glycaemic control and reduce cardiovascular risk factors in people with diabetes.
3. Available studies report the following potential measures to restrict weight gain or induce weight loss in people with type 2 diabetes taking insulin: using insulin detemir and adjunctive medications, following dietary energy restrictions and increasing physical activity, behavioural interventions and the frequency of clinical support.

Key words

- Insulin
- Obesity
- Weight loss

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1. The proportion of adults who are obese is continuing to rise, and this brings with it an increased risk of type 2 diabetes and its complications.
2. As poor glycaemic control confers an increased risk of complications, it is important to initiate insulin therapy, when required, in a timely manner; however, both people with type 2 diabetes and their clinicians can be reluctant to do so for fear of weight gain.
3. Multiple research studies have concluded that there is an inevitable gain in body weight after insulin initiation for adults with type 2 diabetes, but there have been few studies that have specifically explored weight changes in obese adults with type 2 diabetes on insulin therapy.

One message I am consistently reminded of by obese adults with type 2 diabetes and healthcare professionals alike, is that insulin therapy causes weight gain. However, from my clinical experience not all insulin-treated adults with type 2 diabetes will inevitably gain weight, even those who are already obese. So how do some obese adults manage to limit weight gain or even lose weight on insulin treatment? This article will consider the published literature on weight changes following insulin initiation and discuss ways to promote positive weight changes in people taking insulin, whether or not they have experienced weight gain following initiation.

Prevalence of obesity, type 2 diabetes and insulin therapy in adults

In 2012, about 25% of adults were classified as obese (BMI ≥ 30 kg/m²) in the UK (Health and Social Care Information Centre [HSCIC], 2014a), and obese adults are five times more likely to be diagnosed with type 2 diabetes compared with healthy weight adults (Gatineau et al, 2014). In the UK, the percentage of obese adults is predicted to rise to 50% of women and 60% of men by 2050 (Butland et al, 2007). With this projected surge in adult obesity rates, a similar increase in the prevalence of adults with type 2 diabetes is also predicted. This has also led to an increase in insulin use for the management of type 2 diabetes; using real-world data, the rate of adult insulin users with a diagnosis of type 2 diabetes has trebled to 4.34 per 1000 of the UK population from 1991 to 2010 (Holden et al, 2014). Insulin use has risen in tandem with increasing obesity and type 2 diabetes rates, and rates are expected to continue rising rapidly.

Consequences and benefits of insulin initiation

Obese adults with uncontrolled type 2 diabetes have an increased risk of long-term complications such as cardiovascular disease, amputations, blindness, depression, kidney disease and premature mortality (Gatineau et al, 2014); therefore, it is important to initiate insulin treatment to improve glucose control when necessary in combination with other medications and lifestyle interventions.

Several studies conducted on overweight and

obese adults with type 2 diabetes found weight loss is associated with improved glycaemic control, lipid profile, blood pressure and reduced cardiovascular risk (Markovic et al, 1998; Anderson et al, 2003; Ridderstråle et al, 2006; Feldstein et al, 2008). Weight loss has also been associated with longer life expectancy (Lean et al, 1990). In a trial of 10 insulin-treated obese adults with type 2 diabetes, an association was established between a significant weight loss of 50% of excess weight and reduced basal endogenous glucose production and improved insulin sensitivity of the liver, adipose tissue and skeletal muscle (Jazet et al, 2008), thus showing the benefits of weight loss.

Evidence for weight gain in obese adults with type 2 diabetes on insulin therapy

Multiple research studies have concluded that there is an inevitable gain in body weight after insulin initiation for adults with type 2 diabetes (Riddle et al, 2003; Holman et al, 2007; Pontiroli et al, 2011), but there have been few studies that have specifically explored weight changes in obese adults with type 2 diabetes on insulin therapy.

In a longitudinal study including obese adults with type 2 diabetes, the obese participants were less likely to gain weight than the leaner participants after insulin initiation (Jansen et al, 2011). Other studies have concurred with this finding (Jazet et al, 2008; Jansen et al, 2010), though results from the CREDIT (Cardiovascular Risk Evaluation in people with type 2 Diabetes on Insulin Therapy) study demonstrated that weight gain was similar for those who were more obese compared to those that were less obese (Balkau et al, 2014).

It has been reported in various studies that soon after insulin initiation, there is an initial weight gain in obese adults with type 2 diabetes followed by weight stabilisation. Jansen and colleagues (2011) have published one of the quickest rates of weight gain in the initial 9 months after starting insulin among adults with a higher BMI. Weight regain was initially between 0.52 (0.4–0.7) kg/month for the first 9 months, and then weight regain reduced to 0.1 kg/month (average gain +1.2 kg/year).

Weight stabilisation has been shown to occur 2–3 years after insulin initiation (Larger et al, 2001). A similar weight outcome was described by

Watson et al (2011) who analysed a retrospective database of 3783 adults with type 2 diabetes over a 24-month period following insulin initiation in primary care. The authors reported that the greatest weight gain was at 6 months after insulin initiation (+2.0 kg) in the obese group, and that there was a negative correlation between weight gain and baseline BMI.

A 9-year study in Iran has also identified a 0.3% weight loss and a 0.2% weight gain in the obese and morbidly obese insulin-treated adults with type 2 diabetes respectively (Janghorbani and Amini, 2009), which suggests baseline BMI may have a role in changes in weight. One study has shown that obese adults with a previous myocardial infarction event and type 2 diabetes who have begun insulin treatment had a significant increase in weight regain of 2.3 (1.5–3.2) kg and incidence of reinfarction (hazard ratio 2.5; $P=0.011$), but the increased risk of reinfarction was not related to the increase in weight gain (Aas et al, 2009).

Weight management factors for adults with type 2 diabetes on insulin therapy

Although there have been few studies investigating the factors related to weight management for obese adults with type 2 diabetes who have begun insulin, some conclusions have been made to suggest ways to mitigate weight regain after insulin initiation.

Insulin initiation: timing, type and dose

The potential to regain weight after insulin initiation in adults with type 2 diabetes can be a psychological barrier to agreeing to treatment (Korytkowski, 2002; Snoek, 2002). By initiating insulin before HbA_{1c} rises to very high levels, significant weight gain can be avoided. In fact, when blood glucose is well controlled, insulin users have been shown to gain minimal body weight (+0.5 kg) over a 24-month period (Huizinga et al, 2008).

The choice of insulin type on initiation also appears to have an impact on subsequent body weight. Researchers have demonstrated a -0.5 kg weight loss after 26 weeks with insulin detemir with or without dietary interventions in obese people (30.0–34.9 kg/m²), and up to -2.0 kg weight loss in severely obese adults (35.0–39.9 kg/m²) with dietary intervention and in morbidly obese

adults (40–45 kg/m²) with insulin detemir alone (Niswender et al, 2014). Weight loss in adults with a BMI higher than 35 kg/m² after insulin detemir initiation has also been confirmed by Raslova and colleagues (2007). Furthermore, research using data from adults with type 2 diabetes on insulin therapy in all BMI groups has reported lower weight gain with insulin detemir, especially if used once daily, compared with insulin glargine (Rosenstock et al, 2006; Meneghini et al, 2007; Pontiroli et al, 2011), and lower weight gain with insulin glargine relative to prandial or premixed insulin (Davies and Khunti, 2008; Freemantle et al, 2013). However, none of the preceding studies were specific for obese adults only.

Limiting the total insulin dose can also minimise weight gain (Balkau et al, 2014), and this may be achieved by using other anti-diabetes medicines in combination pharmacotherapy.

Combination pharmacotherapy

An example of the benefits of combination medications were described in an observational study by Schreiber et al (2008) when 596 obese adults with type 2 diabetes were treated with insulin glargine plus a variety of oral glucose-lowering medication over 32 months in clinical practice. At the end of the study, Schreiber and colleagues reported a resulting weight loss of 4.4±10.7 kg ($P<0.0001$) in the obese group.

i) Metformin

Studies on adults with type 2 diabetes have shown a weight neutral or modest weight loss effect with adjunctive metformin use (Golay, 2008), especially in obese adults (United Kingdom Prospective Diabetes Study [UKPDS] Research Group, 1998). A particular study on 71 insulin-treated obese adults reported reduced HbA_{1c}, cholesterol and BMI levels with the addition of metformin to insulin, with or without a sulphonylurea (Johnson et al, 1998).

ii) Other medications

Other pharmacological agents in combination with insulin appear to induce weight loss in obese adults with type 2 diabetes. For instance, after 12 months' use, empagliflozin with insulin and exenatide with insulin reduced body weight by 2.4–2.5 kg

Page points

1. By initiating insulin before HbA_{1c} rises to very high levels, significant weight gain can be avoided. When glycaemic control is good, insulin users have been shown to gain minimal body weight.
2. The type of insulin also appears to be important, with evidence suggesting that insulin detemir results in weight loss.
3. Combination pharmacotherapy with agents such as metformin can reduce insulin dose and thus reduce potential weight gain.

Page points

1. Sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists have weight-lowering effects, while dipeptidyl peptidase-4 inhibitors are weight-neutral and can improve glycaemic control without the need to increase insulin dose.
2. Bariatric surgery and lifestyle interventions also have a part to play in reducing weight gain post-insulin initiation.

(Rosenstock et al, 2014) and 12.8 ± 7.5 kg (Nayak et al, 2010) in their respective study populations. Research on adults with type 2 diabetes and a range of body weights has identified the weight-lowering or weight neutral effects of type 2 diabetes medicines. Glucagon-like peptide 1 (GLP-1) receptor analogues (Russell-Jones and Khan, 2007) and sodium–glucose cotransporter 2 (SGLT2) inhibitors (Tahrani et al, 2013) are weight lowering, and dipeptidyl peptidase-4 inhibitors are described as weight-neutral (Deacon, 2011).

Medicines that are prescribed for the concomitant management of type 2 diabetes and its complications can also have a positive or neutral effect on weight (e.g. the cholesterol-lowering drug colesvelam is weight-neutral [Pedersen, 2013]). Orlistat can also be prescribed to obese people with type 2 diabetes for weight loss (Kelley et al, 2002).

Bariatric surgery

Specific studies on insulin-treated obese people with type 2 diabetes who have undergone bariatric surgery are rare. Results from one particular study with morbidly obese people with type 2 diabetes highlighted significant reductions in body weight (-33.6 kg) after Roux-en-Y gastric bypass (RYGB) surgery after 1 year compared to baseline, versus minimal weight gain (0.6 kg) in the diabetes support and education group (Khoo et al, 2014).

Lifestyle interventions

It is well known that lifestyle interventions can increase insulin sensitivity and support reductions in insulin dose requirements that may go on to augment weight loss.

i) Dietary intervention

A small study over a 1-year period conducted by Aas et al (2005) of 38 overweight and obese adults with type 2 diabetes randomised to an intensive lifestyle intervention (ILI); ILI with insulin initiation; or insulin initiation alone reported weight changes of -3.0 kg, $+3.5$ kg and $+4.9$ kg respectively. There were similar reductions in HbA_{1c} for each intervention group. The researchers showed intensive lifestyle interventions can limit weight gain and even cause weight loss. However, the ILI groups regained weight after the study finished, possibly due to reduced adherence to recommendations.

One study using meal replacements described restricting dietary energy to ~ 1172 kcal/day as a method to reduce body weight. Fifteen insulin-treated obese adults took part and, after 12 weeks following the diet, there was a 7.1% decrease in weight (Kempf et al, 2014). At 1.5-year follow up, weight loss was sustained at -6.3% of baseline weight. A greater energy restriction of ~ 450 kcal/day was imposed on 10 insulin-treated (>30 units/day) obese adults with type 2 diabetes in the study by Jazet et al (2008). This diet was followed until 50% excess weight reduction was achieved (the mean time to target weight was 17 weeks). In this study, significant weight loss was demonstrated despite insulin therapy and other glucose-lowering medications being stopped during the study, showing diet alone can cause significant weight loss. Although small, the preceding studies suggest energy restriction in obese individuals with type 2 diabetes on insulin therapy may result in significant weight loss.

Other dietary interventions such as the Mediterranean diet, low glycaemic index diet and low carbohydrate diet do not appear to have been studied in obese adults with type 2 diabetes on insulin therapy. From my clinical experience, insulin-treated obese adults who reduce excessive total carbohydrate intake toward the recommended minimum of ~ 130 g/day, dependent on activity levels, are significantly more likely to lose weight or reduce weight gain.

ii) Physical activity intervention

Maintaining recommended physical activity levels has been identified as supporting weight loss in adults with type 2 diabetes (Wing, 2014). In the UK, physical activity levels in obese adults have significantly decreased over recent years. Data from 2012 reported 32% of obese men and 19% of obese women were not meeting physical activity recommendations (HSCIC, 2014b), so it is imperative that physical activity levels are increased to reduce weight gain and encourage weight loss.

In a study by Jansen et al (2010), the authors noted that insulin-treated adults with large weight gains had significantly lower physical activity levels compared with those that did not gain weight (2275 ± 385 vs 2632 ± 734 kcal/day; $P=0.005$ respectively). Therefore, early weight gain

prevention is imperative as weight control may become more difficult as time goes on due to reduced activity levels.

Adherence to lifestyle interventions

The above studies show that weight loss is possible with lifestyle interventions such as dietary energy restrictions and increased physical activity levels. So why are there contradictory weight outcomes between different studies? One possible answer could lie in people's compliance and adherence to lifestyle recommendations.

Adherence and compliance are often the greatest barriers to diabetes management (Mosnier-Pudar, 2009). It has been shown that insulin users have higher adherence to advice relating to insulin and other medications than to diet and physical activity; indeed diet and physical activity compliance rates are low (DiMatteo, 2004; Broadbent et al, 2011). Therefore, people with diabetes are more likely to adhere to insulin regimens rather than lifestyle recommendations.

Favourable weight outcomes were attained by improved adherence in a recent multi-centre randomised control trial: the Look AHEAD (Action for Health in Diabetes) trial. After a mean follow-up of 9.6 years in overweight and obese adults with type 2 diabetes, this trial reported a 6% weight loss in the intensive lifestyle intervention group compared with a 3.5% weight loss in the usual care group (Wing, 2014). Crucially, obese adults and insulin users were able to lose weight at a similar rate to non-insulin users by 4 years (approximately -4.3% of initial weight [Wadden et al, 2011; Unick et al, 2013]). There did not appear to be an investigation into weight outcomes in individuals who were both obese and users of insulin. The three significant factors contributing to successful long-term weight loss in the Look AHEAD trial were frequency and quality of support, increased physical activity levels and dietary energy restrictions. Ways to improve adherence through increased frequency of support for adults, using behavioural techniques, appear to be important in managing weight in the long-term.

Conclusion

Weight gain in obese insulin-treated adults with type 2 diabetes has been commonly observed in

multiple studies, but some studies have demonstrated weight loss, particularly the Look AHEAD study. Strategies to mitigate weight gain, or induce weight loss, from currently available research include the following: choosing insulin detemir; using adjunctive medications such as metformin, SGLT2 inhibitors and GLP-1 receptor agonists; undergoing RYGB surgery if appropriate; dietary energy restrictions and increasing physical activity levels. Adherence to lifestyle recommendations appears to be associated with likelihood of weight loss, and more frequent support and behavioural interventions can improve adherence to lifestyle interventions. ■

Aas AM, Bergstad I, Thorsby PM et al (2005) An intensified lifestyle intervention programme may be superior to insulin treatment in poorly controlled type 2 diabetic patients on oral hypoglycaemic agents: results of a feasibility study. *Diabet Med* **22**: 316–22

Aas AM, Ohrvik J, Malmberg K et al for the DIGAMI 2 investigators (2009) Insulin-induced weight gain and cardiovascular events in patients with type 2 diabetes. A report from the DIGAMI 2 study. *Diabetes Obes Metab* **11**: 323–9

Anderson JW, Kendall CW, Jenkins DJ (2003) Importance of weight management in type 2 diabetes: review with meta-analysis of clinical studies. *J Am Coll Nut* **22**: 331–9

Balkau B, Home PD, Vincent M et al (2014) Factors associated with weight gain in people with type 2 diabetes starting on insulin. *Diabetes Care* **37**: 2108–13

Broadbent E, Donkin L, Stroh JC (2011) Illness and treatment perceptions are associated with adherence to medications, diet, and exercise in diabetic patients. *Diabetes Care* **34**: 338–40

Butland B, Jebb S, Kopelman P et al (2007) *Tackling obesity: Future Choices - Project Report (2nd edition)*. UK Government's Foresight Programme, London

Davies M, Khunti K (2008) Insulin management in overweight or obese type 2 diabetes patients: the role of insulin glargine. *Diabetes Obes Metab* **10**(Suppl 2): 42–9

Deacon CF (2011) Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review. *Diabetes Obes Metab* **13**: 7–18

DiMatteo MR (2004) Variations in patients' adherence to medical recommendations: quantitative review of 50 years of research. *Medical Care* **42**: 200–9

Feldstein AC, Nichols GA, Smith DH et al (2008) Weight change in diabetes and glycemic and blood pressure control. *Diabetes Care* **31**: 1960–5

Freemantle N, Balkau B, Home PD (2013) A propensity score matched comparison of different insulin regimens 1 year after beginning insulin in people with type 2 diabetes. *Diabetes Obes Metab* **15**: 1120–7

Gatineau M, Hancock C, Holman N et al (2014) *Adult obesity and type 2 diabetes*. Public Health England, Oxford. Available at: <http://bit.ly/1M1w4sm> (accessed on 19.01.15)

Golay A (2008) Metformin and body weight. *Int J Obes* **32**: 61–72

Health and Social Care Information Centre (2014a) *Health survey for England 2012: Summary of key findings*. HSCIC, Leeds. Available at: <http://bit.ly/1g0P1e8> (accessed on 29.01.15)

Page points

1. Increasing patient adherence and compliance is an important way to mitigate weight gain; it has been shown that insulin users have higher adherence to advice relating to insulin and other medications than diet and physical activity.
2. Strategies to mitigate weight gain, or induce weight loss, from currently available research include: choosing insulin detemir; using combination medications such as metformin, sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists; undergoing Roux-en-Y gastric bypass surgery if appropriate; setting dietary energy restrictions and increasing physical activity levels.

“Adherence to lifestyle recommendations appears to be associated with an increased likelihood of weight loss, and more frequent support and behavioural interventions can improve adherence to lifestyle interventions.”

- Health and Social Care Information Centre (2014b) *Statistics on obesity, physical activity and diet: England 2014*. HSCIC, Leeds. Available at: <http://bit.ly/Z020dv> (accessed on 29.01.15)
- Holden SE, Gale EA, Jenkins-Jones S, Currie CJ (2014) How many people inject insulin? UK estimates from 1991–2010. *Diabetes Obes Metab* **16**: 553–9
- Holman RR, Thorne KI, Farmer AJ et al (2007) Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Engl J Med* **357**: 1716–30
- Huizinga MM, Niswender KD, Gebretsadik T et al (2008) Insulin use and weight maintenance in well-controlled type 2 diabetes: A prospective cohort study. *Obesity* **16**: 1933–7
- Janghorbani M, Amini M (2009) Patterns and predictors of long-term weight change in patients with type 2 diabetes mellitus. *Ann Nutr Metab* **54**: 111–8
- Jansen HJ, Vervoort G, van der Graaf M, Tack CJ (2010) Pronounced weight gain in insulin-treated patients with type 2 diabetes mellitus is associated with an unfavourable cardiometabolic risk profile. *Neth J Med* **68**: 359–66
- Jansen HJ, Hendriks JC, de Galan BE et al (2011) Contribution of change in glycosylated haemoglobin to insulin associated weight gain: results of a longitudinal study in type 2 diabetic patients. *Endocrine* **39**: 190–7
- Jazet IM, Schaart G, Gastaldelli A et al (2008) Loss of 50% of excess weight using a very low energy diet improves insulin-stimulated glucose disposal and skeletal muscle insulin signalling in obese insulin-treated type 2 diabetic patients. *Diabetologia* **51**: 309–19
- Johnson M, Krosnick A, Carson P et al (1998) A retrospective chart review of uncontrolled use of metformin as an add-on therapy in type 2 diabetes. *Clin Ther* **20**: 691–8
- Kelley DE, Bray GA, Pi-Sunyer FX et al (2002) Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes. *Diabetes Care* **25**: 1033–41
- Kempf K, Schloot NC, Gartner B et al (2014) Meal replacement reduce insulin requirement, HbA_{1c} and weight long-term in type diabetes patients with >100U insulin per day. *J Hum Nutr Diet* **27**(Suppl 2): 21–7
- Khoo CM, Chen J, Pamuklar Z, Torquati A (2014) Effects of Roux-en-Y gastric bypass or diabetes support and education on insulin sensitivity and insulin secretion in morbidly obese patients with type 2 diabetes. *Ann Surg* **259**: 494–501
- Korytkowski M (2002) When oral agents fail: practical barriers to starting insulin. *Int J Obes Relat Metab Disord* **26**(Suppl 3): S18–24
- Larger E, Rufat P, Dubois-Laforgue D, Ledoux S (2001) Insulin and weight gain: myth or reality? *Diabet Metab* **27**: 23–7
- Lean ME, Powrie JK, Anderson AS, Garthwaite PH (1990) Obesity, weight loss and prognosis in type 2 diabetes. *Diabet Med* **7**: 228–33
- Markovic TP, Campbell LV, Balasubramanian S et al (1998) Beneficial effect on average lipid levels from energy restriction and fat loss in obese individuals with or without type 2 diabetes. *Diabetes Care* **21**: 695–700
- Meneghini LF, Rosenberg KH, Koenen C et al (2007) Insulin detemir improves glycaemic control with less hypoglycaemia and no weight gain in patients with type 2 diabetes who were insulin naive or treated with NPH or insulin glargine: clinical practice experience from a German subgroup of the PREDICTIVE study. *Diabetes Obes Metab* **9**: 418–27
- Mosnier-Pudar H, Hochberg G, Eschwege E et al (2009) How do patients with type 2 diabetes perceive their disease? Insights from the French DIABASIS survey. *Diabet Metab* **3**: 220–7
- Nayak UA, Govindan J, Baskar V et al (2010) Exenatide therapy in insulin-treated type 2 diabetes and obesity. *QJM* **103**: 687–94
- Niswender K, Piletic M, Andersen H et al (2014) Weight change upon once-daily initiation of insulin detemir with or without dietary intervention in overweight or obese insulin-naive individuals with type 2 diabetes: results from the DIET trial. *Diabetes Obes Metab* **16**: 186–92
- Pedersen SD (2013) Impact of newer medications for type 2 diabetes on body weight. *Curr Obes Rep* **2**: 134–41
- Pontiroli AE, Miele L, Morabito A (2011) Increase of body weight during the first year of intensive insulin treatment in type 2 diabetes: systematic review and meta-analysis. *Diabetes Obes Metab* **13**: 1008–19
- Raslova K, Tamer SC, Clauson P, Karl D (2007) Insulin detemir results in less weight gain than NPH insulin when used in basal bolus therapy for type 2 diabetes mellitus, and this advantage increases with baseline body mass index. *Clin Drug Investig* **27**: 279–85
- Ridderstråle M, Gudbjörnsdottir S, Eliasson B et al (2006) Obesity and cardiovascular risk factors in type 2 diabetes: results from the Swedish National Diabetes Register. *J Intern Med* **259**: 314–22
- Riddle MC, Rosenstock J, Gerich J et al (2003) The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* **26**: 3080–6
- Rosenstock J, Davies M, Home PD et al (2006) Insulin detemir added to oral anti-diabetic drugs in type 2 diabetes provides glycaemic control comparable to insulin glargine with less weight gain. *Diabetes* **55**: A132
- Rosenstock J, Jelaska A, Frappin G et al (2014) Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycaemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. *Diabetes Care* **37**: 1815–23
- Russell-Jones D, Khan R (2007) Insulin-associated weight gain in diabetes – causes, effects and coping strategies. *Diabetes Obes Metab* **9**: 799–812
- Schreiber SA, Ferlinz K, Haak T (2008) The long-term efficacy of insulin glargine plus oral antidiabetic agents in a 32-month observational study of everyday clinical practice. *Diabet Technol Ther* **10**: 121–7
- Snoek FJ (2002) Breaking the barriers to optimal glycaemic control – what physicians need to know from patients’ perspectives. *Int J Clin Pract Suppl* **129**: 80–4
- Tahrani AA, Barnett AH, Bailey CJ (2013) SGLT inhibitors in management of diabetes. *Lancet Diabetes Endocrinol* **1**: 140–51
- UK Prospective Diabetes Study (UKPDS) Group (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* **352**: 854–65
- Unick JL, Beavers D, Bond DS et al (2013) The long term effectiveness of a lifestyle intervention in severely obese individuals. *Am J Med* **126**: 236–42
- Wadden TA, Neiberg RH, Wing RR et al (2011) Four-year weight losses in the Look AHEAD study: factors associated with long-term success. *Obesity* **19**: 1987–98
- Watson L, Wilson BP, Alsop J, Kumar S (2011) Weight and glycaemic control in type 2 diabetes: what is the outcome of insulin initiation? *Diabet Obes Metab* **13**: 823–31
- Wing RR (2014) Implications of Look AHEAD for clinical trials and clinical practice *Diabet Obes Metab* **16**: 1183–91