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

Online learning opportunity

See page 61 for details.

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.

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/m^2) 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;

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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 diabesity.
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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Page points

1. 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.
2. The potential to regain weight after insulin initiation in adults with type 2 diabetes can be a psychological barrier to agreeing to treatment.
3. By initiating insulin before HbA_{1c} rises to very high levels and weight is lost through poor glycaemic control, significant weight gain could be avoided.

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/m^2), and up to ~2.0 kg weight loss in severely obese adults (35.0–39.9 kg/m^2) with dietary intervention and

in morbidly obese adults (40–45 kg/m^2) with insulin detemir alone (Niswender et al, 2014). Weight loss in adults with a BMI higher than 35 kg/m^2 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 determir, 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 (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 colesevelam 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

Page points

1. Finding the optimal insulin timing, type and dose can minimise weight gain.
2. Combination pharmacotherapy can reduce insulin dose and reduce potential weight gain.
3. Bariatric surgery and lifestyle interventions also have a part to play in reducing weight gain post-insulin initiation.

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.

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 (DiMattteo, 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. ■

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"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."

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Online CPD activity

Visit www.diabetesonthenet.com/cpd to record your answers and gain a certificate of participation

Participants should read the preceding article before answering the multiple choice questions below. There is ONE correct answer to each question. After submitting your answers online, you will be immediately notified of your score. A pass mark of 70% is required to obtain a certificate of successful participation; however, it is possible to take the test a maximum of three times. A short explanation of the correct answer is provided. Before accessing your certificate, you will be given the opportunity to evaluate the activity and reflect on the module, stating how you will use what you have learnt in practice. The CPD centre keeps a record of your CPD activities and provides the option to add items to an action plan, which will help you to collate evidence for your annual appraisal.

1. According to Health and Social Care Information Centre 2012 figures, what PERCENTAGE of the UK adult population have a BMI of 30 kg/m² or higher? Select ONE option only.

A. 10
B. 25
C. 33
D. 50
E. 60

2. According to 2010 data, what approximate PERCENTAGE of adults in the UK with type 2 diabetes use insulin? Select ONE option only.

A. 0.5
B. 5
C. 10
D. 15
E. 20

3. Janner et al (2011) compared the weight of obese adults with type 2 diabetes to non-obese adults with type 2 diabetes before and after initiation of insulin. Which of the following is the MOST appropriate statement about their findings? Select ONE option only.

A. Both groups gained the same amount of weight.
B. Both groups lost weight.
C. The leaner patients were more likely to lose weight.
D. The obese patients were less likely to gain weight.
E. The obese patients were more likely to gain weight.

4. Approximately how long after insulin initiation for a person with type 2 diabetes is any weight gain MORE likely to stabilise? Select ONE option only.

A. 1 month
B. 2 months
C. 3 months
D. 6 months
E. 12 months

5. According to recent evidence, initiation of which one of the following insulins is MOST likely associated with lower weight gain and/or weight loss in obese people with type 2 diabetes? Select ONE option only.

A. Humulin® M3
B. Lantus®
C. Levemir®
D. NovoMix® 30
E. Insuman® Basal

6. According to recent evidence, people with type 2 diabetes requiring insulin are MOST likely to comply with advice relating to which one of the following? Select ONE option only.

A. Diet
B. Insulin use
C. Physical activity
D. Weight loss

7. A 47-year-old man has type 2 diabetes and was initiated onto Insuman® Comb 15 12 months ago. He is still gaining weight and finding he needs to snack regularly between meals and before going to bed. Which of the following alternative insulins would MOST likely reduce his need for snacking between meals? Select ONE option only.

A. Humulin® I
B. Humulin® M3
C. Insulatard®
D. Insuman Basal®
E. Lantus®

8. A 58-year-old obese woman has type 2 diabetes and continuing poor glycaemic control despite taking metformin 1 g twice daily. Her renal function is normal. She chooses to start insulin rather than additional oral anti-diabetes medicines. Which is the MOST appropriate advice about her metformin? Select ONE option only.

A. Continue the same dose.
B. Decrease the dose.
C. Increase the dose.
D. Stop the metformin.
E. Switch to a sulphonylurea.

9. Which of the following glucagon-like peptide-1 receptor agonist medications, if any, have a licence for combination with insulin? Select ONE option only.

A. Exanatide twice daily
B. Liraglutide once daily
C. Lixisenatide once daily
D. All of the above
E. None of the above

10. Sodium–glucose cotransporter 2 inhibitors have a direct action on which of the following? Select ONE option only.

A. Adipose tissue
B. Kidney
C. Liver
D. Pancreas
E. Small intestine