Obesity

A glimpse into "Look AHEAD"

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The American Diabetes Prevention Study (DPS) was a landmark study that, together with other RCTs, demonstrated that an intensive lifestyle intervention (ILI) was able to significantly reduce T2D development in high-risk individuals (Knowler et al, 2002; Thomas et al, 2010). The Look AHEAD (Action for Health in Diabetes) study was subsequently designed to examine the impact of an ILI in overweight/obese people with T2D compared with a diabetes support and education programme (Look AHEAD Research Group, 2006). The authors defined a target individual weight loss of at least 10%. Weight loss was maintained using reduced calorie intake and increased physical activity (≥175 min/week). The primary study outcome was the incidence of cardiovascular (CV) events. However, a reduced observed CV event rate resulted in expansion of the primary end-point definition, and a resultant study extension (Brancati et al, 2012).

The Look AHEAD study included over 5000 people (aged 45–76 years) with T2D and obesity. Study results illustrated that ILI successfully reduced body weight and improved glycaemic control. The ILI achieved greatest weight loss in the first year; this was partially maintained at 4 years at which point approximately 5% of the initial body weight was lost by the ILI group compared with the education group. The ILI group also had improved glycaemic control, blood pressure, lipid profile and physical fitness (Look AHEAD Research Group, 2010), and a reduced incidence of non-alcoholic fatty liver (Lazo et al, 2010). In the Sleep AHEAD sub-study, significant improvements in sleep apnoea were observed in the ILI group (Foster, 2009).

Over the past 2 years, several notable ancillary studies and observations from Look AHEAD have increased our understanding of diabetes and its response to ILI. Look AHEAD participants who maintained their weight in the first year were most likely to further maintain weight loss and improved CV risk markers (Neiberg et al, 2012). An important factor associated with better long-term weight loss outcomes was the frequency of group session attendance, highlighting the importance of frequent contact with healthcare professionals in chronic condition management (Wadden et al, 2011). More recently, 11 risk alleles for obesity identified through genome-wide association studies were examined in Look AHEAD (McCaffery et al, 2012). Associations with increased food frequency and food selection were observed and will hopefully inform the development of future, more individualised interventions for weight loss and T2D.

Reduced mobility is a significant problem in obesity, resulting in disability. Look AHEAD researchers recently reported on the impact of ILI on mobility (Rejeski et al, 2012; summarised alongside), using six of 11 items from the Short-Form Health Survey (SF-36) physical functioning subscale. Clinical disability was divided into four states (good to severe mobility). A graded exercise treadmill test assessed fitness. At baseline there was an increase in BMI and a reduction in physical fitness from State 1 to 4. Those in the ILI group had a 48% reduction in mobility-related disability compared with the support and education programme group ($P<0.001$). The investigators tested the contributions of weight loss and physical activity to these improvements using path analysis. Both factors were found to be important in the impact of ILI on mobility, but the effect of weight loss was greater. Thus, it can be concluded that weight loss and physical activity are important in reducing disability in obese people with T2D.

In conclusion, results from the Look AHEAD study highlight the complexities of obesity, T2D and the necessity of a holistic approach to patient care. ILI has an important role to play in improving outcomes for patients. The look AHEAD ILI intervention, however, is intense and it is currently unclear whether it is possible to implement this widely or if it is cost-effective. It would be interesting to know if less-intensive approaches are as effective. Despite these uncertainties, the current provision of patient support for lifestyle change is grossly inadequate, and, given the significant benefits of ILI, must be taken more seriously.

Brancati FL et al (2012) Midcourse correction to a clinical trial when the event rate is underestimated. *Clin Trials* **9**: 113–24

Foster GD (2009) The Sleep AHEAD study. *Arch Intern Med* **169**: 1619–26

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

Lazo M et al (2010) Effect of a 12-month intensive lifestyle intervention on hepatic steatosis in adults with type 2 diabetes. *Diabetes Care* **33**: 2156–63

Look AHEAD Research Group (2006) A description of the lifestyle intervention and the evidence supporting it. *Obesity (Silver Spring)* **14**: 737–52

Look AHEAD Research Group (2010). Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus. *Arch Intern Med* **170**: 1566–75

McCaffery JM et al (2012) Obesity susceptibility loci and dietary intake in the Look AHEAD Trial. *Am J Clin Nutr* **95**: 1477–86

Neiberg RH et al (2012) Patterns of weight change associated with long-term weight change and cardiovascular disease risk factors *Obesity (Silver Spring)* 13 Feb [Epub ahead of print]

Thomas GN et al (2010) A systematic review of lifestyle modification and glucose intolerance in the prevention of type 2 diabetes. *Curr Diabetes Rev* **6**: 378–87

Wadden TA et al (2011) Four-year weight losses in the Look AHEAD study: factors associated with long-term success. *Obesity (Silver Spring)* **19**: 1987–98

NEJM

Mobility decline in T2D can be slowed with weight loss and fitness

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

1 The authors of the Look AHEAD (Action for Health in Diabetes) study set out to compare the effect on self-reported mobility limitation of an intensive lifestyle intervention (ILI) with a diabetes education programme, in obese adults with T2D.

2 Individuals ($n=5016$) were randomly assigned to the ILI group ($n=2514$) or diabetes education group ($n=2502$) and followed for 4 years. People in the education group attended three group sessions per year, which focussed on nutrition, exercise and support.

3 Annual mobility, weight loss and fitness were measured throughout follow-up in both treatment groups. The effect of the two interventions on mobility decline, and how this was influenced by weight loss and fitness, was evaluated.

4 The authors defined four categories of disability. Over the course of the study, a higher percentage of people from the ILI group remained in the "good-mobility" category compared with those in the diabetes education group.

5 Compared with the diabetes education group, there was a relative reduction in mobility severity of 48% in the ILI group ($P<0.001$). This was found to be mediated by weight loss and fitness improvement ($P<0.001$ and $P<0.001$).

6 The authors concluded that mobility decline in obese adults with T2D can be slowed with improvements to fitness and weight loss and that this has clinical importance in an ageing population with T2D.

Rejeski WJ, Ip EH, Bertoni AG et al (2012) Lifestyle change and mobility in obese adults with type 2 diabetes *N Engl J Med* **366**: 1209–17

"Improved glycaemic control is better achieved with 12-month medical therapy plus bariatric surgery than with medical therapy alone in uncontrolled T2D."

NEJM

Bariatric surgery vs medical therapy in uncontrolled T2D

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

1 The relative efficacy of bariatric surgery and medical therapies for the treatment of uncontrolled T2D has not been extensively investigated. The authors of the STAMPEDE (Surgical Treatment and Medication Potentially Eradicate Diabetes Efficiently) trial set out to compare the effects of intensive medical therapy with bariatric surgery on glycaemic control improvements in obese individuals with T2D.

2 A total of 150 eligible individuals aged 20–30 years, with a BMI between 27 and 43 kg/m^2 and an HbA_{1c} level of <53 mmol/mol (7.0%) were randomised to intensive medical therapy alone (n=41) or intensive medical therapy with surgery (Roux-en-Y gastric bypass surgery [n=50] or sleeve gastrectomy [n=49]). The primary study outcome was the percentage of people with HbA_{1c} ≤42 mmol/mol (6.0%) at 12 months following treatment randomisation.

3 Intensive medical therapy included the use of more recent antidiabetes drug treatments, lipid-lowering therapy, weight management (people were encouraged to participate in the WeightWatchers® programme), counselling on lifestyle aspects of diabetes management (every 3 months by a diabetes educator), and frequent home glucose monitoring.

4 Body weight, blood pressure, waist and hip circumference, HbA_{1c} and fasting plasma glucose levels were measured at baseline and follow-up (at 3, 6, 9 and 12 months).

5 At 12 months, significantly more people in the bariatric surgery and sleeve gastrectomy groups achieved an HbA_{1c} of ≤42 mmol/mol (6.0%) compared with the intensive medical therapy group (P=0.002 and P=0.008, respectively). The 12-month HbA_{1c} levels were also significantly lower in both surgical groups than in the medical therapy group (P<0.01 for both comparisons).

6 Over 12 months, people in the medical therapy group took increasingly more antidiabetes medications per day, whereas this number decreased significantly for both surgical groups (P<0.001 for both comparisons).

7 Surgery yielded significantly greater weight loss and changes in BMI and waist circumference compared with medical therapy. Weight loss and BMI changes were more pronounced following gastric bypass surgery than following sleeve gastrectomy (P=0.02 and P=0.03, respectively).

8 The authors concluded that improved glycaemic control is better achieved with 12-month medical therapy plus bariatric surgery than with medical therapy alone in uncontrolled T2D.

Schauer PR, Kashyap SR, Wolski K et al (2012) Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *N Engl J Med* **366**: 1567–76

DIABETES, OBESITY AND METABOLISM

Vitamin D_3: Effect on diabetes risk in African American individuals

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

1 The researchers aimed to determine the effect of vitamin D_3 supplementation on insulin secretion, insulin sensitivity and glycaemic control in overweight African American individuals with early diabetes or prediabetes, a population in which vitamin D status is generally poor.

2 In a randomised, placebo-controlled, parallel-group trial lasting 12 weeks, people (n=89; age ≥40 years) were randomised to either vitamin D_3 supplementation (4000 IU/day; to be taken with the first meal; n=43) or placebo (n=46), and stratified by age. Baseline characteristics were obtained using a questionnaire, which was repeated at follow-up.

3 Oral glucose tolerance testing was used to measure study outcomes measures at two follow-up visits.

4 Baseline 25-hydroxyvitamin D concentration was around 40 nmol/L in both groups. Vitamin D_3 supplemetation increased this concentration to 81 nmol/L.

5 Compared with the placebo group, insulin sensitivity decreased and insulin secretion increased in the vitamin D_3 group (both reached significance; P=0.034 and P=0.024, respectively). Vitamin D_3 supplementation had no effect on glycaemia.

6 The authors concluded that in obese African American people, vitamin D_3 supplementation for 3 months corrects vitamin D_3 insufficiency but does not alter the pathophysiology of prediabetes.

Harris SS, Pittas AG, Palermo NJ (2012) A randomized, placebo-controlled trial of vitamin D supplementation to improve glycaemia in overweight and obese African Americans. *Diabetes Obes Metab* **14**: 789–94

"In obese African Amerian people, 3-month vitamin D_3 supplementation corrects vitamin D_3 insufficiency but does not alter the pathophysiology of prediabetes."

PEDIATRIC DIABETES

Obese young people at risk of T2D need further evaluation

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

1 In this pilot study, the authors aimed to identify clinical factors predictive of risk for progression to T2D in obese youth.

2 Using retrospective data, young people (aged 8–20 years) who met the American Diabetes Association screening criteria for T2D and had normal fasting plasma glucose (OBng; n=86) or who had T2D (D; n=44) were compared for: BMI standard deviation for age and gender (BMIz); and insulin resistance expressed by homeostatic model assessment (HOMA-IR). The OBng group underwent further latent class analysis.

3 Comparison of the OBng and D groups revealed that a positive family history of T2D (overweight first- or second-degree relative with T2D) was significantly associated with development of youth-onset T2D (P<0.008). Measures of BMIz, age, gender and pubertal stage were similar across both groups.

4 In the OBng group, BMIz was significantly correlated with insulin resistance (r=0.33, P<0.002) but not with FPG (r=0.04, P=0.69). Latent class analysis revealed three classes with increasing BMIz and HOMA-IR; only class three (mean BMIz, 2.65) was significantly associated with a positive family history of T2D.

5 The authors concluded that the study findings indicate that further evaluation of obese young people (rather than fasting plasma glucose screening alone) could identify a third more individuals at risk of T2D who will benefit from preventative interventions.

Greig F, Hyman S, Wallach E et al (2012) Which obese youth are at increased risk for type 2 diabetes? Latent class analysis and comparison with diabetic youth. *Pediatr Diabetes* **13**: 181–8

DIABETIC MEDICINE

Metformin therapy increases postprandial GLP-1

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

1 The authors of this prospective, observational study investigated the long-term effects of chronic metformin therapy on postprandial levels of endogenous appetite regulatory hormones (glucagon-like peptide-1 [GLP-1], dipeptidyl peptidase-4 [DPP-4] and active ghrelin) in drug-naive obese people with T2D.

2 At the first clinic visit, individuals aged 47–69 years (n=8; six male) with an average HbA_{1c} of >86 mmol/mol (10%) had fasting GLP-1, DDP-4 and ghrelin concentrations measured. Measurements were repeated at 12 time points over 6 hours following a mixed meal at the same clinic visit.

3 Individuals commenced metformin monotherapy, titrating the daily dose upwards from 500 mg over 6–8 weeks until adequate metabolic control was established. Postprandial hormone measurements were repeated at 3 months.

4 At 3 months, postprandial ghrelin activity did not change significantly, DPP-4 levels were consistently lower than at baseline, although this did not reach significance, and GLP-1 concentrations were higher at all 12 time points (P=0.017). No significant weight change occured in the study.

5 This was the first study to look at the long-term effects of metfomin on endogenous appetite regulatory hormone levels. The authors concluded that chronic metformin therapy causes a significant, sustained postprandial rise in GLP-1 in obese people with T2D, and this could point the way to another of its glucose-lowering mechanisms.

Thondam SK, Cross A, Cuthbertson DJ et al (2012) Effects of chronic treatment with metformin on dipeptidyl peptidase-4 activity, glucagon-like peptide 1 and ghrelin in obese patients with type 2 diabetes mellitus. *Diabet Med* **29**: e205–10

NATURE

ChREBP-ß isoform: A novel target for diabetes treatment

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

1 A major pathogenic factor of T2D and cardiovascular disease is impaired insulin action in peripheral tissues. Increased release of fatty acids from adipose tissue contributes to obesity-related insulin resistance.

2 The uptake of glucose into adipose tissue is controlled by the expression of the insulin-responsive GLUT4 glucose transporter, which has a central role in systemic glucose metabolism.

3 The researchers of this animal study investigated how altering the expression of adipose tissue GLUT4 in mice altered glucose homestasis. In doing so, they aimed to gain insight into potential new therapeutic targets for the management of T2D.

4 Global gebe expression was analysed in mice with and without adipose-specific GLUT4.

5 The study results indicated that adipose tissue GLUT4 regulated the expression of carbohydrate-responsive element-binding protein (ChREBP), a regulator of adipose tissue lipogenesis and glycolysis.

6 The authors identified a potent and novel isoform of ChREBP, which was expressed in a glucose-dependent manner (ChREBPß); this isoform had a beneficial effect on glucose homeostasis in mice.

7 The authors concluded that their findings have key clinical implications for T2D management. In obese humans, ChREBPß expression correlates with insulin sensitivity, indicating that it could well be a novel theraputic target in diabetes treatment.

Herman MA, Peroni OD, Villoria J et al (2012) A novel ChREBP isoform in adipose tissue regulates systemic glucose metabolism. *Nature* **484**: 333–8

"Chronic metformin therapy causes a significant, sustained postprandial rise in GLP-1 in obese people with T2D, and this could point the way to another of its glucose-lowering mechanisms."