The number of obese people in the UK has risen dramatically over the last 20 years. Compelling evidence emerged over the same time that obesity causes diabetes, rather than being two sides of the same metabolic coin. Despite considerable advances in our understanding of the underlying molecular biology, medicating our way out of obesity and type 2 diabetes – Mark Greener discovers – is unlikely.

Rather, parents, health care professionals and society need to get young children on the right track.

The combination of abundant food and sedentary habits helped drive a dramatic increase in adult obesity during the last 20 years. According to the Health and Social Care Information Centre, the proportion of men who were obese rose from 13.2% in 1993 to 26.0% in 2013. The proportion of women who were obese increased from 16.4% to 23.8% during the same time. The proportions that were overweight (including obesity) increased from 57.6% to 67.1% in men and from 48.6% to 57.2% in women.

As the 2015 Milan Declaration: A Call to Action on Obesity, issued by the European Association for the Study of Obesity (easoo.org/wp-content/uploads/2015/06/EASOMilanDeclaration2015.pdf), notes ‘obesity, beyond being in some cases a highly disabling and fatal disease per se, contributes to numerous ‘disabling and fatal’ non-communicable diseases. Indeed, Cambridge University researchers estimate that a body mass index (BMI) of at least 30kg/m² accounted for 337,000 of the 9.2 million deaths among European men and women during 2008.¹

In particular, type 2 diabetes (T2D) shows an unequivocal, strong and mutually reinforcing relationship with obesity. In a study of the Framingham cohort performed between 2000 and 2005, 25.5% of 50-year-old people without diabetes were obese. But 61.8% of those with diabetes were obese. In 60-year-old people, the proportions were 33.0% and 67.4% respectively.² In another study, adults with a BMI of at least 40kg/m² were 7.37 times more likely to be diagnosed with diabetes than those of healthy weight.³ ‘Family history, which includes ethnic background, and age are strong risk factors for T2D. There’s a very steep increase in the prevalence of diabetes as age increases,’ says Jonathan Pinkney, Professor of Endocrinology and Diabetes at Plymouth University. ‘However, weight gain is the most significant modifiable risk factor for diabetes and substantial weight loss usually has a profoundly beneficial effect on diabetes.’

Part of the mechanism

Professor Pinkney notes that obesity ‘is an integral part of the mechanism’ that directly leads to T2D. ‘However, weight gain’s importance varies between people, partly because of their genetic constitution,’ he told Practical Diabetes. ‘Some people are genetically capable of coping with the weight gain because of good insulin secretion, whereas in others, the same weight gain leads to diabetes.’

Diabetes results from a range of abnormalities – partly inherited and partly related to ageing and weight gain – which influence insulin’s production and action. The abnormalities affect a range of organs including the pancreas, liver, muscle, fat and intestines. Professor Pinkney notes that adipokines – a group of more than 600 chemical messengers released by fat cells⁴ – and increases in free fatty acids may provide part of the explanation why weight gain results in T2D. ‘Good evidence supporting the importance of many of these different molecular mechanisms in diabetes has emerged over the last 20 years,’ he says. Inevitably, pharmacologists are targeting these molecular aberrations for a new generation of drugs for obesity and T2D. ‘Targeting the molecular mechanism to develop a single, highly effective treatment for weight gain – a penicillin for obesity – would be wonderful,’ Professor Pinkney comments. ‘But the actions of insulin and the body’s control of food intake are complex and there doesn’t seem to be a final common pathway. Personally, I think that a single “magic bullet” drug for obesity or for diabetes is very unlikely.’

Nevertheless, therapeutic innovations are providing an ever wider range of treatment options for many people with diabetes. ‘One area of current interest is the well-known tendency of many drugs used in the treatment of type 2 diabetes to promote weight gain, which, for people who are already often overweight or obese, is contrary to the overall treatment aims,’ Professor Pinkney says.

For instance, a meta-analysis of 62 randomised controlled trials lasting between three and 12 months’ duration found that sulphonylureas, thiazolidinediones, insulin glargine and alogliptin/pioglitazone were associated with an average weight gain of between 1.19 and 2.44kg. In contrast, sodium glucose co-transporter inhibitors, glucagon-like peptide 1 analogues, miglitol and empagliflozin/linagliptin reduced body weight by 1.15–2.26kg.⁵ A 26-week study assessing insulin degludec/liraglutide – recently launched in the UK as Xultophy – reported weight loss of 2.7kg from baseline.⁶

‘The choice of drug treatment for diabetes is one factor that influences body weight. The beneficial changes in weight with these “weight-neutral” hypoglycaemics are relatively modest, but they are still useful clinically,’ Professor Pinkney remarks. ‘However, I don’t really feel they are game changers. We won’t medicate our way out of diabetes and obesity.’

‘In general, people with diabetes taking oral drugs don’t attribute the weight gain to a particular drug. In clinical studies, weight gain has been a reason for non-compliance with oral therapies. But these were informed patients and I don’t see much of this in my practice,’ adds Gwen Hall, Diabetes Specialist Nurse, Haslemere Health Centre, Surrey. ‘However, weight gain can be an issue, particularly with insulins. People with diabetes may be reluctant to increase the dose because of weight gain. But any reductions in weight are clinically valuable. Every little helps!’
Lack of resources presents a greater barrier in Ms Hall’s practice than iatrogenic weight gain. ‘The number of patients who receive structured education about T2D is lamentable,’ she comments.

However, if patients are motivated – if they have begun the cycle of change – counselling and support from health care professionals can make a big difference, comments Ms Hall.

**A cut above**

In contrast to medical treatments, T2D can enter remission after bariatric surgery, which restores normal, or greatly improves, glucose levels. In one study, T2D entered remission in 13% of patients who lost weight by lifestyle changes compared to 73% who received laparoscopic adjustable gastric banding.5 We know that many people with T2D enter remission after bariatric surgery. However, it is still not clear how surgery produces the remissions,’ Professor Pinkney says. ‘If we could understand that mechanism, it might be possible to develop treatments that produce the same results but without surgery. That would be an amazing breakthrough.’

However, bariatric surgery attracts critics. ‘Some people argue that bariatric surgery only benefits a few people and it’s too expensive,’ Professor Pinkney says. ‘Approximately 5.4% of adults in England – about two million people – are eligible for bariatric surgery,6 which costs between £3000 and £11 505 depending on the procedure and the post-surgical care (www.bbc.co.uk/news/health-25766253). ‘Critics feel the money would be better spent on public health interventions,’ he says. ‘Unfortunately, there’s no good evidence that public health interventions to tackle obesity make much difference once adults have developed T2D.’

Against this background, tailoring treatment may bring the best results. ‘We need to find the right treatment for each person,’ Professor Pinkney says. ‘Bariatric surgery works for some people, but it’s not for everyone. Lifestyle treatments will help other people, while some need medicines. It’s important we have a range of treatments.’

**Tackling the source**

The modern environment – with its high-fat fast-foods, advertising and supersize meals – overwhelms the body’s ability to regulate food intake. Tackling the problem may require a marked shift in society. ‘Individuals are vulnerable to changes in food production, processing and marketing and to changes in physical work and transportation,’ the Milan Declaration comments. ‘Many of these changes are linked to obesity. We need to consider whether obesity in itself is a disease or rather a symptom of a diseased society.’

‘I’m confident that society will eventually address the issue,’ Professor Pinkney says. ‘A decade or two ago it wouldn’t have been remotely acceptable for smokers to stand outside. Now the idea is spreading worldwide. We’ve also already seen the political will among certain indigenous groups to try to tackle obesity and T2D more effectively.’

For example, the Pima people live in southern Arizona, near the Gila River. In a series of studies starting in early 1960s, researchers discovered that 50% of the Pima had diabetes. Ninety-five percent of the Pimas with diabetes were overweight (diabetes. niddk.nih.gov/dm/pubs/pima/pathfind/pathfind.htm).

Initially, biologists blamed the genes for such high risks of diabetes, suggesting that they may express a human analogue of mice homozygous for the ob gene. These ob/ob mice exhibit, for example, marked obesity, a diabetes-like syndrome, impaired fertility and poor wound healing. ‘We now know that indigenous peoples are not “outliers”. These astonishingly high rates of obesity and diabetes arise from the change to a more western lifestyle. We’ve seen similar patterns in Pacific islanders, Australasia and south Asians, and it is obvious that obesity and diabetes are now widespread on every continent,’ Professor Pinkney notes. ‘The adoption of the “western lifestyle” results in weight gain and increased risks of cardiovascular disease and diabetes for most human populations. Today, many indigenous groups see the seriousness of obesity and diabetes on a par with cancer or HIV. It is hoped that in time these changing perspectives will exert the political leverage necessary to tackle the issue.’

Nevertheless, Professor Pinkney concedes that there is currently not the political will to address the issue in the UK. In part, he suggests, the government is probably reluctant to take on complicated vested interests in the multinational food industry. ‘Unless society as a whole wants to improve everyone’s diet and lifestyle, it is difficult for individuals to sustain their efforts. People find it really difficult to lose weight and then keep it off,’ he says. ‘If it is left entirely to individual choice, I doubt if we will ever see the UK adult population slim down.’

So, Professor Pinkney suggests focusing on the early origins of obesity and diabetes. In the 2013/2014 school year, 9.5% of children in reception (4–5 years of age) were obese and 22.5% were overweight (including obese). By year 6 (10–11 years of age), the proportions reached 19.1% and 33.5% respectively.

Ms Hall says: ‘We need to limit junk food. We need easy access to the types of exercise people want to do. Healthy food needs to be the same price or cheaper than junk food. And supermarkets should not promote unhealthy food. It should be pushed to the back of the shelves.’

Ms Hall also stresses the importance of educating parents and patients. ‘We need to look at portion sizes,’ she says. ‘I have many patients who eat a healthy diet, but they just eat too much. We need to address alcohol consumption, which is just empty calories. We need to educate parents dispelling any anxiety they have that they could trigger anorexia.’

‘We must do more to tackle obesity in early childhood through to adolescence, when the weight gain really gets going,’ Professor Pinkney concludes. ‘Life is a bit like a train journey. If your train starts from Paddington station, then the set of points determining whether you end up in Oxford or Penzance is just outside the station. Once you are on the right track you tend to stay there. But once you are on the wrong track it’s very hard to change.’

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**References**

References are available online at www.practicaldiabetes.com.
References


