Achieving integrated, cohesive care of diabetes, obesity and cardiometabolic risk with an awareness of the obesity paradox

David Haslam

This article discusses the metabolic syndrome and the fact that many drugs may benefit one element of the syndrome but are detrimental to others. It also discusses the obesity paradox – whereby obesity becomes protective against mortality after a vascular clinical event – and warns of its complexities. Whereas traditional glucose-lowering agents reduce the risk of diabetic complications by their primary action – reducing HbA_{1c} – they have unwanted side effects that damage health, often through weight gain and hypoglycaemia, and sometimes they can increase the risk of cardiovascular events, fractures, possible bladder cancer and heart failure. Newer glucose-lowering agents should be prioritised in primary care to limit damage done by older agents. Glucagon-like peptide-1 agonists, dipeptidyl peptidase-4 inhibitors and sodium–glucose cotransporter-2 inhibitors have additional effects of improving the composite-associated metabolic syndrome risk factors, so clinicians no longer have to "make do" with diabetes drugs that have damaging side effects.

The malign influence of obesity is most easily recognised through its association with insulin resistance and metabolic syndrome, which is the coexistence of obesity with such ostensibly diverse risk factors as dyslipidaemia, hypertension and diabetes. The "metabolic syndrome" became officially recognised in 1988 when Gerald Reaven, during his Banting lecture at the American Diabetes Association conference, introduced the concept of the coexistence of the clustering of conditions to a global audience. Other modern physicians such as Kylin and Vague had noted that the separate conditions tended to occur in the same person, but Reaven brought the term into common usage although he preferred the term "syndrome X", explaining that some aspects – such as blood hypercoagulability – are not metabolic (Reaven, 1988).

The criteria for the syndrome have changed over time, the most recent incarnation being the pronouncement by the International Diabetes Federation (IDF) that places abdominal obesity as the only "must have" factor in attaining the syndrome alongside raised blood pressure, abnormal lipid profile and abnormal glycaemic control (Alberti, 2005; Alberti et al, 2005). The IDF underlined the importance of the syndrome, stating: "With the metabolic syndrome driving the twin global epidemics of type 2 diabetes and cardiovascular disease there is an overwhelming moral, medical and economic imperative to identify those individuals with metabolic syndrome early, so that lifestyle interventions and treatment may prevent the development of diabetes and/or cardiovascular disease" (International Diabetes Federation, 2006).

As certain diseases coexist and must be considered as separate components of one overarching state it is imperative to "make every contact count" and optimise the identification of obese individuals, engaging and screening for coexisting conditions whenever possible (regardless of the absurdities of the qualities and outcomes framework which perversely incentivises sustained obesity). Although the metabolic syndrome has been useful in emphasising the coexistence of these conditions and supporting cohesive screening policies, it has perhaps caused other conditions related to obesity, such as sleep apnoea, polycystic ovarian syndrome

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Article points

1. Traditional drugs used to control diabetes often have an adverse effect on other aspects of the metabolic syndrome and will often cause weight gain.
2. Newer glucose-lowering drugs are both effective in managing diabetes and do not adversely effect other aspects of the metabolic syndrome.
3. The obesity paradox is complex and supports the practice of individualised care.

Key words

- DPP-4 inhibitors
- GLP-1 agonists
- Metabolic syndrome
- Obesity
- Obesity paradox
- SGLT-2 inhibitors

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"Treating people with type 1 diabetes using insulin can induce weight gain which can result in iatrogenic metabolic syndrome."

and depression to be overlooked and this should be rectified.

Clinicians encounter problems when managing disparate aspects of the metabolic syndrome comprehensively. Glucose-lowering agents may cause weight gain and when treating excess weight there is a tendency to raise blood pressure. In treating high blood pressure or abnormal lipid profiles, there is a tendency to induce or aggravate diabetes… and so on.

The challenge when managing individuals with any component of the metabolic syndrome is to consider all the disparate elements at once and avoid managing individual factors in isolation. This has not been easy given the drawbacks of traditional pharmacological agents and the limited success of lifestyle interventions. There are now treatments which do not present these problems. Telmisartan (Suksomboon et al, 2012) is an example of an agent which while it targets one element – blood pressure – it also improves other areas of the metabolic syndrome. It is an antihypertensive agent that also has a significant impact on insulin resistance and reduces fasting plasma glucose, effects not seen with other angiotensin receptor blockers or other classes of blood pressure drugs.

Integrated management of diabetes and metabolic syndrome

Of the total amount of money spent on treating type 2 diabetes in the UK only 6.1% is spent on glucose-lowering agents, whereas 68.6% is spent on in-patient management, and almost 10% on outpatient costs where attempts to lower glucose levels have been less than fully effective (Kanavos et al, 2012). Two-and-a-half times as much is spent on prescribing drugs for conditions related to diabetes for patients with diabetes, suggesting that the cost of glucose-lowering agents *per se* can be considered minor compared with the costs of not prescribing or mis-prescribing these agents.

The DCCT (Diabetes Control and Complications Trial) recently published the results of a follow-up study about damage caused by insulin. DCCT studied people with type 1 diabetes, demonstrating that good glycaemic control reduces the risk of complications. In 1993, the same cohort of patients was recruited for the on-going Epidemiology of Diabetes Interventions and Complications (EDIC) study, which showed a 42% reduced risk of any cardiovascular event and a 57% reduced risk of non-fatal heart attack, stroke or death from cardiovascular causes with intensive glucose control. The recent follow-up proposes an alarming concept: treating people with type 1 diabetes using insulin can induce weight gain, which can result in iatrogenic metabolic syndrome. The quartile from EDIC with most weight gain increased from BMI 24 kg/m^2 to an obese 31 kg/m^2, displayed increased waist circumference, more severe deterioration in HbA_{1c} and higher total cholesterol, raised low-density lipoprotein (LDL) with sinister small dense LDL-particles and raised blood pressure. Even more alarming, intima-media thickness was greater in those who had gained a lot of weight and coronary artery calcification also occurred more frequently.

Conversely, the Look AHEAD study (Wing et al, 2013) showed that long-term weight loss can be sustainable and is linked to reductions in lipids and blood pressure, but the Look AHEAD intervention may be too intensive to be transferable to primary care. However, the Steno-2 study demonstrated how important a multidisciplinary approach is when treatments look beyond glycaemic control at risk factors such as blood pressure and lipid levels. With intensive treatment over almost 8 years, the risk of both macro- and microvascular events were reduced by about 50% (Gaerde et al, 2003) and maintained in the long-term (Gaerde et al, 2008).

Obesity and disease risk

Studies such as Framingham (Hubert et al, 1983), the Nurses' Health Study (Colditz et al, 1990) and the Health Professionals' Study (Chan et al, 1994) clearly demonstrate the strong link between obesity, cardiovascular disease and diabetes. The proposed mechanism centres upon insulin resistance, reduction in adiponectin (Hara et al, 2007) with increased abdominal adiposity, plus the dangerous influence of inflammatory cytokines such as TNF-alpha and IL-6.

There are causative links that occur long before the patient enters the clinic, which are public health issues – poor dietary macronutrient selection and lack of physical activity being mainly to blame. Once the public health catastrophe of

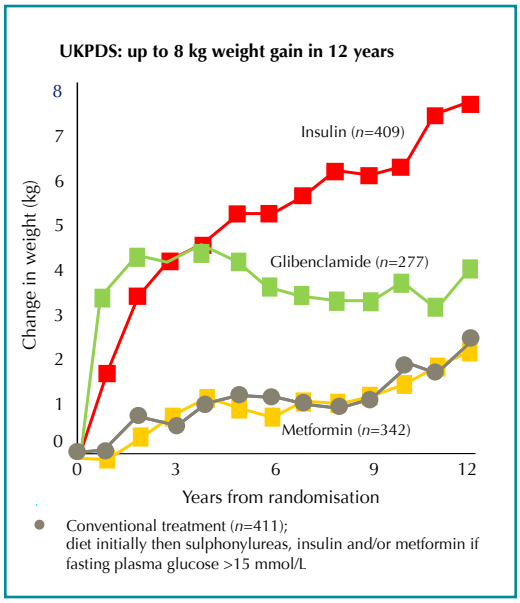

Figure 1. The impact of some commonly used diabetes therapies on weight gain. Source: UK Prospective Diabetes Study (UKPDS) Group (1998). Copyright (1998), with permission from Elsevier.

obesity has occurred, weight loss is difficult to achieve in primary care as shown by trials such as Counterweight (Counterweight Project Team, 2008) and CAMWEL (Camden Weight Loss; Nanchahal et al, 2012), which struggled to help people achieve and maintain meaningful weight loss.

The complexities of integrated management of the metabolic syndrome can be demonstrated by:

- Statins, which improve lipid profile but increase the risk of diabetes.
- Sibutramine, which induces weight loss but raises blood pressure.
- Niacin, which increases HbA_{1c} while lowering cholesterol.
- Torcetrapib, which was withdrawn from phase III trials despite enormous improvements in lipid profile because of an increase in blood pressure and stroke risk.
- Beta-blockers, which reduce blood pressure but increase the risk of obesity partly by inducing more sedentary behaviour.
- Beta-blockers and thiazide diuretics, which increase the risk of diabetes.

Traditional glucose-lowering agents improve one aspect of the metabolic syndrome while worsening others, particularly weight. After insulin was introduced in 1922, diabetes stopped being a fatal illness – one of the greatest moments in medical history. However, insulin causes detrimental weight gain and hypoglycaemia, despite many advances which have culminated in the production of degludec which is a genuinely long-acting insulin that minimises nocturnal hypoglycaemia, allowing flexible dosage regimens. Until recently, the evolution of drugs to manage diabetes was slow and each new drug was beset with side effects, especially weight gain which is both a harmful and demoralising burden for patients who are being encouraged to lose weight. In ACCORD (Gerstein et al, 2008), a study of intensive versus conservative treatment of diabetes, 28% of patients gained >10 kg.

Other glucose-lowering agents have had different adverse effects on weight and metabolic syndrome. Metformin is weight neutral and confers early and long-term macrovascular protection against cardiovascular events and mortality. Sulphonylureas cause harmful weight gain, and dangerous hypoglycaemia, while pioglitazone induces weight gain and possible adverse cardiovascular events, pathological fractures in women, worsening of heart failure and a small increased risk of bladder cancer (electronic Medicines Compendium, 2013). The ADOPT study (Kahn et al, 2006) and UK Prospective Diabetes Study (UKPDS) Group (1998) have clearly demonstrated the capacity to induce weight gain by commonly used agents (*Figure 1*).

Newer glucose-lowering agents and metabolic syndrome

The UK Prospective Diabetes Study (Stratton et al, 2000) suggests that reducing HbA_{1c} is the foremost priority of glucose-lowering agents, as each 1% reduction in HbA_{1c} leads to reductions of 21% in diabetes-related mortality, 37% in microvascular complications, 43% reduction in amputation or fatal peripheral blood vessel disease, 14% in myocardial infarction (MI) and 12% in stroke.

Recently developed glucose-lowering agents induce improved glycaemic control but do not worsen, and often improve, other aspects of the metabolic syndrome and should be considered early in the treatment pathway if excess weight is a problem. Many newer drugs are based upon the incretin system, by which L-cells of the gut, secrete glucagon-like peptide-1 (GLP-1) into the circulation when stimulated by an oral glucose load, which in

Page points

1. The integrated management of the metabolic syndrome is complex, as traditional glucose-lowering agents can worsen some aspects of it, particularly the gaining of weight.
2. Each new drug to manage diabetes has been beset with adverse side effects, especially weight gain.
3. Recently developed glucose-lowering agents should be considered early in the treatment pathway if excess weight is a problem.

"Recently developed glucose-lowering agents induce improved glycaemic control but do not worsen and often improve other aspects of the metabolic syndrome and should be considered early in the treatment pathway if excess weight is a problem."

turn stimulates pancreatic insulin secretion and inhibits glucagon production. Natural GLP-1 is broken down by the enzyme dipeptidyl peptidase-4 (DPP-4). Therefore, levels of GLP-1 can be increased by using synthetic GLP-1 – the injectable drugs exenatide, liraglutide and lixisenatide – or by inhibiting DPP-4 using the oral agents sitagliptin, vildagliptin, saxagliptin, linagliptin and, after its anticipated launch in the UK, alogliptin.

DPP-4 inhibitors

DPP-4 inhibitors reduce HbA_{1c} by 0.5–1% (5.5–10.9 mmol/mol) (Amori et al, 2007) and are considered weight neutral (Nathan et al, 2009). Although some people gain weight slightly whereas others lose weight (Cobble, 2012), one study showed a mean weight loss of 0.96 kg with sitagliptin (Pratley et al, 2010). DPP-4 inhibitors do not have a significant effect on blood pressure or a consistently demonstrated benefit on lipids (Yanai et al, 2012), although it is thought they have direct cardiovascular benefits promoting vascular repair with possible cardiovascular protection when vascular damage has occurred (Jose and Inzucchi, 2012). One meta-analysis compared patients treated with saxagliptin with individuals on other agents or placebo and reported a 57% risk reduction in a composite end point of cardiovascular death, MI or stroke (Frederich et al, 2010; Jose and Inzucchi, 2012). However, a more recent study indicated that saxagliptin did not significantly increase or decrease rates of cardiovascular events and provided no cardiovascular benefits for those with a history of established cardiovascular disease (Scirica et al, 2013). Another study demonstrated that alogliptin did not significantly increase the rates of cardiovascular events in individuals with a recent history of acute coronary syndrome (White et al, 2013).

GLP-1 analogues

GLP-1 analogues have additional benefits when compared with DPP-4 inhibitors in enhancing satiety via a central mode of action and by delaying gastric emptying, and this is a major element of their efficacy. Patients may lose significantly more weight, with superior reductions in HbA_{1c} than with DPP-4 inhibitors. Liraglutide is subject to trials in anticipation of gaining a licence for the treatment of obesity for people with or without diabetes: the SCALE study has been designed to assess weight maintenance after 5% weight loss induced by a low calorie diet and has demonstrated a further 6.2% weight loss with small but significant improvements in cardiometabolic risk (Wadden et al, 2013). Another trial demonstrated weight loss, accompanied by a decrease in prevalence of metabolic syndrome of 59% over 2 years (Astrup et al, 2012). Liraglutide-induced weight reduction is mainly from fat, not lean tissue mass, and from the problematic intra-abdominal area rather than subcutaneous stores (Jendle et al, 2009). Several studies suggest GLP-1 agonists improve blood pressure and lipids (Buse et al, 2009), although this may be through weight loss alone (Jose and Inzucchi, 2012). Exenatide taken once-weekly demonstrates a powerful reduction in HbA_{1c} of 1.4% (15.3 mmol/mol) in meta-analysis, alongside modest but significant reductions in blood pressure and lipids (Grimm et al, 2013), and lixisenatide has a significant but slightly less powerful effect on HbA_{1c} and weight than the other GLP-1 agonists (Petersen et al, 2013).

SGLT-2 inhibitors

Sodium–glucose cotransporter-2 (SGLT-2) inhibitors are new drugs that prevent reabsorption of glucose from the proximal tubule of the kidney, allowing around 300 calories/day of glucose to be excreted in urine with an associated reduction in weight (Bolinder et al, 2012). They also induce a significant reduction in systolic blood pressure and triglycerides (Riser Taylor and Harris, 2013). A lower rate of cardiac events was seen in individuals with type 2 diabetes taking dapagliflozin against comparators in a meta-analysis (Ptaszynska et al, 2013). Whereas most glucose-lowering agents enhance the metabolism of sugar, SGLT-2 inhibition goes a step further by eliminating excess sugar from the body.

The obesity paradox

Although obesity is implicated as a cause of a variety of cardiometabolic diseases and cancer, its presence may be protective against mortality once these conditions have occurred. It has been said that, "The idea that a known risk factor somehow transforms into a 'protective' agent after an occurrence of a vascular clinical event is both surreal and troubling" (Katsnelson and Rundek, 2011). This phenomenon has been termed the "obesity paradox".

It is known that increased BMI is a determinant for heart failure: a Framingham 14-year follow-up study (Kenchaiah et al, 2002) of 5881 participants, found a graded increased risk of heart failure with increasing BMI: for every unit increase in BMI, risk of heart failure increased by 5% in men and 7% in women. However, once heart failure had occurred there was an entirely different story. A meta-analysis of 28 209 recruits (Oreopoulos et al, 2008) demonstrated that obese patients had reduction in cardiovascular mortality of 40% and all-cause mortality of 33%. In one study, among 12 000 veterans, underweight men with low fitness had the highest mortality and highly-fit overweight men the lowest of any subgroup. Overweight and obese men with moderate fitness had mortality rates similar to those of a highly fit normal-weight reference group (McAuley et al, 2010).

In a review of studies representing 250 000 patients with coronary artery disease, cardiovascular and total mortality outcomes were better in overweight and "mildly" obese patients compared with those of "normal" weight (Romero-Corral et al, 2006). The INVEST (Uretsky et al, 2007) study included 22 500 individuals with hypertension plus coronary artery disease, and demonstrated a lower risk of death and major cardiovascular events in the overweight and obese compared with those with normal weight.

Various explanations have been suggested for the paradox: it may be that fat does actually exert a protective influence in certain conditions through an unknown mechanism possibly through improved metabolic reserve, or it could be that obesity meant that individuals were identified as high-risk earlier, allowing the protective influence of statins and anti-hypertensive agents to have been present for longer. An interesting thesis suggests that obese people who had heart failure "thrust upon them" through weight gain, are naturally less susceptible to the disease, therefore, equally naturally less prone to poor prognosis, and might not have developed the condition had they stayed lean (Arena and Lavie, 2010).

Other theories are that lower weight might be smoking related, or due to intercurrent illness, or the fact that BMI is used inappropriately as a measure of body morphology, although in later studies these factors are adjusted for (Lavie et al, 2010). A *post-hoc* analysis of the PROactive study of pioglitazone addressed the issue, with interesting results (Doehner et al, 2012). The lowest mortality in individuals with type 2 diabetes and cardiovascular disease in those with BMI 30–35 kg/m^2; in contrast, those with BMI <22 kg/m^2 had a higher all-cause mortality. Weight loss was associated with increased total mortality, increased cardiovascular mortality, and all-cause hospitalisation: weight loss of ≥7.5% body weight (seen in 18.3% of patients) was the strongest cut-point for impaired survival but weight gain was not associated with increased mortality. Notably, BMI rather than body morphology was used, possibly explaining the anomaly. It is known that the positive relationship between obesity and mortality is attenuated with age, under which circumstance excess weight may be better at acting as a protective factor in established chronic disease (Adams et al, 2006).

Conclusion

Clinicians are now in a position to be able to manage all aspects of the metabolic syndrome cohesively, without dangerous and demoralising side effects such as weight gain. Drugs such as sulphonylureas, which cause these effects, should be relegated in favour of agents that promote simultaneous improvement of all the elements of the metabolic syndrome, rather than sacrificing one in favour of another. However, the obesity paradox suggests that individualised care is more important than ever, and lifestyle and healthy nutritional advice should be enhanced by medicines that lower glucose but promote general health not weight gain. ■

"The obesity paradox suggests that individualised care is more important than ever and lifestyle and healthy nutritional advice should be enhanced by medicines which lower glucose but promote general health not weight gain"

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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 UKPDS data, which SINGLE one of the following shows the LEAST relative risk reduction for each 1% reduction in HbA_{1c}?
Select ONE option only.

A. Amputation or fatal peripheral blood vessel disease
B. Diabetes-related mortality
C. Microvascular complications
D. Myocardial infarction
E. Stroke

2. According to the International Diabetes Federation (IDF), which SINGLE one of the following is NOT an essential criterion for a diagnosis of "metabolic syndrome"?
Select ONE option only.

A. Abdominal obesity
B. Abnormal glycaemic control
C. Abnormal lipid profile
D. Body mass index (BMI) >35 kg/m^2
E. Raised blood pressure

3. In people with metabolic syndrome, which SINGLE one of the following anti-hypertensives can also significantly benefit insulin resistance and reduce fasting blood sugars?
Select ONE option only.

A. Bisoprolol
B. Doxazosin
C. Indapamide
D. Ramipril
E. Telmisartan

4. Which SINGLE one of the following statements is evidence-based?
Select ONE option only.

A. Aspirin benefits all people with diabetes aged over 30
B. Beta-blockers increase the risk of obesity
C. Sibutramine reduces blood pressure in people with type 2 diabetes
D. Statins increase the risk of cardiovascular disease mortality
E. Thiazide diuretics reduce the risk of diabetes

5. Which SINGLE one of the following studies provides evidence for the association between strict glucose control and iatrogenic metabolic syndrome?
Select ONE option only.

A. EDIC
B. Framingham
C. Health Professionals' Study
D. Nurses' Health Study
E. Steno-2

6. According to ADOPT and UKPDS figures, which SINGLE treatment was associated with the MOST weight gain?
Select ONE option only.

A. Glibenclamide
B. Insulin
C. Metformin
D. Repaglinide
E. Rosiglitazone

7. Which SINGLE one of the following anti-diabetic agents can benefit people with diabetes by delaying gastric emptying?
Select ONE option only.

A. Biguanides
B. DPP-4 inhibitors
C. GLP-1 analogues
D. SGLT-2 inhibitors
E. Sulfonylureas

8. According to the PROactive study, people with type 2 diabetes and cardiovascular disease had the LOWEST mortality in which weight range?
Select ONE option only.

A. BMI 20–21 kg/m^2
B. BMI 22–25 kg/m^2
C. BMI 26–29 kg/m^2
D. BMI 30–35 kg/m^2
E. BMI 36–38 kg/m^2

9. Which SINGLE one, if any, of the following studies showed sustainable, meaningful weight loss in people with diabetes in a primary care setting?
Select ONE option only.

A. CAMWEL
B. Counterweight
C. Look AHEAD
D. Nurses' Health Study
E. None of the above

10. Which SINGLE one of the following statements BEST demonstrates the term "obesity paradox"?
Select ONE option only.

A. Treatment of people with diabetes unintentionally causes weight gain
B. Antidiabetic agents that induce weight gain are associated with a lower cancer risk
C. Obesity can be a protective factor in people with heart failure
D. Obesity is a rising epidemic despite multiple public health campaigns