The obesity paradox: Behind the theory

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The rules by which clinicians managed obesity and diabetes used to be simple. Sushruta (India, 600 BC), Hippocrates (Greece, 400 BC) and Avicenna (Persia, 980 AD) all agreed that diet and activity were the basic cornerstones of a healthy lifestyle.

Since then there have been some mavericks and some pioneers; the philosopher, Hieronymus Cardanus believed that trees out-live men because of their immobility and advised against even the slightest activity; Paracelsus made giant strides forward in patient care and public health but also believed nymphs, gnomes, giants, dwarves, incubi and succubae ruled the natural world, so might not be considered particularly reliable.

In 1797, Scottish army physician, John Rollo, first introduced the low carbohydrate diet for his obese patient with diabetes, Captain Meredith. Arsenic, strychnine, mercury, dinitrophenol, pokeberry, tobacco and other toxins have been periodically recommended by physicians to manage obesity over recent centuries, but tended to have some side-effects and, thankfully, are no longer used for obesity or diabetes.

In 1922, management of diabetes was revolutionised when 14-year-old Leonard Thompson was the first person to be successfully treated with insulin, transforming diabetes into a treatable rather than terminal illness. So far, so good; this complex disease can be treated with a simple choice of options: diet, activity and insulin.

Things started to get complicated with the development of newer types of insulin, metformin, sulphonylureas, acarbose, and thiozoladinediones; these are all important drugs in managing diabetes, but each one is burdened by clutter, ranging from hypoglycaemia, diarrhoea, fractures, heart failure and especially weight gain – entirely counterproductive in people in whom weight loss is desirable.

A recent follow-up of the DCCT (Diabetes Control and Complications Trial) describes people with type 1 diabetes having metabolic syndrome thrust upon them due to insulin-induced weight gain.

To make matters worse, whilst glucose-lowering agents may cause weight gain, drugs targeting other individual aspects of the metabolic syndrome have unintended consequences. Statins lower cholesterol, but can increase the risk of diabetes; niacin also has been shown to increase HbA_{1c}, whilst torcetrapib induced enormous improvements in lipid profile but was withdrawn from trials because of an increase in blood pressure and stroke risk. Beta-blockers reduce blood pressure, but increase obesity risk partly by promoting sedentary behaviour, and they, and thiazide diuretics, increase the risk of diabetes.

Weight-loss drugs, such as dexfenfluramine, were withdrawn due to heart valve defects and primary pulmonary hypertension, whereas sibutramine induced excellent weight loss, but increased blood pressure and pulse, and was withdrawn due to an increase in non-fatal cardiovascular events (although it was ultimately realised that subjects who lost weight on sibutramine benefitted from reduced mortality).

Only now, with the emergence of DPP-4 inhibitors, GLP-1 mimetics and SGLT-2 inhibitors, do clinicians no longer have to be resigned to putting up with the clutter and people with diabetes can benefit from blood pressure improvements, weight loss and a possible reduction in cardiovascular risk.

Adding to the complexity has been the fact that studies such as ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation), VADT (Veterans Affairs Diabetes Trial) and UKPDS (UK Prospective Diabetes Study) have torn up the rule book, demonstrating that individualisation of care is crucial, and that people of different ages, different stages of their condition and with varying degrees of risk all have unique therapeutic needs. A paper in *The Lancet* (Currie, 2010) demonstrated the risk of pursuing overambitious targets in individuals taking

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sulphonylureas or insulin as they demonstrated increased mortality when HbA_{1c} was driven below 53 mmol/mol (7%).

The obesity paradox

The obesity paradox adds a newly recognised "spanner in the works" with regard to individualisation of care. Although obesity is a cause of various cardiometabolic diseases and cancer, its presence may be protective against mortality once those conditions exist. Katsnelson and Rundek (2011) have said:

> *"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."*

It is known that excess weight is a factor in heart failure. The Framingham Heart Study has shown 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 (Kenchaiah et al, 2002). However, once heart failure occurs obese individuals have a reduced cardiovascular mortality of 40% and all-cause mortality of 33% (Oreopoulos et al, 2008). In one study of 12 000 veterans, underweight men with low fitness suffered highest mortality and highly-fit overweight men the lowest. 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). A review of studies comprising 250 000 people with coronary artery disease, cardiovascular and total mortality outcomes were more favourable in overweight and "mildly" obese people compared with normal weight (Romero-Corral et al, 2006)

Various explanations for the obesity paradox have been proposed: it is possible that fat does actually exert a protective influence in certain conditions, possibly through improved metabolic reserve. Alternatively, the presence of obesity may ensure that individuals are identified as high-risk earlier, allowing the protective influence of statins and antihypertensive agents to have been present for longer.

An interesting theory suggests that obese people who have heart failure because of 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 related to smoking, or intercurrent illness, or the fact that BMI is a poor measure of body morphology, although in recent 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 occurred in those with BMI 30–35 kg/m^2, in contrast to those with BMI <22 kg/m^2 who had higher all-cause mortality. Weight loss was associated with increased total mortality, increased cardiovascular mortality, and all-cause hospitalisation.

The current aging, fattening population also impacts upon decision making in obesity and diabetes. An elderly obese individual with any BMI will have a higher fat mass than their younger counterpart, because of sarcopenia and ectopic fat deposition; therefore their treatment will be different and weight loss might be inappropriate. It is known that the positive relationship between obesity and mortality is attenuated with age, under which excess weight may be better at acting as a protective factor in established chronic disease (Adams et al, 2006).

Individualised care

Management of obesity and diabetes is complex and should be governed by unique individual needs and characteristics, not cost. Of the total cost of diabetes, glucose-lowering agents make up 7.8%, whereas inpatient, outpatient and drugs for comorbidities make up the rest (see http://bit.ly/1pEEbUZ). In other words, the cost of getting treatment right is minor compared to the cost of getting it wrong, and any increase in drug costs will make significant savings elsewhere.

Rationing of glucose-lowering agents based on cost is preventing clinicians managing individuals to the best of their ability. A useful analogy is that you wouldn't show a great artist like Rubens the whole range of available colours but tell him he can only use black and brown because they're cheap. Treatment of obesity and diabetes is a skilled art and the whole range of colours should be available. ■

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