Forget polypharmacy for type 2 diabetes! Weight management is a better investment

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'I've got my life back' exclaims a participant from the Diabetes UK–funded Diabetes Remission Clinical Trial (DiRECT). She is not the first to use that expression, reflecting a 2014 national survey by the James Lind Alliance. People living with type 2 diabetes (T2D) ranked as their number one priority for research 'whether T2D can be cured or reversed'. Diabetes UK, a patient–professional charity, funded DiRECT to answer that very question.

"*When doctors told me that my pancreas was working again, it felt fantastic, absolutely amazing! I don't think of myself as a diabetic anymore. I get all my diabetes checks done, but I don't feel like a diabetic.*" – Isobel, DiRECT participant.

"*By the end of it, my 16 tablets a day went down to zero, and my blood pressure which was sky-high went back to normal. I felt 10 years younger!*" - DiRECT participant

For people living with diabetes, a significant motivation is the release from the need to take medications. Compliance with prescriptions for T2D and hypertension are frequently poor [17]. Many people dislike becoming reliant on medications: feeling 'too young' to become a chronic disease patient dependent on lifelong clinical treatment. Some reported unpleasant side effects.

Both patient preference, and also a focus on the underlying cause of disease, point towards weight management as offering a more pro-active and fundamental management than drugs, with remission as the primary target of modern diabetes treatment. Medications provide only a second-best solution, but necessary when substantial weight loss is not achieved or (less frequently, in about 15%) does not result in remission.

Figure 1 - Overview.

The thinking was simple. Until ~40 years ago, T2D only affected older people. With an average age of onset of ~70 years, relatively few lived long enough to run into serious difficulties from their diabetes. The worldwide epidemic of overweight and

obesity has changed all that, teaching us that T2D is a nutritional disease: almost nobody gets T2D unless they become overweight. And with earlier weight gains, the average age at diagnosis has fallen dramatically to ~50 years, so many more people are getting T2D and most now live long enough to get its painful and disabling complications: premature heart disease, kidney failure and dialysis, neuropathies (including dementia), infections, amputations, blindness and polypharmacy.

Literally hundreds of drugs have been developed and licenced worldwide, at colossal research expense, but all these drugs can do for people with T2D is reduce their haemoglobin A1c by a maximum of 1–2% [1]. Their use is complicated, depending on the presence of cardiovascular complications, some subclinical [2], and limited by a range of side effects. Moreover, as none of them stop disease progression or greatly reduce complications or mortality, people with T2D need to increase doses and take multiple drugs to reduce other weight-related risks, especially antihypertensives and lipid-lowering agents. Biguanides, sodium–glucose co-transporter-2 inhibitors and glucagon-like peptide (GLP) agonists do have evidence of very modest cardiovascular disease risk reduction, but they come with side effects and none address the full 'ominous octet' of obesity-related pathologies causing T2D and its complications [3]. We should not deny their value, but without correcting the underlying obesity-driven disease process, T2D still shortens lives by 5–6 years on average, despite all the medications [4].

People with T2D would prefer a better solution, and so would healthcare funders. Polypharmacy has become the norm, but it is expensive and still leaves people 'diabetic' and facing serious complications.

DiRECT is a major strategic research initiative funded by Diabetes UK as a collaboration between the University of Glasgow and the University of Newcastle. Mike Lean and Roy Taylor had seen hospital beds gradually filling up with more and more people with ghastly complications of T2D. Based on their observations and their extensive diabetes research careers around nutrition, metabolism and body fat, they both proposed that T2D might actually be reversible, at least in its early stages.

The way that weight gain causes T2D, by overloading susceptible people's body fat stores until the excess fat starts to fill up and damage the liver and pancreas, had been established by detailed metabolic studies at Newcastle University: a 15-kg weight loss removed that ectopic fat [5]. Meanwhile, the Glasgow team demonstrated effectiveness in achieving and sustaining a 10- to 15-kg weight loss for the Counterweight Plus weight management programme, without surgery [6], having previously published observational research suggesting that with a 15-kg weight loss, the life expectancy of people was almost the same as people who had never had diabetes [7].

Diabetes UK brought the two teams together as a strategic research initiative. This globally recognized study showed that providing Counterweight Plus, entirely within a routine primary care setting, resulted in 'remission' (off all glucose-lowering medication and diagnostic tests indicating no longer diabetic) for almost half the participants at Year 1. The standard care control group had only 4% remissions. Results were best for those who lost 15 kg; 86% free from diabetes at 1 year and 83% after 2 years [8, 9]—the same as with bariatric surgery [10]. A massive paradigm shift was starting in the management of T2D.

Step forward to non-drug management, which tackles excess fat in the liver and pancreas, the only modifiable risk factor. With significant weight loss of ~10–15 kg, fat levels in the liver and pancreas drop sharply, reducing insulin resistance, which in most cases allows the pancreatic beta cells to burst back into action [11]. A small

proportion of patients, ~15–20% remain diabetic despite losing ≥15 kg; some just need even greater weight loss, but there may be other factors such as previous pancreatitis. The majority, who are no longer diabetic, in line with the loss of liver and pancreas fat detected with magnetic resonance measurements, had a rapid restoration of their first-phase insulin responses and a gradual return over 12 months to completely normal total insulin secretion capacity [12].

Obesity is also a growing problem for people with type 1 diabetes, aggravating control and complications. Remission of type 1 diabetes is not possible by diet, but weight loss can greatly reduce insulin requirements [13, 14]. Radical weight management interventions such as total diet replacement (TDR) demands close monitoring of blood glucose and adjustment of insulin doses.

Traditional 'healthy eating' lifestyle approaches do not achieve the magnitude of weight loss required for remission of T2D. Counterweight Plus is a structured, long-term, professionally supported weight management programme. It involves an initial TDR phase using an 830 kcal/day formula diet product and appointments with trained dietitians or nurse practitioners. This TDR period provides rapid guaranteed weight loss of 15–20 kg if followed properly for ~12 weeks. Trained practitioners guide the person to reflect on habits, motivations, influences, environment and resources, which need to be addressed when food is reintroduced. Long-term maintenance of weight loss is critical to sustain remission of the disease. Relapse to diabetes was entirely explained by weight regain [9].

Success has been replicated in different T2D populations, with similar strategies, notably the Diabetes Intervention Accentuating Diet and Enhancing Metabolism I (DIADEM-I) trial in Qatar, which also utilized a phase of TDR and phased food reintroduction and weight loss maintenance. In a younger population with a shorter duration of T2D, the remission rate at 12 months was 60% [15].

Clinical services now face demands from people living with T2D, and from service funders, to adopt the highly cost-effective non-surgical approaches in the management of overweight and obesity demonstrated in DiRECT. The UK National Health Service (NHS) spent almost £1.1 billion for diabetes medications alone in 2019—this figure increasing by 5% (i.e. £50 million) annually as diabetes prevalence rises and newer drugs become available. Detailed cost-effectiveness analysis of DiRECT modelled into routine NHS diabetes care showed that the intervention cost was compensated for by savings from fewer drug prescriptions and fewer referrals and admissions, compensating 56% of the intervention costs (£1411 per participant) in just the 2-year observed data in DiRECT. Over a lifetime, the intervention will increase quality-adjusted life years significantly, yet will 'save' £1337 per participant [16]. These estimates assume that people would gradually relapse to diabetes at the same annual rate as observed in DiRECT and conservatively assumed all patients will relapse to diabetes by Year 10, thereafter incurring usual costs for diabetes care and complications. Thus the current DiRECT intervention is cheaper than carrying on without it!

In summary, evidence points to substantial weight loss, sufficient to clear ectopic fat from the liver and pancreas, as the cornerstone for management of T2D. Modern GLP-1 agonist medications are very effective and, if the price allows, could valuably complement optimal dietary advice when needed for effective weight loss. However the critical keystone, yet to be perfected, is long-term maintenance of that weight loss, and diet is essential, as no drugs are yet licenced for weight maintenance.

Conflict of Interest Statement

Prof Lean reports grants from Diabetes UK and Novo Nordisk, and advisory board and lecturing honoraria from Novo Nordisk, Merck, Lilly and Sanofi outside the submitted work. Ms McCombie reports personal fees from Counterweight Ltd outwith the submitted work. Dr Xin declares no conflict of interest.

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