

Prevention and Reversal of type 2 diabetes: highlights from a symposium at the 2018 Diabetes UK Annual Professional Conference

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Bulleled Novelty Statement

- **The NHS Diabetes Prevention Programme is performing well and expanding**
- **In 2018, England became the first country in the world to achieve universal coverage with a Type 2 diabetes prevention programme**
- **Common Type 2 diabetes is a condition of excess fat in liver and pancreas in susceptible people**
- **The underlying processes can be reversed to normal in short duration disease, resulting in long term normoglycaemia**
- **The mass provision of weight loss support is feasible as a vital part of our clinical strategy to prevent diabetes**

Abstract

Aim This symposium covers the gamut of Type 2 diabetes prevention, reversing established Type 2 diabetes, population level delivery of weight loss programmes and the person insights into achieving and retaining substantial weight loss.

Results The NHS prevention programme was launched in 2016 with 49% accepting the invitation to participate and 52% of these completing the intervention. By March 2018, mean weight loss was 3.2kg reflecting considerable health benefits. Established Type 2 diabetes is now known to be a reversible condition in the early years, and the underlying mechanism is the removal of the excess fat from within liver and pancreas in these susceptible individuals. The Diabetes Remission Clinical Trial has shown that around half of a primary care population of people with Type 2 diabetes of less than 6 years duration can be returned to non-diabetic blood glucose control which lasts at least 12 months. This raises the question of population level intervention to achieve weight loss. The success of some mass weight loss programmes requires to be recognized. Reframing mass provision of weight loss support should be a vital part of our clinical strategy to prevent and treat Type 2 diabetes. However, the current obesogenic environment is a reality in which individuals must live. A personal account of achieving substantial and maintaining substantial weight loss provides invaluable insight into practical problems encountered. All health professionals dealing with weight control should assimilate and reflect upon this understanding.

Conclusions Effective prevention and long term reversal of Type 2 diabetes is feasible. The impact upon the individual must be considered during delivery of advice and support

Introduction

This symposium deals with the critically important matter of retaining health if type 2 diabetes threatens. Recent encouraging data from the NHS Diabetes Prevention Programme are discussed. The possibility of preventing onset of type 2 diabetes has been accepted for some time, but the potential for long-term return to normal of non-diabetic blood glucose control is still being assimilated by health care professionals. The simple factor driving this common condition is now established –excess fat within liver and pancreas in susceptible individuals. There is a clear message for the wider population, which if successful, could see a fall in incidence and prevalence of type 2 diabetes. Prevention or reversal of established type 2 diabetes impinges upon real people living real lives. Even though the actions required to reverse type 2 diabetes are straightforward, the human cost of this has to be recognized, and the personal account included in the symposium conveys very necessary understanding.

The NHS Diabetes Prevention Programme (JV)

The prevalence of diabetes in England has increased from 2.3 million in 2009/10 [1] to 3.0 million in 2015/16 [2]. Over 90% of people with diabetes have Type 2 diabetes [3]. The associated complication and premature mortality burden is borne by individuals, their families and carers [4], and by the NHS [5]. Randomised controlled trials in those with impaired glucose tolerance have demonstrated that onset of Type 2 diabetes can be prevented or delayed through behavioural interventions [6; 7].

A strategy for future healthcare in England, published in 2014, suggested a focus on prevention to manage demand, and proposed a national Type 2 diabetes prevention programme [8]. The Healthier You: NHS Diabetes Prevention Programme was therefore developed to prevent or delay onset of Type 2 diabetes in adults already identified to be at high risk, defined as having non-diabetic hyperglycaemia (HbA_{1c} 42-47 mmol/mol (6.0 – 6.4%) or fasting plasma glucose 5.5-6.9 mmol/l). Individuals identified following an NHS Health Check [9], through retrospective searches of general practice records for qualifying blood tests, or through routine clinical practice, are offered a place on a behavioural intervention. This approach is outlined in NICE Public Health Guideline PH38 [10], and will be complemented by the population-

level interventions to tackle obesity, the major modifiable risk factor for Type 2 diabetes, outlined in the UK Government's Childhood Obesity Plan [11].

Following a commissioned evidence review [12], an expert reference group developed a service specification for behavioural interventions and their delivery, which informed a national procurement for intervention providers. Four service providers were appointed, each with the ability to provide the behavioural interventions in localities across England. The behavioural interventions enable weight loss, increased physical activity and improved nutrition through a minimum of 13 face-to-face group-based sessions, over at least 9 months, constituting at least 16 hours of contact time. Local health economies, partnerships of Clinical Commissioning Groups and Local Authorities who have responsibility for commissioning healthcare and public health services, chose from the available national service providers. They undertook to identify and refer a target number of eligible individuals into the programme, based on local expected prevalence of those at risk as well as on enabling infrastructure.

Formative evaluation has already been conducted [13], and a clinical and cost-effectiveness evaluation of the Programme has been commissioned by the National Institute for Health Research that will report in 2021.

Financial year 2016/17 constituted the first wave of national roll-out, during which the Programme was implemented across approximately 50% of England. Between June 2016 and end of March 2017, there were 43,603 referrals received, 16% higher than expected. Of those referred, 49% attended the initial assessment, higher than the 40% modelled uptake. Data on referrals, uptake, and participant characteristics were published [14]. As well as demonstrating referral numbers and percentage uptake in excess of prior modelled values, characteristics of attendees suggested that the programme was reaching those who are both at greater risk of developing Type 2 diabetes and who typically access healthcare less effectively (e.g. black and minority ethnic groups and those resident in deprived areas).

The second wave of national roll-out occurred during the Financial year 2017/18 during which Programme implementation reached approximately 75% of England, and by the end of March 2018, 182,000 referrals had been received and 78,000 individuals had attended an initial assessment (initial assessment precedes attendance

at group-based interventional sessions). There can be a delay of up to 6 months from referral before participants attend one of the interventional sessions, related to among other factors, establishing recommended group sizes and due to participant preferences. The interventions themselves take between 9 and 12 months to complete, so that by the end of March 2018, only around 4,500 participants had completed interventions. From this cohort, it was established that:

1. Of those who attended at least one interventional session, 52% completed the intervention, where completion is defined as attendance at more than 60% of sessions (aligned to the Provider payment model, whereby Providers are paid only as participants reach each of 5 milestones, with 60% or more attendance at sessions at each milestone required for achievement of payment).
2. Mean weight loss for completers was 3.2kg (3.1 to 3.4kg), 3.7kg if those of normal body-mass index at commencement were excluded. This was greater than had been predicted from the initial evidence review. Mean weight loss for all (intention-to-treat, last observation carried forward) was 2.3kg (2.2 to 2.4kg).

Financial year 2018/19 has constituted the final wave of national roll-out, and by Summer 2018, England became the first country in the world to achieve universal geographical coverage with a Type 2 diabetes prevention programme. By September 2018, over 280,000 had been referred into the programme, and over 20,000 participants had been associated with cohorts that had completed the programme. Data associated with this 20,000 cohort will be published shortly.

The Department of Health and Social Care's Mandate to NHS England for 2018-19 [15] requires the programme to deliver 100,000 interventions per year by 2020, but implementation is ahead of schedule and this target will be reached in 2019. Given the early success of the Programme, an announcement was made on 30th November 2018 that the Programme resources and capacity would be expanded over the next few years to achieve delivery of 200,000 interventions per year.

The evidence for remote or digital delivery of interventions to prevent or delay onset of Type 2 diabetes is weaker than for group-based face-to-face interventions. However, digital modes of delivery have the potential for greater reach and lower unit

cost. These issues are being considered in a major uncontrolled pilot of digital prevention interventions conducted in live service environments as part of the Healthier You Programme.

The Provider Framework is currently being re-procured, allowing opportunity to apply learning from the first 3 years of implementation. In contrast to the characteristics of initial attendees as previously described [14], retention on Programme has been poorer in those from black and minority ethnic groups and in those resident in deprived areas, and modifications to the Provider payment model moving forward will further incentivize retention of these specific groups. Attendance and retention is also poorer in those of working age, and via the re-procured Provider Framework, Providers will in future offer remote/digital modes of Programme delivery for those who decline or fail to attend the face-to-face standard offer. Further expansion of digital offers will be informed by the Healthier You Digital Pilot outlined above, due to report in early 2020.

Data from the National Diabetes Audit in England will support Programme delivery evaluation from 2018/19, expanding from population-wide surveillance of those with diagnosed diabetes to also include those with non-diabetic hyperglycaemia. Data will be systematically extracted from primary care systems for those coded with any of the descriptors consistent with high risk of Type 2 diabetes. The extraction has been piloted [16] and, within data quality limits, will permit longitudinal tracking of individuals with non-diabetic hyperglycaemia. Linkage of this and service datasets from the Programme will allow evaluation of targeted prevention on type 2 diabetes incidence, longer-term incident microvascular and cardiovascular complications, and mortality. This is the first national clinical audit of those at high risk that will provide such longitudinal evaluation data.

Those identified as being at risk of type 2 diabetes can avoid development of the disease, but it is likely that there will be continuing clinical presentation. Recent research has clarified the nature of type 2 diabetes and has led to demonstration that full health can be regained.

Understanding type 2 diabetes and its reversibility (RT)

In 2006, it became possible to postulate a simple single mechanism as the cause of Type 2 diabetes [17]. The hypothesis was presented in a plenary lecture to Diabetes UK and the subsequent study, funded by Diabetes UK, was powered to test this. Was it possible that people with type 2 diabetes could stop medication and return to normal plasma glucose control during negative energy balance and if so, what were the underlying mechanisms? Because the effect size postulated was so large, only a small group size was needed to demonstrate statistical significance. The DIABETES UK project grant of £125,000 turned out to be good value for money.

The resulting Counterpoint study used a very low calorie liquid formula diet, supplemented with non-starchy vegetables [18]. This was empirically designed to be acceptable for people going about their normal daily life yet able to achieve 15kg weight loss. The mean weight change was 15.3kg in 8 weeks, and this allowed the time course of return to normal fasting plasma glucose to be established. But importantly, the study examined the pathophysiological processes thought to be responsible. Within 7 days, plasma glucose had normalised due to a 30% fall in liver fat causing normalisation of liver insulin sensitivity. However, the most striking change was the reawakening of the beta cell with first phase insulin response slowly increasing to normal over 8 weeks.

There was intense interest from people with diabetes about the possibility of escaping the disease, and because of this, the information on how-to-do-it was placed on a website. The subsequent emails showed that motivated individuals were able to achieve around 15kg weight loss at home and that this resulted in reversal of type 2 diabetes in 73% with less than 4 years duration of type 2 diabetes, 56% with 4-8 years and 43% with more than 8 years duration [19].

Counterpoint was an acute study designed to test a hypothesis, and its results raised two major questions. Could the return to normal glucose metabolism be maintained during normal eating but avoidance of weight regain? Would people with long duration type 2 diabetes benefit similarly? The second study used the same dietary intervention, but was followed by a stepped return to normal foodstuffs, informed by the description by Counterpoint participants that suddenly returning to normal food was difficult. This was the Counterbalance study (Counteracting Beta cell failure by Long term Action to Normalize Calorie intake) [20]. After the re-introduction of normal food over 2 weeks, then monthly follow up with personal advice about food

quantity, normal beta cell function and normal plasma glucose control persisted for at least 6 months. It also showed that with increasing duration of type 2 diabetes, the chance of returning to the non-diabetic state gradually decreased [21]. Clearly there was potential for wider roll out if a suitable delivery system could be designed, preferably to operate in primary care, and the early results of Counterbalance informed the decision to conduct the Diabetes Remission Clinical Trial (DiRECT) with people in the first 6 years of type 2 diabetes.

DIABETES UK played a major role in the genesis of DiRECT. Separately from the above studies on the pathophysiology of reversal of type 2 diabetes, Mike Lean had developed framework for delivery of effective weight loss in obesity *per se* in primary care. This showed that one third of obese individuals were able to sustain weight losses of over 15kg at one year [22]. Individual grant applications to set up a larger study of diabetes reversal in primary care from both RT and ML were turned down and Diabetes UK recommended a collaboration. An application based upon synergy of knowledge of how type 2 diabetes could be reversed and the training system for Primary Care staff was successful in being funded.

The 12 month results of DiRECT conclusively demonstrated the feasibility of achieving remission of type 2 diabetes in routine Primary Care. The 8 hours of structured training for practice nurses (or dietitians if available) resulted in almost half of those recruited returning to non-diabetic control which persisted up to one year after the start of the intervention [23]. Given that recruitment for DiRECT was rapidly oversubscribed and that a remarkable 30% of all invited volunteered to participate, the wide applicability has been demonstrated.

The psychological mechanisms underlying motivation and overcoming barriers have been identified. One particularly striking result was the very clear benefit of involving spouse, partner or social contacts in the decision to lose weight and during the period of weight loss and subsequent maintenance. The Tyneside cohort underwent detailed metabolic testing. This confirmed that adequate weight loss is always accompanied by normalisation of liver fat, hepatic fat export and pancreas fat, but even in the first 6 years of type 2 diabetes some individuals had beta cells which had already undergone full dedifferentiation [24]. There was a tendency for this to be commoner in people with longer diabetes duration, but clearly reflected genetic factors relating to beta cell durability under continued metabolic stress. The bottom line of all the metabolic

studies can be simply stated. Type 2 diabetes is a state of excess fat inside liver and pancreas and removal of this allows return to non-diabetic glucose control.

A formal economic analysis of the first 12 months of DiRECT has indicated the extent of value for money to taxpayers.

Although the first year results of DiRECT are exciting, the 2nd year outcomes will determine for the extent of benefit to the whole population of people with type 2 diabetes. Retention in the study has been good. The data on avoidance of weight regain and maintenance of remission will be separately reported.

Targetted prevention programmes are essential, but if politicians and health care authorities could take effective action to modify the obesogenic environment, more widespread benefit could accrue.

The success to date of population control of weight (PA)

Can mass provision of weight loss support ever be a realistic strategy to prevent diabetes in the UK? The evidence suggests it can and the major block to making this happen is the way that we, as clinicians, think about weight loss.

The first block is that most overweight people and clinicians do not realise that the benefits of a weight loss attempt are long-lasting, even if the weight loss is temporary. We perceive recurrent weight loss attempts negatively- we call it yo-yo dieting- and in popular culture in Britain we perceive this as harmful [25]. Clinicians, who are not taught the science of weight loss, believe this too.[26] However, the evidence does not support this common belief. The diabetes prevention trials randomised people to a weight loss programme or usual care.[27; 28] They showed initial weight loss in the intervention arm was followed by almost total weight regain on average, but the incidence of diabetes remains lower than the control group for the duration of follow-up thus far, apparently permanently. Weight loss also lowers blood pressure and improves lipid profile and there is growing evidence that temporary improvements in both risk factors reduces the incidence of cardiovascular disease.[29-33]

The second block is that we perceive overweight people as not motivated to lose weight because they rarely achieve weight loss [26]. However, we should instead view this as a failure of clinicians to engage with and offer their patients support because doing so makes a difference. A trial examined patients' responses to offering weight loss support in primary care to people who had a BMI of at least 30kg/m² [34; 35]. Eighty-three percent of those waiting to see 137 general practitioners volunteered and we excluded people who appeared to be motivated by dint of already acting on their weight, leaving 1882 participants in the trial. GPs were trained to offer support in a 30-second behaviourally informed opportunistic intervention at the end of a routine consultation. When GPs did so, 77% of apparently unmotivated patients accepted a referral to a 12-week behavioural weight loss programme and most of those, 40% of the total, started the programme. Those who attended had lost 4.7kg on average at one year follow-up, which is similar to that achieved by apparently motivated people who seek out weight loss support.[36; 37] As a result of this, weight loss at one year in all those offered support as part of the brief intervention was 2.4kg, 1.4kg greater than that achieved by the control group. It appears that clinicians can easily generate motivation to lose weight and achieve weight loss in their patients but prefer not to do so.

Thirdly, we as clinicians have a cultural block about engaging with weight loss and implementing the findings of this trial.[26] But suppose we could overcome this block and implement the findings- what then? We examined the impact on the incidence of disease, quality adjusted life years, and associated health service costs in relation to the costs of delivering brief interventions using the UK Health forum microsimulation model for the years from 2015 to 2020. We assumed that everyone who visited a GP and who had a BMI of at least 30kg/m² received a brief intervention and compared this scenario where no one did. (Although the work is unpublished, it used a similar approach to published modelling based on the trial).[38] The model predicted that it would reduce the incidence of diabetes, hypertension, and coronary heart disease by 11%, 11%, and 13% relative to natural trend and be cost-saving within a few years of implementation. If GPs were to overcome this block, this work would add three hours a year to their workload, but the prize for doing so in health

gain, reduced workload from reduced incidence of disease, and the financial benefit to the nation is great.

In conclusion, we need three reframings. We need to reframe weight loss followed by weight regain as a partial amelioration of the problem of obesity but a permanent gain for health. We can use this to spur re-engagement with a weight loss effort. We need to view patients' failure to lose weight as a reflection of *our* failure to offer support to do so. And we need to reframe mass provision of weight loss support as a vital part of our clinical strategy to prevent diabetes. The prize for doing so is great.

The data from DiRECT establish the feasibility of reversal of Type 2 diabetes in primary care but do not adequately reflect the human dimension. Lives have to be lived during and after any period of weight loss. This personal account provides insight for all health care professional.

A personal insight into reversing type 2 diabetes (David Paul)

I've become the unlikely "poster boy" for the 800 calorie a day starvation diet to reverse Type 2 Diabetes in the hugely successful DiRect study. I was one of the original volunteers recruited and in my case it has worked spectacularly well. I shall remain indebted to the researchers for the rest of my life, all be it that I'm still a bit of a chunky chap who to the untrained eye does not appear to have ever starved in his life.

I lost four stones (~25 Kg) in 12 weeks, in the first seven days of living on just four shakes a day my blood sugar level dropped from 13.4 to just 4.9 and more than two years on it's still at around that 4.9 level. I remain free of the physical and mental burden of being diabetic.

But the challenge of living on four shakes a day during the actual diet is as nothing compared to trying to keep that weight off once you're allowed to resume eating normal food and get the green light to once again darken the doorway of your favourite pub.

Frankly, it's a daily battle. If you're like me, the sort of bloke who can eat and drink until the bathroom scales are buckling, then what's to stop you just piling the pounds back on again after your days on the diet start to fade in the memory?

Well in my case it's the sheer fear of becoming diabetic once again. Having shed so much weight I don't want to go back to being constantly haunted by thoughts I might go blind from diabetes or have a foot amputated, or fearing that I'm destined to keel over from a stroke.

So to that end I tried initially to control my meal portion size. Fat chance! I was given a hefty book packed with several hundred calorie counted meals by one of the diabetes nurses. I took one look, laughed at it and stuffed it in the glove compartment of my car. Two years on it's still in the car. Unread and unwanted and it will never make it into the kitchen. So the portions I served myself at meal times were too big and a few pounds piled on. Disaster.

The next plan was to go on that 5-2 diet, where you eat sensibly for five days and hardly eat at all for the other two. If I'd been able to eat sensibly I'd never have become diabetic in the first place. I suspected it wouldn't work, and it didn't. And a few more pounds piled on. Disaster.

So I joined my local council gym. £32 a month to sit on an exercise bike. I don't know which was worse, the tedium of pedalling and getting nowhere while listening to the lassies on the bikes beside me, debating which of the muscle bound hunks nearby that they liked the look of the most, or the tedium of hooking in my headphones to watch endless re-runs of Master Chef or Homes Under The Hammer on the computer screen on that dreaded exercise bike each night.

And then I realised that having spent two hours burning off calories in the gym I'd get home raging with thirst and hunger and the first thing I'd do was dive into the fridge for a cold beer and a lump of cheese to keep me going until dinner. I'd tell myself it didn't matter because I must have just burned off hundreds of calories. And a few more pounds piled on. Disaster.

So then sitting around the table after Christmas Dinner - and I'd just had the full works and was making serious inroads into the port and cheese - my family has a little tradition where we go public with any plans or ambitions we might have for the year ahead. To everyone's surprise, including me, and to guffaws of laughter all round, I

blurted out that in 2018 I would cycle from Land's End to John O'Groats, a 1,000 mile ride in 14 days. I had no idea whether I'd manage it, but having said it at the very least I'd have to try to do it and surely all the training I'd need and the actual ride itself, around 80 miles a day, would keep my weight down and ensure I remained diabetes free?

So I went online and found a firm called Peak Tours that run what cyclists call "LEJOG" - shorthand for a Land's End To John O'Groats ride. And later that same day I delved into the garage and dug out my old bike, which hadn't seen daylight for a decade or more. I rode one mile down the road and a mile back. By the time I got home my thighs were on fire, my lungs were burning and I had to have a lie down. 1,000 miles in a fortnight? What was I thinking?

But then I thought about how depressed and miserable I'd been having eaten and drunk my way into a Type 2 Diabetes diagnosis, which until the Newcastle diet came along was a life sentence, and realised I'd just have to get back on the saddle.

So I did and bit by bit I increased my regular bike rides and within a few months a 50 mile ride was easy, soon it was 60 and 70 miles, day after day. I bought a very expensive new bike and even took the plunge and invested in some lycra cycling gear. Stepping out of the front door dressed head to toe in lycra is a big moment for a chap like me. It's an unforgiving fabric. I looked like a sausage on the brink of bursting. But you know what? Lycra actually does the job it's meant to. It makes cycling easier, you stay warmer and drier and can therefore cycle for longer and I decided I didn't care what I looked like, or what passing motorists thought, and a fair few motorists made me well aware of their thoughts I can assure you! Because by riding my bike the pounds were melting away, at last I'd discovered a way of keeping my weight under control while still being able to eat and drink a fair few of the things I love.

So I did the 1,000 mile Land's End to John O'Groats ride last September. It was quite a challenge not due to the cycling, because I'd done enough training> The hard bit was not piling on the weight because I had to stay in a different pub every night for two weeks with a bunch of two dozen other cyclists. Often it would be a Wetherspoons where the giant mixed grill at a bargain bucket £10 often proved just irresistible along with a fair few helpings of the £2 a pint guest ale and then the whisky of the week once we had all pedalled into Scotland.

So the net result was I cycled eight hours a day for 14 days, covered the 1,000 miles up hill and down dale, burning off countless calories and in that gruelling fortnight I lost the grand total of just seven pounds in weight. But I'd had the time of my life and was at least a little bit slimmer at when I got to the God forsaken town they call John O'Groats, being slimmer after a holiday was a first for me.

But that was during the first year of DiRECT. The future stretches out. As a result this September I'll be back in the saddle again riding the length of France from Caen in Normandy to Nice on the Mediterranean coast - another 1,000 mile trip. The cycling will be just as tough as the Land's End ride, but not piling on the weight will again be far harder - the wine will be better and there will inevitably be a lot more cheese. But thanks to this research programme I'm a different person. My attitude towards food and how much I eat has been recalibrated and as a result my life has been totally transformed.

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