THE LATEST ON WHY AND HOW

As NHS England's remission programme gets underway, Senior Research Communications Officer **Dr Faye Riley** takes a look at the latest DiRECT findings and what's next for remission research.

Featuring Isobel Murray, who has been in remission from type 2 diabetes for six years after taking part in the DiRECT trial.

The striking findings from the Diabetes UK-funded DiRECT trial have rightly been celebrated for transforming the way we about think of type 2 diabetes. And now, with the launch of NHS England's low-calorie diet remission programme, thousands will be able to benefit from DiRECT's ground-breaking findings.

GPs in 10 areas of England are now able to refer patients who have been diagnosed with type 2 diabetes in the last six years onto the programme. These sites will test DiRECT in the 'real world' over the course of a year. People with type 2 diabetes will receive a low-calorie total diet replacement and support to keep weight off through virtual one-to-ones, group sessions or digital support.

This comes on top of similar programmes rolling out as part of the Scotland Healthier Future type 2 diabetes prevention framework and a planned small pilot across four Health Boards in Wales.

It's a fantastic moment and the culmination of years of hard work from our researchers and supporters. We've come a long way since we first awarded Professor Roy Taylor a research grant back in 2008 to study the effects of a low-calorie diet in 11 people.

"The launch of the NHS England programme to reverse type 2 diabetes is an exciting moment. It is the practical outcome of a 12-year series of research studies – from hypothesis of the cause of type 2 diabetes to proof of the underlying mechanisms, then real-life application," explains Prof Taylor, co-leader of the DiRECT trial.

And, most importantly, it means more lives will be changed. "People with type 2 diabetes who have put their diabetes into remission frequently tell us

THE WHAT, OF REMISSION

how it has changed their lives," says Bridget Turner, Diabetes UK's Director of Policy, Campaigns and Improvement. "We are so pleased to see that others will now have the same opportunity and hope that it won't be too long before more remission programmes are rolled out across the country."

In order to assist healthcare professionals in having constructive conversations about remission, we developed an Information Prescription, which is available to download from GP IT systems or at www.diabetes.org.uk/up-info-prescription. We also have lots more information and resources at www.diabetes.org.uk, including recipes and meal planners.

Speaking volumes

Along with helping to change lives right now, DiRECT is also revealing further insights into how type 2 diabetes can be put into remission. In the team's most recent paper[1], we learnt more about the dramatic changes remission can cause inside the body.

We've known for some time that the pancreas in people with type 2 diabetes is around 20–30% smaller than in people without the condition and is more irregularly shaped. But it has never been clear if this is the cause or a result of developing type 2 diabetes.

To understand what happens to the pancreas when people go into remission, the researchers studied 64 participants from the DiRECT trial and 64 people without type 2 diabetes. Using MRI scans, they measured the volume, shape, and amount of fat in the pancreas, and followed how these changed over two years on the trial.

They found that the size of the pancreas in people who were in remission had increased by 20% – returning to almost normal size. Their pancreas shape was also restored, and levels of fat in the pancreas fell.

By comparison, in people taking part in DiRECT who did not go into remission, the increase in pancreas volume was far smaller, and the pancreas shape showed little change. Similarly, only responders showed early and sustained improvement in beta cell function.

Previous research from the DiRECT team revealed that the function of beta cells normalises as a result of remission of type 2 diabetes. However, beta cells only make up around 1% of the pancreas, and these latest findings are the first time we've seen that remission causes positive changes to the whole of the pancreas. Insulin can promote tissue growth and these findings suggest that when insulin production drops in type 2 diabetes, this could cause the pancreas to shrink. When healthy insulin levels are restored thanks to remission, we appear to see a reversal of this process.

Prof Taylor thinks it's not only convincing evidence of a return to normal state when in remission, but says the findings will bring hope for people living with type 2 diabetes. "It will be enormously encouraging for anyone with type 2 diabetes to learn that their small pancreas can return to normal size. Knowing what a treatment actually does inside the body is both motivating and reassuring," he explained.

Can we predict remission?

DiRECT has shown clearly that remission is linked to the degree of weight loss. At two years, 79% of people who had lost between 10 and 15kg were in remission, rising to 82% of people who lost more than 15kg. But we can't tell from the outset who will or won't lose significant amounts of weight. Intensive weight management programmes aren't easy and require huge efforts from the individuals taking part, as well as placing demands on healthcare services. So if we could spot who is more likely to go into remission, or who might benefit from other approaches, it could help to maximise the benefits of DiRECT-style interventions.

With this in mind, the DiRECT team looked at demographic and clinical data to search for factors that could be assessed before or early on in treatment to predict remission success. After weight loss itself, the strongest predictor was the number of diabetes medications prescribed at the start of the study. Fewer medications increased the participants' chances of being in remission at the one- and two-year mark. And the odds of remission were lowest for those prescribed sulfonylureas and metformin. It's likely this measure is indicative of type 2 diabetes progression. Those who require more medications might have more advanced type 2 diabetes, and so their beta cells are less likely to recover.

Findings also showed that people with anxiety or depression were less likely to go into remission and may benefit from additional support in weight management interventions. Baseline BMI, fasting insulin, fasting C-peptide and diabetes duration did not predict remission.

But overall, the findings showed that remission was frequent across the board. While some variables could be linked with remission success, none were sufficient to identify people for whom remission isn't likely to be possible[2]. That's encouraging and reassuring for millions of people living ▶

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PHOTO: IAN JACOBS

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with type 2 diabetes worldwide, and the DiRECT team concluded that remission should be considered a realistic goal for anyone within six years of a diagnosis.

The next chapter

DiRECT is continuing to follow up participants and will keep on answering important questions about long-term remission and its biology. But to make sure remission is a possibility for more people, we needed DiRECT to be the beginning of our journey, not the end. So last year, we hosted a workshop to identify the most urgent priorities for future remission research.

We brought together people living with diabetes with experts in different research fields, including bariatric surgery, weight management interventions and gut hormones to uncover gaps and opportunities, and set a direction of travel. They came up with a set of recommendations in four key areas that were published recently[3]: These are set out below.

A shot in the arm for remission research

We’ve partnered with the National Institute for Health Research (NIHR) and their Programme Grants for Applied Research scheme. Together we’re making funding available for research which investigates the implementation, in primary care, of approaches to help people recently diagnosed with type 2 diabetes go into remission. These may be new interventions or approaches that complement existing programmes, which are designed to boost engagement or effectiveness.

Applications may, for example, focus on different diet-based remission programmes, behavioural therapies to help support weight loss maintenance, strategies to improve psychosocial support for people attempting remission, or ways to combine pharmacotherapy with nutrition-based approaches.

“We’re excited to be partnering again with Diabetes UK – the Covid-19 crisis has highlighted just how important research is for the health and wealth of the nation,” says Rajinder Flora, Assistant Director for NIHR’s Programme Grants for Applied Research scheme. “By working together to help more people with type 2 diabetes go into remission, we hope we can make a big difference in people’s lives and help to make our healthcare system more effective too.”

Stage 1 applications close on 25 November and you can find out more by going to: **www.diabetes.org.uk/up-apply-grant**

Through the implementation of DiRECT, coupled with stimulating new remission research and areas of exploration, we have an opportunity to give millions of people living with type 2 diabetes a better quality of life. Isobel Murray, who has been in remission for six years after taking part in DiRECT, sums up just what remission means. “When I was first told that my diabetes went into remission, I felt absolutely ecstatic. Almost six years later, that feeling is still with me. Over the last few years, I’ve been able to lead a normal life again,” Isobel says.

“It took only a few months to do the plan and to get my life back – it was worth every minute. I feel 10 years younger now and I will do everything in my power to never go back to how things were before.”

PHOTO: DIABETES UK

Key recommendations

1. **The biology of remission.** We need to understand how weight loss leads to beta cell recovery in some and not others; unpick the role of gut hormone therapy in remission; and identify novel biomarkers which could be used to predict response to remission interventions in the future.
2. **How to personalise lifestyle approaches based on biology, patient choice and subtypes.** We need to build a greater understanding of the role low-carbohydrate diets could have, and understand how effective interventions can be in different black and minority ethnic communities, making sure we get more diversity in future research.
3. **The most effective approaches to implementation of lifestyle interventions.** We must work out the best ways to deliver interventions in real-world settings, along with assessing health economic implications. We need to know how interventions can best support people to keep weight off; the psychological impact of remission; and explore barriers to bariatric surgery.
4. **The best approaches to combining therapies.** We need to explore the effectiveness of using different approaches to remission – including gut hormones, other drugs, lifestyle approaches and bariatric surgery – in tandem with each other. Also, to determine how we can effectively stratify type 2 diabetes and align remission interventions with the individual.

We want to work alongside funders, researchers, healthcare professionals, and the wider health system to see these research gaps being filled. And, excitingly, there’s already action being taken with our partners.

References

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