

# THE DIRECT ROUTE TO TYPE 2 REMISSION?

Diabetes UK recently awarded funds to a groundbreaking clinical trial of a low-calorie liquid diet for Type 2 diabetes. The charity's Research Communications Officer, **Dr Richard Elliott**, meets the researchers who want to put Type 2 into remission – and keep it there

Not everyone with Type 2 diabetes is overweight, but weight gain, and becoming overweight even before reaching the level of obesity, are the most important modifiable risk factors for the condition. They are also the reasons why Type 2 has now transformed from a problem of old age into a global epidemic that now affects overweight and obese people of all ages. Surgical operations, such as gastric banding and gastric bypass, are potential solutions because they lead to dramatic weight loss, which can put Type 2 diabetes into remission for up to 80 per cent of patients. Such treatments, however, are expensive, invasive and carry a risk of surgical complications, all of which mean that they can often only be offered as a last resort, and are not available to the vast majority of people with Type 2 diabetes.

In 2011, Diabetes UK funded a pilot study at Newcastle University that aimed to clarify the mechanisms underlying Type 2 diabetes and the induction of remission and replicate the effects of bariatric surgery using diet alone. Under close supervision from a medical team, 11 people with Type 2 underwent an intensive low-calorie liquid diet for eight weeks and achieved startling results. After only a week, levels of fat in the participants' livers had decreased sharply and the insulin sensitivity of the liver had returned to normal. After eight weeks, levels of fat in the pancreas had also decreased and insulin production had returned to normal. Everyone who took part had put their Type 2 diabetes into remission, with an average weight loss of around 15kg. Some participants later regained weight but, after three months of normal eating with no special follow-up, most still had non-diabetic blood glucose control. The liquid diet used in the study was challenging and by no means a quick fix for Type 2 diabetes, but the mere possibility of Type 2 remission without surgery proved to be a revelation for researchers. Professor Roy Taylor, who led the study, said: "Our findings were enormously exciting. We had demonstrated that by changing calorie intake we could change fat levels in the liver and pancreas and return both insulin sensitivity and insulin production to normal."

Over the same period, Professor Mike Lean, an expert in human nutrition and diabetes at the University of Glasgow, was leading a study of a similar liquid diet, to establish how the lower calorie intake and weight loss can be sustained within routine NHS practice without surgery. After a year, 44 per cent of the patients whose follow-up weight was available (at least a third of those who entered the trial) had managed to lose over 15kg.

## Taking the next step

Diabetes UK was quick to see the value of bringing these pieces of evidence together. In 2012, the charity called for new research ideas to bring this approach a step closer to

the clinic. Now, after a careful review process, Diabetes UK has awarded the largest-ever research grant in its 79-year history, to support a new study that was due to begin in October. With over £2.4m from the charity, Prof Lean and Prof Taylor will work in partnership with Counterweight Ltd, the dietitian-led UK weight management provider, to compare the long-term effects of a new approach to weight management with the best diabetes care that is currently available. The aim of DiRECT (Diabetes REmission Clinical Trial) is to help people with Type 2 diabetes become, and remain, non-diabetic in the long term and to compare this approach with the best possible standard treatment over two years.

This time around, the low-calorie liquid diet that was used in previous studies will be combined with a long-term structured plan for weight control. The aim is not just to demonstrate remission, but to evaluate the potential of this approach for widespread use in general practice. Prof Taylor explained: "We know that changes in calorie intake can produce changes in body composition that put Type 2 diabetes into remission – at least in some people. Now we're moving from a short study focused on underlying mechanisms to one that is long term and more practical. We need to evaluate how well people do using this approach and uncover problems that might be faced. Our work will focus on long-term outcomes and standard clinical care because the ultimate goal is to help people with Type 2 diabetes to change their eating habits for life through routine visits to their own GP."

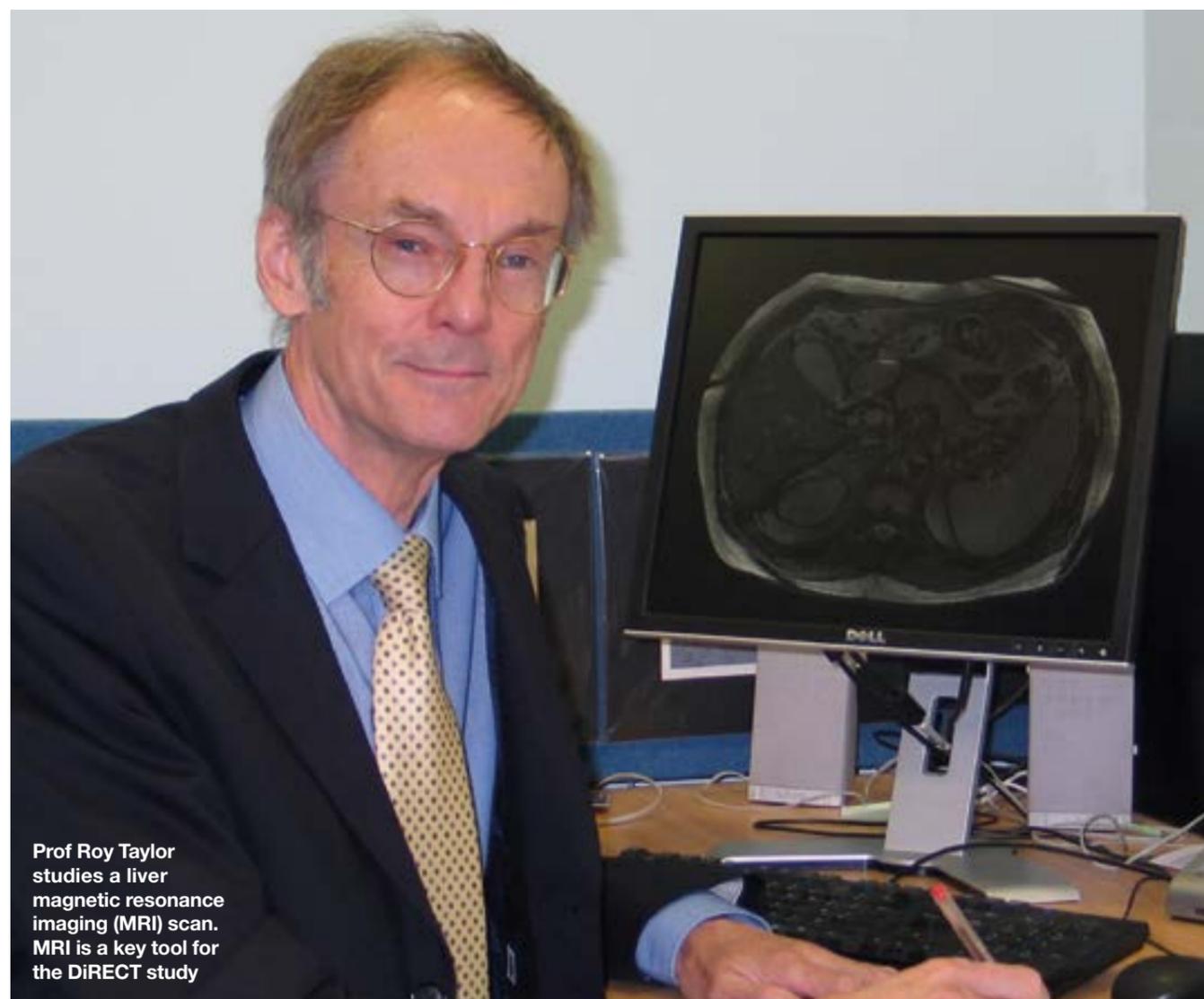
Over the next year, the researchers will invite GP practices across Scotland and Tyneside to help them recruit 240 people aged 20–65 who are overweight and have been diagnosed with Type 2 diabetes in the last six years. The study will not be accepting individual patients directly. Participants at half the practices will be allocated to receive the best-available Type 2 diabetes care, as laid out in current clinical guidelines. The participants at the remaining practices will receive a low-calorie liquid diet, and will then be reintroduced gradually to normal food. They will receive expert support to help them maintain their weight loss in the long term. This study will also consider a wide range of variables (which include genetics, metabolism, psychological attitudes and physical activity) and is the only way to tell if a low-calorie liquid diet is practical and more effective in the long term than the current best-available treatments for Type 2 diabetes.

The setting for the study has been carefully chosen, as Prof Lean explained: "There are now millions of people with Type 2 diabetes in the UK and they can't all be trailing into hospital once a year for help with weight loss – that simply isn't going to do the job. If this new approach is ever going to be useful for people with diabetes, they need to be seen much more frequently, and in a supportive environment that is easily accessible. This study will break important new ground because our observations and measurements of the new weight control plan will all take place within routine primary care."

Some of the participants from Tyneside will also undergo metabolic studies and magnetic resonance imaging (MRI) scans at Newcastle University to help the researchers understand in precise detail how significant weight loss contributes to Type 2 diabetes remission. "The MRI investigation is one of the most exciting parts of this project and will build upon what we have already observed," said Prof Taylor. "Our original study measured what happens to levels of fat in the pancreas and the liver during Type 2 remission, but we still don't know what happens to those levels in the long term. By extending our observations of the exact mechanisms involved, this study will show us what happens inside the body when Type 2 diabetes first appears. It will also reveal what happens when Type 2 diabetes goes into remission and the durability of changes that make it disappear. By the end of the study, we should know how to identify people who can use this approach to achieve Type 2 diabetes remission and in how many people the change will be long term. That's the really practical aspect of this study, because we want to make a difference to the management of Type 2 diabetes that will help people for life."

Only when the results of this work are in can Diabetes UK think about advocating any changes to the existing dietary recommendations for overweight people who have Type 2 diabetes.

"The current guidelines on healthy balanced eating are good," Prof Lean emphasised. "The reason for doing this research is that we don't know at present whether the extra effort, and stress, of following a very restrictive diet will indeed bring benefits in the long term. Although benefits are possible, we know that weight regain after liquid diets has been common in the past, and could have harmful effects. We need to study sufficient numbers of people for long enough to be sure that the benefits outweigh the costs."



Prof Roy Taylor studies a liver magnetic resonance imaging (MRI) scan. MRI is a key tool for the DiRECT study

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**Making a quantum leap**

Both researchers emphasise that the approach on trial is intensive, challenging and will not be suitable for everyone with Type 2 diabetes. Gallstones are a possible risk of intensive weight loss, but this is uncommon (in one pilot study, one out of 116 patients was confirmed as having gallstones) and should be less common with the planned low-calorie liquid diet, as it is less restrictive than those used previously.

Dr Matthew Hobbs, Diabetes UK Head of Research, said: "The 2011 study and evidence from bariatric surgery have shown us that Type 2 diabetes can be put into remission. As exciting as these findings are, there is much about low-calorie diets that we do not yet understand. We don't know whether this diet will put Type 2 diabetes into remission in the long term and we don't know if it will be possible to predict what sort of person will do best. Even more fundamentally, this kind of diet is certainly not an easy option or a 'quick fix'. Study participants on the diet will be consuming so few calories that they are likely to feel hungry for quite a lot of the time. Those who complete the diet will also have to maintain a healthy lifestyle to stop their Type 2 diabetes coming back. Moreover, there are real questions about what proportion of people will be able to stick to this diet for the length of time needed for it to be effective.

"Until these questions are answered, we are not in a position to recommend that general dietary guidelines for people with Type 2 diabetes are changed, or to advise the NHS to offer this diet as a treatment option. That uncertainty is exactly why we are supporting these researchers with this grant. This new study should provide the evidence we need in order to give definitive

answers to these questions."

Despite the challenges involved, both researchers think that this study could lead to a dramatic shift in our understanding of Type 2 diabetes. Prof Lean said: "There has been huge media interest related to our previous research in this area and many people might want (or think they want) this kind of treatment – but first we need to prove that it actually works in primary care. It's therefore very important that we do this research and that healthcare professionals and people with Type 2 help us to compare our new experimental approach with the highest standards of existing care. We've also got to be clear that the weight-loss plan we're testing is not going to be easy. It's going to be hard work for our research participants and, even though we're going to support them as best we can, some are going to find it difficult."

"We're confident that some people with Type 2 diabetes will be able to achieve remission, because we've seen it happen before. But, what we really want to know is, how many can do it, and are we able to identify those for whom it is not worth making the effort. We don't want to ask people to work hard on this until we're sure it will bring long-term benefits."

Type 2 diabetes will always be a serious health condition, requiring serious personal and medical attention. But, perhaps it won't always be seen as a permanent condition



that worsens – inevitably – over time, until it is ultimately managed using insulin. If this study shows that intensive weight management can bring about and maintain Type 2 remission in the long term, it could completely overturn this point of view.

Specifically, it could lead to significant changes in the way that Type 2 diabetes is managed by the NHS and provide an accessible way to help people with Type 2 live for longer and with fewer complications, without the need for weight-loss surgery.

Prof Lean explained: "I've looked after a lot of patients with Type 2 diabetes and I've seen dreadful complications creeping up inexorably. I'm hoping we can change that. First, we – as a profession – need to recognise that there's no such thing as 'mild diabetes'. Type 2 diabetes is a very serious condition and medications, whether it's insulin, sulfonylureas, metformin or something else, will, for the most part, only help patients to manage the symptoms. They have small effects that are of great value in reducing complications, but they won't correct the disease process.

"In that respect, I think that our management of Type 2 diabetes has, to some extent, missed the point for the last 100 years. The point is that Type 2 typically develops only when you get a big waist. Physical activity plays a part of course, but the main thing is being overweight and obesity, and that has been known for a

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**Prof Mike Lean hopes to change thinking on the management of obesity and Type 2 diabetes**



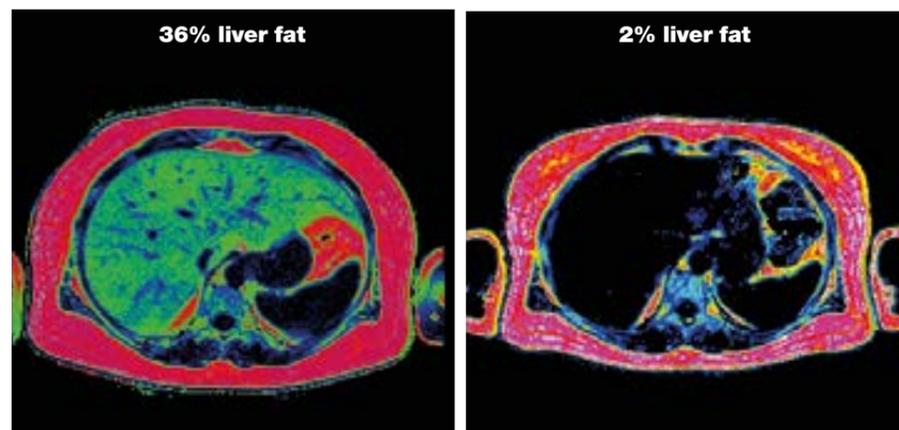
very long time. So far, we as doctors and researchers have ducked this because, as a profession, we have not focused our efforts and resources on helping people to lose weight – and perhaps by not understanding how incredibly difficult it is for seriously obese people with Type 2 diabetes to reduce their weight and to keep it off. Hopefully this study will help to change our thinking on obesity and show that, if we can help people to lose weight using this approach, we can help a lot of people with Type 2 diabetes to turn it around. If we're successful, healthcare professionals in primary care will be able to offer a high proportion of their Type 2 patients the possibility of remission as well as the pathway to help them get there."

DiRECT will take five years to complete and is only just getting under way, but Prof Lean is optimistic about the practical improvements that could be achieved. "If our analysis shows that this approach to weight loss and weight management is both effective and cost-effective, our aim will be to produce a programme that can be implemented in the NHS as soon as possible," he said.

Prof Taylor is also confident of major advances to come in our understanding and management of Type 2 diabetes. "With this study we are exploring uncharted terrain. We know where we're trying to get to and we know that there will be challenges along the way. We don't yet have a full map to guide us and at the end there will be details left to unravel and other questions to ask. Nevertheless, I believe that this study will lead to a quantum leap forward in understanding of how best to manage Type 2 diabetes."

**i** Recruitment for this study is only taking place via selected GP practices in Scotland and Tyneside. Individual patients are not being recruited directly. Further information is available at [www.diabetes.org.uk/direct](http://www.diabetes.org.uk/direct)

- Further information and findings from the pilot studies that led to DiRECT are available at: <http://dx.doi.org/10.1007/s00125-011-2204-7>; <http://dx.doi.org/10.3399/bjgp13X663073>; [www.ncl.ac.uk/magres/research/diabetes/reversal.htm](http://www.ncl.ac.uk/magres/research/diabetes/reversal.htm)
- Results from DiRECT will be published in *Update* and on the Diabetes UK website as soon as they are available. Until then, it is important that people with Type 2 diabetes know about the existing guidelines on healthy, balanced eating and do their best to follow them. Our guides to a healthy lifestyle and eating well with Type 2 diabetes are at: [www.diabetes.org.uk/guide-to-diabetes](http://www.diabetes.org.uk/guide-to-diabetes)



**In Prof Taylor's pilot study of the low-calorie liquid diet in Type 2 diabetes, magnetic resonance image (MRI) scans (left) showed tangible evidence of reductions in liver fat levels**