

Work leading up to and timeliness of DiRECT

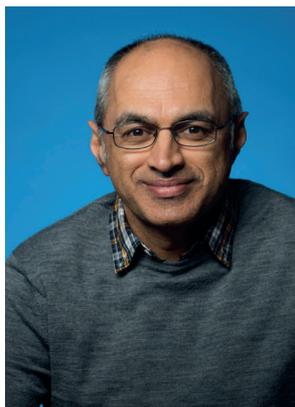
Naveed Sattar, Professor of Metabolic Medicine at the University of Glasgow, discusses obesity, liver fat and why DiRECT can help people with Type 2 diabetes

the link between obesity and diabetes risk has been known for many years, but that it is much stronger (by more than a factor of 10-fold) than the link between obesity and heart disease is not fully appreciated. For example, whereas a body mass index (BMI) of 35 equates to a two- to four-fold higher risk for heart disease compared with a BMI of 21, for diabetes, this BMI difference brings about a greater than 40-fold higher risk. As a result, BMI forms a major part of all diabetes risk scores throughout the world. It is of no surprise therefore that intentional weight loss is a recommended target for all our patients with diabetes, though in reality, few currently manage to achieve and sustain meaningful weight loss.

The nation's rising body weights have inevitably contributed to a rising prevalence of diabetes. From around 1% prevalence in the 1970s, the UK prevalence now sits closer to 6%, although admittedly, improved life expectancy and better survival of people with diabetes have also contributed to this rise in prevalence. We also began to see Type 2 diabetes in young adults and even children, with the first reports of the latter in the early 2000s. And these days we face a problem with more and more younger people developing Type 2 diabetes, a group in whom the condition worsens more rapidly. Indeed, plentiful evidence suggests the earlier one develops Type 2 diabetes, the greater excess risk for a range of complications and the greater loss of life years from diabetes.

The role of liver fat

But why does obesity lead to Type 2 diabetes? The search for the mechanisms linking weight gain and diabetes has been going on for years, and I was able to contribute a little to this. In the early 2000s, we showed that the liver enzyme, ALT predicted development of diabetes and that its increase over time and sustained elevation, together with triglyceride levels, accompanied the transition to diabetes in men from the West of Scotland Study. As ALT rises with more liver fat, these data led us to speculate hepatic fat accumulation as important to development of diabetes. I recall Roy Taylor congratulating me on this paper, as he was looking for evidence to support his developing theories.



PROFESSOR NAVEED SATTAR is a clinically active academic with wide experience in diabetes and cardiovascular epidemiology, biomarkers, guidelines and trials. He is Professor of Metabolic Medicine at the University of Glasgow and has written over 800 peer reviewed papers, including many in major medical journals. He is of South Asian heritage and so has a strong family history of Type 2 diabetes, adding to his interest in all aspects of the condition. He continues to work in lifestyle and drug trials, and recognises the need for both to improve health outcomes. Above all, he really enjoys collaborating with wonderful colleagues all over the world.

Of course, little did I know at the time that Roy and his team were undertaking much more elegant studies to make these and other connections. Their accumulated evidence has shown that a gain of ectopic fat in the liver and pancreas contributes to the development of Type 2 diabetes via emerging mechanisms. Furthermore, Roy and others showed that different people have different BMI set points beyond which they start to gain more of this harmful ectopic fat. Men seem to have a lower BMI set point for diabetes (a finding, we also contributed to), as well as those with family histories of diabetes and many ethnicities, and in each case, there is emerging evidence of ectopic fat gains at lower BMIs.

Why weight loss matters

Regardless of mechanisms, if all the above facts hold true, substantial weight loss ought to reverse Type 2 diabetes. Multiple bariatric surgery studies have now shown this to be true, so that many people with Type 2 diabetes have completely normalised their glucose levels after surgery and are off all their therapies. Remarkably, this also included some who were on insulin, providing early evidence that the pancreatic beta cells were not in fact lifeless, but in many cases their functions might actually be recoverable.

Of course, many people do not want to have Type 2 diabetes and few are willing to undergo surgery to reverse it. So, could novel dietary methods work? Roy Taylor and his team showed this to be possible in the short term with low-calorie diets, with accompanying reductions in ectopic fat. But what about sustaining such weight loss over the longer term? Fortunately, Mike Lean and his team had been working out how to help people sustain weight loss after a low-calorie diet, and so, a meaningful collaboration was born out of which the DiRECT trial was designed and conducted. The timeliness of DiRECT is important, given still rising obesity levels, and its results provide further evidence that research into determining how best to help people lose and sustain weight loss can have remarkable benefits. DiRECT is by no means the end of the road, but more of a beginning and stimulus to others in the community to extend and improve these concepts for the benefits of our patients.