

Type 2 diabetes remission associated with renal and cardiovascular benefits

Achieving type 2 diabetes remission at any point during the 12 years of the Look AHEAD trial was associated with a 33% lower rate of chronic kidney disease (CKD) and a 40% lower rate of cardiovascular disease (CVD) compared with those not achieving remission, according to this *post hoc* analysis published in *Diabetologia*. There was a dose–response relationship, with those achieving remission for at least four visits having a 55% and 49% lower rate of CKD and CVD, respectively, compared to those not achieving remission. Compared with the control group receiving normal diabetes education and support (irrespective of remission achievement), in those who achieved remission with intensive lifestyle support, there was a 40% reduction in CKD and a 23% reduction in CVD, with even greater reductions in those who achieved persistent remission over at least four visits. In the overall sample, 12.7% of participants achieved remission at 1 year (11.2% of those in the intensive lifestyle group and 2.0% in the diabetes education and support group), declining to 7.2% versus 2.1% in the two groups at year 4 and to 3.7% versus 1.95% at 12 years. Comparing those achieving remission with those who did not, there was a small (2%) net increased weight loss overall but a larger (8%) difference in those who achieved extended remission. Remission was also more likely in those with a shorter duration of type 2 diabetes and in those with lower baseline HbA_{1c}. Whether there should be greater focus on reducing CKD and CVD by pursuing remission via intensive lifestyle interventions (which may have additional long-term health benefits) or by optimising drug therapy remains under debate. What is clear is that both options should be discussed so that people can make an informed choice.

Type 2 diabetes remission is recognised as an achievable goal based on findings from bariatric surgery and lifestyle interventions in the DiRECT and DIADEM-I studies. Bariatric surgery studies have shown that remission is associated with reductions in risk of chronic kidney disease (CKD), cardiovascular disease (CVD) and mortality.

In this *post hoc* observational analysis published in *Diabetologia*, Gregg and colleagues used data collected during the Look AHEAD (Action for Health in Diabetes) study to explore whether similar benefits on CKD and CVD might be achievable when using lifestyle intervention to achieve remission.

The prespecified renal outcome was the incidence of high-risk or very-high-risk CKD, defined using KDIGO criteria as ACR >30 mg/mmol regardless of

eGFR, ACR >3 mg/mmol and eGFR <60 mL/min/1.73 m², or eGFR <45 with ACR <3 mg/mmol. The prespecified cardiovascular outcome was a composite of death due to cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke or hospitalisation for angina.

In the Look AHEAD study (Look AHEAD Research Group, 2013), participants with excess weight/obesity and type 2 diabetes were randomised to either an intensive lifestyle intervention or normal diabetes support and education. The lifestyle intervention group received both weekly group and individual lifestyle sessions for the first 6 months, then three ongoing sessions per month for the next 6 months. They received two contacts per month during years 2–4 and were encouraged to attend monthly support sessions in years 4–12. This is



Pam Brown
GP in Swansea

Citation: Brown P (2024) Diabetes Distilled: Type 2 diabetes remission associated with renal and cardiovascular benefits. *Diabetes & Primary Care* 26: 33–5



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a significantly greater lifestyle intervention than could be delivered in most UK practices and of longer duration than in the NHS Type 2 Diabetes Path to Remission Programme.

People in the lifestyle group were encouraged to follow a 1200–1800 kcal/day diet low in fat and saturated fat, and to take at least 175 minutes per week of brisk walking or equivalent moderate-intensity activity. Behavioural strategies including self-monitoring and problem solving were taught, and liquid meal replacements were available in year 1 to help achieve dietary goals. In contrast, the normal diabetes support and education group were offered three group sessions annually, without individualised behavioural support.

Participants in Look AHEAD had a mean age of 59 years, mean diabetes duration of 6 years and mean BMI of 35.8 kg/m². Follow-up visits and blood testing occurred annually for 4 years and then every 2 years up to the final follow-up at 12 years. Although the 2022 consensus definition of diabetes remission is HbA_{1c} <48 mmol/mol with no medication for at least 3 months, or 6 months if using lifestyle alone (Riddle et al, 2021), this *post hoc* study assigned remission status to people not receiving any glucose-lowering medication who had HbA_{1c} <48 mmol/mol at a single time point, described as an “epidemiological definition” for remission.

Results

Data on 4402 participants for the CKD assessment and 4132 participants for the CVD assessment were analysed. Overall, 12.7% of the sample met the criteria used here for remission on at least one follow-up – primarily driven by the 11.2% of participants in the lifestyle group who achieved remission in year 1. Remission prevalence gradually decreased to 7.2% by year 4 in the intervention group, whereas it remained stable at around 2% across the years in the control group. By year 12, the prevalence of remission was low but remained twice as high in the intervention group than in controls (3.7% vs 1.95%).

Those who achieved remission at any stage had a 33% lower rate of CKD and a 40% lower rate of CVD than those who did not achieve remission. There was a dose–response relationship, such that

those achieving persistent remission across four or more visits had a 55% lower rate of CKD and a 49% lower rate of CVD compared with those not achieving remission.

Those who achieved remission at any stage had greater weight loss: mean weight loss of 7.3 kg at 1 year and 4.5 kg at 4 years, compared with 4.0 kg and 2.2 kg at 1 and 4 years, respectively, in those in the intervention group who did not achieve remission. Mean weight loss was greater in those who achieved persisting remission for at least four visits (12.3 kg and 9.6 kg at 1 and 4 years, respectively).

Comparison with other remission trials

These findings make for interesting comparison with other studies of type 2 diabetes remission, DiRECT (Lean et al, 2018) and DIADEM-I (Taheri et al, 2020). In Look AHEAD, weight loss in the intervention group in years 1 and 2 was similar to that achieved in DiRECT (9.5% and 5.3% at the same time points), yet remission rates were much lower, at 12% versus 46% at 1 year, and 10% versus 36% at 2 years.

In the DIADEM-I study in the Middle East, participants were younger and with shorter duration of type 2 diabetes than in DiRECT, and the net weight loss of 6.1% was associated with a 61% remission rate at 1 year compared with 12% in the control group. Both DIADEM-I and DiRECT used an initial total meal replacement eating plan providing around 800–850 kcal/day for 12 weeks to achieve rapid initial weight loss.

In Look AHEAD, as in the DiRECT study, those with short duration of diabetes, low starting HbA_{1c} and greater weight loss were most likely to achieve remission and, therefore, experience reduced CKD and CVD.

The authors discuss potential pathways by which diabetes remission could reduce the risk of CKD, CVD and other long-term outcomes. Those achieving remission lost slightly more weight, and weight loss is associated with multiple benefits, including improved glucose, blood pressure, insulin resistance, inflammation and liver fat levels. In the original Look AHEAD study, those achieving 10% weight loss in year 1 had a 21% lower CVD risk (Look AHEAD Research Group, 2016). The reduction

in HbA_{1c} may have a positive benefit on the vascular endothelium and reduce progression of atherosclerosis. The recommended intensive lifestyle changes, including improved diet quality and high rates of physical activity, may also have contributed.

The authors postulate that the initial 12-week total meal replacement resulting in early rapid weight loss in DiRECT and DIADEM-I may have somehow contributed to the higher remission rates in the first 2 years in these studies despite the similar weight loss to that achieved in Look AHEAD.

Discussion

What is emerging from remission studies is that, although remission can be achieved in people with varying duration of type 2 diabetes, actively pursuing remission using lifestyle measures is most effective within the first few years of type 2 diabetes (mean 3 years and all <6 years in DiRECT, versus mean 6 years in Look AHEAD). This should encourage us to discuss and support motivated people to pursue remission early after diagnosis.

The weight regain beyond 1 year in those who were successful in achieving intentional weight loss reflects the pattern commonly seen in most weight loss studies, with the weight nadir achieved around 6–12 months and with regain thereafter. This has been partly attributed to the “weight set point” concept, whereby the body will decrease activity and increase hunger and food consumption unconsciously, ensuring that weight regain occurs back to the starting point (and usually slightly higher) unless changes in food types (e.g. reducing ultra-processed food) are made. Better understanding of interventions to help people achieve weight maintenance may improve longer-term remission rates and, hence, increase the cardiovascular and renal benefits seen here.

The authors raise the dilemma of whether national and public health programmes should focus on trying to reduce CKD and CVD risk using intensive lifestyle intervention to target diabetes remission, or whether reduction in CKD

and CVD outcomes are best achieved through optimal drug management. Given that we now have drugs which help achieve and maintain significant weight reduction, making remission more achievable, and given that those same drugs can significantly reduce CKD progression and CVD outcomes, optimising lifestyle advice and drug therapy is likely to have synergistic benefits.

It is important to remember that people with type 2 diabetes are at increased risk of CVD and that, [as highlighted in a recent *Diabetes Distilled*](#), this risk may remain elevated even if diabetes remission is achieved. Drugs to reduce this risk, such as statins and RAAS inhibitors, may be indicated even if glycaemia is well controlled without glucose-lowering medications.

Implications for practice

Many people remain unaware that type 2 diabetes remission is possible or that weight loss is important in achieving this. Most of us will not be able to access the level of support that was available in Look AHEAD, DiRECT or DIADEM-I, but we can signpost to remission programmes and, if we feel unable to provide weight loss advice ourselves, we can refer to our dietetic and weight management services. At the same time, we need to avoid clinical inertia and go ahead with prescribing those drugs that can reduce complications, morbidity and mortality even if HbA_{1c} is at target. Such a two-pronged approach is likely to make more impact than either strategy alone.

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