

REMISSION IN ADULTS WITH TYPE 2 DIABETES

Position statement August 2021

Why have we produced this position statement?

Diabetes UK has recognised that remission can occur in people diagnosed with type 2 diabetes, for a number of years. The Covid 19 pandemic of 2020/21 has highlighted the devastating effect of living with diabetes, and the elevated health risks of living with diabetes and overweight or obesity [1]. A key strategic outcome of Diabetes UK is to increase the numbers of people with type 2 diabetes going into remission. This position statement has been produced to set out the definition of type 2 diabetes remission and what we know and say about the ways that this might occur. It also makes some recommendations about what needs to happen to ensure wider access to interventions that support remission in people with type 2 diabetes. It is timely as we welcome the publication of an international consensus report on the definition and interpretation of remission in type 2 diabetes remission [2].

How did we develop this position?

We have reviewed the evidence and sought the views of a wide group of stakeholders. In 2017 we held a workshop attended by people with diabetes, health care professionals and researchers to inform our interim recommendations. Since then we have been working with experts from the American Diabetes Association (ADA), and the European Association for the Study of Diabetes (EASD) to agree a definition of type 2 diabetes remission.

A wider group including Diabetes UK's Council of Health Care Professionals (CHP), researchers and other clinicians were asked to comment on the final draft.

What do we say about this issue?

Key points and recommendations

- Type 2 diabetes remission is possible through **weight loss, following intensive dietary changes or bariatric surgery**
- Diabetes UK defines type 2 diabetes remission as a sustained metabolic improvement where HbA1c levels return to below 6.5% (48mmol/mol) and which is sustained for at least 3 months in the absence of glucose-lowering medications
- The health benefits of weight loss are huge, even if remission does not occur. It reduces the risk of developing other conditions and may lead to reducing or stopping blood glucose lowering medications and could reduce the risk of serious harm from coronavirus.
- As there is insufficient evidence on the impact of remission on specific diabetes complications, everyone who is in remission should continue to receive regular monitoring at least annually including retinal screening, and ongoing support for self-management, tailored to their specific needs

- We welcome and support the introduction of pilot remission services in the NHS in England and Northern Ireland and services in Scotland based on the low-calorie diet approach
- Bariatric surgery should be more widely available for people with type 2 diabetes who meet NICE criteria
- More research is needed to understand different means of going into remission and maintaining it, the long-term impact of remission on complications and remission in different population groups including children and young people with type 2 diabetes.

A note on terminology: Diabetes UK's position is that the term "remission" currently best reflects the situation where HbA1c levels return to below the diagnostic criteria for diabetes and the person is relieved of diabetes symptoms without glucose lowering medications, without downplaying the risk of relapse and essential need for ongoing review. There is currently no evidence that this state could remain permanently. For this reason, Diabetes UK does not support the use of the term "cure" and any other that suggests a permanent situation. We know that people with type 2 diabetes, and some within the healthcare system, sometimes talk about reversal of diabetes. Whilst we will sometimes use this term to engage people with the concept of remission and to ensure they are accessing our information and advice on remission we consider the term "remission" to be more accurate.

Why is remission in type 2 diabetes important?

For people with type 2 diabetes and their healthcare team, the possibility of being able to go into remission can provide motivation and hope – something to aim for. It can help to improve how people engage with their diabetes management not only because of the need to reduce the risk of complications, but also because there is a possibility of minimising the day-to-day impact of their condition. In 2018, a Diabetes UK survey of people who said they had put their type 2 diabetes into remission for any period of time, or had attempted to do so, 38% of those who had tried this said it had improved the way that they feel and a quarter (26%) had reduced their diabetes medication. Over half (51%) had reduced their blood glucose levels (HbA1c) regardless of whether they actually went into remission.

For the local health economy, there are benefits in the reduction of the cost of medications and treatment of diabetes complications. One study showed that the use of a DiRECT-style approach to remission is not only predicted to improve the life expectancy of people living with type 2 diabetes but to result in an average saving to the NHS of £1337 per person over their lifetime. Compared to standard care, the DiRECT-style approach would be cost saving within 6 years [3].

When more clinical evidence is available, it may be possible to reduce the recommended frequency of follow up and monitoring in people who are in remission.

What is type 2 diabetes in remission?

We have worked with other diabetes organisations internationally to agree consistent criteria to define diabetes remission.

We define type 2 diabetes remission as a sustained metabolic improvement:

- HbA1c levels returned below 6.5% (48mmol/mol) and sustained for at least three months without glucose-lowering medications
- In situations where an HbA1c test is determined to be an unreliable marker of chronic glycaemic control, fasting plasma glucose <7.0 mmol/L or eA1c <6.5% calculated from CGM values can be used as alternate criteria
- To evaluate the effectiveness of a remission programme, HbA1c or fasting plasma glucose levels should be measured before and no sooner than 3 months after the start of the programme and withdrawal of any glucose-lowering medication
- Subsequent testing to determine long-term maintenance of a remission should be done at least yearly thereafter.

How can people with type 2 diabetes go into remission?

Obesity remains the most potent modifiable risk factor for type 2 diabetes. Between 80- 90% of people with type 2 diabetes have obesity or overweight [4, 5]. Weight loss can improve or normalise the underlying mechanisms causing type 2 diabetes [6].

Different studies have reported various rates of remission depending on the intervention, the criteria for defining remission and the study design among other factors.

Intensive lifestyle interventions

Various dietary interventions such as low-fat diets, low-carbohydrate diets, Mediterranean diets, very low-calorie diets, and meal replacements have been used to induce weight loss in people with type 2 diabetes [7]. However, only a few studies have reported remission of type 2 diabetes through lifestyle interventions. Diabetes UK recommends an individualised approach.

The UK DiRECT study which randomised people with type 2 diabetes into a weight management programme, including a low-calorie meal replacement diet followed by a stepped food reintroduction and supportive follow up in Primary Care, reported 46% of participants were in remission after a year and 36% after two years [8,9]. Crucially, in the DiRECT study, one year remission rate of 86% was reported in participants who lost 15kg or more. This informed Diabetes UK's recommendation that people with obesity or overweight should aim for a weight loss of approximately 15kg as soon as possible after diagnosis of type 2 diabetes [7].

The recent DIADEM-1 study from Qatar which replicated the DiRECT approach in people with type 2 from the Middle East and North Africa found that 61% of participants were in

remission after a year [11]. A US non-randomised study which aimed to induce ketosis through a low-carbohydrate diet reported type 2 diabetes remission rates of 25% at year 1 and 18% at year 2 [11, 12].

Historically, the Look Ahead study, an intensive lifestyle intervention using a low-fat diet for weight loss, reported a remission rate of 11.5% after a year and 7% at 4 year follow up [13]. Another RCT which involved an intervention with a Mediterranean diet also reported a remission rate of 15% after a year and 5% at 6 year follow up [14].

It is difficult to adequately compare the results from these interventions due to the differences in characteristics of participants such as duration of diabetes, baseline BMI and HbA1c levels as well as the definition of remission used in the different studies. There are also differences in the methodology employed by the researchers. However, evidence indicates that just as different dietary approaches have been shown to induce weight loss, remission can occur using different diets. The results from these interventions also show that though remission rates are significantly higher in the intervention groups, some people in the control groups also achieved remission. These results confirm reports that remission can also occur spontaneously in usual care settings without specialist intensive intervention [14, 15]. Diabetes UK recognises that some people may attempt remission on their own and recommends that they receive support to ensure that whatever dietary approach they choose is safe and evidence based.

Remission through lifestyle interventions appears more likely in people newly diagnosed with type 2 diabetes and those with lower baseline HbA1c levels [13, 14, 15, 16]. To date, remission has occurred through weight loss in people who have obesity or overweight. However, there is ongoing research such as the ReTUNE study to understand whether a low-calorie diet can put people with type 2 diabetes, but with less weight to lose into remission [17].

There are currently some pilot remission services in England using the low-calorie diet approach which explore different ways of delivering the intervention. Some are mirroring the DiRECT approach of one to one support, some are piloting a group based intervention, and others are piloting support delivered digitally. Data from the DROPLET study [18], a Total Meal Replacement (TDR) programme with weekly behavioural support for 12 weeks and monthly support for three months also informed the pilots. We look forward to seeing the results of these and for the most effective approaches to be rolled out more widely.

Where meal replacement products are used as part of a remission intervention our position is that the NHS should provide these free to the person with type 2 diabetes.

Bariatric (metabolic) surgery

Different remission rates have been reported depending on the bariatric surgery procedure used, criteria for defining remission among other factors. An international consensus statement endorsed by 45 international diabetes associations including Diabetes UK and the ADA reported that type 2 diabetes remission occurs in about 30–60% of patients following surgery [19].

There is not enough long-term data to know whether bariatric surgery can lead to life-long remission, although remission of up to 15 years has been reported [20]. Generally, the median diabetes-free years for people with type 2 diabetes who have undergone bariatric surgery is about 8 years, depending on the procedure [19] and available data suggest fewer people remain in remission over time. Studies have reported relapse rates of approximately 20% at 3 years and 25 – 35% at 5 years post-surgery [21, 22].

Current evidence suggests that pre-operative BMI is not a strong predictor of whether surgery will lead to remission, and if relapse is likely [19, 23, 24]. Two meta-analyses and a systematic review indicate that better remission rates are obtained in younger people with higher residual beta cell function, a shorter duration of diabetes, a smaller waist circumference, higher preoperative high-density lipoprotein, lower preoperative total cholesterol, triglycerides and low-density lipoprotein levels [25, 26]. Limited evidence suggests that the risk of relapse may be associated with factors such as older age at surgery, longer duration of diabetes, poor baseline glycaemic control, baseline insulin use and female sex [22, 27]. Although some studies have confirmed the intuition that long term weight regain could predict relapse [27, 28], a more recent larger study failed to establish this association [22].

Whilst most of the long-term benefits of bariatric surgery can be attributed to weight loss, it has been suggested that some improvements in glucose control may occur independent of weight loss [29], via changes in gut hormone levels, the microbiota, bile acid metabolism, intestinal glucose metabolism and nutrient sensing [22].

NICE guidance recommends that people with type 2 diabetes who meet certain criteria should be offered bariatric surgery. We support this and would like to see more people with type 2 being offered this option as a treatment which could lead to remission. Our weight management position statement makes recommendations about widening access to all tiers of weight management services including bariatric surgery.

Insight from GPs and commissioners in England, commissioned by Diabetes UK, found that there were a number of barriers for people with type 2 diabetes to accessing bariatric surgery, including a lack of clear pathway and a lack of full provision of weight management services in some areas. Health care professionals' perceptions of bariatric surgery, its place in a treatment pathway for people with type 2 diabetes and negative views of people living obesity also impacted on referral to services where they did exist. Where there were clear pathways and good provision of weight management services people were more likely to get referred and perceptions of the benefits of bariatric surgery as a treatment for type 2 diabetes were more positive.

How should remission be discussed with a person with type 2 diabetes?

Health care professionals should provide consistent, evidence-based information to a person with type 2 diabetes about the possibility of remission, as a goal of treatment, at diagnosis and in the first few years following diagnosis. This might be particularly pertinent during discussions to start or increase blood glucose lowering medication, during significant life events and at early onset of diabetes complications as insight suggests people are more likely

to seek remission at these times. The discussions about the potential to reduce or stop blood glucose lowering medication could offer extra motivation for the person to better engage with their diabetes management and encourage maintenance of healthy lifestyle changes and weight loss.

When someone has reached remission, it will be beneficial to recognise this and the contribution made by the person to improving their health. It might be helpful to discuss how they intend to maintain the changes they have made and how their family and friends may be able to help - and also make people aware of peer support, such as that provided by Diabetes UK local groups and online forums.

It will be important to stress that little is known about how remission affects the risk of the macro and microvascular complications of type 2 diabetes in the long-term. Therefore, people should be coded as in remission (rather than resolved) to ensure that they continue to be called for annual checks including referral for retinal screening and monitoring of complications. If they have existing complications, they should be encouraged and supported to continue in current care pathways (e.g. with foot protection team). In addition, remission will need to be actively maintained. The person's need for diabetes education and continued weight maintenance should be reviewed regularly and they should be referred as appropriate if it is assessed that they could benefit, in order to maintain their diabetes in remission.

People who are in remission from type 2 diabetes should also continue to be offered free flu vaccination.

What is the impact of remission on diabetes complications?

Little is known about the effect of diabetes remission on new-onset diabetes complications or progression of existing complications. A long-term follow-up observational study found that bariatric surgery was associated with higher remission rates and fewer microvascular and macrovascular diabetes complications [25].

Although systematic reviews have suggested that bariatric surgery may protect against new cases of diabetic retinopathy [31], and its progression [32] in people with type 2 diabetes, a recent UK study has shown that bariatric surgery does not guarantee improvement in progression or prevention of diabetic retinopathy, despite improved HbA1c in 86% of people with type 2 diabetes, and 42% achieving normalised HbA1c [33]. Therefore, it is recommended by the UK National Screening Committee that people diagnosed with diabetes continue with retinal screening for life, even if they are in remission [34].

There is also limited evidence suggesting that bariatric surgery may prevent the incidence and progression of albuminuria and stop the decline of renal function [35]. However, data is limited to suggest that surgery guarantees protection against nephropathy.

Bariatric surgery has also been reported to reduce risk factors of cardiovascular disease (CVD) [19,36] and a recent observational study has also reported a significantly lower incident MACE in people with type 2 diabetes who undergo bariatric surgery [37]. Though these reports are encouraging, it is likely that that people with diabetes who attain remission

remain at higher risk of CVD complications compared to the general population so regular monitoring of CVD risk factors including lipids and blood pressure is recommended [19].

For these reasons, Diabetes UK recommends that all people who reach remission should be monitored at least annually for complications until further evidence is developed. The same targets for risk factors such as blood pressure and lipids should apply.

How does remission apply to people with type 1 diabetes?

People with type 1 diabetes who undergo islet cell or whole pancreas transplantation may come off insulin injections at least for a short time. However, type 1 diabetes is an autoimmune condition and that underlying pathophysiology never goes away. Therefore, our current discussions of remission apply specifically to people with type 2 diabetes.

How does remission apply to children with type 2 diabetes?

Type 2 diabetes appears to be more aggressive in children than in adults, leading to a more rapid decline of beta-cell function [38]. Though some studies have reported the effect of bariatric surgery in children with type 2 diabetes, remission of type 2 diabetes in children is not widely reported in literature. However, bariatric surgery in children is uncommon in the UK, and NICE recommends this as an option only in centres that have dedicated paediatric facilities for caring for children and young people with diabetes [39]. Therefore, more work is needed before the issues, and long-term implications, of remission in the context of children with type 2 diabetes can be adequately discussed.

Recommendations for further work to support roll out and implementation

Remission of type 2 diabetes should be systematically coded on GP systems and audited through the National Diabetes Audit and similar, to inform further research and monitoring.

Diabetes UK's priorities for type 2 diabetes remission research has been discussed with various stakeholders including researchers, people with type 2 diabetes and other experts in the field. Findings from these discussions have been published [41]. There is also a need for further research into:

- the longer-term outcomes of people who have achieved remission. The impact on diabetes complications requires particular investigation.
- the factors associated with likelihood of relapse and those factors that support maintenance of remission.
- the issues, and long-term implications, of remission in children with type 2 diabetes.

The policy implications of remission coding on people with diabetes and the health care system also need to be further explored.

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