

## Diabetes UK interim position statement on remission in adults with Type 2 diabetes

Diabetes UK recognises that remission can be achieved in people previously diagnosed with Type 2 diabetes. This interim position statement has been produced to address the lack of consistency and the confusion amongst healthcare professionals, people with diabetes and the general public about the terminology used to describe this and the claims made about the effectiveness of various interventions. Diabetes UK considers that the use of the term 'remission' currently best reflects the situation where someone is relieved of diabetes symptoms and the need for management with blood glucose lowering medications, without downplaying the risk of relapse and essential need for ongoing review. There is currently no evidence that this state could be achieved permanently. For this reason Diabetes UK does not support the use of the term 'cure' and any other that suggests a permanent situation.

In drafting this statement, the evidence was reviewed and the views of a wide group of stakeholders were sought through face-to-face meetings and email/telephone correspondence. A workshop attended by people with diabetes, healthcare professionals, researchers and Diabetes UK staff was convened to review the draft and seek consensus on recommendations. A wider group including Diabetes UK's Council of Health Care Professionals (CHP), researchers and other clinicians were also asked to comment on the final draft.

Although, Diabetes UK had originally set out to recommend criteria for defining and coding diabetes remission, this was not possible as there was no consensus. Therefore, Diabetes UK is planning further work to ensure consistency.

### Key points

- Type 2 diabetes remission is possible through intensive lifestyle changes or bariatric surgery.
- Diabetes UK recognises that there are different criteria for defining diabetes remission, and will work with relevant stakeholders during the first half of 2018 to agree a consistent criteria for the UK.
- The benefits of intensive lifestyle interventions and bariatric surgery are huge, even if remission is not achieved, and may lead to reduction or stopping blood glucose lowering medications as well as reducing risk factors for other conditions.
- As there is insufficient evidence on the impact of remission on diabetes complications, everyone who achieves remission should continue to receive regular monitoring at least annually including retinal screening, and ongoing support for self-management tailored to their specific needs.
- More research is needed to understand the long term impact of remission on complications and the impact on local health economies.

## Why is remission in Type 2 diabetes important?

For people with Type 2 diabetes and their healthcare team the possibility of achieving remission can provide motivation and hope – something to aim for. It can help to improve how people engage in their diabetes management, not only because of the need to reduce risk of complications, but also because there is a possibility of minimising the day-to-day impact of their condition.

For the local health economy there are benefits in reduction of the cost of medications and diabetes complications. When more evidence is available, it may be possible to reduce recommended frequency of follow up and monitoring in people who have achieved remission.

## What is Type 2 diabetes in remission?

Different criteria have been used in research and clinical practice including the American Diabetes Association's criteria<sup>1</sup>, which differentiates between partial and complete remission<sup>2</sup>, and one recently proposed by a UK research group<sup>3</sup>.

Achieving UK wide consensus on the criteria for remission is critical as implementing these criteria will have a huge impact on local organisations and the care of people with diabetes. Diabetes UK is planning a wider discussion to agree consistent criteria to define diabetes remission, and coding, in the UK, following extensive discussions with people with diabetes, GPs, diabetes consultants, other healthcare professionals and researchers.

## How can remission be achieved in people with Type 2 diabetes?

Obesity remains the most potent modifiable risk factor for Type 2 diabetes. Between 80–90% of people with Type 2 diabetes are overweight or obese<sup>4, 5</sup>. Weight loss can improve or normalise the underlying mechanisms causing Type 2 diabetes<sup>6</sup>.

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

Intensive lifestyle interventions that result in weight loss have been reported to lead to about 10–15% remission rates at one-year follow-up<sup>7</sup>. However, evidence for long-term remission following lifestyle interventions is anecdotal and limited.

Various dietary interventions such as low fat diets, low carbohydrate diets, Mediterranean diets, very low-calorie diets, and meal replacements have been used to achieve weight loss in people with Type 2 diabetes<sup>8</sup>. Diabetes UK recommends an individualised approach.

The Counterbalance study tested the theory that normal blood glucose levels could be achieved through a very low-calorie diet and showed that those people with shorter duration Type 2 diabetes who achieved normal glucose control maintained this for at least six months<sup>9</sup>. However, results from the larger long-term DiRECT study may be able to confirm longer-term remission in routine Primary Care using a low-calorie diet and supportive follow up<sup>10</sup>.

The Look Ahead study, which aimed at weight loss through intensive lifestyle intervention, reported a remission rate of 7% at four-year follow-up<sup>11</sup>. The Predimed study which involved an intervention with Mediterranean diets also reported remission rate of 5% at six-year follow-up<sup>12</sup>. Although remission rates in both the Look Ahead and Predimed studies were significantly higher in the intervention groups, some people in the control groups also achieved remission<sup>11, 12</sup>. These results confirm reports that remission can also be achieved in usual care setting without specialist intensive intervention<sup>12, 13</sup>.

Remission through lifestyle interventions appears more likely in people newly diagnosed with Type 2 diabetes and those with lower baseline HbA1c<sup>9, 11-13</sup>.

## Bariatric (metabolic) surgery

Different remission rates have been reported depending on the 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<sup>15</sup>.

To date, there is no reliable data to view surgery as a permanent cure, although remission of up to 15 years has been reported<sup>16</sup>. Generally, the median diabetes-free years for people with Type 2 diabetes undergoing surgery is about eight years, depending on the procedure<sup>15</sup> and available data suggest an erosion of remission over time. Some studies have reported relapse rates of approximately 20% at three years and 25–35% at five years<sup>17, 18</sup>.

Current evidence suggests that BMI per se is not a strong predictor of diabetes remission success from surgery or relapse<sup>15, 19</sup>. Instead, two meta-analyses and a systematic review have suggested 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 and fewer other complications of shorter durations<sup>20, 21</sup>. 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 gender<sup>18, 22</sup>. Although some studies have confirmed the intuition that long term weight regain could predict relapse<sup>22, 23</sup>, a more recent larger study failed to establish this association<sup>18</sup>.

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<sup>24</sup>, via changes in gut hormones, microbiota, bile acid metabolism, intestinal glucose metabolism and nutrient sensing<sup>18</sup>.

## How should remission be discussed with a person with Type 2 diabetes?

Once there are agreed criteria for remission, healthcare professionals could consistently talk to a person with Type 2 diabetes about the possibility of remission, as a goal of treatment, at diagnosis and at regular reviews. This might be particularly pertinent during discussions to start or increase blood glucose lowering medication. 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 achieved remission it will be beneficial to recognise this and the contribution made by the person to improving their health. However, it is always important to stress that Type 2 diabetes is largely a cardiovascular condition and that little is known about how remission affects risk of the macro and microvascular complications in the long-term. Therefore, all should still continue to have annual checks including referral for retinal screening and monitoring of complications, and if they have existing complications, they should be encouraged and supported to continue in current care pathways (eg, with the 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.

## What is the impact of remission on diabetes complications?

Little is known about the actual effect of diabetes remission on new onset diabetes complications or progression of existing complications. A long-term follow-up observational study has concluded that bariatric surgery was associated with higher remission rates and fewer microvascular and macrovascular diabetes complications<sup>25</sup>.

Although systematic reviews have suggested that bariatric surgery may protect against new cases of diabetic retinopathy<sup>26</sup>, and its progression<sup>27</sup> 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<sup>28</sup>. Therefore, it is recommended that people diagnosed with diabetes continue with retinal screening for life, even if they are in remission<sup>28, 29</sup>.

There is also limited evidence suggesting that bariatric surgery may prevent the incidence and progression of albuminuria and stop the decline of renal function<sup>30</sup>. However, data is limited to suggest that surgery guarantees protection against nephropathy.

Bariatric surgery has also been reported to reduce risk factors of cardiovascular diseases (CVD)<sup>15, 31</sup> although evidence for CVD events as primary outcome is lacking<sup>15</sup>. It is reasonable to assume 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<sup>15</sup>.

For these reasons Diabetes UK recommends that all people who achieve 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, this discussion of remission applies 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 more destructive decline of beta-cell function<sup>32</sup>. Remission of Type 2 diabetes in children is not widely reported in literature, with the exception of a few studies that have reported the effect of bariatric surgery. 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<sup>33</sup>. 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**

There is a need for UK-wide consensus on how diabetes remission is defined. Diabetes UK is planning this piece of work for the first half of 2018 to involve all the relevant stakeholders.

When we have agreed criteria, remission of Type 2 diabetes should be systematically coded and audited to inform further research and monitoring.

There is 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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