

# Is remission of type 2 diabetes mellitus real?

**T**ype 2 diabetes mellitus has traditionally been considered a progressive condition, with an inexorable loss of pancreatic  $\beta$ -cell function resulting eventually in insulin dependency. Advances in management can flatten this trajectory with reversal of hyperglycaemia and dyslipidaemia improving pancreatic  $\beta$ -cell function,<sup>1</sup> at least temporarily. This can be achieved by augmenting insulin secretion and/or reducing endogenous insulin requirements. Strategies to reduce endogenous insulin requirements include ameliorating insulin resistance, reducing carbohydrate intake, or increasing glucose disposal. Such strategies are achieved with combination pharmacotherapy and modification of health-related behaviours, making a glycated haemoglobin (HbA<sub>1c</sub>) level of  $\leq 6.5\%$  a feasible and durable target.

It is also possible to achieve and maintain an HbA<sub>1c</sub> level of  $\leq 6.5\%$  for a variable period without pharmacotherapy by a substantial ( $> 10\%$ ) reduction in adiposity achieved via metabolic surgery<sup>2</sup> or aggressive caloric restriction.<sup>3-6</sup> Diabetes Australia, together with the Australian Diabetes Society, in accordance with international consensus<sup>7-9</sup> defines remission as achieving an HbA<sub>1c</sub> level of 6.5% or less and maintaining it for at least 3 months without glucose-lowering therapy. This is not a cure and does not imply normal glucose metabolism. The underlying genetic, environmental and comorbid factors resulting in the initial diagnosis of type 2 diabetes persist. Furthermore, innate physiology makes a reduction in adiposity achieved by caloric restriction alone extremely difficult to maintain. Without additional intervention, it is expected that for most individuals a progressive increase in HbA<sub>1c</sub> above 6.5% will ultimately occur.<sup>3,6</sup>

## Benefits and risks and of aiming for remission

Tight control of glycaemia slows, prevents or reverses microvascular diabetes complications. To date, there are no data that remission per se confers additional benefit. Inattention to cardiovascular risk factor management may be deleterious, particularly in individuals who feel their condition is less serious while in remission.

For people with obesity, particularly if severe and with suboptimally or poorly controlled type 2 diabetes, weight loss of 10–15% of bodyweight is generally necessary for diabetes remission to occur. This magnitude of weight loss has other benefits on weight-related comorbidities, including cardiovascular disease, obstructive sleep apnoea, metabolic liver disease, and osteoarthritis.

Although most weight loss is fat mass, loss of lean body mass also occurs, which will be cumulative if there are cycles of weight loss and weight gain, and abrogated but not eliminated by resistance activity. Frail individuals should generally not be encouraged to attempt remission if significant weight loss is required.

One of the major benefits of the concept of remission is to provide hope and motivation to people with type 2 diabetes.<sup>10</sup> Distress may improve with a sense of control of the condition. There are also potential licensing and insurance benefits in not having a diagnosis of overt diabetes. On the other hand, not achieving or not sustaining remission may be perceived as individual failure and increase diabetes-related distress.<sup>11-13</sup>

## Methods of achieving remission

### Nutrition and lifestyle interventions

Weight loss, carbohydrate restriction and physical activity each have independent benefits for glycaemia. Generally, for remission to occur, weight loss is necessary.

**Intensive lifestyle intervention.** In the Look AHEAD study, an intensive lifestyle intervention resulted in remission in 11.5% and 7.3% of individuals at year 1 and 4, respectively, compared with 2% at both time points in the control group.<sup>3</sup>

**Very low calorie diets.** The United Kingdom-based DiRECT study<sup>6,14</sup> used a total diet replacement formula (825–853 kcal/day) for 12–20 weeks, followed by stepped food re-introduction (2–8 weeks), and then structured support for weight loss maintenance. The 1-, 2-, and 5-year remission rates were 46%, 36% and 11% in the intervention group compared with 24%, 3% and 3.4%, respectively, in the usual care group. Sustained remission related to the magnitude and maintenance of weight loss. There were 50% less, predominantly diabetes related, serious adverse events in the intervention group. Only 28% of eligible individuals elected to enter the study so this is probably a best case scenario in a selected motivated population.

**Therapeutic carbohydrate restriction.** The more carbohydrate intake is restricted, the greater the benefit for glycaemia and dyslipidaemia.<sup>4,5</sup> Restriction of carbohydrate intake to the point of ketosis may aid short term maintenance through suppression of hunger. Although there are independent benefits of weight reduction and carbohydrate restriction, the differences in the glycaemic effects of ketogenic, Mediterranean, moderate carbohydrate, and low glycaemic index diets were only significantly related to the mean weight change.<sup>5,15,16</sup> The Mediterranean diet has the best data currently for longer term cardiovascular outcomes.<sup>17</sup> A diet where processed foods, sugared drinks, and alcohol are minimised or eliminated will achieve substantial carbohydrate reduction.

### Metabolic surgery

Metabolic surgery is indicated for people with type 2 diabetes and body mass index  $\geq 30 \text{ kg/m}^2$ .<sup>18</sup> The optimal procedure is a Roux-en-Y gastric bypass. Remission occurs in over 80% of patients at 2–3 years,<sup>19-21</sup> and in one small study, maintenance of remission was reported in 38% of patients at 10 years.<sup>19</sup>

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## Pharmacological interventions

By the current definition, remission cannot exist while glucose-lowering drug therapy is continued. However, drug therapy can allow some recovery of  $\beta$ -cell function that can persist for a period after cessation of drug therapy.<sup>22</sup> Glucagon-like peptide 1 (GLP-1) receptor agonists, and newer even more powerful therapies — such as dual GLP-1 receptor and glucose-dependent insulinotropic polypeptide (GIP) agonists; triple agonists of receptors for GLP-1, GIP and glucagon; and combinations of GLP-1 and amylin receptor agonists — can reduce body weight by up to 20%.<sup>23</sup> Although bariatric surgery has been found to confer greater weight loss than GLP-1 receptor agonists, the improvements in glycaemia are similar.<sup>24</sup> Sustained benefit requires ongoing medication use.

## Factors affecting achieving and maintaining remission

Currently, bariatric surgery is associated with the best data for durability of diabetes remission,<sup>25-27</sup> predictors of which are shorter duration of diabetes (<6 years), preserved  $\beta$ -cell function, and weight loss at 2 years.<sup>28</sup>

Maintaining long term nutritional modulation is notoriously difficult and requires substantial practical and emotional support. Most people losing 10–15% weight will regain almost all of it by 5 years without adjunctive pharmacotherapy or metabolic surgery.<sup>29</sup>

In adults, type 1 diabetes is frequently misdiagnosed as type 2 diabetes — up to 39% in one study.<sup>30</sup> Such people and those with monogenic diabetes, type 3c (insulin deficient due to primary pancreatic disease such as pancreatitis) diabetes, and hybrid diabetes with irreversible insulin deficiency generally will not achieve remission without transplantation.

Realistic expectations are critical to a nuanced discussion regarding potential diabetes remission.

## Future directions

Evidence that diabetes remission translates into better outcomes of diabetes-related complications and other comorbidities is needed. Real world translation of proof-of-concept research studies and use in minority populations including Indigenous Australians are required.

All modalities used to induce remission can be applied with benefit in individuals across the spectrum of glycaemic disturbance. Remission should not be seen as the sole goal of these interventions — primary prevention of type 2 diabetes in at-risk individuals, and improvement in glycaemic control and other cardiovascular risk factors in all people living with type 2 diabetes, particularly if optimal lifestyle behaviours are adopted, will have substantial health benefits. Reducing HbA<sub>1c</sub> levels from 9% to 7% is likely to achieve more health improvement than dropping them from 6.7% to 6.4%.

Greater and more equitable access to metabolic surgery, particularly for those with severe obesity, judicious use of weight- and glucose-lowering pharmacotherapy,

and support for nutritional modulation are required. The optimal approach to individualising management, support and empowerment of patients remains to be determined. Furthermore, providing optimal public health messaging and a supportive food environment remains a translational challenge despite advances in knowledge.

Glucose-lowering therapies such as metformin, sodium-glucose cotransporter 2 inhibitors and GLP-1 receptor agonists are increasingly used for non-glycaemic benefits, including weight control, with withdrawal contra-indicated irrespective of remission. Studies are required to demonstrate the benefit-risk ratio of adjunctive pharmacotherapy to maintain remission, and to determine whether a lower HbA<sub>1c</sub> cut-off should be applied.

## Summary

Remission of type 2 diabetes, as currently defined, is achievable with a variety of management modalities but is not a cure. The benefits of remission, as opposed to those of weight loss and improvement in glycaemia, on health outcomes are not yet established. A reduction in carbohydrate intake is beneficial, feasible and effective without the need to be ketogenic, and is most easily achieved by elimination of processed foods and alcohol. Unintended consequences such as excess loss of lean body mass, suboptimal overall nutrition, and distress from unrealistic or overpromised expectations need to be avoided. Similarly, we must avoid a singular focus on remission and being medication free to the exclusion of overall cardiac risk reduction and attention to detection and management of other comorbidities including sleep disorders, depression and anxiety, health literacy, and social determinants of health.

Structured programs to initiate and provide support need to be embedded in primary care, where most potential remission candidates are seen, and must be supported by public health initiatives relating to community-wide improvement in nutrition and physical activity.

Based on current data relating to durability of remission, adjunctive pharmacotherapy will be required for most patients, and wider and more equitable availability of metabolic surgery for those with the most severe obesity must be prioritised.

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