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Cite this as: *BMJ* 2025;388:r40
http://doi.org/10.1136/bmj.r40

SGLT2 inhibitors and dietary calorie restriction for type 2 diabetes remission

Combined strategy is effective but questions remain

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The view that the hyperglycaemia associated with type 2 diabetes is inexorably progressive was challenged by the publication of the DiRECT study in 2018.[1 2] Through a mean weight loss of 10 kg achieved by a period of total diet replacement (often referred to as the "soups and shakes" diet), 46% of participants achieved remission of type 2 diabetes at 12 months. The longer term sustainability of the remission achieved is less clear, with 36% still in remission at two years in the DiRECT study but only 13% at five years with continued support.[3 4] The English NHS Type 2 Diabetes Path to Remission Programme provides access to similar interventions in the real world for people within six years of diagnosis of type 2 diabetes and body mass index >27 (appropriately adjusted according to ethnicity), with 12 month remission rates of approximately 30%.[5] Around 35 000 people have now been referred into the national programme.

The linked study by Liu and colleagues (doi:10.1136/bmj-2024-081820) investigated the combined effect of the sodium-glucose cotransporter-2 (SGLT-2) inhibitor dapagliflozin with calorie restriction on remission of type 2 diabetes over 12 months.[6] They used a moderate calorie restriction (reduction by 500-750 kcal/day) for participants in both arms, which they argue is more practical and acceptable than the more restrictive total diet replacement approach adopted in DiRECT. Participants were randomised 1:1 to dapagliflozin or placebo. This multicentre randomised controlled trial was conducted across China, including 328 patients with type 2 diabetes of less than six years' duration, body mass index >25, and age between 20 and 70 years. Metformin was the only antihyperglycaemic drug allowed at baseline. Wraparound behavioural change support was deployed, with two monthly glycated haemoglobin (HbA1c) measurements assessing remission over 12 months. Remission of type 2 diabetes was defined as HbA1c <6.5% and fasting glucose of <7.0 mmol/L in the absence of any glucose lowering medication for at least two months. Metformin use at baseline was continued together with either placebo or dapagliflozin for at least four months. If glycaemic thresholds were met after this point, metformin was stopped first followed by discontinuation of dapagliflozin or placebo.

Remission of type 2 diabetes was achieved in 44% of participants in the calorie restriction plus dapagliflozin group over a 12 month period (median 9 months) compared with 28% in those on calorie restriction alone (risk ratio 1.56, 95% confidence interval 1.17 to 2.09). Changes in body weight were modest (−5.0 kg in the combined group versus −3.2 kg in the calorie restriction alone group). The study also showed benefits of dapagliflozin on body fat mass, systolic blood pressure, high density lipoprotein cholesterol, and triglyceride. Two serious adverse events (admission to hospital for urinary tract infections) were reported in the dapagliflozin group, with mild and moderate adverse events being similar across the two groups.

The study highlights important considerations around the remission levels in both study groups. In the calorie restriction plus dapagliflozin arm, despite a mean body weight loss of only 5 kg, remission levels were comparable to those observed at 12 months in the DiRECT trial, in which a 10 kg mean weight loss was achieved.[2] In the calorie restriction alone arm, despite a mean weight loss of only 3.2 kg, remission levels were also impressive and comparable to those seen in the real world in the NHS Type 2 Diabetes Path to Remission Programme with a much greater calorie restriction (just over 800 kcal/day) and mean weight loss of 9.4 kg. Could participants' baseline characteristics have influenced these results? Early evaluation of the NHS Type 2 Diabetes Path to Remission Programme shows that shorter duration of type 2 diabetes and lower baseline HbA1c are independent predictors of higher remission rates.[5] Liu and colleagues report a short median duration of diabetes of 0.3 years and 0.2 years in the dapagliflozin and placebo arms, respectively.[6] This is a notably shorter duration than in both the DIADEM-I and DiRECT trials in addition to the Path to Remission Programme, the last two of which also reported slightly higher baseline HbA1c values.[2 5 7]

Metformin was taken by approximately half of the participants in each study arm and continued for at least four months, in contrast to the DiRECT trial in which this was stopped on initiation of total diet replacement. We also note the use of a shorter two month time off glucose lowering drugs criterion in the definition of remission. Although previously defined in the DiRECT trial,[2] this short duration could potentially include higher numbers of transient diagnoses of remission. Ethnicity in the linked study may also have influenced remission levels, although this is less clear; in an adult Chinese population remission of type 2 diabetes was achieved in 47% of participants following three months of intermittent calorie restriction, despite body weight loss of only 5.93 kg and a mean duration of diabetes of more than six years.[8]

The marked increase in type 2 diabetes remission levels with the addition of dapagliflozin to moderate calorie restriction is notable, showing the efficacy of this combination strategy. Mechanistically, SGLT-2

inhibitor driven glycosuria results in a more selective energy deficit that mimics the effects of dietary calorie restriction on energy metabolism, possibly permitting less dietary calorie restriction for a similar effect size.[9]

Total diet replacement interventions for remission of type 2 diabetes have been successfully implemented at a population level for eligible and willing people with recent onset of type 2 diabetes.[5] A challenge is long term sustainability of remission related to maintenance of weight loss,[10] and a combination strategy may be attractive in the new era of obesity pharmacotherapy.[11] Aside from the potent glycosuric effects of SGLT-2 inhibitors, newer incretin mimetics achieve potent weight loss and high levels of normoglycaemia.[12 13]

Should such glucose lowering drugs be discontinued at the point of remission, and is the loss of cardiovascular/renal protection offset by the delay in type 2 diabetes? Can specific drug mechanisms be harnessed for a more individualised approach to remission of type 2 diabetes? Despite the low adverse event rate highlighted in this study, the drug safety profile in a combined strategy also needs to be evaluated. The optimal balance of lifestyle components needs to be considered; achieving remission through less intense calorie restriction may prove more inclusive at the population level and may also serve to reduce interventional unit cost. Despite these uncertainties, SGLT-2 inhibitors are now co-first line drugs (with metformin) for many patients with type 2 diabetes.[14] The study by Liu and colleagues supports more research into combined approaches to achieving successful and sustainable remission of type 2 diabetes.[6]

Competing interests: The BMJ has judged that there are no disqualifying financial ties to commercial companies. The authors declare the following other interests: JV was the national clinical director for diabetes and obesity at NHS England from April 2013 to September 2023 and in this role was directly involved in the establishment of the NHS Type 2 Diabetes Path to Remission Programme in England.

Provenance and peer review: Commissioned; not externally peer reviewed.

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