

CARBOHYDRATE RESTRICTION IN THE MANAGEMENT OF TYPE 2 DIABETES

The Evidence

- 1. RCTs**
- 2. Systematic reviews**
- 3. Critical reviews, narrative reviews**
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- 5. Pre-diabetes**
- 6. Digital interventions**
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*Carbohydrate restriction has become an increasingly popular treatment method in the management of type 2 diabetes, metabolic syndrome and pre-diabetes.
There is considerable evidence to support its use.*

1. RCTs

There have been 22 randomised control studies comparing the use of low carb diets compared to low fat diets in type 2 diabetes. The first study was published in 2004. The studies range in length of follow up from three months to two years.

In all 22 studies, the low carb diets were associated with a reduction in HbA1c, the primary outcome measure used. In 19/22 studies, the reduction in HbA1c was greater in the low carb versus the low fat diets, and 14/19 were statistically significant. None of the three studies in which the low fat showed greater reduction in HbA1c were significant.

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2. Systematic Reviews and meta-analyses

Twenty two systematic reviews/meta-analyses have looked at the relationship between low carb diets and T2D. Two recent (2022) studies have been published.

The study by Jahedi et al (2022) evaluated the dose-dependent effect of carbohydrate restriction in patients with type 2 diabetes. Fifty trials with 4291 patients were identified. At 6 months, compared with a carbohydrate intake between 55%–65% and through a maximum reduction down to 10%, each 10% reduction in carbohydrate intake reduced HbA1c, fasting plasma glucose and body weight. There were also reductions in total cholesterol, LDL cholesterol, triglycerides, and systolic blood pressure (SBP). Levels of HbA1c, FPG, body weight, TG, and SBP decreased linearly with the decrease in carbohydrate intake from 65% to 10%.

Apekey et al (2022) reviewed twenty-two RCTs comprising 1391 mostly obese participants with T2D. At 3 months, a LC vs. LF diet significantly reduced HbA1c levels, mean difference (95% CI) of -0.41% (-0.62, -0.20). LC diet significantly reduced body weight, BMI, fasting insulin and triglycerides and increased total cholesterol and HDL-C levels at the short-to-intermediate term, with a decrease in the requirement for antiglycaemic medications at intermediate-to-long term

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3. Critical reviews, narrative reviews

A number of critical and narrative reviews have also been published.

Of particular interest is the study by Brown et al published in 2021. A group of specialist dietitians and medical practitioners was convened, supported by the British Dietetic Association and Diabetes UK, to discuss dietary approaches to T2DM and consequently undertook a review of the available clinical trial and practice audit data regarding dietary approaches to remission of T2DM.

They stated that “current available evidence suggests that a range of dietary approaches, including low energy diets (mostly using TDR) and low carbohydrate diets, can be used to support the achievement of euglycaemia and potentially remission. The most significant predictor of remission is weight loss and, although euglycaemia may occur on a low carbohydrate diet without weight loss, which does not meet some definitions of remission, it may rather constitute a ‘state of mitigation’ of T2DM. This technical point may not be considered as important for people living with T2DM, aside from that it may only last as long as the carbohydrate restriction is maintained. The possibility of actively treating T2DM along with the possibility of achieving remission should be discussed by healthcare professionals with people living with T2DM, along with a range of different dietary approaches that can help to achieve this.”

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4. Other studies

In addition to the RCTs, various other types of studies (non-randomised, cohort etc) have been published.

Of particular interest is the paper by Unwin et al. Dr David Unwin is a GP in England who had been managing his patients with T2D with a low carb approach for a number of years. In 2020 he published his results.

“By 2019, 128 (27%) of the practice population with T2D and 71 people with prediabetes had opted to follow a lower carbohydrate diet for a mean duration of 23 months. For patients with T2D, the median (IQR) weight dropped from of 99.7 (86.2, 109.3) kg to 91.4 (79, 101.1) kg, $p < 0.001$, while the median (IQR) HbA1c dropped from 65.5 (55, 82) mmol/mol to 48 (43, 55) mmol/mol, $p < 0.001$. For patients with prediabetes, the median (IQR) HbA1c dropped from 44 (43, 45) mmol/mol to 39 (38, 41) mmol/mol, $p < 0.001$. Drug-free T2D remission occurred in 46% of participants. In patients with prediabetes, 93% attained a normal HbA1c. Since 2015, there has been a relative reduction in practice prescribing of drugs for diabetes leading to a T2D prescribing budget £50 885 per year less than average for the area”.

Another paper from David Unwin published in 2023 showed that *“a low-carbohydrate diet-based approach was able to achieve major weight loss with substantial health and financial benefit. It resulted in 20% of the entire practice T2D population achieving remission and for 97% of those interested in the approach, sustained for an average of 33 months. Those patients who started with ‘younger’ diabetes and lower HbA1c were far more likely to achieve remission with 77% of those adopting a low-carbohydrate approach in the first year of their T2D achieved remission. Those in the non-remission, ‘mitigation’ group achieved unexpectedly greater, clinically important improvements in diabetic control with the diet. This represents an important ‘window of opportunity’ for further investigation. People with established long-term T2D, which may be poorly controlled could benefit from looking carefully at reducing sugar and starchy carbohydrates”.*

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5. Pre-diabetes

There are a small number of studies looking at the association of pre-diabetes and low carb diet.

McKenzie and colleagues followed 96 patients with prediabetes (age 52 (10) years; 80% female; BMI 39.2 (7.1) kg/m²) who received a continuous remote care intervention focused on reducing hyperglycemia through carbohydrate restricted nutrition therapy for two years in a single arm, prospective, longitudinal pilot study. Two-year retention was 75% (72 of 96 participants). 51% of participants (49/96) met carbohydrate restriction goals as assessed by blood beta-hydroxybutyrate concentrations for more than one-third of reported measurements. Estimated cumulative incidence of normoglycemia (HbA1c < 5.7% without medication) and type 2 diabetes (HbA1c ≥ 6.5% or <6.5% with medication other than metformin) at two years were 52.3% and 3%, respectively.

McKenzie AL, Athinarayanan SJ, McCue JJ, et al. Type 2 diabetes prevention focused on normalization of glycemia: a two-year pilot study. *Nutrients* 2021, 13, 749. <https://doi.org/10.3390/nu13030749>

In a 2022 study by Dorans et al at an academic medical center in New Orleans, Louisiana. 150 patients with HbA1c at pre-diabetic levels were randomized to a low-carbohydrate diet intervention or usual diet for six months. Compared with the usual diet group, the low-carbohydrate diet intervention group had significantly greater 6-month reductions in HbA1c (net difference, -0.23%; 95% CI, -0.32% to -0.14%; P < .001), fasting plasma glucose (-10.3 mg/dL; 95% CI, -15.6 to -4.9 mg/dL; P < .001), and body weight (-5.9 kg; 95% CI, -7.4 to -4.4 kg; P < .001).

Dorans KS, Bazzano LA, Qi L, et al. Effects of a low-carbohydrate dietary intervention on hemoglobin a1c: a randomized clinical trial. *JAMA Netw Open*. 2022 Oct 3;5(10):e2238645. doi: 10.1001/jamanetworkopen.2022.38645.

In an earlier study by Rohling et al (2020) 141 persons with prediabetes were randomised into either a control group with lifestyle intervention only or a lifestyle intervention group accompanied with a low carb diet. Compared with the control group, significantly more intervention participants converted to normoglycemia after 52 weeks (50% vs. 31%; p < 0.05)

Röhling M, Kempf K, Banzer W, et al. Prediabetes conversion to normoglycemia is superior adding a low-carbohydrate and energy deficit formula diet to lifestyle intervention. A 12-month subanalysis of the ACOORH Trial. *Nutrients*. 2020 Jul 7;12(7):2022. doi: 10.3390/nu12072022. PMID: 32646010; PMCID: PMC7400892.

6. Digital interventions

More recently, digitally delivered programs in both the UK and the US have shown efficacy in managing Type 2 diabetes.

(a) RCTs

In this pilot feasibility study, overweight adults (body mass index ≥ 25) with type 2 diabetes (glycated hemoglobin [HbA_{1c}] 6.5%-9.0%) were randomly assigned to a 32-week online intervention (n=12) or an online diet program based around a plate method diet (n=13) to assess the impact of each intervention on glycemic control and other health outcomes. At 32 weeks, participants in the intervention group reduced their HbA_{1c} levels more (0.8%) than participants in the control group (0.3%). More than half of the participants in the intervention group (6/11, 55%) lowered their HbA_{1c} to less than 6.5% versus 0% (0/8) in the control group (P=.02). Participants in the intervention group lost more weight (12.7 kg) than participants in the control group (3.0 kg). Participants in the intervention group lowered their triglyceride levels (-60.1 mg/dL) more than participants in the control group (-6.2 mg/dL). Dropout was 8% (1/12) and 46% (6/13) for the intervention and control groups, respectively

Saslow LR, Mason AE, Kim S, et al. An online intervention comparing a very low-carbohydrate ketogenic diet and lifestyle recommendations versus a plate method diet in overweight individuals with type 2 diabetes: a randomized controlled trial. *J Med Internet Res* 2017, 19, 16, doi:10.2196/jmir.5806

A Chinese study in subjects with pre-diabetes reported that mobile app-based low-carbohydrate dietary guidance led to significant improvements in postprandial hyperglycemia. Additionally, the low-carbohydrate dietary guidance had a beneficial impact on weight, BMI, body fat mass, percentage of body fat, visceral fat area, triglyceride levels, dietary habits and exercise/physical activity

Chen XY, Su HH, Kunii D, et al. The effects of mobile-app-based low-carbohydrate dietary guidance on postprandial hyperglycemia in adults with prediabetes. *Diabetes Therapy* 2020, 11, 2341-2355, doi:10.1007/s13300-020-00906-x.

(b) Non-RCTs

The study from the UK by Saslow et al (2018) reviewed results from the digital Low Carb program on *diabetes.co.uk* which has had over 400,000 participants. Of the 743 participants in the study with a starting HbA_{1c} at or above the type 2 diabetes threshold of 6.5%, 195 (26.2%) reduced their HbA_{1c} to below the threshold while taking no glucose-lowering medications or just metformin. Of the participants who were taking at least one hypoglycemic medication at baseline, 40.4% (289/714) reduced one or more of these medications. Almost half (46.40%, 464/1000) of all participants lost at least 5% of their body weight. Overall, glycemic control and weight loss improved, especially for participants who completed all 10 modules of the program. For example, participants with elevated baseline HbA_{1c} ($\geq 7.5\%$) who engaged with all 10 weekly modules reduced their HbA_{1c} from 9.2% to 7.1% (P<.001) and lost an average of 6.9% of their body weight (P<.001).

Saslow LR, Summers C, Aikens JE, Unwin DJ Outcomes of a digitally delivered low-carbohydrate Type 2 diabetes self-management program: 1-year results of a single-arm longitudinal study *JMIR Diabetes* 2018;3(3):e12

A further study by Summers et al demonstrated that glycemic control and weight loss improved on the digital program, particularly for participants who completed more than nine core lessons in the program over 12 months. The mean HbA_{1c} went from 58.8 mmol/mol at baseline to 54.0 mmol/mol, representing a mean reduction of 4.78 mmol/mol (SD 4.60; $t_{31}=5.87$; $P<.001$). Results showed an average total body weight reduction of 4.17%, with an average weight reduction of 3.85 kg (SD 2.49; $t_{31}=9.27$; $P<.001$) at the 12-month follow-up point.

Summers C, Tobin S, Unwin D. Evaluation of the low carb program digital intervention for the self-management of type 2 diabetes and prediabetes in an NHS England general practice: single-arm prospective study. *JMIR Diabetes*. 2021 Sep 9;6(3):e25751. doi: 10.2196/25751.

In the USA, the digitally delivered **Virta Health** program has published results annually comparing a cohort of patients who self-selected to participate in the metabolic and continuous care intervention (CCI) for T2D and a comparison group of patients who self-selected to participate while receiving their usual care (UC) from their own medical providers and diabetes education program.

The one year results showed HbA_{1c} declined from 59.6 to 45.2 mmol mol⁻¹, weight declined 13.8kg and T2D medication prescription other than metformin declined from 56.9% to 29.7. Insulin therapy was reduced or eliminated in 94% of users; sulfonylureas were entirely eliminated in the CCI. No adverse events were attributed to the CCI.

Hallberg SJ, McKenzie AL, Williams PT, et al. Effectiveness and safety of a novel care model for the management of type 2 diabetes at 1 year: an open-label, non-randomized, controlled study. *Diabetes Therapy* 2018;9:583-612, doi:10.1007/s13300-018-0373-9.

The 2 year results demonstrated use of any glycemic control medication (excluding metformin) among participants declined (from 55.7 to 26.8%) including insulin (-62%) and sulfonylureas (-100%). There was also resolution of diabetes (reversal, 53.5%; remission, 17.6%) in the treatment group.

Athinarayanan SJ, Adams RN, Hallberg SJ, et al. Long-term effects of a novel continuous remote care intervention including nutritional ketosis for the management of type 2 diabetes: a 2-year non-randomized clinical trial. *Front Endocrinol* 2019 Jun 5;10:348. doi: 10.3389/fendo.2019.00348

And after 3.5 years.

This abstract by McKenzie et al showed that 50.2% of diabetes medications and 71.4% of diabetes medications other than metformin were discontinued. 45.5% (65/143) of participants achieved HbA_{1c} <6.5% with either no medication (34/65, 52%) or only metformin (31/65, 48%) at 3.5 y; 37.8% of participants maintained this status from 1 through 3.5 y of treatment. 22% of participants achieved diabetes remission at 3.5 y, and 17.5% of participants maintained remission status from 2 through 3.5 y of treatment. This demonstrates that clinically meaningful improvements across multiple markers of metabolic risk can be sustained in patients with T2D who selected treatment with this treatment regimen for 3.5 y.

McKenzie A, Athinarayanan S, Adams R, et al. A continuous remote care intervention utilizing carbohydrate restriction including nutritional ketosis improves markers of metabolic risk and reduces diabetes medication use in patients with type 2 diabetes over 3.5 years. *J Endocr Soc.* 2020 May 8;4(Suppl 1):SUN-LB113. doi: 10.1210/jendso/bvaa046.2302. PMID: PMC7208790

And after 5 years

At five years, there were persistent improvements in weight from 116.4 to 107.6 kg, fasting insulin from 25.8 to 24.5 mIU/L (, and HOMA-IR from 9.1 to 6.6 (all adjusted p-values <0.05). Total diabetes medications were reduced 46.6%, and 59.9% excluding metformin were deprescribed. The percent of patients prescribed diabetes medications significantly decreased at 5 years (from 85.2% to 71.3%; p<0.01). Despite less medication use, HbA1c improved from 7.5 to 7.2% (-0.3%, 95%CI [-0.6, 0.0], unadjusted p-value<0.05) .

They concluded that *“over 5 years follow-up, the VLCI with CRC showed excellent retention, sustained clinically significant weight loss, and stable glycemic control with reduced dependency on antidiabetes medications.”*

Athinarayanan SJ , Vantieghem M, Mckenzie AI, et al. Five-year weight and glycemic outcomes following a very-low-carbohydrate intervention including nutritional ketosis in patients with type 2 diabetes. *Diabetes* 2022;71(Supplement_1):832-P

7. Defeat Diabetes

Defeat Diabetes is a digital program available as an app or web-based developed by a group of Australian medical specialists and dietitians. It is a comprehensive program which educates and provides practical advice about following a restricted carbohydrate approach in type 2 diabetes. Thus far, more than 8000 subscribers have followed the program.

The effectiveness of the program is being measured in two ways, by annual surveys of subscribers, and by a formal research study at a La Trobe university.

Defeat Diabetes conducted a survey of the initial cohort of subscribers from January 2021 after three months adherence to the Defeat Diabetes app-based program.

The results from the survey were as follows:

- 63% of those with type 2 diabetes were in remission, and all others had reported significant decreases in blood glucose levels
- 100% of participants previously taking insulin were able to discontinue its use
- nearly 30% of participants had reduced or stopped diabetes management medications
- 100% of subscribers who tracked waist measurement reporting a decrease in waist size with 80% reporting a waistline measurement decrease of five centimetres or more (a clothing size)
- 62% of subscribers reported an overall feeling of health and wellbeing improvement after three months
- 84% of participants declared that the program had changed their views on what 'healthy eating' means
- 38 per cent of participants felt an increase in energy levels after three months.

A second survey was performed in 2023

- 66% who recorded their HbA1c reduced their HbA1c from >6.5 to <6.4
- 68% of men who recorded their HbA1c reduced their HbA1c from >6.5 to <6.4
- 63% with prediabetes who recorded their HbA1c were able to achieve an HbA1c of <5.9
- 41% of members who recorded their HbA1c reduced their HbA1c from >6.5 to <6.4 and were able to stop or reduce medication
- 92% of members who recorded their weight achieved weight loss, on average 8 kg
- 27% of members who recorded their weight were able to lose 10 kg or more
- 82% of members who recorded their waistline measurements were able to achieve a reduction, on average 6cm
- 25% of members who recorded their waistline measurements lost 10cm or more

Defeat Diabetes has commissioned a research project under the supervision of Professor George Moschonis, Director of the Human Nutrition & Dietetics Research Lab at *La Trobe University*, Melbourne. The study is entitled "*Effectiveness of digitally delivered continuous*

care intervention (Defeat Diabetes) on the self-management of type 2 diabetes. A 12-month single-arm, pre-post intervention study” and is being conducted by PhD student Despina Kolivas. The protocol has been published.

Kolivas D, Fraser L, Schweitzer R, Brukner P, Moschonis G. Effectiveness of a digitally delivered continuous care intervention (defeat diabetes) on type 2 diabetes outcomes: a 12-month single-arm, pre–post intervention study. *nutrients*. 2023; 15(9):2153. <https://doi.org/10.3390/nu15092153>

The study is being supported by 140 GPs around Australia who have agreed to refer patients to the study and monitor their progress. Recruitment is nearly complete.

Preliminary three-month data from 49 subjects has shown :

- improvement of glycemic control in 39/49
- 26 of the 49 have reduced their HbA1c levels to non-diabetic levels - they are in remission
- average weight loss has been 4.3 kg in three months
- many have reduced their diabetes and/or blood pressure medications