



What predicts drug-free type 2 diabetes remission? Insights from an 8-year general practice service evaluation of a lower carbohydrate diet with weight loss

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ABSTRACT

Background Type 2 diabetes (T2D) is often regarded as a progressive, lifelong disease requiring an increasing number of drugs. Sustained remission of T2D is now well established, but is not yet routinely practised. Norwood surgery has used a low-carbohydrate programme aiming to achieve remission since 2013.

Methods Advice on a lower carbohydrate diet and weight loss was offered routinely to people with T2D between 2013 and 2021, in a suburban practice with 9800 patients. Conventional 'one-to-one' GP consultations were used, supplemented by group consultations and personal phone calls as necessary. Those interested in participating were computer coded for ongoing audit to compare 'baseline' with 'latest follow-up' for relevant parameters.

Results The cohort who chose the low-carbohydrate approach (n=186) equalled 39% of the practice T2D register. After an average of 33 months median (IQR) weight fell from 97 (84–109) to 86 (76–99) kg, giving a mean (SD) weight loss of –10 (8.9)kg. Median (IQR) HbA1c fell from 63 (54–80) to 46 (42–53) mmol/mol. Remission of diabetes was achieved in 77% with T2D duration less than 1 year, falling to 20% for duration greater than 15 years. Overall, remission was achieved in 51% of the cohort. Mean LDL cholesterol decreased by 0.5 mmol/L, mean triglyceride by 0.9 mmol/L and mean systolic blood pressure by 12 mm Hg. There were major prescribing savings; average Norwood surgery spend was £4.94 per patient per year on drugs for diabetes compared with £11.30 for local practices. In the year ending January 2022, Norwood surgery spent £68 353 per year less than the area average.

Conclusions A practical primary care-based method to achieve remission of T2D is described. 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. It appears that T2D duration <1 year represents an important window of opportunity for achieving drug-free remission of diabetes. The approach can also give hope to those with poorly controlled T2D who may not achieve remission, this group had the greatest improvements in diabetic control as represented by HbA1c.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ The idea of drug-free remission of type 2 diabetes (T2D) gives hope to many and can be achieved in different ways.
- ⇒ Sugary and starchy foods worsen blood glucose control so a low-carbohydrate diet is a logical first step.

WHAT THIS STUDY ADDS

- ⇒ Advice and ongoing guidance on a low-carbohydrate diet in primary care can achieve improved diabetic control 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.
- ⇒ Those in the non-remission, 'mitigation' group achieved unexpectedly greater, clinically important improvements in diabetic control with the diet

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Seventy-seven per cent of those adopting a low-carbohydrate approach in the first year of their T2D achieved remission. 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.

INTRODUCTION

In 2021, the *British Dietetic Association* published a review of dietary strategies for drug-free remission of type 2 diabetes (T2D),¹ which stated that 'total dietary replacements and low-carbohydrate diets have been demonstrated as being effective in facilitating weight loss and remission of T2D'. However, meta-analyses do not always support a focus on low-carbohydrate diets to achieve either weight loss or remission of diabetes.^{2,3} There is a need for hard data on outcomes of such an approach and to examine what clinical aspects help it succeed.

In this paper, we examine real-world data from a cohort based in a UK primary care clinic offering a low-carbohydrate approach to people with T2D from 2013 to 2021. The physiological mechanisms behind remission induced by dietary weight loss were first demonstrated in 2011.⁴ Since then the idea of drug-free T2D remission has gained international momentum.⁴⁻⁷ We now have an international consensus on the definition of remission; a glycated haemoglobin (HbA1c) <48 mmol/mol sustained for >3 months in the absence of diabetes medication.⁸ Earlier practice audits showed significant improvements in: HbA1c,^{9,10} lipids and blood pressure (BP) (this despite 'deprescribing' 20% of antihypertensive drugs),¹¹ renal function¹² and liver function.¹³ Not only were major health improvements demonstrated but also substantial drug-budget savings.¹⁰

This analysis of our 8-year dataset explores which factors predict remission, its durability and the glycaemic control of those not achieving remission.

METHODS

Advice on lowering dietary carbohydrate was offered routinely by our team of nine specially trained GPs and three practice nurses to patients with T2D (defined as HbA1c >48 mmol/mol on two occasions) starting in March 2013 (online supplemental file 1, low-carbohydrate protocol). Our protocol includes important information around the deprescribing of both drugs for BP and T2D; both BP and blood glucose were often found to improve to an extent requiring a medication review.¹¹ Checking and discussing body weight was the first step in every consultation, then the low-carbohydrate diet was offered as an option alongside clear and simplified explanations of key physiological principles emphasising: that good diabetic control is about avoiding the damage caused by blood sugars spikes, that 'time in range' matters,¹⁴ a high blood sugar is often a reflection of foods eaten recently, glucose and insulin levels change in response to different foods, starchy carbohydrates comprise many glucose molecules causing significant blood sugar elevation and how weight loss was part of the process. (online supplemental file 2).

We view high blood sugars as an interesting puzzle rather than a problem, one to be explored collaboratively with the patient. In cases where weight or HbA1c began to climb after an initial improvement we observed early on that most patients had actually increased their carbohydrate consumption (carb creep). Often a quick telephone call would motivate change.

Many of our less experienced clinicians worried that talking about obesity could be considered 'fat shaming.' We encouraged them to explain that weight loss could really help peoples' health and to ask if they were interested to work collaboratively to achieve this. In this way, we supplied relevant information and then checked if the person wanted to go ahead before giving more specific advice.

For those who opted for the lower carbohydrate programme, baseline weight and blood results were ascertained alongside dietary advice as part of routine GP or practice nurse consultations. Weight was measured at each visit, the level of ongoing support was tailored to patient choice and clinical need. In addition to 10 min 'one-to-one' appointments (we estimate an average of three consultations per patient, per year) the practice offered optional 90 min evening group sessions, approximately every 6 weeks. Group sessions included relatives who were encouraged to attend as some patients relied on others for food shopping or cooking. Group sessions provided a forum for people to offer practical support to others and training new staff. On average 25 patients attended each session. From the onset of the COVID-19 pandemic, these group sessions were hosted as online Zoom meetings. This enabled us to send a link to these meetings inviting every person in the practice with T2D. This was particularly important for patients wanting a 'refresher'.

Educational resources were produced to support patients and staff. The low-carbohydrate diet sheet (online supplemental file 3) outlines suitable sources of food. Glycaemic load data were also presented to encourage a reduced intake of sugary and starchy foods. For example, replacing breakfast cereals, rice, bread and potatoes with, full-fat dairy, eggs, green leafy vegetables, meat, fish, berries and nuts (with sensitivity to each patient's socio-cultural dietary needs and preferences). From 2018, staff training was formalised through completion of a Royal College of General Practitioners e-learning module on T2D and the glycaemic index, written by one of the authors.¹⁵

This paper forms part of an ongoing audit of service provision. An iterative process necessitating regular updates of the protocol and practice-wide sharing of 'what works' based on audits like this. As a result, our methods have improved since 2013. The tendency for results to deteriorate after initial promise led to us focusing on effective maintenance of dietary change. We suggested people look ahead to the challenges of holidays, Christmas and birthdays, times when so many diets fail. We encouraged patients to look out for weight gain at these times and take action. Computer generated graphs of all metrics measured were sent out as patient feedback (the reception staff call this 'The happy post'). Around 2016, we became aware of another possible behavioural factor causing our patients to regain weight: 'food addiction'.¹⁶ In response, we supported people to identify and completely avoid their 'trigger foods'.

Further behaviour changes were enabled by encouraging participants to consider their individual hopes and health goals, the resources available to them, setting realistic next steps and enabling the individual to notice what works for them (online supplemental file 4).¹⁷ We would highlight the power that the hope of drug-free remission brings to people with T2D. This model was key to maintaining the motivation of our clinical team and helping it

evolve. Finally, in terms of behaviour change we learnt to ask how people learn best: Did they prefer a leaflet, book or App?

Exclusion criteria were severe mental illness, terminal illness and eating disorders

Routine clinical data were collected from March 2013 to April 2021. Baseline measurements of weight and BP were made at the surgery and blood tests (HbA1c, lipid profiles) by the local NHS phlebotomy clinic. Frequency of blood tests depended on clinical need and risk assessment as part of standard care. Some patients found it challenging to fit fasting blood tests into their lifestyle patterns, so our results include a greater number of incomplete data sets for lipid profiles than other measures.

Statistical analyses were performed with R V.4.0.2. Summaries of baseline and follow-up data are shown as median and the IQR (IQR, 25th percentile, 75th percentile) for non-normally distributed continuous variables like age, weight, HbA1c, lipid profile and BP. More normally distributed continuous variables like duration of diet are presented as mean (SD). Comparisons between baseline and latest follow-up continuous variables were made using the Wilcoxon signed rank test for paired samples. A $p < 0.05$ was considered statistically significant.

Baseline and latest follow-up distributions of data are presented as box and whisker plots, the box represents the median value and the IQR, the red dot indicates the mean value and the upper and lower whiskers indicate either, the minimum/maximum value, or 1.5 times the IQR.

Linear regression models were fitted with HbA1c reduction as the outcome and baseline HbA1c as the predictor. Logistic regression models were fitted with remission occurrence as the outcome and gender, baseline age, baseline weight, baseline HbA1c and duration of T2D as predictors.

RESULTS

By the end of the 8-year period (March 2013–April 2021), Norwood surgery had a T2D disease register of 473 people, of whom 186 (39%) chose the low-carbohydrate approach. Of these, 114 (61%) were male, and the median (IQR) age at baseline was 63 (54, 73) years. Mean (SD) duration of follow-up was 33 (27) months. 37.6% of the cohort were people within 1 year of diagnosis.

For the whole cohort commenced on the low-carbohydrate programme median (IQR) weight fell from 97 (84–109) to 86 (76–99) kg, giving a mean (SD) weight loss of -10 (8.9) kg; $p < 0.001$. Median (IQR) HbA1c dropped from 63 (54–80) to 46 (42–53) mmol/mol; $p < 0.001$. The median (IQR) triglyceride dropped from 2.1 (1.4–3.2) to 1.4 (1.0–1.9) mmol/L; $p < 0.001$. The median (IQR) systolic BP dropped from 140 (134–150) to 132 (122–138) mm Hg; $p < 0.001$. The median (IQR) total cholesterol decreased from 4.9 (4.1–5.7) to 4.3 (3.6–5.0) mmol/L; $p < 0.001$. The median (IQR) total cholesterol

to High-Density Lipoprotein (HDL) ratio decreased from 4.0 (3.0–5.0) to 3.9 (3.0–4.4); $p < 0.001$ (table 1, figure 1 and online supplemental file 5).

Data for baseline and latest follow-up both for remission and non-remission subcohorts are compared further down in table 1. The mean (SD) weight change was -12 (9.2) kg for the remission group compared with -8.6 (8.4) kg for the non-remission group (non-significant). No patients achieved remission without some weight loss, though in three patients it was one kg or less. The distribution of weight change between the remission and non-remission groups is shown in figure 2. In the remission group HbA1c dropped by a mean (SD) of 17 (15) mmol/mol compared with 24 (21) mmol/mol for the non-remission group. The remission group also started with a lower baseline HbA1c (figure 3 and table 2). This group had been on the diet for a mean (SD) of 37 (42) months compared with 31 (23) months for the non-remission group.

Data on baseline figures comparing the remission group with the non-remission group are shown in table 2. Only two metrics showed significant difference: Baseline median (IQR) HbA1c for the remission group was 54 (50–62) mmol/mol compared with 75 (65–91) mmol/mol for the non-remission group ($p < 0.001$). Baseline median (IQR) for time since diagnosis was 2 (0.0–68) months for the remission group compared with 72 (28–127) months for the non-remission group ($p < 0.001$). The remission group were more likely to be diagnosed recently and have a significantly lower baseline HbA1c. All other baseline metrics: age, weight, blood lipids and BP were not significantly different between remission and non-remission groups.

A linear regression model fitted with HbA1c reduction as the outcome and baseline HbA1c as the predictor demonstrated a highly significant relationship $R^2 = 0.74$; $p < 0.0001$ (figure 4 and online supplemental file 6). Those starting with the highest HbA1c were more likely to achieve the greatest improvements in HbA1c but were less likely to achieve remission (logistic regression, online supplemental file 7). Figure 4 also shows that 178 patients showed an improved HbA1c, only 5 (3%) had a worse result at latest follow-up.

Recent diagnosis (< 1 year) of diabetes was an important predictor of remission (see figure 5, online supplemental file 7). In the first year after diagnosis 77% of those given low-carbohydrate advice achieved a HbA1c of < 48 mmol/mol while not taking any diabetic medication. The comparable figures for established T2D were 35%, 31%, 44% and 20% for durations of 1–5, 5–10, 10–15 and greater than 15 years. By April 2021, 94 people had achieved remission, this was 51% of those choosing a low-carbohydrate approach and 20% of the total practice T2D disease register (table 3).

Prediction of remission with logistic regression models looking at baseline data on HbA1c, weight, age, gender and time since diagnosis (online supplemental files 9 and 10) showed that only a lower baseline HbA1c and less time

Table 1 Comparing baseline and latest follow-up data for 186 patients with T2D advised on a low-carbohydrate diet, with breakdown into two subgroups; 94 patients who achieved remission and 92 patients who did not

	Baseline measure median (IQR)	Latest follow-up median (IQR)	Difference Mean (SD)	P value	Matched pairs n (%)
1. Cohort of 186 T2D participants who chose a low-carbohydrate diet mean (SD) duration of diet: 33 (27) months mean (SD) time from diagnosis to diet start: 64 (69) months					
Age (years)	63 (54–73)	–	–	–	–
Weight (kg)	97 (84–109)	86 (76–99)	–10 (8.9)	<0.001	181 (97)
HbA1c (mmol/mol)	63 (54–80)	46 (42–53)	–21 (19)	<0.001	183 (98)*
Serum cholesterol (mmol/L)	4.9 (4.1–5.7)	4.3 (3.6–5.0)	–0.5 (0.9)	<0.001	107 (58)
HDL cholesterol (mmol/L)	1.1 (1.0–1.3)	1.2 (1.0–1.5)	+0.1 (0.3)	0.002	114 (61)
Total chol/HDL ratio	4.0 (3.0–5.0)	3.9 (3.0–4.4)	0.5 (0.9)	<0.001	102 (58)
Calculated LDL cholesterol (mmol/L)	3.6 (2.9–4.5)	3.1 (2.5–3.6)	–0.5 (0.9)	<0.001	100 (54)
Triglyceride (mmol/L)	2.1 (1.4–3.2)	1.4 (1.0–1.9)	–0.9 (1.2)	<0.001	108 (58)
Systolic BP (mm Hg)	140 (134–150)	132 (122–138)	–12 (16)	<0.001	128 (69)
Diastolic BP (mm Hg)	80 (78–90)	78 (70–80)	–5.8 (9.7)	<0.001	128 (69)
2. Cohort of 94 T2D participants achieving remission mean (SD) duration of diet: 35 (31) months Mean (SD) time from diagnosis to diet start: 43 (65) months					
Age (years)	63 (54–72)	–	–	–	–
Weight (kg)	96 (84–111)	83 (74–100)	–12 (9.2)	<0.001	90 (96)
HbA1c (mmol/mol)	54 (50–62)	43 (39–45)	–17 (15)	<0.001	91 (97)*
Serum cholesterol (mmol/L)	5.0 (4.0–5.4)	4.2 (3.6–5.1)	–0.4 (1.0)	0.002	48 (51)
HDL cholesterol (mmol/L)	1.1 (1.0–1.3)	1.3 (1.0–1.6)	+0.2 (0.3)	<0.001	51 (54)
Total chol/HDL ratio	4.2 (3.1–5.0)	4.0 (3.0–4.4)	–0.5 (0.9)	0.001	46 (49)
Calculated LDL cholesterol (mmol/L)	3.6 (2.8–4.1)	3.1 (2.5–3.6)	–0.5 (1.1)	0.001	43 (46)
Triglyceride (mmol/L)	1.9 (1.3–3.0)	1.3 (0.9–1.7)	–0.9 (1.3)	<0.001	46 (49)
Systolic BP (mm Hg)	140 (136–155)	132 (121–140)	–14 (18)	<0.001	63 (67)
Diastolic BP (mm Hg)	80 (78–90)	76 (70–80)	–7 (10)	<0.001	63 (67)
3. Cohort of 92 T2D participants not achieving remission mean (SD) duration of diet: 31 (23) months Mean (SD) time from diagnosis to diet start: 84 (68) months					
Age (years)	62 (55–73)	add data	–	–	–
Weight (kg)	97 (86–108)	89 (79–99)	–8.6 (8.4)	<0.001	91 (99)
HbA1c (mmol/mol)	75 (65–91)	54 (49–60)	–24 (21)	<0.001	92 (100)
Serum cholesterol (mmol/L)	4.8 (4.2–5.8)	4.3 (3.6–4.8)	–0.5 (0.9)	<0.001	59 (64)
HDL cholesterol (mmol/L)	1.2 (1.0–1.3)	1.1 (1.0–1.4)	0.0 (0.2)	0.315	63 (68)
Total chol/HDL ratio	4.0 (3.0–5.1)	3.8 (2.9–4.6)	0.5 (1.0)	<0.001	56 (61)
Calculated LDL cholesterol (mmol/L)	3.5 (2.9–4.7)	3.1 (2.4–3.7)	–0.6 (0.8)	<0.001	57 (62)
Triglyceride (mmol/L)	2.2 (1.6–3.2)	1.6 (1.1–2.4)	–0.8 (1.2)	<0.001	62 (67)
Systolic BP (mm Hg)	140 (132–149)	132 (124–138)	–11(13)	<0.001	65 (71)
Diastolic BP (mm Hg)	80 (76–85)	78 (70–80)	–4.1 (8.9)	<0.001	65 (71)
*HbA1c is known for all participants at latest follow-up for classification as ‘in remission’, however, baseline HbA1c is not known for three participants. BP, blood pressure; HbA1c, Glycated Haemoglobin; HDL, High-Density Lipoprotein; LDL, Low-Density lipoprotein ; T2D, type 2 diabetes.					

since diagnosis of T2D were good predictors of remission. Taken together these two factors could predict remission with an accuracy (95% CI) of 79% (72% to 84%), 73% sensitivity, 85% specificity.

Interrogation of the Openprescribing website for the year ending January 2022 revealed that of the 16 local GP practices that make up Southport and Formby Clinical Commissioning Group Norwood Surgery spent £68 353 less on drugs for diabetes than is average for the area (online supplemental file 11).

DISCUSSION

In our cohort of 186 patients on the lower carbohydrate programme for an average of 33 months, average weight fell by 10 kg and HbA1c by 21 mmol/mol, with significant reductions in Low-Density Lipoproteine(LDL) cholesterol, triglyceride, systolic and diastolic BP. HDL cholesterol increased significantly. Together these form some of the major risk factors not just for T2D but also for cardiovascular disease. T2D remission was achieved by 51% of the cohort, 20% of the practice T2D disease register.

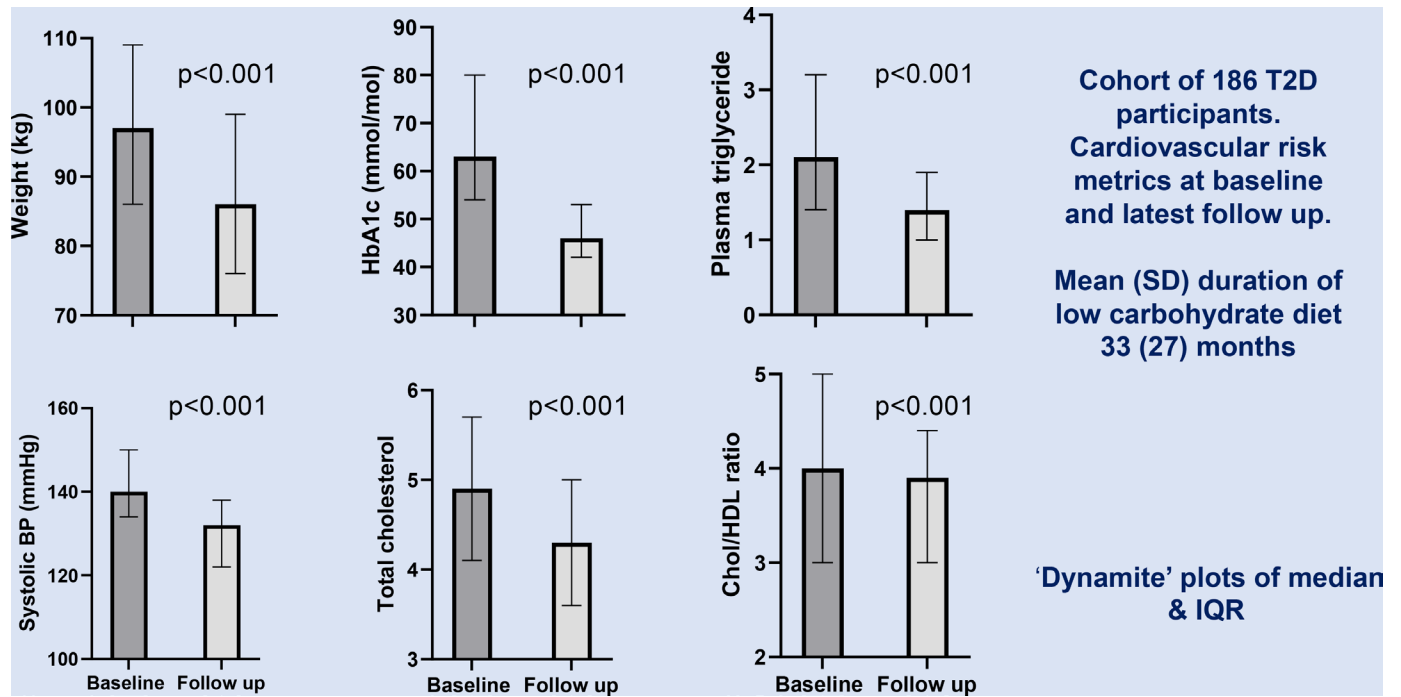


Figure 1 Change in weight, metabolic parameters and systolic blood pressure in the cohort of 186 patients with T2D followed up for an average of 33 months. BP, blood pressure; T2D, type 2 diabetes. HDL High-Density Lipoprotein

These outcomes are very different from those reported in many low-carbohydrate diet studies and reasons must be considered. The striking observation is the substantial fall in weight, not always seen in studies of this dietary approach.^{23 18} Weight loss was observed in the only other study of a low-carbohydrate diet which achieved good rates of remission of T2D.⁷ Delivery by a trusted health professional and frank discussion of the importance of weight loss would appear to have been important in bringing about the observed effects. Consistent long-term management was achieved by the primary care team.

Ongoing support is essential in preventing a return to old habits. It is possible that for some people food, much like nicotine and alcohol may be addictive.¹⁶ This may explain why highly processed foods can be so challenging to give up permanently.¹⁹ We have found the idea of food addiction can help people better understand their relationship with food. Ongoing benefits from this approach depend on sticking with the diet and long-term weight loss. One of our patients commented 'this is a lifestyle rather than a diet'. Our programme is diet focused, the addition of exercise may well improve results further.²⁰ An important part of the programme is the continued monitoring of weight allowing early detection of 'slipping back'. For the most people, increasing weight and HbA1c is simply a reflection of 'carb creep', clinicians should recognise this. It is not that the diet itself has failed, it is a failure of dietary adherence. For many people, this situation simply requires a phone call to ask 'have you any idea why your blood has become more sugary?' Such close personal follow-up was observed to be effective. We found that most people knew that carbs had crept back and realised they needed to return to what had worked

before. This is where our open-access group work via Zoom helps. Those needing a refresher can join without an appointment. Rarely, we have seen the worrying scenario of rising HbA1c despite significant weight loss. Clearly missed diagnosis of type 1 diabetes or pancreatic cancer should be considered. We have also learnt that anticipating and discussing challenging situations such as Christmas and holidays in advance helped our patients to plan *before* problems arose. For the many whose control slips, we have found it is helpful to ask afterwards 'What

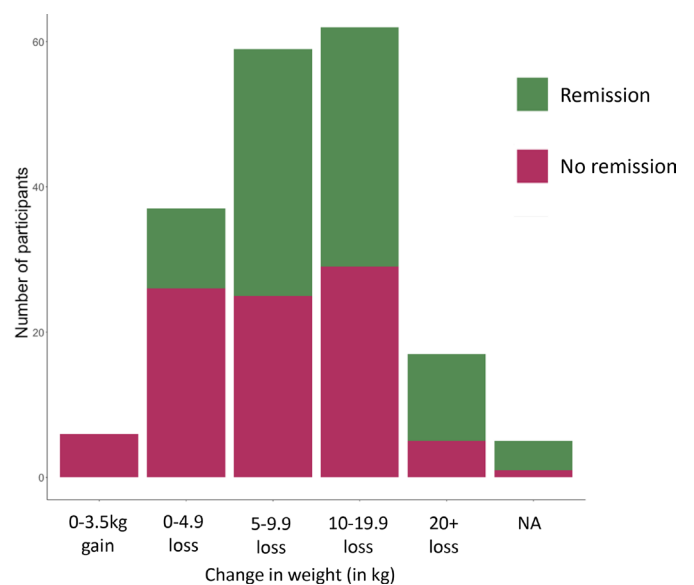
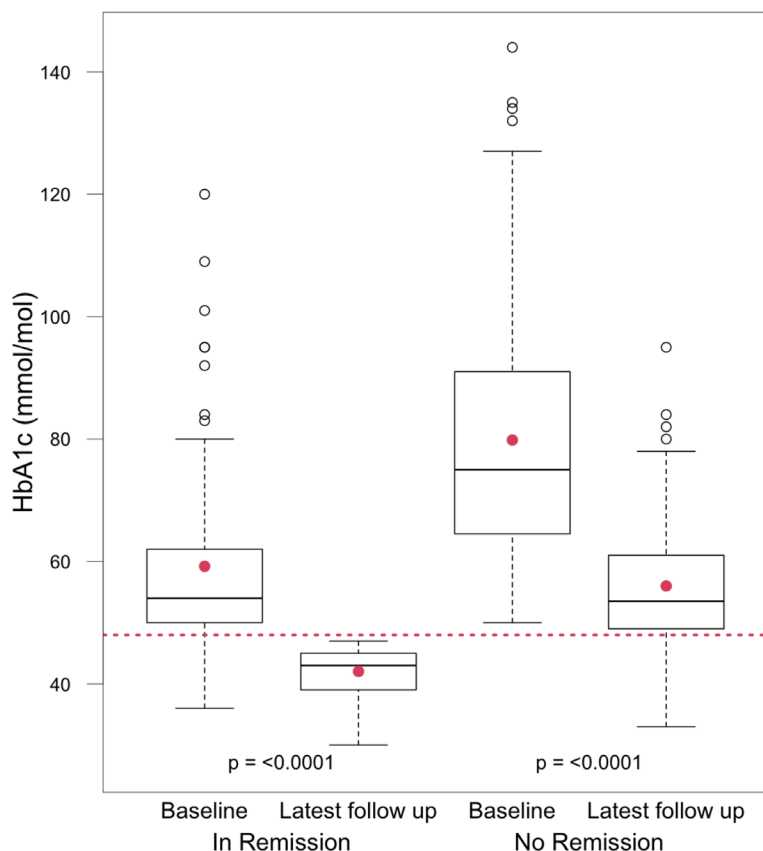


Figure 2 Number of patients divided into those who achieve remission and those who do not plotted against change in weight (in kg). NA, not applicable.



- 1. Those who achieve remission start with a lower average HbA1c.
- 2. Those who do not achieve remission show a greater improvement in HbA1c

The horizontal dotted line is at 48 mmol/mol. Individuals below this line may have achieved remission

Figure 3 Baseline and latest follow-up HbA1c figures in mmol/mol divided into remission and no-remission groups shown as box and whisker graphs. Mean duration of the low-carbohydrate diet 33 months. HbA1c, Glycated Haemoglobin

could you do differently next time?’. With empathy and ongoing support our mistakes can be an opportunity to learn.

An essential component of our success appears to be the offer of hope while supporting people to consider different approaches to T2D. It may seem challenging

to enthuse those with long-standing T2D who have poor diabetic control. However, previous qualitative research suggests that changing to a dietary approach to manage diabetes is well accepted, particularly in people with T2D for up to 6 years.^{21 22} Although we found remission rates to be lower in those with longstanding T2D, those in this

Table 2 Comparing baseline data for a cohort of 186 people with T2D who chose a low-carbohydrate diet segregated into: (1) the group who go on to achieve remission; (2) the group who do not achieve remission

Baseline metric	Remission group n=94 on the diet for a mean(SD) of 35 (31) months Median (IQR)	Non-remission group n=92 on the diet for a mean(SD) of 31 (23) months Median (IQR)	P value
Time since diagnosis (Months)	2.0 (0.0–68)	72 (28–127)	<0.001
HbA1c (mmol/mol)	54 (50–62)	75 (65–91)	<0.001
Age (years)	63 (54–72)	62 (55–73)	0.903
Weight (kg)	96 (84–111)	97 (86–108)	0.850
Serum cholesterol (mmol/L)	5.0 (4.0–5.4)	4.8 (4.2–5.8)	0.817
HDL cholesterol (mmol/L)	1.1 (1.0–1.3)	1.2 (1.0–1.3)	0.799
Calculated LDL cholesterol (mmol/L)	3.6 (2.8–4.1)	3.5 (2.9–4.7)	0.736
Triglyceride (mmol/L)	1.9 (1.3–3.0)	2.2 (1.6–3.2)	0.058
Systolic BP (mm Hg)	140 (136–155)	140 (132–149)	0.307
Diastolic BP (mm Hg)	80 (78–90)	80 (76–85)	0.097

BP, blood pressure; HbA1c, Glycated Haemoglobin; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; T2D, type 2 diabetes.

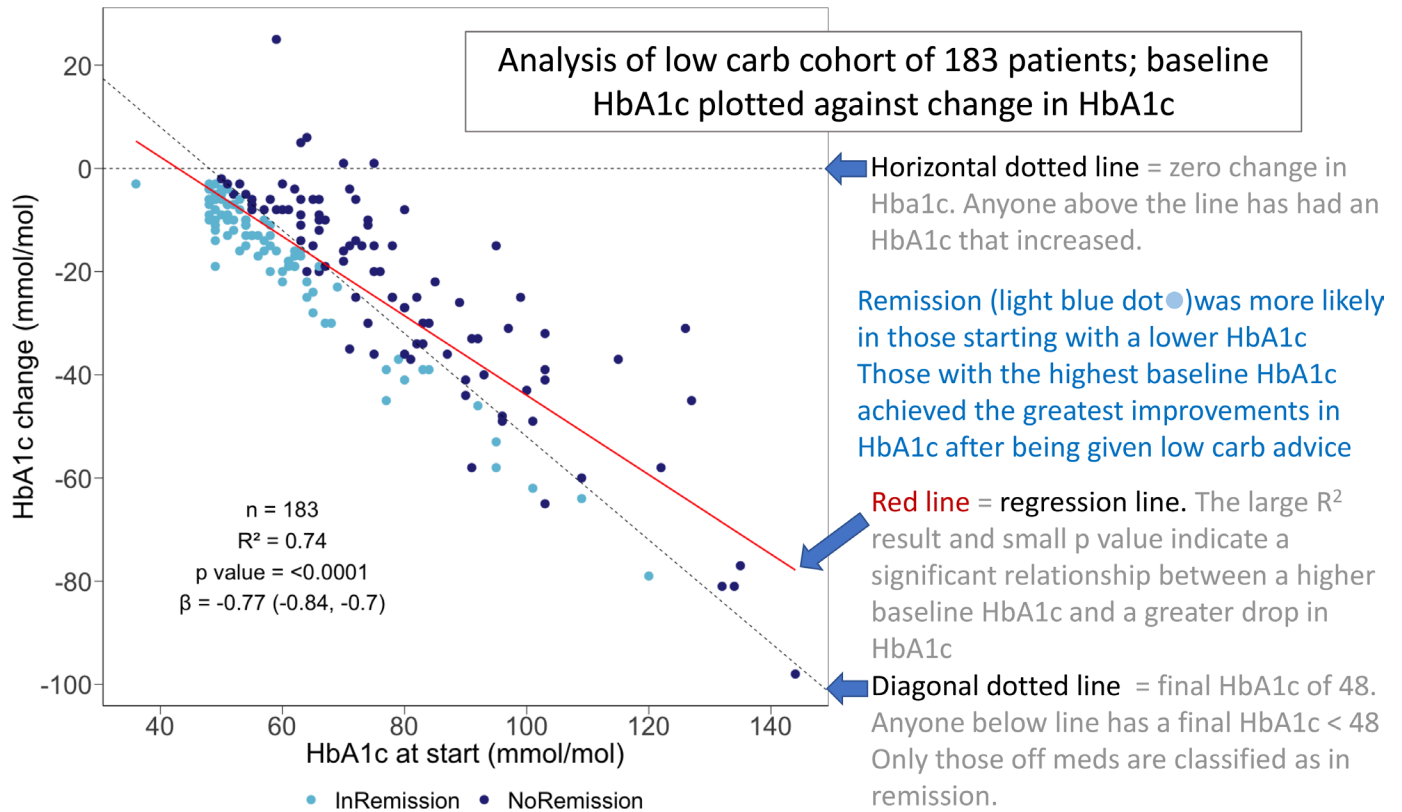


Figure 4 Regression analysis of the improvement in HbA1c over an average of 33 months with respect to baseline HbA1c. HbA1c, glycated haemoglobin.

high-risk group still benefit significantly from reducing their carbohydrate intake and losing weight in terms of greatly improved diabetic control. Perhaps the most important messages from this audit is that clinical benefit does not depend on achieving remission.

The T2D remission rate at the Norwood surgery has improved every single year since 2017 as shown in table 3. We are becoming increasingly effective. Why is this? We believe that offering hope of a better future is essential, coupled with clear messages delivered by supportive

peers and professionals. Follow-up with honest feedback is essential. A very helpful motivational technique is to offer our patients dietary change as an alternative to life-long medication. Interestingly, when offered this choice not a single person in 8 years chose lifelong medication but renewed their dietary efforts.

Seventy-seven per cent of those opting to try the low-carbohydrate-based programme in the first year following diagnosis achieved remission as shown in figure 4. Our data clearly show that the best chance of

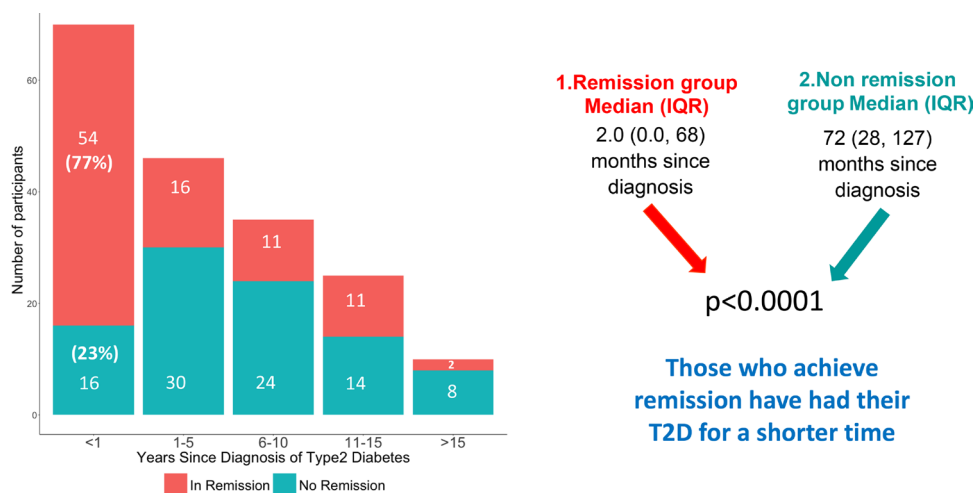


Figure 5 A cohort of 186 patients with T2D on a low-carbohydrate diet for an average of 33 months stratified according to years since diagnosis, comparing baseline data for time since diagnosis of T2D between the remission group (n=94) and non-remission group (n=92). T2D, type 2 diabetes.

Table 3 Norwood practice data on T2D remission March 2015–April 2021

Data collected to:	Mean duration of low-carbohydrate approach	No of T2D cases in remission HbA1c<48*	No of choosing the approach	Remission rate for people who choose the low-carbohydrate approach	No of patients with T2D on the diabetic register	Overall remission rate for practice
March 2017	13 months	15	48	31%	416	4%
May 2018	20 months	41	106	39%	454	9%
January 2019	22 months	59	123	48%	469	13%
March 2020	30 months	68	143	48%	485	14%
April 2021	33 months	94	186	51%	473	20%

*T2D remission defined as: previous diagnosis of T2D by WHO criteria and HbA1c <6.5% (<48 mmol/mol) without antidiabetes medication. As per McCombie *et al.*³⁹ in mmol/mol.
HbA1c, Glycated haemoglobin; T2D, type 2 diabetes .

remission is in those with T2D for least time, consistent with previous observations.^{23–25} The remission rate drops after that first year, suggesting that those leaving it longer are missing an important window of opportunity. We should focus on ‘metabolic age’ (duration of T2D) rather than chronological age. We found that those people who achieve remission start with a lower HbA1c. This may be anticipated, but there is still hope for those starting with a higher HbA1c. Those with the highest HbA1c at baseline were most likely to see the biggest improvements in HbA1c on reducing dietary carbohydrate as shown in [figure 4](#) (although five patients achieved remission despite starting with a HbA1c >90 mmol/mol). This gives hope to those with poorly controlled T2D who are more likely to achieve significant mitigation than remission and avoid medication. Finally looking at [figure 4](#), it can be seen that only 5 out of 183 (3%) participants choosing a low-carbohydrates approach recorded a worsening HbA1c result.

The role of weight loss in remission is important.²⁶ Our findings support this, with none achieving remission without weight loss. A commonly reported patient finding was how surprised they were not to feel hungry on this diet. Interestingly randomised controlled trials have shown a low-carbohydrate diet may both increase energy expenditure²⁷ and reduce appetite,²⁸ which would make weight loss much easier. The studies which have revealed the physiological changes underlying remission demonstrate the considerable reduction in liver fat content associated with weight loss. In a primary care series of people apparently free of liver disease, liver fat decreased from the very high level of 16.0% to just 3.1%.²⁴ This completely reverses the liver insulin resistance which causes fasting hyperglycaemia. It also resulted in a sharp reduction in exported triglyceride from the liver to all ectopic sites including the pancreas. This decrease in pancreatic fat supply permits relief of the metabolic stress which causes beta cell dysfunction.^{4 24 29} It is likely that weight loss by any means can induce remission. Other studies of remission have used a relatively high carbohydrate, low calorie approach and clinical studies of food-based

approaches or bariatric surgery both achieve remission.^{25 30} The question is which approach is safe, effective and most acceptable to patients? The present data demonstrate a highly effective method in primary care which allows continued avoidance of weight regain. In a study of adults with screen-detected T2D, weight loss of ≥10% early in the disease was associated with a doubling of remission at 5 years.³¹

The rising cost of drug treatments for T2D is of great concern, especially in an ageing population and an obesity epidemic. The substantial prescribing savings documented in this audit are therefore of profound importance. It is clear that medication will be required for many people with T2D especially those with longer duration disease. However, The National Institute for Health and Care Excellence guidelines on T2D focus more on medication while paying scant attention to diet.³² The management of most diseases is based on knowledge of pathophysiology but this new understanding of the nature of T2D³⁰ has not yet been incorporated into such guidelines. Change is underway, guided by the National Health Service (NHS) England diabetes remission programme.³³ Major national savings in prescribing costs for T2D are achievable. It is also important to appreciate the potential risks of some medications. SGLT2 inhibitors can cause potentially fatal ketoacidosis.³⁴ A practical summary is included in online supplemental file 1, doctor/nurse protocol.

Limitations are common to all practice-based service evaluations of this kind. The lack of randomisation introduces the risk of selection bias as those least motivated to return to health are less likely to embark on the programme. It is unlikely that cases are ‘cherry picked’ given the high average baseline HbA1c (63 mmol/mol). The absence of a control group means we cannot compare this dietary intervention directly with routine care. We acknowledge the risk of reporting bias as we rely on each persons’ word regarding dietary adherence, however, the mean weight loss of 10 kg suggests significant dietary change. We cannot be certain of the exact nature of the change or the balance of the different macronutrients in the diet of participants. The magnitude of average improvement and the fact

this cohort are a large proportion (39%) of the known T2D disease register of a UK NHS practice with 9800 patients is encouraging, as is the observation that this approach has been shown to help people with T2D in other UK general practices.^{35 36}

CONCLUSIONS

In England alone, the National Diabetes Audit 2020–2021 data release³⁷ confirmed that over one million people have poorly controlled T2D with a HbA1c >58 mmol/mol. This has important implications for mortality as the UK National Diabetes Audit and Office of National Statistics estimate that each year spent with HbA1c >58 mmol/mol loses a patient around 100 days of life.³⁸ Novel solutions to this problem must be identified as routine UK NHS care is clearly insufficient. In this context our cohort improved average HbA1c from 63 mmol/mol to 46 mmol/mol. Norwood surgery has supported people with T2D reduce dietary carbohydrates and lose weight for over 8 years. This has delivered significant improvements in HbA1c with 20% of the practice's population achieving drug-free T2D remission. There have also been a range of important cardiovascular risk factor improvements. Diabetes drug savings are £68 353 per year compared with the local average. These savings are likely to be dwarfed by cost savings from reduced complications of T2D and days lost from work. Our findings show that a low-carbohydrate intervention with weight loss can be particularly effective in delivering remission for those with either a lower HbA1c or who have had diabetes for a shorter time. It can also give hope to those with poorly controlled T2D who had the greatest improvements in HbA1c.

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Contributors DU initiated the approach in the practice, designed the infographics and wrote the initial drafts. JU organised and ran the group consultations, also training all clinical staff in using patients' own goals and feedback to implement change. CD did the statistics, produced the tables, the boxplots and regression models. ST supported the approach within the practice and co-edited the manuscript. RT advised on data interpretation and co-edited the manuscript. DU is responsible for the overall content as guarantor.

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Supplementary File. Insights from a general practice service evaluating a lower carbohydrate diet in patients with type 2 diabetes mellitus over 8 years: what predicts successful drug-free remission and what happens to those who do not achieve this goal? Unwin D. et al. 2022

Item 1. Doctor/Nurse protocol Norwood Surgery: T2D, prediabetes, lower carb dietary option

Doctor/Nurse protocol Norwood Surgery: T2D, prediabetes, lower carb dietary option (this document is under regular review, please let DJU know if it can be improved).

General points

Remember not all low carb diets are necessarily good, for example a diet coke and pepperoni sausage diet is low carb, but not well formulated. A well formulated low carb diet will be full of fibre & essential nutrients(1) see the Norwood low carb diet sheet.

In general, we are trying to avoid the high blood glucose levels that lead to poor health, the new concept of 'time in range'(2) made possible by devices like the Freestyle Libre are a helpful extension of this.

Try to see patients and their high blood sugars as an interesting puzzle rather than a problem. One to be worked out with the patient; so our approach is collaborative.

At the first appointment for those people interested in this approach:

- Explore possible benefits/ risks of a lower carb approach to T2diabetes (eg medications, risk of hypo) and make a start on motivation. The idea of diabetes remission or coming off meds is very motivating for many people. At Norwood 50% of those choosing a low carb diet achieve drug free T2diabetes remission. Of those recently diagnosed (<12 months) the remission rate is 76%.

An example of the type of question you can ask.

'You have a range of different possible futures WRT to your diabetes, which will you choose?' 'In this clinic to date the average weight loss on low carb is 9Kg, is this of interest to you?' etc.,

- Check are the patients interested in the low carb approach, there are others (eg VLCD)?

-Visit basic physiology of sugar starting with the fact that 'your HbA1c shows how sugary your diet has been in the last few months', and explaining sugar can almost be seen as a metabolic poison to someone with T2D.

Ask 'where do you think the sugar has come from in your diet?' (An exception to this is the 'Dawn phenomenon' where overnight gluconeogenesis results in a high fasting glucose)

- Explain dietary sources of glucose with Norwood sugar equivalence infographics(3).

- Give the Norwood standard diet sheet for low carb approach.

- Establish baseline data; Wt., waist, height, bloods; HbA1c, renal, fasting lipids, FBC.

-Enter EMIS computer code 'low carbohydrate diet'.

-Medications

? **Risk of hypoglycaemia** (Insulin, gliclazide) reduce dose/stop but monitor

? **Risk of DKA** (SGL2Inhibitors). Stop, but monitor blood glucose.

? **Risk of hypotension**, explain that with weight loss BP may well improve and medications for this may be reduced or cut back

-Salt; Due to the renal sodium retaining properties of insulin(4) for those with T2D going low carb and therefore lower insulin results in considerable loss of sodium and consequently a diuresis. Patients may well need to increase their salt intake –particularly in the first few weeks of the diet.

-Suggest a review date - often 2 or 4 weeks depending on assessed risks. Perhaps longer for pre-diabetes

On review

Weigh, measure waist, BP. Do medications need to be changed? See above

How is it going? Problems/suggestions

Produce Emis graphs of Weight., HbA1c etc. as feedback to maintain motivation.

Ask about hunger and appetite. Hungry people are unlikely to stick to a diet. Many people who drop the carbs enough also drop their insulin sufficiently to allow them to burn their own fat as fuel(5) -so they become 'fat burners' who are far less hungry. Do they need to drop their carbs a little more so they can burn fat? Another possibility to help with hunger is to increase the dietary protein.

Think about the possibility of 'food addiction' for those who are struggling with cravings or experiencing weight gain(6). If moderation is impossible, rather like someone with an alcohol problem, abstinence from 'trigger foods' may be the answer. Possibly suggest a book; 'Fork in the Road' it's on Amazon.

Do they wish to continue?

Are they happy to share anonymised data for our on-going audit of service provision?(please explain what this means) This extra level of patient data protection is not actually needed for audit but Norwood feels it's good practice.

If so enter Emis GP computer code 'obtaining consent'

Would they like to attend the Zoom group sessions –do they know how to find out when the next one is?

Three worrying patterns wrt HbA1c and weight

1. **If both weight and HbA1c are climbing** the most common reason is 'carb creep' **NOT** failure of the diet needing medication. So check for this by rechecking dietary intakes. Over time many patients drift. It's better to see this as a learning opportunity. We all learn from our mistakes!
2. **Weight loss alongside a climbing HbA1c** is worrying –ask a doctor about this. ? T1D, ?Malignancy
3. **HbA1c 'too good'** eg. 28mmol/mol could the patient be anaemic?

Constipation?

Magnesium supplements can help a lot with this and can help with insulin sensitivity(7)

More fluids

More nuts or green veg

Next steps

Review date and agree next blood test (HbA1c etc.) -usually at 2 months from the start, but this depends on a risk analysis.

Lipid profiles Fasting profiles are preferable as triglyceride/HDL ratios are a better predictor of risk than LDL Lipid profiles usually (but not always) improve on low carb(8)

Remember NICE UK guidelines 1.3.6 Individualise recommendations for carbohydrate and alcohol intake, and meal patterns. **Reducing the risk of hypoglycaemia should be a particular aim for a person using insulin or an insulin secretagogue. [2009]**

Often this is achieved by increasing dietary carbs at the expense of weight gain **An alternative** is to reduce carbs and the drugs involved this has the advantage of weight loss and improvements in BP

Finally, for prescribers Drugs for diabetes and the low carb approach taken from; Murdoch C, Unwin D, Cavan D, Cucuzzella M, Patel M. Adapting diabetes medication for low carbohydrate management of type 2 diabetes: a practical guide. Br J Gen Pract. 2019;69(684):360-1.

For clinicians considering advising a lower carbohydrate diet for patients who are already on anti-diabetic medications, there are three important considerations:

- 1) Whether the drug/diet combination poses a risk of hypoglycaemia. Insulin is an obvious culprit for this as are some oral agents such as gliclazide. Careful measurement of blood glucose, dose reduction and/or cessation of culprit drugs is crucial to patient safety.
- 2) SGLT2 inhibitor drugs; combined with a low carbohydrate diet, have the potential to lead to diabetic ketoacidosis that may be masked by relative normoglycaemia. This class of drugs probably ought to be avoided in this context or at least have the dosage reduced. For some patients with comorbidities such as chronic kidney disease, some experienced practitioners / nephrologists acknowledge the effectiveness of SGLT2s and opt to using both SGLT2 and a low carb diet, BUT this is undertaken with close monitoring and proper attention to the 'sick day rules' for these drugs.
- 3) As demonstrated in our service evaluation data and elsewhere (1), lowering carbohydrate in the diet is associated with a lowering of BP. For patients already on antihypertensive medication, this can lead to symptomatic hypotension requiring dose reduction and/or cessation of culprit drugs.

Prescribing T2D medication in the context of a carbohydrate-restricted diet was the subject of a useful British Journal of General Practice review* that states the diet is safe with metformin, the most commonly prescribed anti-diabetic medication. In addition to deprescribing anti-diabetic medications analysis from the Norwood GP practice on hypertension, published separately (1), shows that 20% of the antihypertensive drugs were also stopped due to significant improvements in BP.

*From Unwin DJ, Tobin SD, Murray SW, Delon C, Brady AJ. Substantial and Sustained Improvements in Blood Pressure, Weight and Lipid Profiles from a Carbohydrate Restricted Diet: An Observational Study of Insulin Resistant Patients in Primary Care. *International Journal of Environmental Research and Public Health*. 2019;16(15):2680.

Useful resources

The Freshwell App free [Freshwell on the App Store \(apple.com\)](https://www.apple.com/uk/app-store/apps/1444444444)

The Reverse Your Diabetes Cookbook: Lose weight and eat to beat type 2 diabetes. Kate Caldesi

https://www.amazon.co.uk/Reverse-Your-Diabetes-Cookbook/dp/0857838571/ref=sr_1_4?crd=2U3I993FVS76V&key

Fork in the Road. Dr Jen Unwin Available only from Amazon. Kindle version also

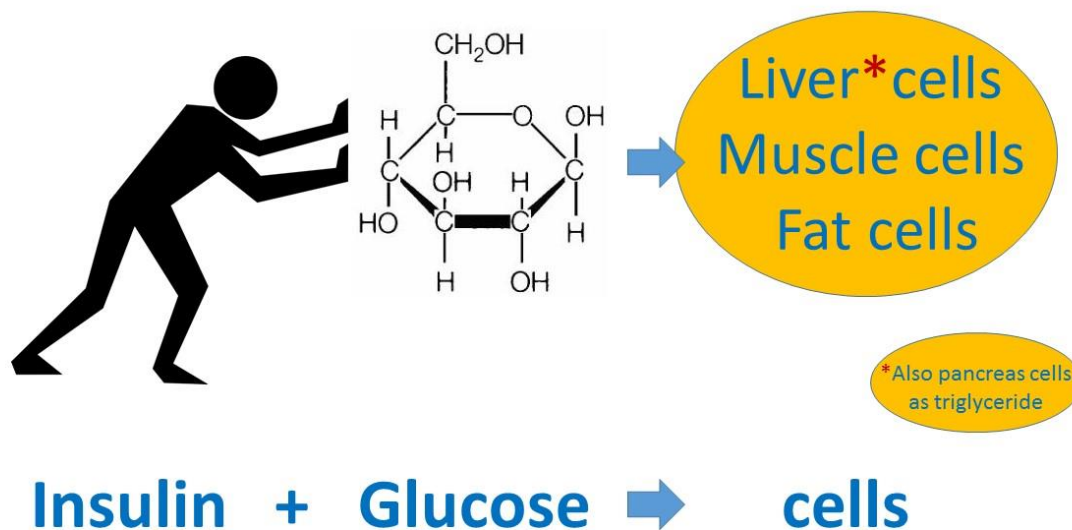
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Item 2. Four infographics used to help people with T2D understand insulin and glucose

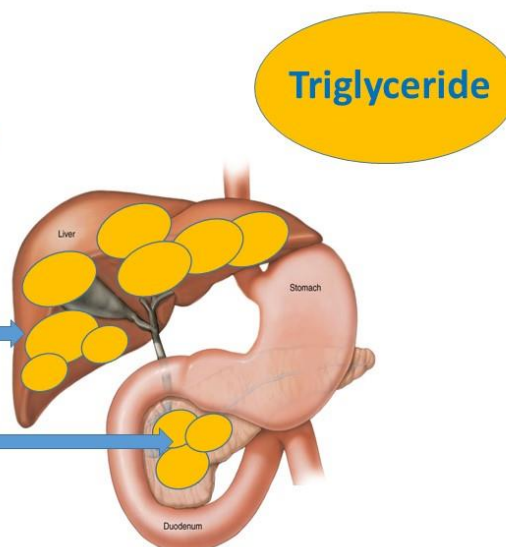
The hormone insulin can be thought of as pushing glucose out of the blood stream and into cells to reduce blood sugar. In some cells it becomes fat



Type 2 diabetes results in part from accumulation of fat in the liver and pancreas

Liver fat: linked to insulin resistance

Pancreatic fat: inhibits B cell function -cannot produce enough insulin



Reversal of type 2 diabetes: Normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Lim EL1, Hollingsworth KG, Taylor R. *Diabetologia.* 2011 Oct;54(10):2506-14. doi: 10.1007/s00125-011-2204-7.

Item 3 A lower carb diet sheet for type 2 diabetes: On the whole for people with T2D we are trying to minimise the damage done over time by high blood sugars. In this condition your metabolism struggles to deal with both sugar itself and the starchy carbohydrates that digest down into surprising amounts of sugar

Sugar – cut it out altogether, although it will be in the blueberries, strawberries and raspberries you are allowed to eat. Cakes and biscuits are a mixture of sugar and starch that make it almost impossible to avoid food cravings; they just make you hungrier!!

Reduce starchy carbs a lot Remember they digest down into surprising amounts of sugar. If possible just cut out the ‘White Stuff’ like bread, rice, pasta, potato, crackers and cereals.

All green veg/salads are fine...Eat as much of these as you can –turn the white stuff green

So that you still eat a good big dinner try substituting veg such as broccoli, courgettes or green beans for your mash, pasta or rice – still covering them with your gravy, Bolognese or curry! Cauliflower rice is now widely available

Tip: try home-made soup – it can be taken to work for lunch and microwaved. Mushrooms, tomatoes, and onions can be included in this.

Fruit is trickier...

Some tropical fruits like bananas, oranges, grapes, mangoes or pineapple have too much sugar in and can set those carb cravings off. Berries are better and can be eaten; blueberries, raspberries, strawberries, apples and pears too.

Eat healthy proteins...

Try basing your meals on non-processed meat like chicken or red meat, eggs (three eggs a day is not too much), fish – particularly oily fish such as salmon, mackerel or tuna –are fine and can be eaten freely. Plain **full fat** yoghurt makes a good breakfast with the berries. Processed meats such as bacon, ham, sausages or salami are not as healthy and should only be eaten in moderation.

Healthy fats are fine in moderation...

Yes, fats can be fine in moderation: olive oil is very useful, butter may be tastier than margarine and could be better for you! Coconut oil is great for stir fries. Four essential vitamins A, D, E and K are only found in some fats or oils. Please avoid margarine, corn oil and vegetable oil.

Beware ‘low fat’ foods. They often have sugar or sweeteners added to make them palatable. Full fat mayonnaise and pesto are definitely on!!

Cheese only in moderation...

It’s a very calorific mixture of fat, and protein.

Snacks: avoid, as habit forming. But un-salted nuts such as almonds or walnuts are OK to stave off hunger. The occasional treat of strong dark chocolate 70% or more in small quantity is allowed.

Eating lots of green veg with protein and healthy fats leaves you properly full in a way that lasts

Alcohol is full of carbs...

Sadly many alcoholic drinks are full of carbohydrate – for example, beer is almost ‘liquid toast’ hence the beer belly!! The odd glass of dry white, red wine or spirits is not too bad if it doesn’t make you hungry afterwards – or just plain water with a slice of lemon.

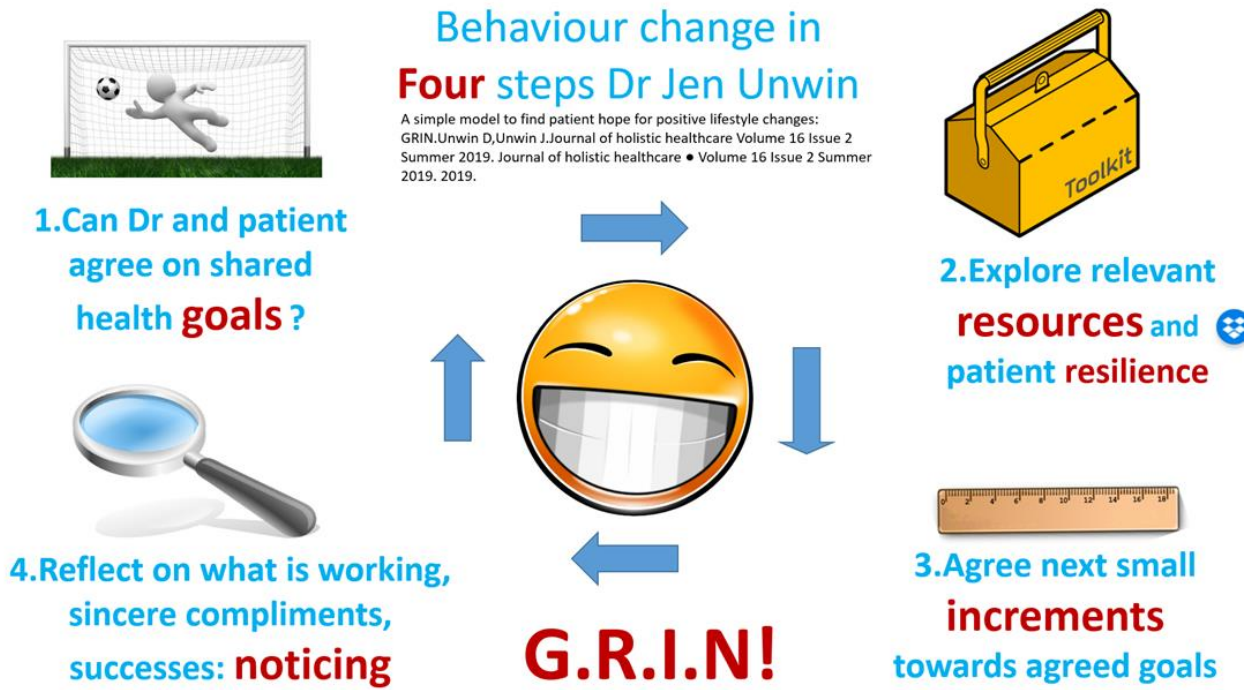
Sweeteners can trick you...

Finally, about sweeteners and what to drink – sweeteners have been proven to tease your brain into being even hungrier, making weight loss more difficult – drink tea, coffee, and water or herb teas. (100ml milk is 1 teaspoon of sugar)

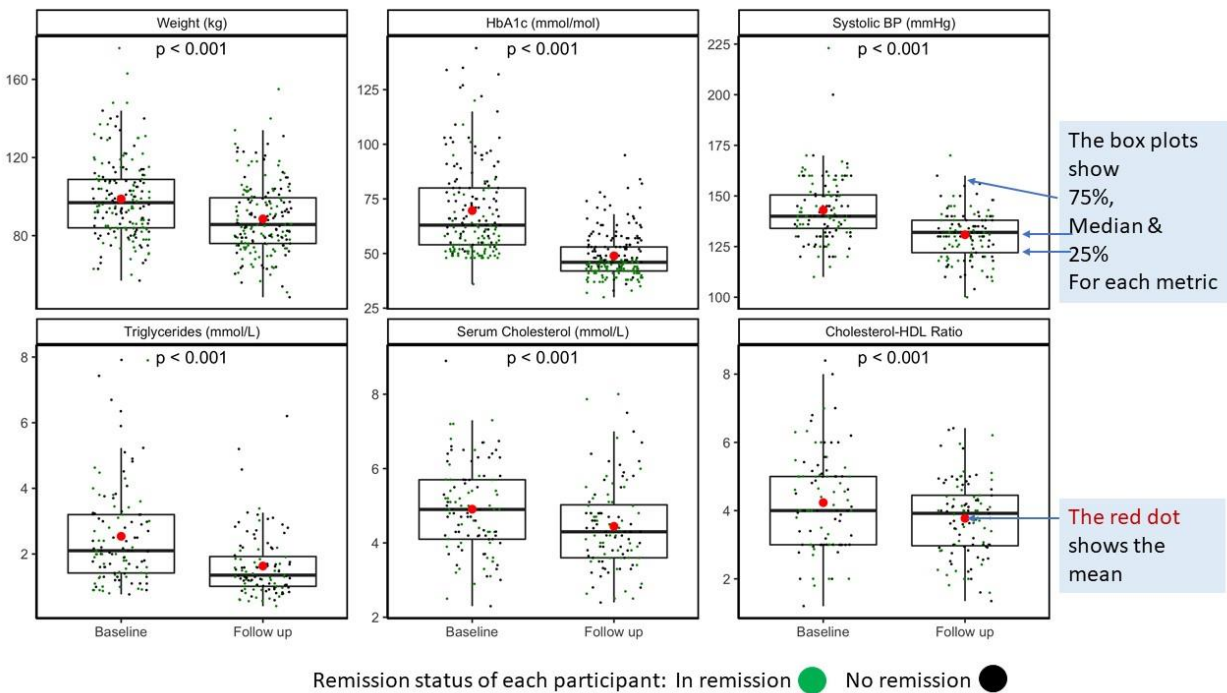
Typically, a low carb diet contains less than 130 grams of carb per day. How low to go depends on many factors. Discuss this with your health care practitioner

Important On prescribed medication? Check this first with your Doctor or HCP before making big changes to your diet. **PS some folk need more salt on a low carb diet**

Item 4. An infographic on goal setting, behavior change and use of feedback



Item 5 A more detailed examination of the data that produced figure 1 showing box plots for the baseline and latest follow up data for six metrics



Item 6 Linear regression model fitted with HbA1c reduction as the outcome and baseline HbA1c as the predictor

Figure x Regression model data for

Call: `lm(formula = HbA1cLoss2 ~ HbA1cStart, data = Data)`

```

Dependent variable:      HbA1cLoss2
HbA1cStart      Coefficient -0.770***
                  Std.error  (0.034)
                  p          <2x10-16
Constant        Coefficient  33.008***
                  Std.error  (2.466)
                  p          <2x10-16

```

```

-----
Observations              183
R2                        0.740
Adjusted R2              0.738
Residual Std. Error      9.500 (df = 181)
F Statistic              514.024*** (df =1; 181)

```

Item 7 Logistic regression model for remission of diabetes as the outcome and baseline HbA1c, weight, age and gender as the predictor

`glm(formula = RemissionNum ~ WeightStart + Age + Gender + HbA1cStart, family = "binomial", data = Data)`

Deviance Residuals:

Min	1Q	Median	3Q	Max
-1.81852	-0.94651	-0.08194	0.78841	2.75309

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	4.649589	2.006606	2.317	0.0205 *
WeightStart	0.007774	0.010141	0.767	0.4433
Age	-0.010272	0.017317	-0.593	0.5531
GenderMale	0.481003	0.362964	1.325	0.1851
HbA1cStart	-0.075745	0.013129	-5.769	7.97e-09 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 250.87 on 180 degrees of freedom

Residual deviance: 192.99 on 176 degrees of freedom

(5 observations deleted due to missingness)

AIC: 202.99 Number of Fisher Scoring iterations: 5

Item 8. Table comparing baseline number of years since diagnosis and the percentage in each category achieving remission

Years since diagnosis of T2 diabetes	Total number of patients choosing a low carb approach	Number achieving remission	Number not achieving remission	Percentage achieving remission
<1 year	70	54	16	77%
1-5 years	46	16	30	35%
6-10 years	35	11	24	31%
11-15 years	25	11	14	44%
15+ years	10	2	8	20%
Total	186	94	92	51%

Item 9 Logistic regression model for remission of diabetes as the outcome and time since diagnosis, baseline; HbA1c, weight, age and gender as the predictor.

A logistic regression model fitted with remission as the outcome with gender, baseline age, baseline weight, baseline HbA1c, and duration of diabetes (in months) found a relationship with both baseline HbA1c and baseline duration of diabetes on remission. A lower baseline HbA1c and a shorter duration of diabetes were significantly related to remission, even after controlling for baseline weight, age and gender (- 0.007/month, p value = 0.010).

The relationship of remission with recent diagnosis was also seen if duration of diabetes was considered as a binary variable of less than 1 year or 1 year or more (-1.29, p value 0.002) Time since diagnosis as a continuous variable.

Statistical work is below

```
glm(formula = RemissionNum ~ WeightStart + Age + Gender + HbA1cStart +
MonthsSinceDiagnosisT2, family = "binomial", data = Data)
```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-1.93009	-0.81937	-0.08784	0.79863	2.83733

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)...	4.249734	2.024828	2.099	0.0358 *
WeightStart ...	0.00578 9	0.010212	0.567	0.5708
Age...	0.001134	0.018167	0.062	0.9502
GenderMale ...	0.539421	0.370737	1.455	0.1457
HbA1cStart...	-0.071033	0.013028	-5.452	4.97e-08 ***
MonthsSinceDiagnosisT2.	-0.007213	0.002815	-2.562	0.0104 *

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 250.87 on 180 degrees of freedom

Residual deviance: 186.17 on 175 degrees of freedom

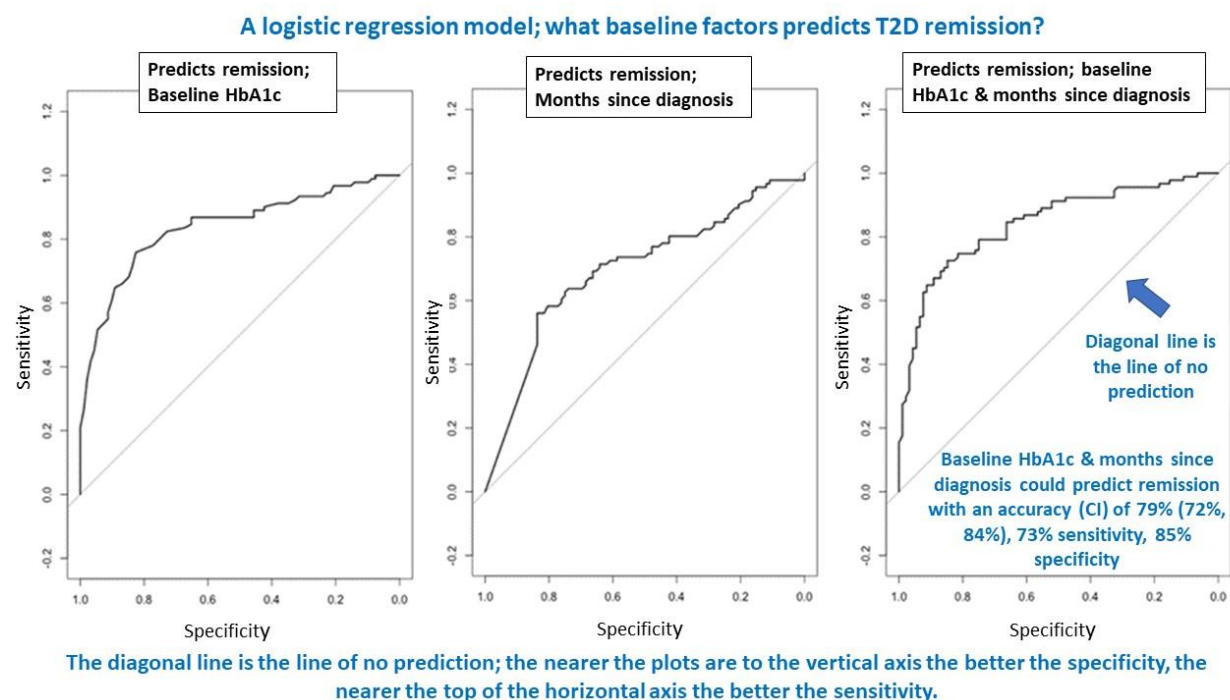
(5 observations deleted due to missingness)

AIC: 198.17

Number of Fisher Scoring iterations: 5

Item 10 Performance of logistic models in predicting remission; an explanation

Logistic regression was carried out to predict remission status using baseline; HbA1c, time since diagnosis or both. For each model the threshold was determined from the ROC curve (pictured; 0.58, 0.62 and 0.61 respectively).



A logistic regression model predicting Remission from baseline HbA1c (as a continuous variable) could predict remission with an accuracy (CI) of 79% (73%, 85%), 76% sensitivity, 83% specificity and an f1 score of 0.78.

A logistic regression model predicting Remission from time since diagnosis (as a continuous variable) could predict remission with an accuracy (CI) of 70% (63%, 76%), 56% sensitivity, 84% specificity and an f1 score of 0.65.

A logistic regression model predicting remission from both baseline HbA1c and baseline months since diagnosis (both continuous variables) could predict remission with an accuracy (CI) of 79% (72%, 84%), 73% sensitivity, 85% specificity and an f1 score of 0.77.

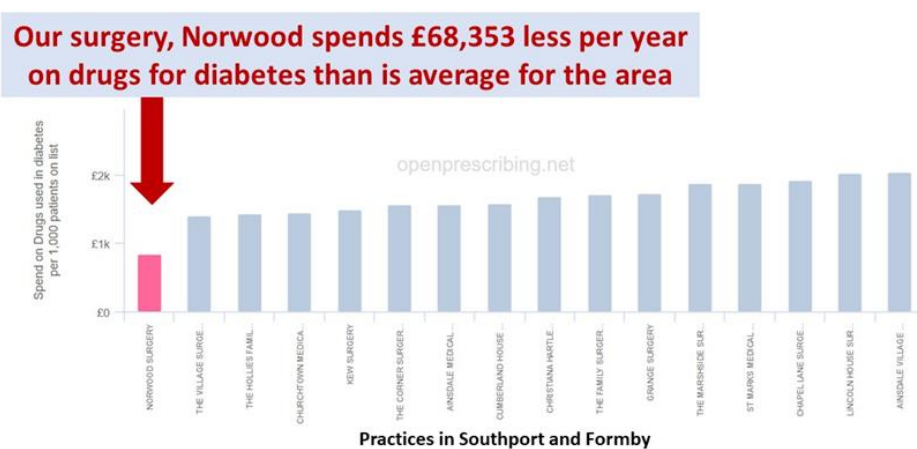
Model data

Predictor	HbA1c	Months since diagnosis	HbA1c+MonthsSinceDiag
accuracy (LCI, UCI)	0.79 (0.73, 0.85)	0.7 (0.63, 0.76)	0.79 (0.72, 0.84)
kappa	0.58	0.4	0.57
mcnemar	0.42	0	0.11
sensitivity	0.76	0.56	0.73
specificity	0.83	0.84	0.85
pos_pred_value	0.81	0.77	0.83
neg_pred_value	0.78	0.66	0.76
precision	0.81	0.77	0.83

recall	0.76	0.56	0.73
f1	0.78	0.65	0.77
prevalence	0.50	0.5	0.5
detection_rate	0.38	0.28	0.36
detection_prevalence	0.46	0.36	0.44
balanced_accuracy	0.79	0.7	0.79

Item 11 Openprescribing data

Spend on antidiabetic drugs (BNF 6.1) vs patients on list by NORWOOD SURGERY and other practices in Southport area. January 2022



(From Openprescribing.net: Accessed march 2022)

Notes on the statistics

There was debate between the authors about which measures of distribution were most accurate, either Median (IQR) or Mean (SD). Table 1 has been designed to encompass both Median IQR and Mean SD so readers can see both. Three of the metrics (HbA1c, Systolic BP & triglyceride levels) have a mean that is greater than the median see, making a normal distribution unlikely. HbA1c is a particularly good example of this starting as it does with a cut off at 48 mmol/mol. Overall we stuck with Median IQR as probably being more accurate (although both appear in the version above). There were data showing a more convincing normal distribution like duration of diet where we used Mean SD.

In collecting our data there is the problem of what to do about people who give up on the low carb diet after a period of time. Since our basic question is about 'what happens to people who chose a low carb diet' We decided to only collect data while we knew the participant was low carb. In the case of those who gave the diet up we stopped collecting data when they were telling us they were still on the diet, so that this became the date of latest follow up This shortening of follow up is thus automatically included in the calculations for average time on the diet.

One of the reviewers asked

Did the patients get other advice besides a low carbohydrate diet, e.g. improving physical activity?

This advice is given to all people with T2D as part of routine UK NHS care. The low carb advice was separate and additional to this.

More on the physiology of T2D, from 2012 Banting lecture by R Taylor. Taylor R. Banting Memorial lecture 2012: reversing the twin cycles of type 2 diabetes. *Diabet Med.* 2013;30(3):267-75.

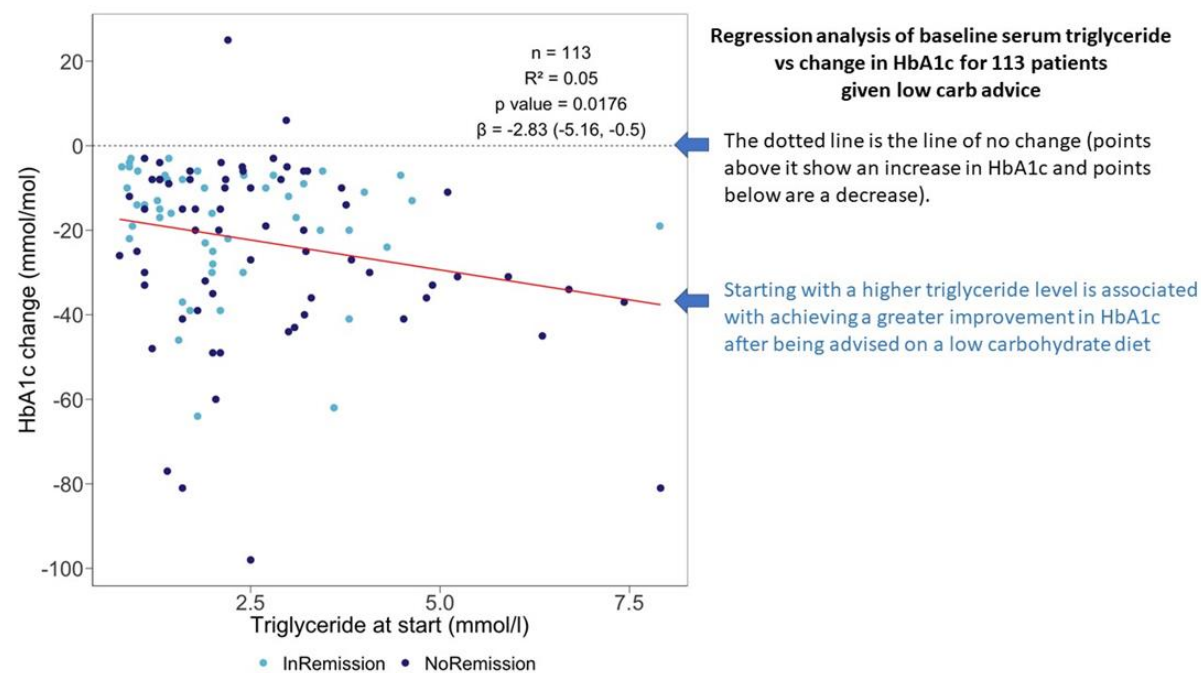
Any excess carbohydrate cannot be stored once the glycogen depots are full. If more glucose is ingested than can be oxidized for energy or stored as glycogen, it has to be turned into fat by the process of de novo lipogenesis. This process only happens in the liver in humans, and triglyceride synthesized in situ is particularly likely to be stored in hepatocytes rather than exported for safe storage in subcutaneous adipose tissue. The newly synthesized fat has three possible fates: it can be oxidized for energy; exported as VLDL in the plasma to be delivered to other tissues or it can be stored in a rather full liver. As de novo lipogenesis is stimulated by insulin, those people who are relatively insulin resistant in muscle—and who therefore have a raised plasma insulin level—are especially likely to accumulate fat in the liver.(9)

Also from 'The Candy study': Sevastianova K, Santos A, Kotronen A, Hakkarainen A, Makkonen J, Silander K, et al. Effect of short-term carbohydrate overfeeding and long-term weight loss on liver fat in overweight humans. *Am J Clin Nutr.* 2012;96(4):727-34.

Volunteers were asked to eat a bag of sweets, drink a 300-ml bottle of Pepsi and 30 ml of fruit juice each day in addition to their usual food. This sucrose overfeeding for 3 weeks brought about a 27% increase in liver fat content. This was associated with a 30% rise in serum alanine aminotransferase (ALT), indicating the associated metabolic stress on hepatocytes(10)

Carbohydrate overfeeding for 3 wk induced a >10-fold greater relative change in liver fat (27%) than in body weight (2%). The increase in liver fat was proportional to that in de novo lipogenesis. Weight loss restores liver fat to normal. These data indicate that the human fatty liver avidly accumulates fat during carbohydrate overfeeding and support a role for DNL in the pathogenesis of NAFLD

Linear regression analysis of baseline serum triglyceride vs change in HbA1c for 113 patients given low carb advice



A linear regression model fitted with HbA1c reduction as the outcome and baseline serum triglyceride as the predictor demonstrated a relationship $R^2 0.05$ $p=0.0176$. Those with a higher triglyceride level at baseline

were likely to achieve a greater improvement in HbA1c. However, no relationship was seen when controlling for baseline HbA1c. Baseline HbA1c and baseline TG are moderately correlated (0.27) therefore high baseline TG may not be independently related.

Supplementary File. Insights from a general practice service evaluating a lower carbohydrate diet in patients with type 2 diabetes mellitus over 8 years: what predicts successful drug-free remission and what happens to those who do not achieve this goal? Unwin D. et al. 2022

Item 1. Doctor/Nurse protocol Norwood Surgery: T2D, prediabetes, lower carb dietary option

Doctor/Nurse protocol Norwood Surgery: T2D, prediabetes, lower carb dietary option (this document is under regular review, please let DJU know if it can be improved).

General points

Remember not all low carb diets are necessarily good, for example a diet coke and pepperoni sausage diet is low carb, but not well formulated. A well formulated low carb diet will be full of fibre & essential nutrients(1) see the Norwood low carb diet sheet.

In general, we are trying to avoid the high blood glucose levels that lead to poor health, the new concept of 'time in range'(2) made possible by devices like the Freestyle Libre are a helpful extension of this.

Try to see patients and their high blood sugars as an interesting puzzle rather than a problem. One to be worked out with the patient; so our approach is collaborative.

At the first appointment for those people interested in this approach:

- Explore possible benefits/ risks of a lower carb approach to T2diabetes (eg medications, risk of hypo) and make a start on motivation. The idea of diabetes remission or coming off meds is very motivating for many people. At Norwood 50% of those choosing a low carb diet achieve drug free T2diabetes remission. Of those recently diagnosed (<12 months) the remission rate is 76%.

An example of the type of question you can ask.

'You have a range of different possible futures WRT to your diabetes, which will you choose?' 'In this clinic to date the average weight loss on low carb is 9Kg, is this of interest to you?' etc.,

- Check are the patients interested in the low carb approach, there are others (eg VLCD)?

-Visit basic physiology of sugar starting with the fact that 'your HbA1c shows how sugary your diet has been in the last few months', and explaining sugar can almost be seen as a metabolic poison to someone with T2D.

Ask 'where do you think the sugar has come from in your diet?' (An exception to this is the 'Dawn phenomenon' where overnight gluconeogenesis results in a high fasting glucose)

- Explain dietary sources of glucose with Norwood sugar equivalence infographics(3).

- Give the Norwood standard diet sheet for low carb approach.

- Establish baseline data; Wt., waist, height, bloods; HbA1c, renal, fasting lipids, FBC.

-Enter EMIS computer code 'low carbohydrate diet'.

-Medications

? **Risk of hypoglycaemia** (Insulin, gliclazide) reduce dose/stop but monitor

? **Risk of DKA** (SGL2Inhibitors). Stop, but monitor blood glucose.

? **Risk of hypotension**, explain that with weight loss BP may well improve and medications for this may be reduced or cut back

-Salt; Due to the renal sodium retaining properties of insulin(4) for those with T2D going low carb and therefore lower insulin results in considerable loss of sodium and consequently a diuresis. Patients may well need to increase their salt intake –particularly in the first few weeks of the diet.

-Suggest a review date - often 2 or 4 weeks depending on assessed risks. Perhaps longer for pre-diabetes

On review

Weigh, measure waist, BP. Do medications need to be changed? See above

How is it going? Problems/suggestions

Produce Emis graphs of Weight., HbA1c etc. as feedback to maintain motivation.

Ask about hunger and appetite. Hungry people are unlikely to stick to a diet. Many people who drop the carbs enough also drop their insulin sufficiently to allow them to burn their own fat as fuel(5) -so they become 'fat burners' who are far less hungry. Do they need to drop their carbs a little more so they can burn fat? Another possibility to help with hunger is to increase the dietary protein.

Think about the possibility of 'food addiction' for those who are struggling with cravings or experiencing weight gain(6). If moderation is impossible, rather like someone with an alcohol problem, abstinence from 'trigger foods' may be the answer. Possibly suggest a book; 'Fork in the Road' it's on Amazon.

Do they wish to continue?

Are they happy to share anonymised data for our on-going audit of service provision?(please explain what this means) This extra level of patient data protection is not actually needed for audit but Norwood feels it's good practice.

If so enter Emis GP computer code 'obtaining consent'

Would they like to attend the Zoom group sessions –do they know how to find out when the next one is?

Three worrying patterns wrt HbA1c and weight

1. **If both weight and HbA1c are climbing** the most common reason is 'carb creep' **NOT** failure of the diet needing medication. So check for this by rechecking dietary intakes. Over time many patients drift. It's better to see this as a learning opportunity. We all learn from our mistakes!
2. **Weight loss alongside a climbing HbA1c** is worrying –ask a doctor about this. ? T1D, ?Malignancy
3. **HbA1c 'too good'** eg. 28mmol/mol could the patient be anaemic?

Constipation?

Magnesium supplements can help a lot with this and can help with insulin sensitivity(7)

More fluids

More nuts or green veg

Next steps

Review date and agree next blood test (HbA1c etc.) -usually at 2 months from the start, but this depends on a risk analysis.

Lipid profiles Fasting profiles are preferable as triglyceride/HDL ratios are a better predictor of risk than LDL Lipid profiles usually (but not always) improve on low carb(8)

Remember NICE UK guidelines 1.3.6 Individualise recommendations for carbohydrate and alcohol intake, and meal patterns. **Reducing the risk of hypoglycaemia should be a particular aim for a person using insulin or an insulin secretagogue. [2009]**

Often this is achieved by increasing dietary carbs at the expense of weight gain **An alternative** is to reduce carbs and the drugs involved this has the advantage of weight loss and improvements in BP

Finally, for prescribers Drugs for diabetes and the low carb approach taken from; Murdoch C, Unwin D, Cavan D, Cucuzzella M, Patel M. Adapting diabetes medication for low carbohydrate management of type 2 diabetes: a practical guide. Br J Gen Pract. 2019;69(684):360-1.

For clinicians considering advising a lower carbohydrate diet for patients who are already on anti-diabetic medications, there are three important considerations:

- 1) Whether the drug/diet combination poses a risk of hypoglycaemia. Insulin is an obvious culprit for this as are some oral agents such as gliclazide. Careful measurement of blood glucose, dose reduction and/or cessation of culprit drugs is crucial to patient safety.
- 2) SGLT2 inhibitor drugs; combined with a low carbohydrate diet, have the potential to lead to diabetic ketoacidosis that may be masked by relative normoglycaemia. This class of drugs probably ought to be avoided in this context or at least have the dosage reduced. For some patients with comorbidities such as chronic kidney disease, some experienced practitioners / nephrologists acknowledge the effectiveness of SGLT2s and opt to using both SGLT2 and a low carb diet, BUT this is undertaken with close monitoring and proper attention to the 'sick day rules' for these drugs.
- 3) As demonstrated in our service evaluation data and elsewhere (1), lowering carbohydrate in the diet is associated with a lowering of BP. For patients already on antihypertensive medication, this can lead to symptomatic hypotension requiring dose reduction and/or cessation of culprit drugs.

Prescribing T2D medication in the context of a carbohydrate-restricted diet was the subject of a useful British Journal of General Practice review* that states the diet is safe with metformin, the most commonly prescribed anti-diabetic medication. In addition to deprescribing anti-diabetic medications analysis from the Norwood GP practice on hypertension, published separately (1), shows that 20% of the antihypertensive drugs were also stopped due to significant improvements in BP.

*From Unwin DJ, Tobin SD, Murray SW, Delon C, Brady AJ. Substantial and Sustained Improvements in Blood Pressure, Weight and Lipid Profiles from a Carbohydrate Restricted Diet: An Observational Study of Insulin Resistant Patients in Primary Care. *International Journal of Environmental Research and Public Health*. 2019;16(15):2680.

Useful resources

The Freshwell App free [Freshwell on the App Store \(apple.com\)](https://www.apple.com/uk/app-store/apps/1444444444)

The Reverse Your Diabetes Cookbook: Lose weight and eat to beat type 2 diabetes. Kate Caldesi

https://www.amazon.co.uk/Reverse-Your-Diabetes-Cookbook/dp/0857838571/ref=sr_1_4?crd=2U3I993FVS76V&key

Fork in the Road. Dr Jen Unwin Available only from Amazon. Kindle version also

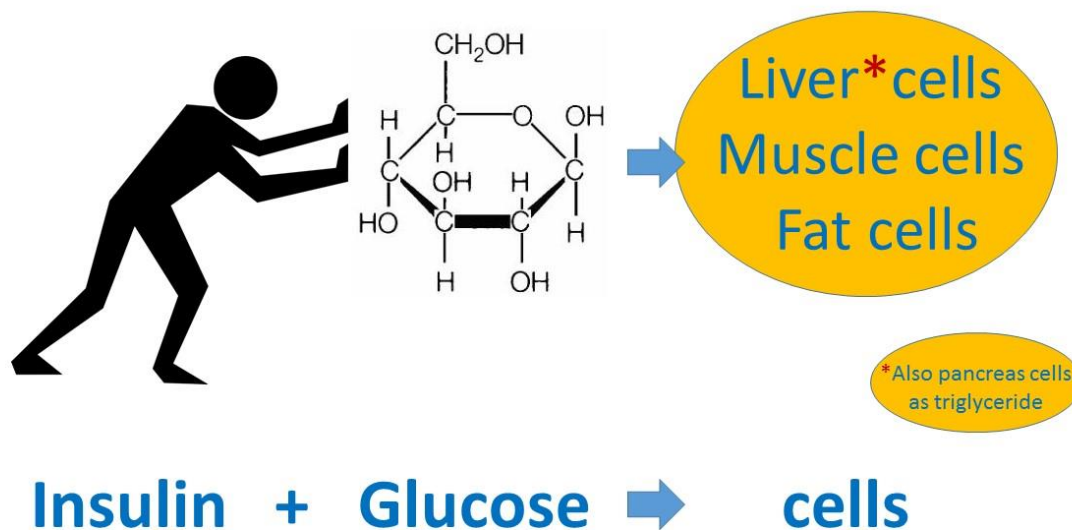
<https://www.amazon.co.uk/s?k=fork+in+the+road+jen+unwin&crd=2UBGTLF924JWE&srefix=fork+in+th%2Caps%2C281>

-
1. Zinn C, Rush A, Johnson R. Assessing the nutrient intake of a low-carbohydrate, high-fat (LCHF) diet: a hypothetical case study design. *BMJ Open*. 2018;8(2):e018846.
 2. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. *Diabetes Care*. 2019;42(8):1593-603.
 3. David Unwin DH, Geoffrey Livesey,. It is the glycaemic response to, not the carbohydrate content of food that matters in diabetes and obesity: The glycaemic index revisited. *Journal of Insulin Resistance*. 2016;2016;1(1), a8. (<https://insulinresistance.org/index.php/jir/article/view/8/11>).
 4. Unwin DJ, Tobin SD, Murray SW, Delon C, Brady AJ. Substantial and Sustained Improvements in Blood Pressure, Weight and Lipid Profiles from a Carbohydrate Restricted Diet: An Observational Study of Insulin Resistant Patients in Primary Care. *International Journal of Environmental Research and Public Health*. 2019;16(15):2680.
 5. Dimitriadis G, Mitrou P, Lambadiari V, Maratou E, Raptis SA. Insulin effects in muscle and adipose tissue. *Diabetes Res Clin Pract*. 2011;93 Suppl 1:S52-9.
 6. Gordon EL, Ariel-Donges AH, Bauman V, Merlo LJ. What Is the Evidence for "Food Addiction?" A Systematic Review. *Nutrients*. 2018;10(4):477.
 7. Morais JBS, Severo JS, de Alencar GRR, de Oliveira ARS, Cruz KJC, Marreiro DDN, et al. Effect of magnesium supplementation on insulin resistance in humans: A systematic review. *Nutrition*. 2017;38:54-60.
 8. Gjuladin-Hellon T, Davies IG, Penson P, Amiri Baghbadorani R. Effects of carbohydrate-restricted diets on low-density lipoprotein cholesterol levels in overweight and obese adults: a systematic review and meta-analysis. *Nutr Rev*. 2018.

9. Taylor R. Banting Memorial lecture 2012: reversing the twin cycles of type 2 diabetes. *Diabet Med.* 2013;30(3):267-75.
10. Sevastianova K, Santos A, Kotronen A, Hakkarainen A, Makkonen J, Silander K, et al. Effect of short-term carbohydrate overfeeding and long-term weight loss on liver fat in overweight humans. *Am J Clin Nutr.* 2012;96(4):727-34.

Item 2. Four infographics used to help people with T2D understand insulin and glucose

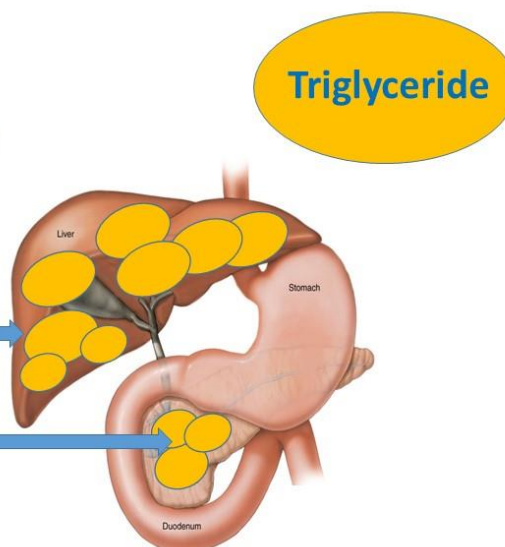
The hormone insulin can be thought of as pushing glucose out of the blood stream and into cells to reduce blood sugar. In some cells it becomes fat



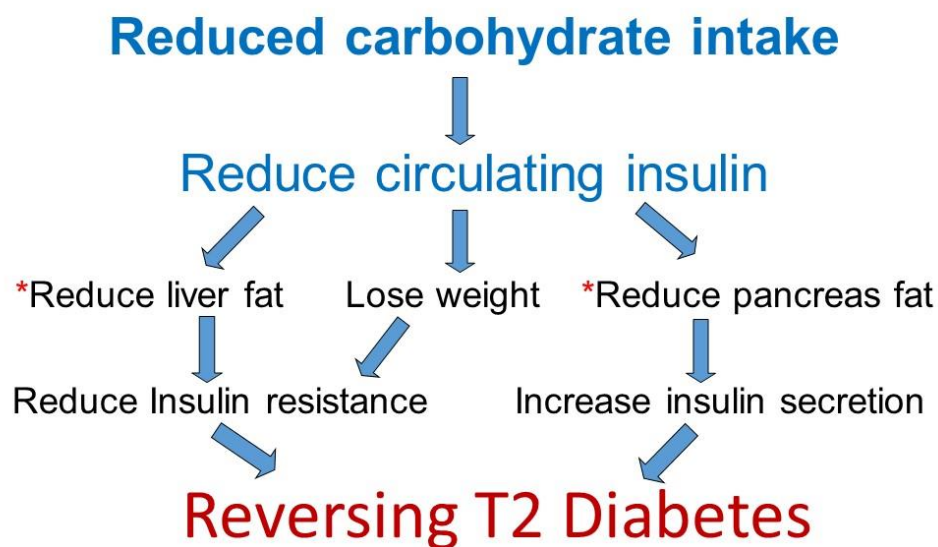
Type 2 diabetes results in part from accumulation of fat in the liver and pancreas

Liver fat: linked to insulin resistance

Pancreatic fat: inhibits B cell function -cannot produce enough insulin

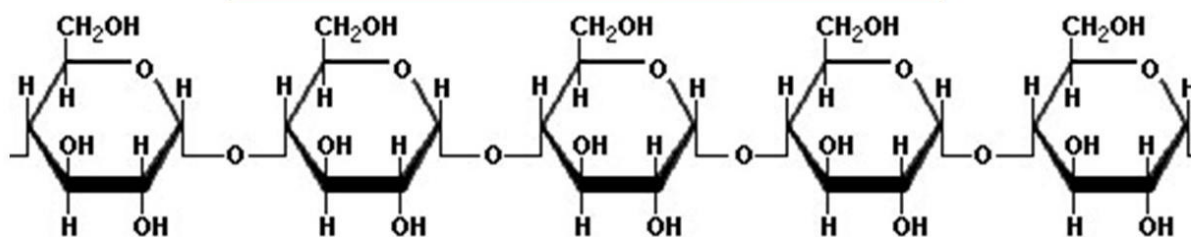


Reversal of type 2 diabetes: Normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Lim EL1, Hollingsworth KG, Taylor R. *Diabetologia.* 2011 Oct;54(10):2506-14. doi: 10.1007/s00125-011-2204-7.



*Reversal of type 2 diabetes: Normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Lim EL1, Hollingsworth KG, Taylor R. Diabetologia. 2011 Oct;54(10):2506-14. doi: 10.1007/s00125-011-2204-7.

A Starch Molecule



Many glucose molecules are linked together – enzymal digestion will break them up again

Item 3 A lower carb diet sheet for type 2 diabetes: On the whole for people with T2D we are trying to minimise the damage done over time by high blood sugars. In this condition your metabolism struggles to deal with both sugar itself and the starchy carbohydrates that digest down into surprising amounts of sugar

Sugar – cut it out altogether, although it will be in the blueberries, strawberries and raspberries you are allowed to eat. Cakes and biscuits are a mixture of sugar and starch that make it almost impossible to avoid food cravings; they just make you hungrier!!

Reduce starchy carbs a lot Remember they digest down into surprising amounts of sugar. If possible just cut out the ‘White Stuff’ like bread, rice, pasta, potato, crackers and cereals.

All green veg/salads are fine...Eat as much of these as you can –turn the white stuff green

So that you still eat a good big dinner try substituting veg such as broccoli, courgettes or green beans for your mash, pasta or rice – still covering them with your gravy, Bolognese or curry! Cauliflower rice is now widely available

Tip: try home-made soup – it can be taken to work for lunch and microwaved. Mushrooms, tomatoes, and onions can be included in this.

Fruit is trickier...

Some tropical fruits like bananas, oranges, grapes, mangoes or pineapple have too much sugar in and can set those carb cravings off. Berries are better and can be eaten; blueberries, raspberries, strawberries, apples and pears too.

Eat healthy proteins...

Try basing your meals on non-processed meat like chicken or red meat, eggs (three eggs a day is not too much), fish – particularly oily fish such as salmon, mackerel or tuna –are fine and can be eaten freely. Plain **full fat** yoghurt makes a good breakfast with the berries. Processed meats such as bacon, ham, sausages or salami are not as healthy and should only be eaten in moderation.

Healthy fats are fine in moderation...

Yes, fats can be fine in moderation: olive oil is very useful, butter may be tastier than margarine and could be better for you! Coconut oil is great for stir fries. Four essential vitamins A, D, E and K are only found in some fats or oils. Please avoid margarine, corn oil and vegetable oil.

Beware ‘low fat’ foods. They often have sugar or sweeteners added to make them palatable. Full fat mayonnaise and pesto are definitely on!!

Cheese only in moderation...

It’s a very calorific mixture of fat, and protein.

Snacks: avoid, as habit forming. But un-salted nuts such as almonds or walnuts are OK to stave off hunger. The occasional treat of strong dark chocolate 70% or more in small quantity is allowed.

Eating lots of green veg with protein and healthy fats leaves you properly full in a way that lasts

Alcohol is full of carbs...

Sadly many alcoholic drinks are full of carbohydrate – for example, beer is almost ‘liquid toast’ hence the beer belly!! The odd glass of dry white, red wine or spirits is not too bad if it doesn’t make you hungry afterwards – or just plain water with a slice of lemon.

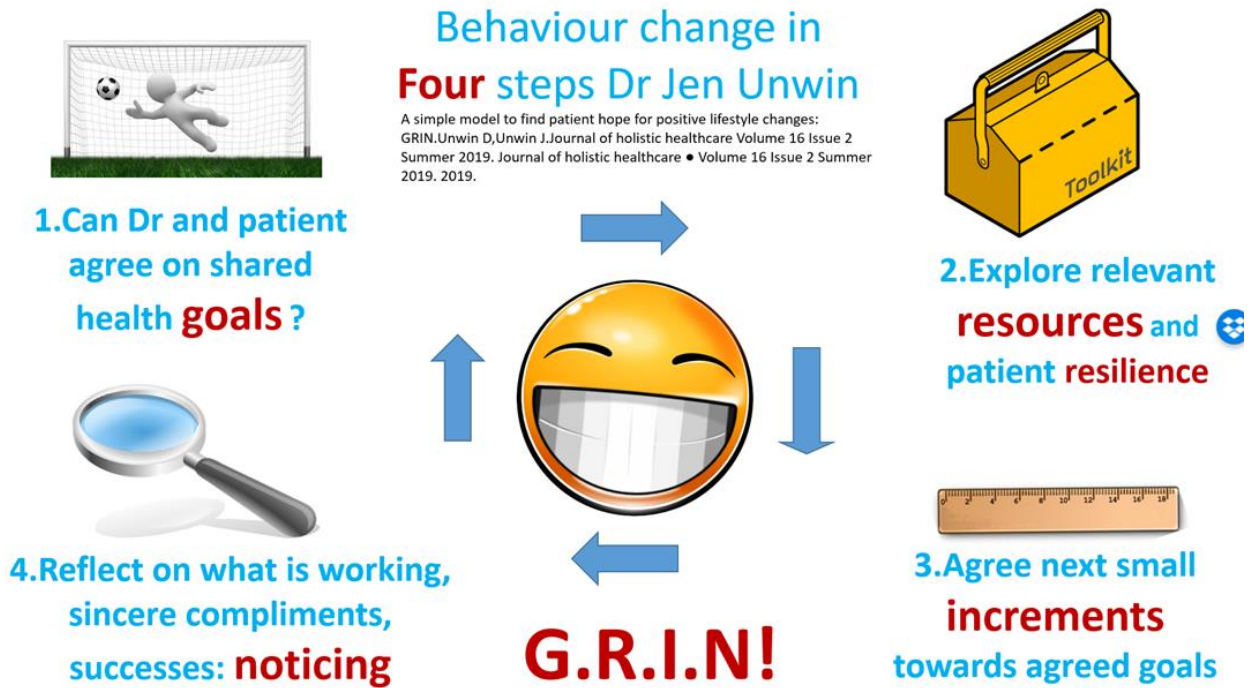
Sweeteners can trick you...

Finally, about sweeteners and what to drink – sweeteners have been proven to tease your brain into being even hungrier, making weight loss more difficult – drink tea, coffee, and water or herb teas. (100ml milk is 1 teaspoon of sugar)

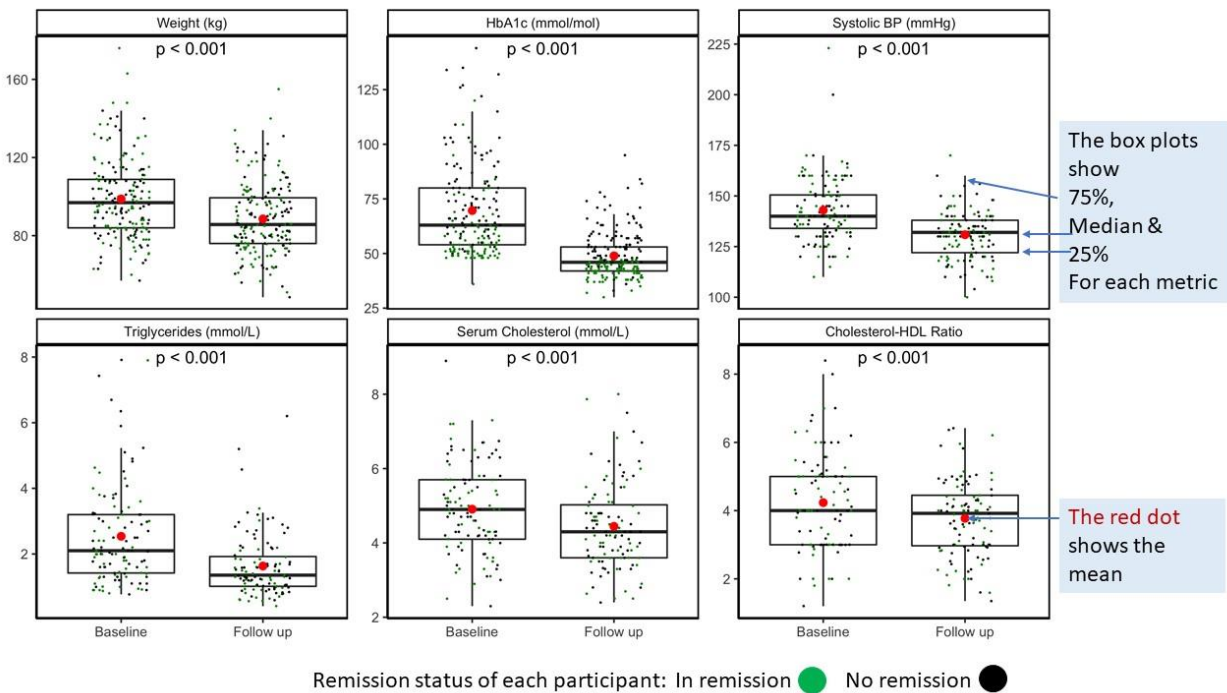
Typically, a low carb diet contains less than 130 grams of carb per day. How low to go depends on many factors. Discuss this with your health care practitioner

Important On prescribed medication? Check this first with your Doctor or HCP before making big changes to your diet. **PS some folk need more salt on a low carb diet**

Item 4. An infographic on goal setting, behavior change and use of feedback



Item 5 A more detailed examination of the data that produced figure 1 showing box plots for the baseline and latest follow up data for six metrics



Item 6 Linear regression model fitted with HbA1c reduction as the outcome and baseline HbA1c as the predictor

Figure x Regression model data for

Call: `lm(formula = HbA1cLoss2 ~ HbA1cStart, data = Data)`

```

Dependent variable:      HbA1cLoss2
HbA1cStart      Coefficient  -0.770***
                  Std.error   (0.034)
                  p           <2x10-16
Constant        Coefficient   33.008***
                  Std.error   (2.466)
                  p           <2x10-16

```

```

-----
Observations              183
R2                        0.740
Adjusted R2               0.738
Residual Std. Error      9.500 (df = 181)
F Statistic               514.024*** (df =1; 181)

```

Item 7 Logistic regression model for remission of diabetes as the outcome and baseline HbA1c, weight, age and gender as the predictor

`glm(formula = RemissionNum ~ WeightStart + Age + Gender + HbA1cStart, family = "binomial", data = Data)`

Deviance Residuals:

Min	1Q	Median	3Q	Max
-1.81852	-0.94651	-0.08194	0.78841	2.75309

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)	4.649589	2.006606	2.317	0.0205 *
WeightStart	0.007774	0.010141	0.767	0.4433
Age	-0.010272	0.017317	-0.593	0.5531
GenderMale	0.481003	0.362964	1.325	0.1851
HbA1cStart	-0.075745	0.013129	-5.769	7.97e-09 ***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 250.87 on 180 degrees of freedom

Residual deviance: 192.99 on 176 degrees of freedom

(5 observations deleted due to missingness)

AIC: 202.99 Number of Fisher Scoring iterations: 5

Item 8. Table comparing baseline number of years since diagnosis and the percentage in each category achieving remission

Years since diagnosis of T2 diabetes	Total number of patients choosing a low carb approach	Number achieving remission	Number not achieving remission	Percentage achieving remission
<1 year	70	54	16	77%
1-5 years	46	16	30	35%
6-10 years	35	11	24	31%
11-15 years	25	11	14	44%
15+ years	10	2	8	20%
Total	186	94	92	51%

Item 9 Logistic regression model for remission of diabetes as the outcome and time since diagnosis, baseline; HbA1c, weight, age and gender as the predictor.

A logistic regression model fitted with remission as the outcome with gender, baseline age, baseline weight, baseline HbA1c, and duration of diabetes (in months) found a relationship with both baseline HbA1c and baseline duration of diabetes on remission. A lower baseline HbA1c and a shorter duration of diabetes were significantly related to remission, even after controlling for baseline weight, age and gender (- 0.007/month, p value = 0.010).

The relationship of remission with recent diagnosis was also seen if duration of diabetes was considered as a binary variable of less than 1 year or 1 year or more (-1.29, p value 0.002) Time since diagnosis as a continuous variable.

Statistical work is below

```
glm(formula = RemissionNum ~ WeightStart + Age + Gender + HbA1cStart +
MonthsSinceDiagnosisT2, family = "binomial", data = Data)
```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-1.93009	-0.81937	-0.08784	0.79863	2.83733

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)...	4.249734	2.024828	2.099	0.0358 *
WeightStart ...	0.00578 9	0.010212	0.567	0.5708
Age...	0.001134	0.018167	0.062	0.9502
GenderMale ...	0.539421	0.370737	1.455	0.1457
HbA1cStart...	-0.071033	0.013028	-5.452	4.97e-08 ***
MonthsSinceDiagnosisT2.	-0.007213	0.002815	-2.562	0.0104 *

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 250.87 on 180 degrees of freedom

Residual deviance: 186.17 on 175 degrees of freedom

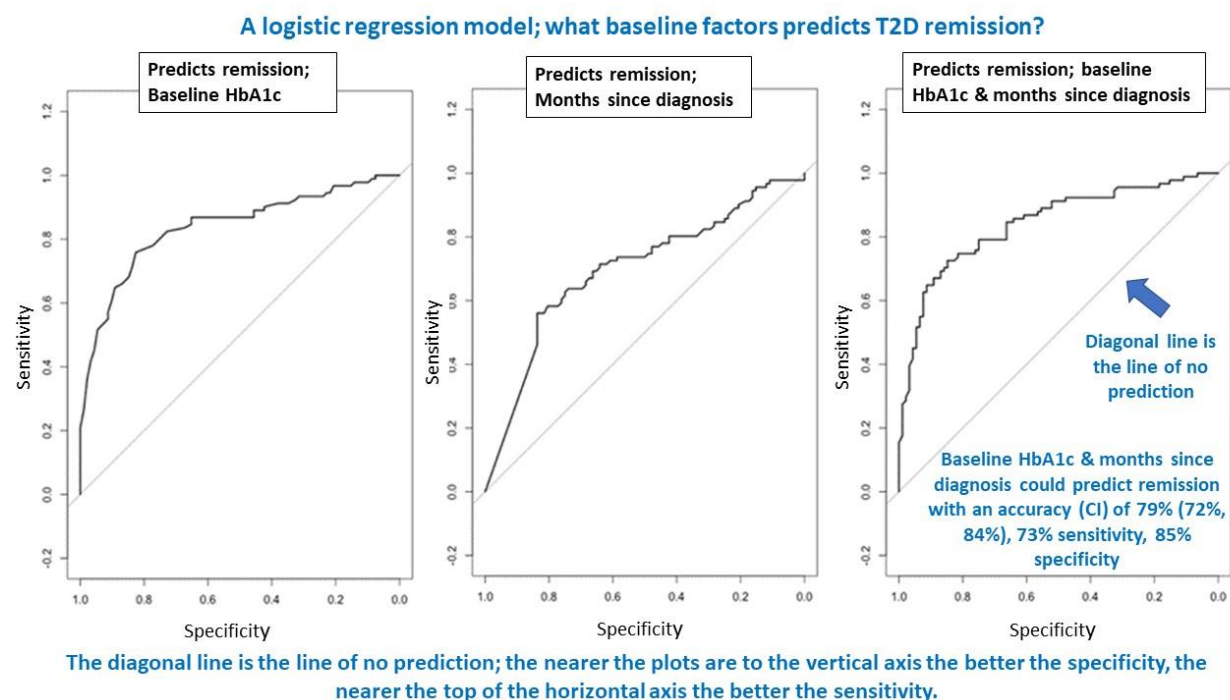
(5 observations deleted due to missingness)

AIC: 198.17

Number of Fisher Scoring iterations: 5

Item 10 Performance of logistic models in predicting remission; an explanation

Logistic regression was carried out to predict remission status using baseline; HbA1c, time since diagnosis or both. For each model the threshold was determined from the ROC curve (pictured; 0.58, 0.62 and 0.61 respectively).



A logistic regression model predicting Remission from baseline HbA1c (as a continuous variable) could predict remission with an accuracy (CI) of 79% (73%, 85%), 76% sensitivity, 83% specificity and an f1 score of 0.78.

A logistic regression model predicting Remission from time since diagnosis (as a continuous variable) could predict remission with an accuracy (CI) of 70% (63%, 76%), 56% sensitivity, 84% specificity and an f1 score of 0.65.

A logistic regression model predicting remission from both baseline HbA1c and baseline months since diagnosis (both continuous variables) could predict remission with an accuracy (CI) of 79% (72%, 84%), 73% sensitivity, 85% specificity and an f1 score of 0.77.

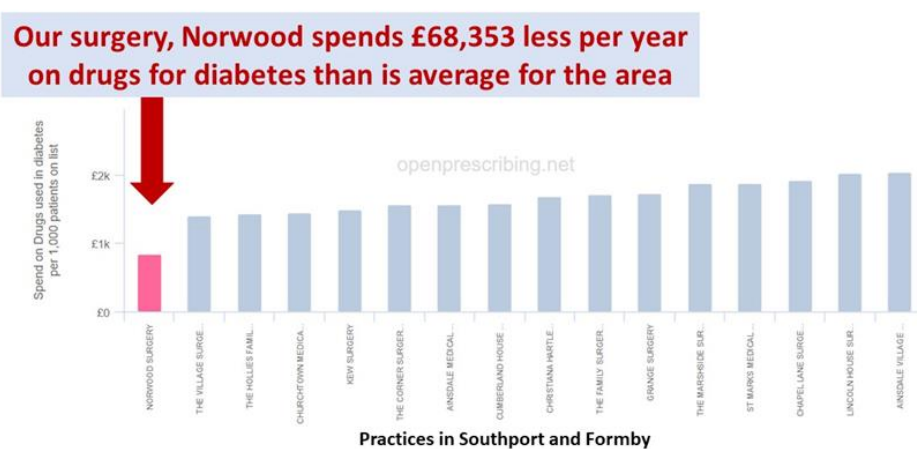
Model data

Predictor	HbA1c	Months since diagnosis	HbA1c+MonthsSinceDiag
accuracy (LCI, UCI)	0.79 (0.73, 0.85)	0.7 (0.63, 0.76)	0.79 (0.72, 0.84)
kappa	0.58	0.4	0.57
mcnemar	0.42	0	0.11
sensitivity	0.76	0.56	0.73
specificity	0.83	0.84	0.85
pos_pred_value	0.81	0.77	0.83
neg_pred_value	0.78	0.66	0.76
precision	0.81	0.77	0.83

recall	0.76	0.56	0.73
f1	0.78	0.65	0.77
prevalence	0.50	0.5	0.5
detection_rate	0.38	0.28	0.36
detection_prevalence	0.46	0.36	0.44
balanced_accuracy	0.79	0.7	0.79

Item 11 Openprescribing data

Spend on antidiabetic drugs (BNF 6.1) vs patients on list by NORWOOD SURGERY and other practices in Southport area. January 2022



(From Openprescribing.net: Accessed march 2022)

Notes on the statistics

There was debate between the authors about which measures of distribution were most accurate, either Median (IQR) or Mean (SD). Table 1 has been designed to encompass both Median IQR and Mean SD so readers can see both. Three of the metrics (HbA1c, Systolic BP & triglyceride levels) have a mean that is greater than the median see, making a normal distribution unlikely. HbA1c is a particularly good example of this starting as it does with a cut off at 48 mmol/mol. Overall we stuck with Median IQR as probably being more accurate (although both appear in the version above). There were data showing a more convincing normal distribution like duration of diet where we used Mean SD.

In collecting our data there is the problem of what to do about people who give up on the low carb diet after a period of time. Since our basic question is about 'what happens to people who chose a low carb diet' We decided to only collect data while we knew the participant was low carb. In the case of those who gave the diet up we stopped collecting data when they were telling us they were still on the diet, so that this became the date of latest follow up This shortening of follow up is thus automatically included in the calculations for average time on the diet.

One of the reviewers asked

Did the patients get other advice besides a low carbohydrate diet, e.g. improving physical activity?

This advice is given to all people with T2D as part of routine UK NHS care. The low carb advice was separate and additional to this.

More on the physiology of T2D, from 2012 Banting lecture by R Taylor. Taylor R. Banting Memorial lecture 2012: reversing the twin cycles of type 2 diabetes. *Diabet Med.* 2013;30(3):267-75.

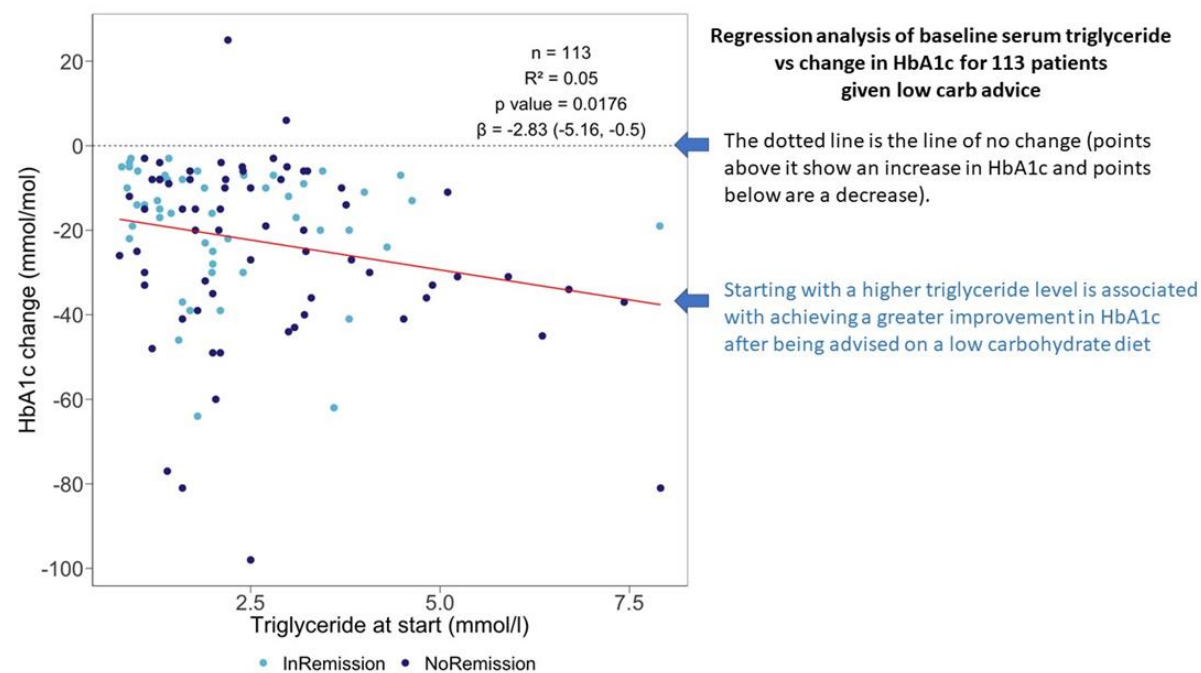
Any excess carbohydrate cannot be stored once the glycogen depots are full. If more glucose is ingested than can be oxidized for energy or stored as glycogen, it has to be turned into fat by the process of de novo lipogenesis. This process only happens in the liver in humans, and triglyceride synthesized in situ is particularly likely to be stored in hepatocytes rather than exported for safe storage in subcutaneous adipose tissue. The newly synthesized fat has three possible fates: it can be oxidized for energy; exported as VLDL in the plasma to be delivered to other tissues or it can be stored in a rather full liver. As de novo lipogenesis is stimulated by insulin, those people who are relatively insulin resistant in muscle—and who therefore have a raised plasma insulin level—are especially likely to accumulate fat in the liver.(9)

Also from 'The Candy study': Sevastianova K, Santos A, Kotronen A, Hakkarainen A, Makkonen J, Silander K, et al. Effect of short-term carbohydrate overfeeding and long-term weight loss on liver fat in overweight humans. *Am J Clin Nutr.* 2012;96(4):727-34.

Volunteers were asked to eat a bag of sweets, drink a 300-ml bottle of Pepsi and 30 ml of fruit juice each day in addition to their usual food. This sucrose overfeeding for 3 weeks brought about a 27% increase in liver fat content. This was associated with a 30% rise in serum alanine aminotransferase (ALT), indicating the associated metabolic stress on hepatocytes(10)

Carbohydrate overfeeding for 3 wk induced a >10-fold greater relative change in liver fat (27%) than in body weight (2%). The increase in liver fat was proportional to that in de novo lipogenesis. Weight loss restores liver fat to normal. These data indicate that the human fatty liver avidly accumulates fat during carbohydrate overfeeding and support a role for DNL in the pathogenesis of NAFLD

Linear regression analysis of baseline serum triglyceride vs change in HbA1c for 113 patients given low carb advice



A linear regression model fitted with HbA1c reduction as the outcome and baseline serum triglyceride as the predictor demonstrated a relationship $R^2 0.05$ $p=0.0176$. Those with a higher triglyceride level at baseline

were likely to achieve a greater improvement in HbA1c. However, no relationship was seen when controlling for baseline HbA1c. Baseline HbA1c and baseline TG are moderately correlated (0.27) therefore high baseline TG may not be independently related.

Supplementary File. Insights from a general practice service evaluating a lower carbohydrate diet in patients with type 2 diabetes mellitus over 8 years: what predicts successful drug-free remission and what happens to those who do not achieve this goal? Unwin D. et al. 2022

Item 1. Doctor/Nurse protocol Norwood Surgery: T2D, prediabetes, lower carb dietary option

Doctor/Nurse protocol Norwood Surgery: T2D, prediabetes, lower carb dietary option (this document is under regular review, please let DJU know if it can be improved).

General points

Remember not all low carb diets are necessarily good, for example a diet coke and pepperoni sausage diet is low carb, but not well formulated. A well formulated low carb diet will be full of fibre & essential nutrients(1) see the Norwood low carb diet sheet.

In general, we are trying to avoid the high blood glucose levels that lead to poor health, the new concept of 'time in range'(2) made possible by devices like the Freestyle Libre are a helpful extension of this.

Try to see patients and their high blood sugars as an interesting puzzle rather than a problem. One to be worked out with the patient; so our approach is collaborative.

At the first appointment for those people interested in this approach:

- Explore possible benefits/ risks of a lower carb approach to T2diabetes (eg medications, risk of hypo) and make a start on motivation. The idea of diabetes remission or coming off meds is very motivating for many people. At Norwood 50% of those choosing a low carb diet achieve drug free T2diabetes remission. Of those recently diagnosed (<12 months) the remission rate is 76%.

An example of the type of question you can ask.

'You have a range of different possible futures WRT to your diabetes, which will you choose?' 'In this clinic to date the average weight loss on low carb is 9Kg, is this of interest to you?' etc.,

- Check are the patients interested in the low carb approach, there are others (eg VLCD)?

-Visit basic physiology of sugar starting with the fact that 'your HbA1c shows how sugary your diet has been in the last few months', and explaining sugar can almost be seen as a metabolic poison to someone with T2D.

Ask 'where do you think the sugar has come from in your diet?' (An exception to this is the 'Dawn phenomenon' where overnight gluconeogenesis results in a high fasting glucose)

- Explain dietary sources of glucose with Norwood sugar equivalence infographics(3).

- Give the Norwood standard diet sheet for low carb approach.

- Establish baseline data; Wt., waist, height, bloods; HbA1c, renal, fasting lipids, FBC.

-Enter EMIS computer code 'low carbohydrate diet'.

-Medications

? **Risk of hypoglycaemia** (Insulin, gliclazide) reduce dose/stop but monitor

? **Risk of DKA** (SGL2Inhibitors). Stop, but monitor blood glucose.

? **Risk of hypotension**, explain that with weight loss BP may well improve and medications for this may be reduced or cut back

-Salt; Due to the renal sodium retaining properties of insulin(4) for those with T2D going low carb and therefore lower insulin results in considerable loss of sodium and consequently a diuresis. Patients may well need to increase their salt intake –particularly in the first few weeks of the diet.

-Suggest a review date - often 2 or 4 weeks depending on assessed risks. Perhaps longer for pre-diabetes

On review

Weigh, measure waist, BP. Do medications need to be changed? See above

How is it going? Problems/suggestions

Produce Emis graphs of Weight., HbA1c etc. as feedback to maintain motivation.

Ask about hunger and appetite. Hungry people are unlikely to stick to a diet. Many people who drop the carbs enough also drop their insulin sufficiently to allow them to burn their own fat as fuel(5) -so they become 'fat burners' who are far less hungry. Do they need to drop their carbs a little more so they can burn fat? Another possibility to help with hunger is to increase the dietary protein.

Think about the possibility of 'food addiction' for those who are struggling with cravings or experiencing weight gain(6). If moderation is impossible, rather like someone with an alcohol problem, abstinence from 'trigger foods' may be the answer. Possibly suggest a book; 'Fork in the Road' it's on Amazon.

Do they wish to continue?

Are they happy to share anonymised data for our on-going audit of service provision?(please explain what this means) This extra level of patient data protection is not actually needed for audit but Norwood feels it's good practice.

If so enter Emis GP computer code 'obtaining consent'

Would they like to attend the Zoom group sessions –do they know how to find out when the next one is?

Three worrying patterns wrt HbA1c and weight

1. **If both weight and HbA1c are climbing** the most common reason is 'carb creep' **NOT** failure of the diet needing medication. So check for this by rechecking dietary intakes. Over time many patients drift. It's better to see this as a learning opportunity. We all learn from our mistakes!
2. **Weight loss alongside a climbing HbA1c** is worrying –ask a doctor about this. ? T1D, ?Malignancy
3. **HbA1c 'too good'** eg. 28mmol/mol could the patient be anaemic?

Constipation?

Magnesium supplements can help a lot with this and can help with insulin sensitivity(7)

More fluids

More nuts or green veg

Next steps

Review date and agree next blood test (HbA1c etc.) -usually at 2 months from the start, but this depends on a risk analysis.

Lipid profiles Fasting profiles are preferable as triglyceride/HDL ratios are a better predictor of risk than LDL Lipid profiles usually (but not always) improve on low carb(8)

Remember NICE UK guidelines 1.3.6 Individualise recommendations for carbohydrate and alcohol intake, and meal patterns. **Reducing the risk of hypoglycaemia should be a particular aim for a person using insulin or an insulin secretagogue. [2009]**

Often this is achieved by increasing dietary carbs at the expense of weight gain **An alternative** is to reduce carbs and the drugs involved this has the advantage of weight loss and improvements in BP

Finally, for prescribers Drugs for diabetes and the low carb approach taken from; Murdoch C, Unwin D, Cavan D, Cucuzzella M, Patel M. Adapting diabetes medication for low carbohydrate management of type 2 diabetes: a practical guide. Br J Gen Pract. 2019;69(684):360-1.

For clinicians considering advising a lower carbohydrate diet for patients who are already on anti-diabetic medications, there are three important considerations:

- 1) Whether the drug/diet combination poses a risk of hypoglycaemia. Insulin is an obvious culprit for this as are some oral agents such as gliclazide. Careful measurement of blood glucose, dose reduction and/or cessation of culprit drugs is crucial to patient safety.
- 2) SGLT2 inhibitor drugs; combined with a low carbohydrate diet, have the potential to lead to diabetic ketoacidosis that may be masked by relative normoglycaemia. This class of drugs probably ought to be avoided in this context or at least have the dosage reduced. For some patients with comorbidities such as chronic kidney disease, some experienced practitioners / nephrologists acknowledge the effectiveness of SGLT2s and opt to using both SGLT2 and a low carb diet, BUT this is undertaken with close monitoring and proper attention to the 'sick day rules' for these drugs.
- 3) As demonstrated in our service evaluation data and elsewhere (1), lowering carbohydrate in the diet is associated with a lowering of BP. For patients already on antihypertensive medication, this can lead to symptomatic hypotension requiring dose reduction and/or cessation of culprit drugs.

Prescribing T2D medication in the context of a carbohydrate-restricted diet was the subject of a useful British Journal of General Practice review* that states the diet is safe with metformin, the most commonly prescribed anti-diabetic medication. In addition to deprescribing anti-diabetic medications analysis from the Norwood GP practice on hypertension, published separately (1), shows that 20% of the antihypertensive drugs were also stopped due to significant improvements in BP.

*From Unwin DJ, Tobin SD, Murray SW, Delon C, Brady AJ. Substantial and Sustained Improvements in Blood Pressure, Weight and Lipid Profiles from a Carbohydrate Restricted Diet: An Observational Study of Insulin Resistant Patients in Primary Care. *International Journal of Environmental Research and Public Health*. 2019;16(15):2680.

Useful resources

The Freshwell App free [Freshwell on the App Store \(apple.com\)](https://www.apple.com/uk/app-store/apps/1444444444)

The Reverse Your Diabetes Cookbook: Lose weight and eat to beat type 2 diabetes. Kate Caldesi

https://www.amazon.co.uk/Reverse-Your-Diabetes-Cookbook/dp/0857838571/ref=sr_1_4?crd=2U3I993FVS76V&key

Fork in the Road. Dr Jen Unwin Available only from Amazon. Kindle version also

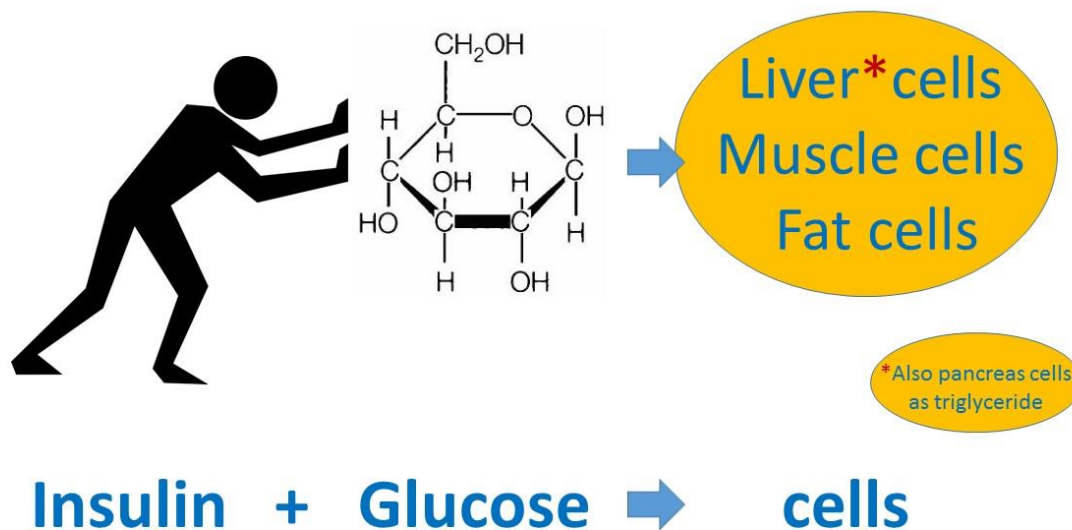
<https://www.amazon.co.uk/s?k=fork+in+the+road+jen+unwin&crd=2UBGTLF924JWE&srefix=fork+in+th%2Caps%2C281>

-
1. Zinn C, Rush A, Johnson R. Assessing the nutrient intake of a low-carbohydrate, high-fat (LCHF) diet: a hypothetical case study design. *BMJ Open*. 2018;8(2):e018846.
 2. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. *Diabetes Care*. 2019;42(8):1593-603.
 3. David Unwin DH, Geoffrey Livesey,. It is the glycaemic response to, not the carbohydrate content of food that matters in diabetes and obesity: The glycaemic index revisited. *Journal of Insulin Resistance*. 2016;2016;1(1), a8. (<https://insulinresistance.org/index.php/jir/article/view/8/11>).
 4. Unwin DJ, Tobin SD, Murray SW, Delon C, Brady AJ. Substantial and Sustained Improvements in Blood Pressure, Weight and Lipid Profiles from a Carbohydrate Restricted Diet: An Observational Study of Insulin Resistant Patients in Primary Care. *International Journal of Environmental Research and Public Health*. 2019;16(15):2680.
 5. Dimitriadis G, Mitrou P, Lambadiari V, Maratou E, Raptis SA. Insulin effects in muscle and adipose tissue. *Diabetes Res Clin Pract*. 2011;93 Suppl 1:S52-9.
 6. Gordon EL, Ariel-Donges AH, Bauman V, Merlo LJ. What Is the Evidence for "Food Addiction?" A Systematic Review. *Nutrients*. 2018;10(4):477.
 7. Morais JBS, Severo JS, de Alencar GRR, de Oliveira ARS, Cruz KJC, Marreiro DDN, et al. Effect of magnesium supplementation on insulin resistance in humans: A systematic review. *Nutrition*. 2017;38:54-60.
 8. Gjuladin-Hellon T, Davies IG, Penson P, Amiri Baghbadorani R. Effects of carbohydrate-restricted diets on low-density lipoprotein cholesterol levels in overweight and obese adults: a systematic review and meta-analysis. *Nutr Rev*. 2018.

9. Taylor R. Banting Memorial lecture 2012: reversing the twin cycles of type 2 diabetes. *Diabet Med.* 2013;30(3):267-75.
10. Sevastianova K, Santos A, Kotronen A, Hakkarainen A, Makkonen J, Silander K, et al. Effect of short-term carbohydrate overfeeding and long-term weight loss on liver fat in overweight humans. *Am J Clin Nutr.* 2012;96(4):727-34.

Item 2. Four infographics used to help people with T2D understand insulin and glucose

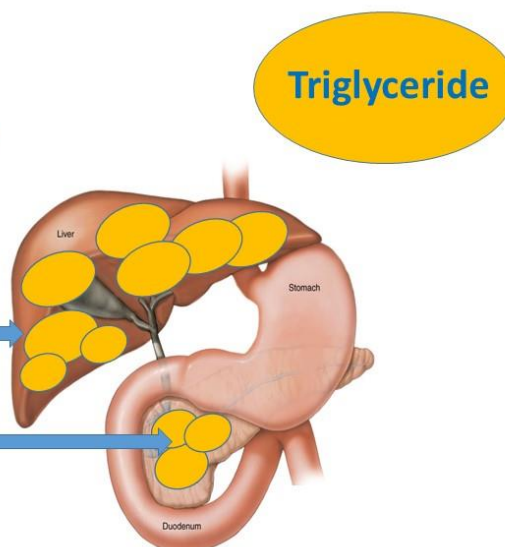
The hormone insulin can be thought of as pushing glucose out of the blood stream and into cells to reduce blood sugar. In some cells it becomes fat



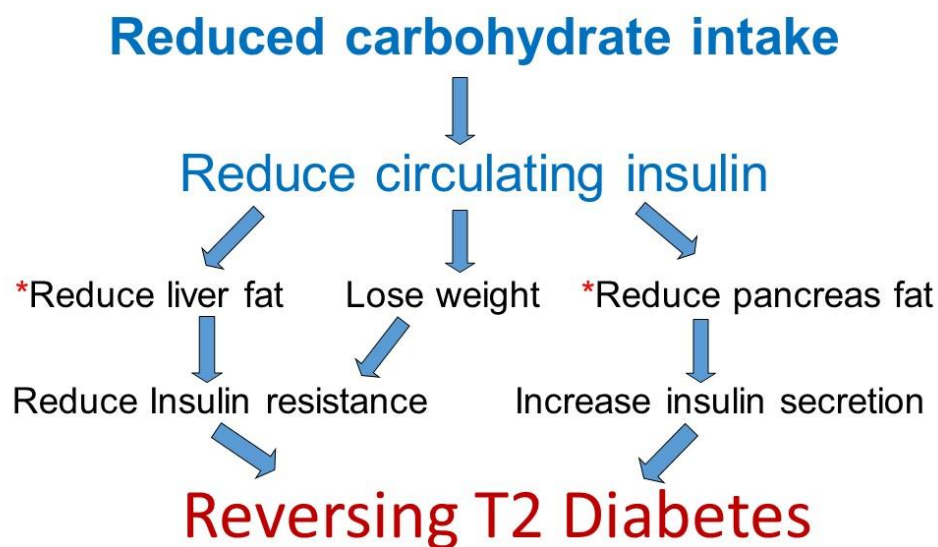
Type 2 diabetes results in part from accumulation of fat in the liver and pancreas

Liver fat: linked to insulin resistance

Pancreatic fat: inhibits B cell function -cannot produce enough insulin

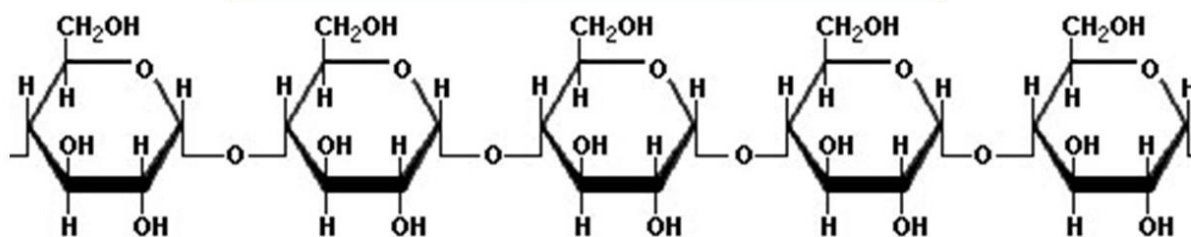


Reversal of type 2 diabetes: Normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Lim EL1, Hollingsworth KG, Taylor R. *Diabetologia.* 2011 Oct;54(10):2506-14. doi: 10.1007/s00125-011-2204-7.



*Reversal of type 2 diabetes: Normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Lim EL1, Hollingsworth KG, Taylor R. Diabetologia. 2011 Oct;54(10):2506-14. doi: 10.1007/s00125-011-2204-7.

A Starch Molecule



Many glucose molecules are linked together – enzymal digestion will break them up again

Item 3 A lower carb diet sheet for type 2 diabetes: On the whole for people with T2D we are trying to minimise the damage done over time by high blood sugars. In this condition your metabolism struggles to deal with both sugar itself and the starchy carbohydrates that digest down into surprising amounts of sugar

Sugar – cut it out altogether, although it will be in the blueberries, strawberries and raspberries you are allowed to eat. Cakes and biscuits are a mixture of sugar and starch that make it almost impossible to avoid food cravings; they just make you hungrier!!

Reduce starchy carbs a lot Remember they digest down into surprising amounts of sugar. If possible just cut out the ‘White Stuff’ like bread, rice, pasta, potato, crackers and cereals.

All green veg/salads are fine...Eat as much of these as you can –turn the white stuff green

So that you still eat a good big dinner try substituting veg such as broccoli, courgettes or green beans for your mash, pasta or rice – still covering them with your gravy, Bolognese or curry! Cauliflower rice is now widely available

Tip: try home-made soup – it can be taken to work for lunch and microwaved. Mushrooms, tomatoes, and onions can be included in this.

Fruit is trickier...

Some tropical fruits like bananas, oranges, grapes, mangoes or pineapple have too much sugar in and can set those carb cravings off. Berries are better and can be eaten; blueberries, raspberries, strawberries, apples and pears too.

Eat healthy proteins...

Try basing your meals on non-processed meat like chicken or red meat, eggs (three eggs a day is not too much), fish – particularly oily fish such as salmon, mackerel or tuna –are fine and can be eaten freely. Plain **full fat** yoghurt makes a good breakfast with the berries. Processed meats such as bacon, ham, sausages or salami are not as healthy and should only be eaten in moderation.

Healthy fats are fine in moderation...

Yes, fats can be fine in moderation: olive oil is very useful, butter may be tastier than margarine and could be better for you! Coconut oil is great for stir fries. Four essential vitamins A, D, E and K are only found in some fats or oils. Please avoid margarine, corn oil and vegetable oil.

Beware ‘low fat’ foods. They often have sugar or sweeteners added to make them palatable. Full fat mayonnaise and pesto are definitely on!!

Cheese only in moderation...

It’s a very calorific mixture of fat, and protein.

Snacks: avoid, as habit forming. But un-salted nuts such as almonds or walnuts are OK to stave off hunger. The occasional treat of strong dark chocolate 70% or more in small quantity is allowed.

Eating lots of green veg with protein and healthy fats leaves you properly full in a way that lasts

Alcohol is full of carbs...

Sadly many alcoholic drinks are full of carbohydrate – for example, beer is almost ‘liquid toast’ hence the beer belly!! The odd glass of dry white, red wine or spirits is not too bad if it doesn’t make you hungry afterwards – or just plain water with a slice of lemon.

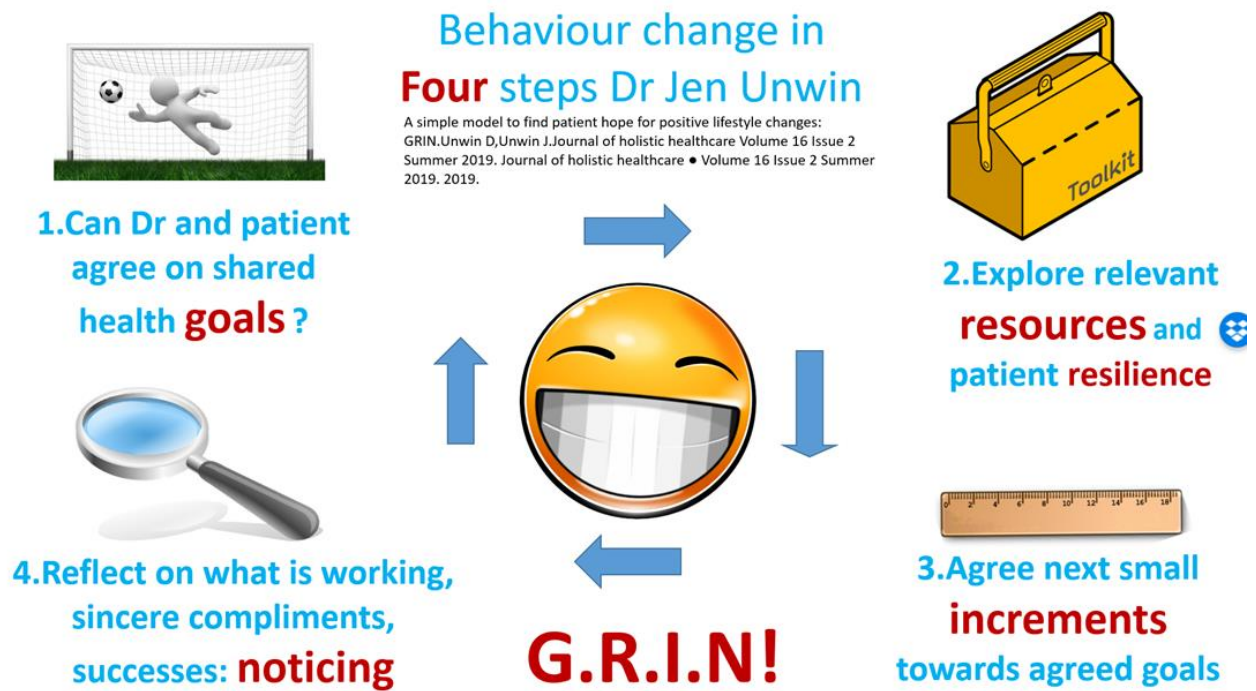
Sweeteners can trick you...

Finally, about sweeteners and what to drink – sweeteners have been proven to tease your brain into being even hungrier, making weight loss more difficult – drink tea, coffee, and water or herb teas. (100ml milk is 1 teaspoon of sugar)

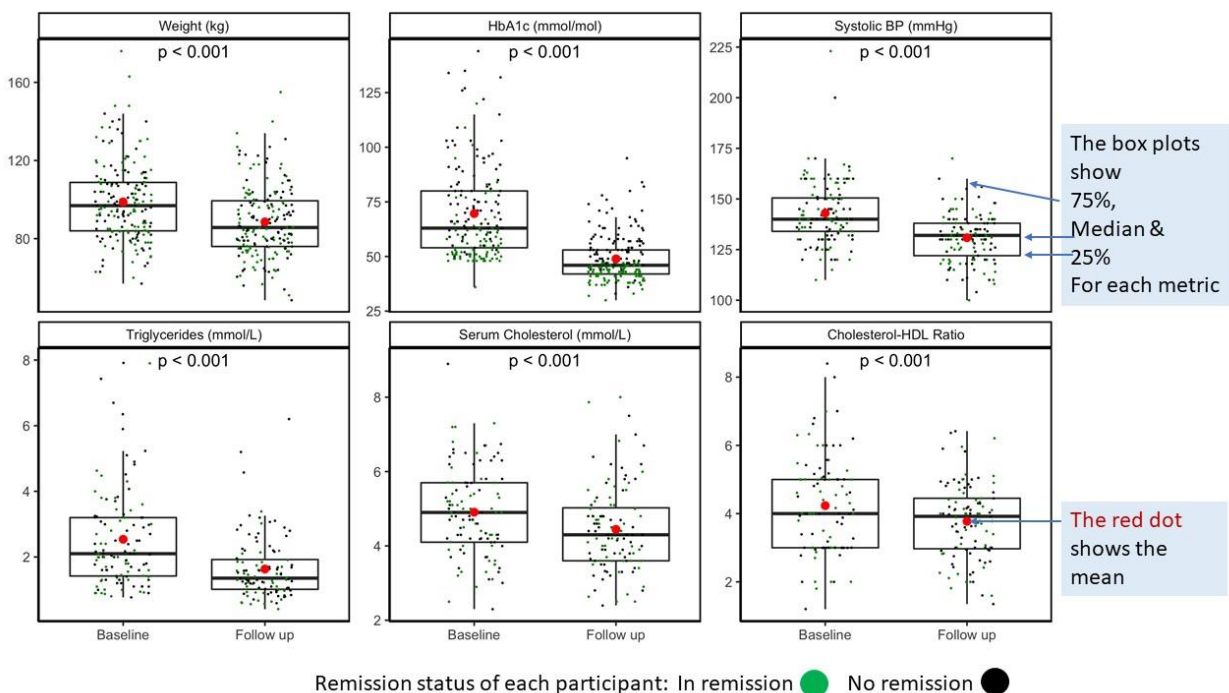
Typically, a low carb diet contains less than 130 grams of carb per day. How low to go depends on many factors. Discuss this with your health care practitioner

Important On prescribed medication? Check this first with your Doctor or HCP before making big changes to your diet. **PS some folk need more salt on a low carb diet**

Item 4. An infographic on goal setting, behavior change and use of feedback



Item 5 A more detailed examination of the data that produced figure 1 showing box plots for the baseline and latest follow up data for six metrics



Item 6 Linear regression model fitted with HbA1c reduction as the outcome and baseline HbA1c as the predictor

Figure x Regression model data for

Call: `lm(formula = HbA1cLoss2 ~ HbA1cStart, data = Data)`

```

Dependent variable:      HbA1cLoss2
HbA1cStart      Coefficient  -0.770***
                  Std.error   (0.034)
                  p          <2x10-16
Constant        Coefficient   33.008***
                  Std.error   (2.466)
                  p          <2x10-16

```

```

-----
Observations              183
R2                        0.740
Adjusted R2              0.738
Residual Std. Error      9.500 (df = 181)
F Statistic              514.024*** (df =1; 181)

```

Item 7 Logistic regression model for remission of diabetes as the outcome and baseline HbA1c, weight, age and gender as the predictor

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15+ years	10	2	8	20%
Total	186	94	92	51%

Item 9 Logistic regression model for remission of diabetes as the outcome and time since diagnosis, baseline; HbA1c, weight, age and gender as the predictor.

A logistic regression model fitted with remission as the outcome with gender, baseline age, baseline weight, baseline HbA1c, and duration of diabetes (in months) found a relationship with both baseline HbA1c and baseline duration of diabetes on remission. A lower baseline HbA1c and a shorter duration of diabetes were significantly related to remission, even after controlling for baseline weight, age and gender (- 0.007/month, p value = 0.010).

The relationship of remission with recent diagnosis was also seen if duration of diabetes was considered as a binary variable of less than 1 year or 1 year or more (-1.29, p value 0.002) Time since diagnosis as a continuous variable.

Statistical work is below

```
glm(formula = RemissionNum ~ WeightStart + Age + Gender + HbA1cStart +
MonthsSinceDiagnosisT2, family = "binomial", data = Data)
```

Deviance Residuals:

Min	1Q	Median	3Q	Max
-1.93009	-0.81937	-0.08784	0.79863	2.83733

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)
(Intercept)...	4.249734	2.024828	2.099	0.0358 *
WeightStart ...	0.00578 9	0.010212	0.567	0.5708
Age...	0.001134	0.018167	0.062	0.9502
GenderMale ...	0.539421	0.370737	1.455	0.1457
HbA1cStart...	-0.071033	0.013028	-5.452	4.97e-08 ***
MonthsSinceDiagnosisT2.	-0.007213	0.002815	-2.562	0.0104 *

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 250.87 on 180 degrees of freedom

Residual deviance: 186.17 on 175 degrees of freedom

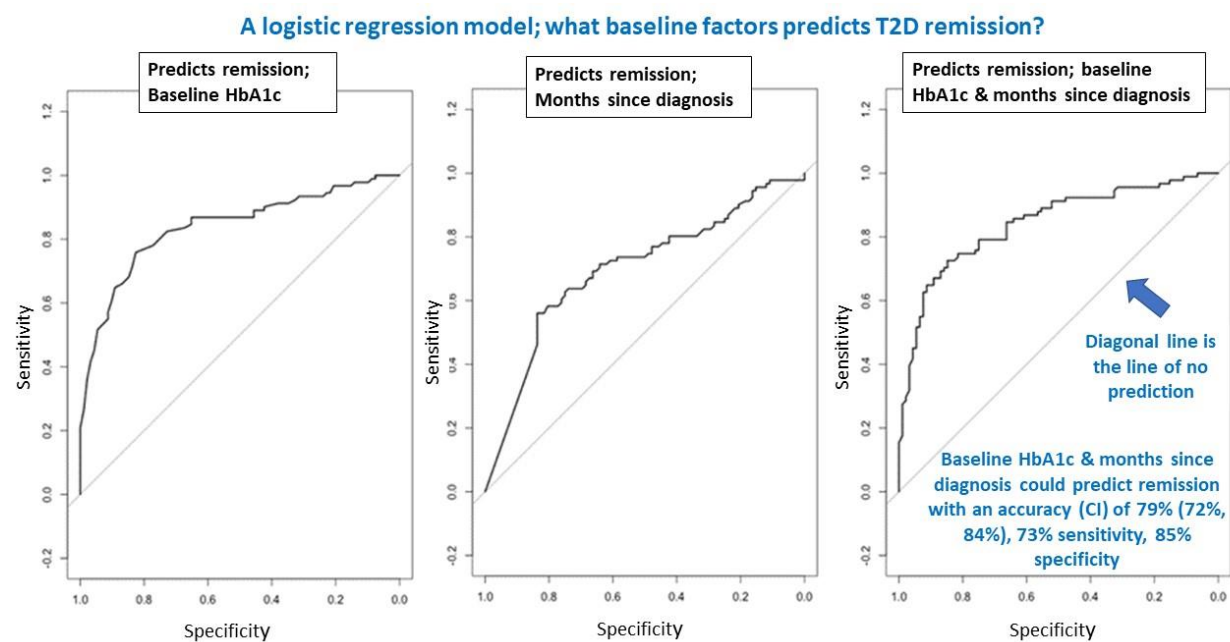
(5 observations deleted due to missingness)

AIC: 198.17

Number of Fisher Scoring iterations: 5

Item 10 Performance of logistic models in predicting remission; an explanation

Logistic regression was carried out to predict remission status using baseline; HbA1c, time since diagnosis or both. For each model the threshold was determined from the ROC curve (pictured; 0.58, 0.62 and 0.61 respectively).



The diagonal line is the line of no prediction; the nearer the plots are to the vertical axis the better the specificity, the nearer the top of the horizontal axis the better the sensitivity.

A logistic regression model predicting Remission from baseline HbA1c (as a continuous variable) could predict remission with an accuracy (CI) of 79% (73%, 85%), 76% sensitivity, 83% specificity and an f1 score of 0.78.

A logistic regression model predicting Remission from time since diagnosis (as a continuous variable) could predict remission with an accuracy (CI) of 70% (63%, 76%), 56% sensitivity, 84% specificity and an f1 score of 0.65.

A logistic regression model predicting remission from both baseline HbA1c and baseline months since diagnosis (both continuous variables) could predict remission with an accuracy (CI) of 79% (72%, 84%), 73% sensitivity, 85% specificity and an f1 score of 0.77.

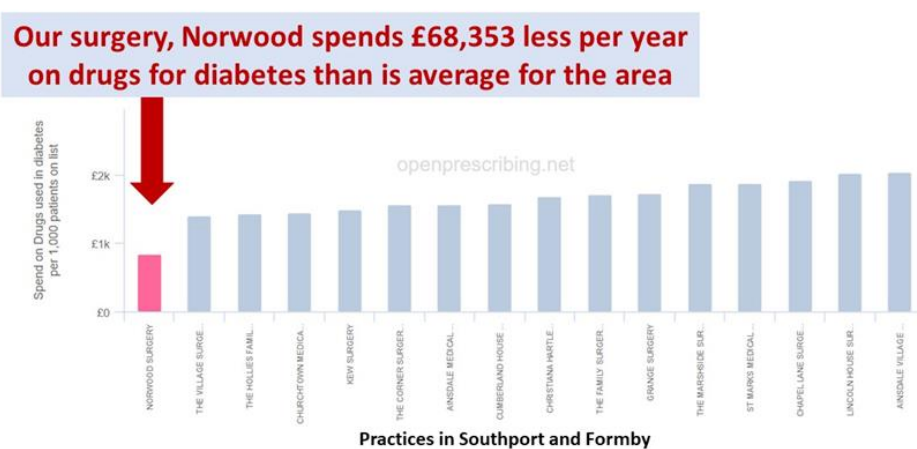
Model data

Predictor	HbA1c	Months since diagnosis	HbA1c+MonthsSinceDiag
accuracy (LCI, UCI)	0.79 (0.73, 0.85)	0.7 (0.63, 0.76)	0.79 (0.72, 0.84)
kappa	0.58	0.4	0.57
mcnemar	0.42	0	0.11
sensitivity	0.76	0.56	0.73
specificity	0.83	0.84	0.85
pos_pred_value	0.81	0.77	0.83
neg_pred_value	0.78	0.66	0.76
precision	0.81	0.77	0.83

recall	0.76	0.56	0.73
f1	0.78	0.65	0.77
prevalence	0.50	0.5	0.5
detection_rate	0.38	0.28	0.36
detection_prevalence	0.46	0.36	0.44
balanced_accuracy	0.79	0.7	0.79

Item 11 Openprescribing data

Spend on antidiabetic drugs (BNF 6.1) vs patients on list by NORWOOD SURGERY and other practices in Southport area. January 2022



(From Openprescribing.net: Accessed march 2022)

Notes on the statistics

There was debate between the authors about which measures of distribution were most accurate, either Median (IQR) or Mean (SD). Table 1 has been designed to encompass both Median IQR and Mean SD so readers can see both. Three of the metrics (HbA1c, Systolic BP & triglyceride levels) have a mean that is greater than the median see, making a normal distribution unlikely. HbA1c is a particularly good example of this starting as it does with a cut off at 48 mmol/mol. Overall we stuck with Median IQR as probably being more accurate (although both appear in the version above). There were data showing a more convincing normal distribution like duration of diet where we used Mean SD.

In collecting our data there is the problem of what to do about people who give up on the low carb diet after a period of time. Since our basic question is about 'what happens to people who chose a low carb diet' We decided to only collect data while we knew the participant was low carb. In the case of those who gave the diet up we stopped collecting data when they were telling us they were still on the diet, so that this became the date of latest follow up This shortening of follow up is thus automatically included in the calculations for average time on the diet.

One of the reviewers asked

Did the patients get other advice besides a low carbohydrate diet, e.g. improving physical activity?

This advice is given to all people with T2D as part of routine UK NHS care. The low carb advice was separate and additional to this.

More on the physiology of T2D, from 2012 Banting lecture by R Taylor. Taylor R. Banting Memorial lecture 2012: reversing the twin cycles of type 2 diabetes. *Diabet Med.* 2013;30(3):267-75.

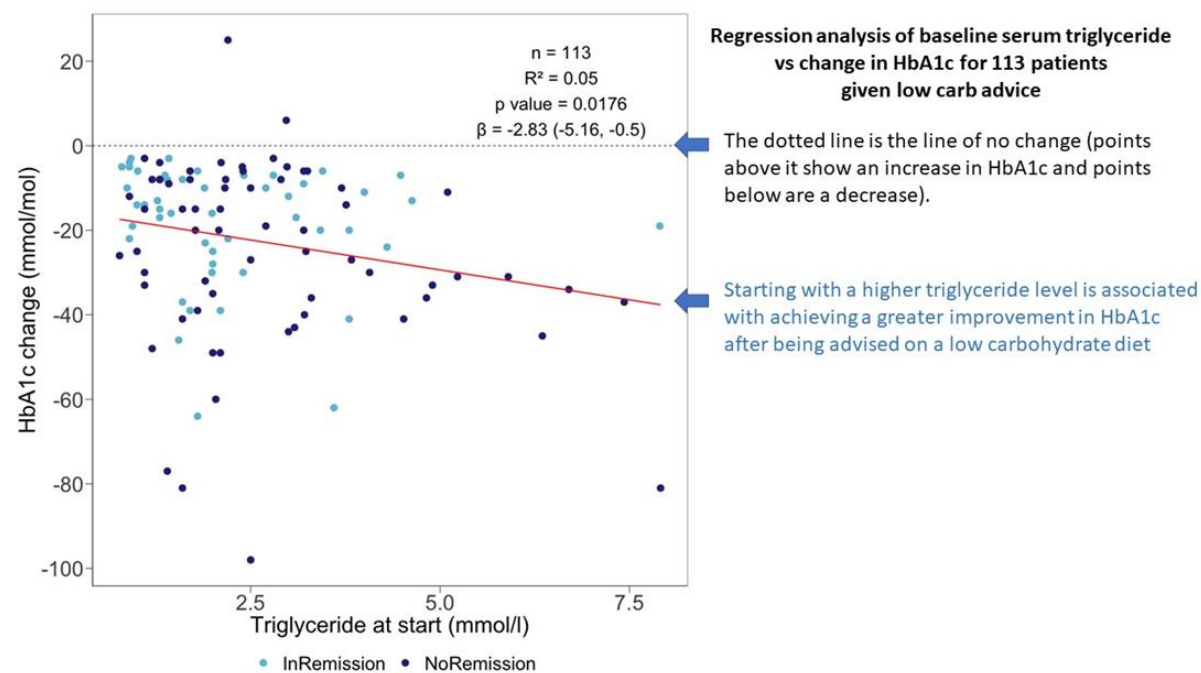
Any excess carbohydrate cannot be stored once the glycogen depots are full. If more glucose is ingested than can be oxidized for energy or stored as glycogen, it has to be turned into fat by the process of de novo lipogenesis. This process only happens in the liver in humans, and triglyceride synthesized in situ is particularly likely to be stored in hepatocytes rather than exported for safe storage in subcutaneous adipose tissue. The newly synthesized fat has three possible fates: it can be oxidized for energy; exported as VLDL in the plasma to be delivered to other tissues or it can be stored in a rather full liver. As de novo lipogenesis is stimulated by insulin, those people who are relatively insulin resistant in muscle—and who therefore have a raised plasma insulin level—are especially likely to accumulate fat in the liver.(9)

Also from 'The Candy study': Sevastianova K, Santos A, Kotronen A, Hakkarainen A, Makkonen J, Silander K, et al. Effect of short-term carbohydrate overfeeding and long-term weight loss on liver fat in overweight humans. *Am J Clin Nutr.* 2012;96(4):727-34.

Volunteers were asked to eat a bag of sweets, drink a 300-ml bottle of Pepsi and 30 ml of fruit juice each day in addition to their usual food. This sucrose overfeeding for 3 weeks brought about a 27% increase in liver fat content. This was associated with a 30% rise in serum alanine aminotransferase (ALT), indicating the associated metabolic stress on hepatocytes(10)

Carbohydrate overfeeding for 3 wk induced a >10-fold greater relative change in liver fat (27%) than in body weight (2%). The increase in liver fat was proportional to that in de novo lipogenesis. Weight loss restores liver fat to normal. These data indicate that the human fatty liver avidly accumulates fat during carbohydrate overfeeding and support a role for DNL in the pathogenesis of NAFLD

Linear regression analysis of baseline serum triglyceride vs change in HbA1c for 113 patients given low carb advice



A linear regression model fitted with HbA1c reduction as the outcome and baseline serum triglyceride as the predictor demonstrated a relationship R^2 0.05 $p=0.0176$. Those with a higher triglyceride level at baseline

were likely to achieve a greater improvement in HbA1c. However, no relationship was seen when controlling for baseline HbA1c. Baseline HbA1c and baseline TG are moderately correlated (0.27) therefore high baseline TG may not be independently related.