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 peperoni 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)

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?crid=2U3I993FVS76V&key

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

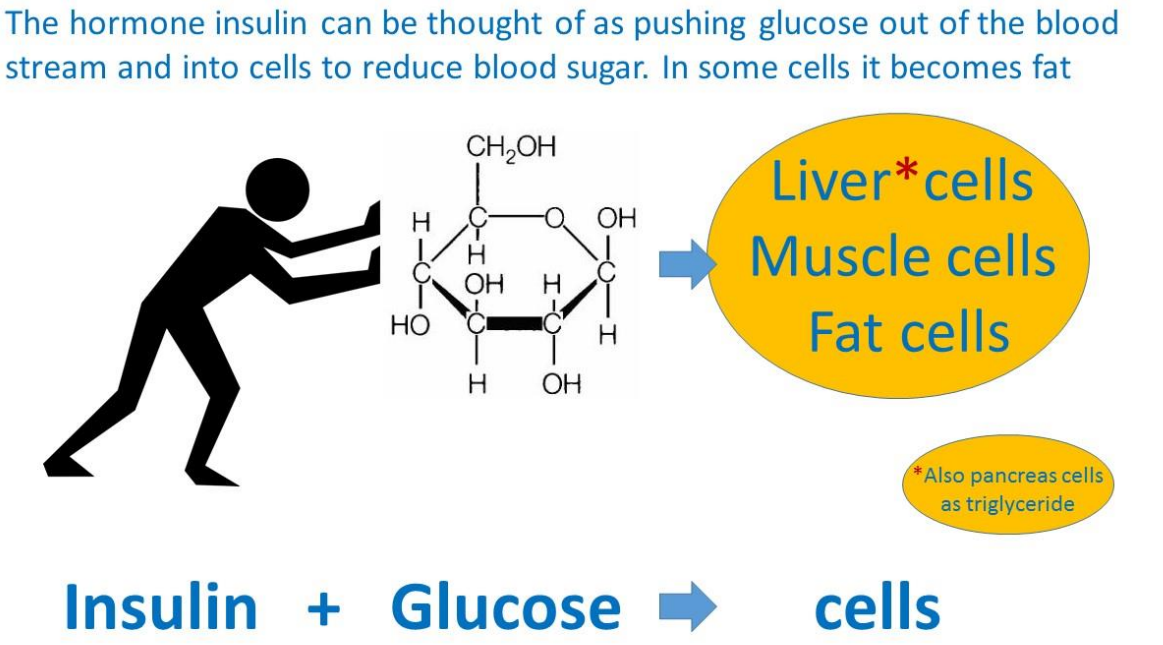
https://www.amazon.co.uk/s?k=fork+in+the+road+jen+unwin&crid=2UBGTLF924JWE&sprefix=fork+in+th%2Caps%2C281

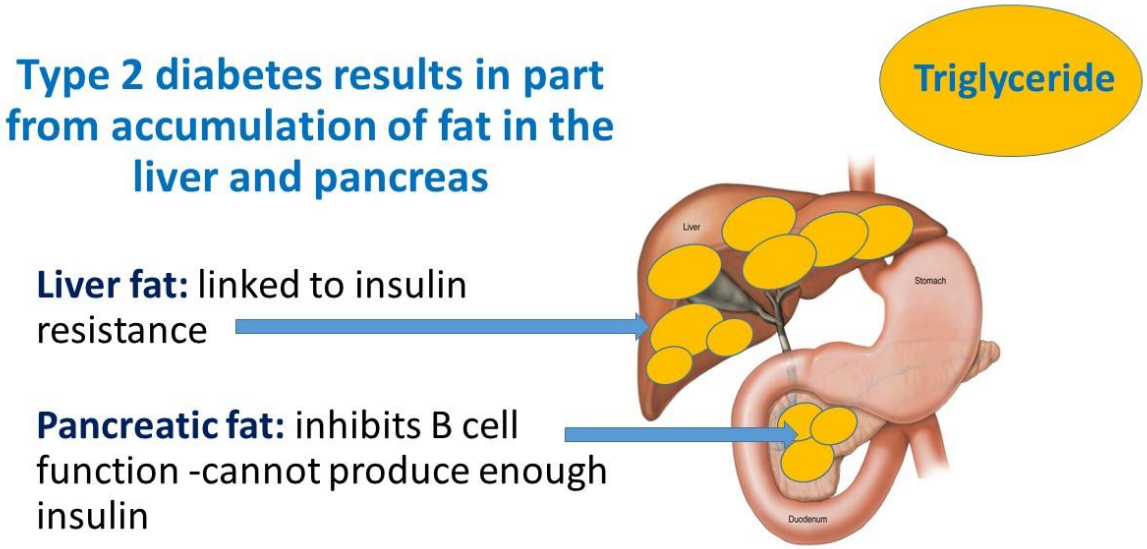
---

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 maters 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.

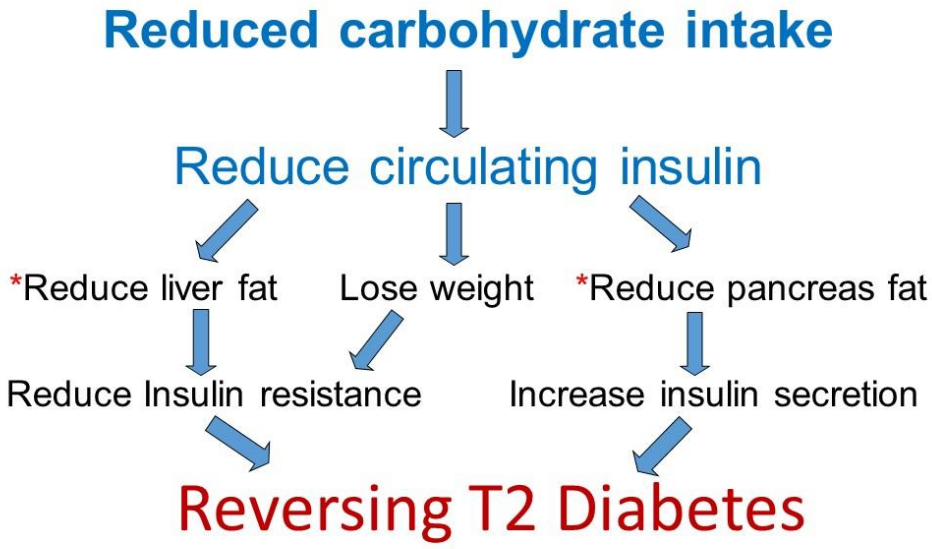
9. Taylor R. Banting Memorial lecture 2012: reversing the twin cycles of type 2 diabetes. Diabet Med. 2013;30(3):267-75.
10. Sevastianova K, Santos A, Kotronen A, Hakkarainen A, Makkonen J, Silander K, et al. Effect of short-term carbohydrate overfeeding and long-term weight loss on liver fat in overweight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

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

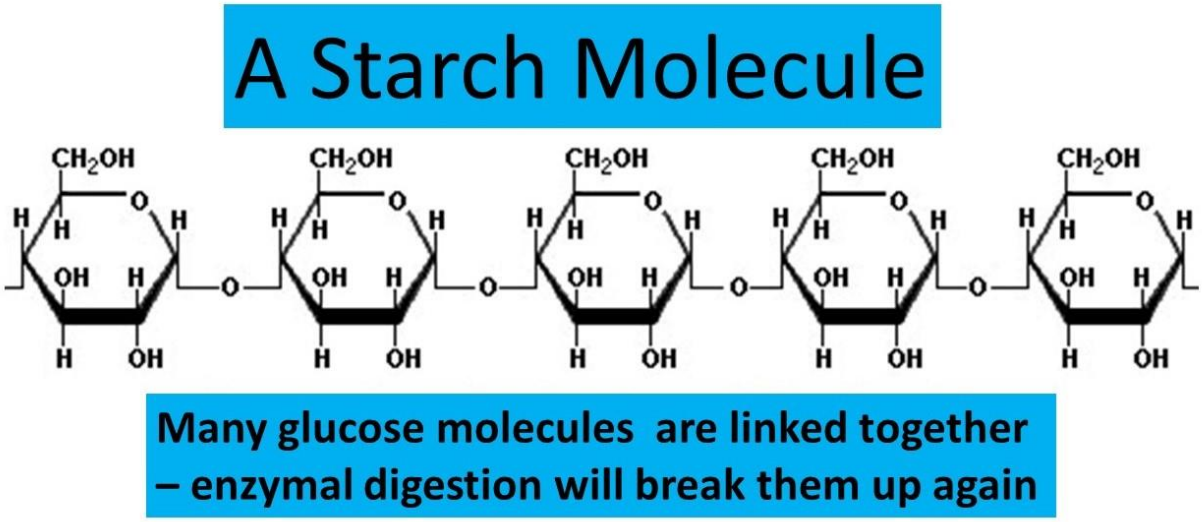




Reversal of type 2 diabetes: Normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Lim EL1, Hollingsworth KG, Taylor R. Diabetologia. 2011 Oct;54(10):2506-14. doi: 10.1007/s00125-011-2204-7.



***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.



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.

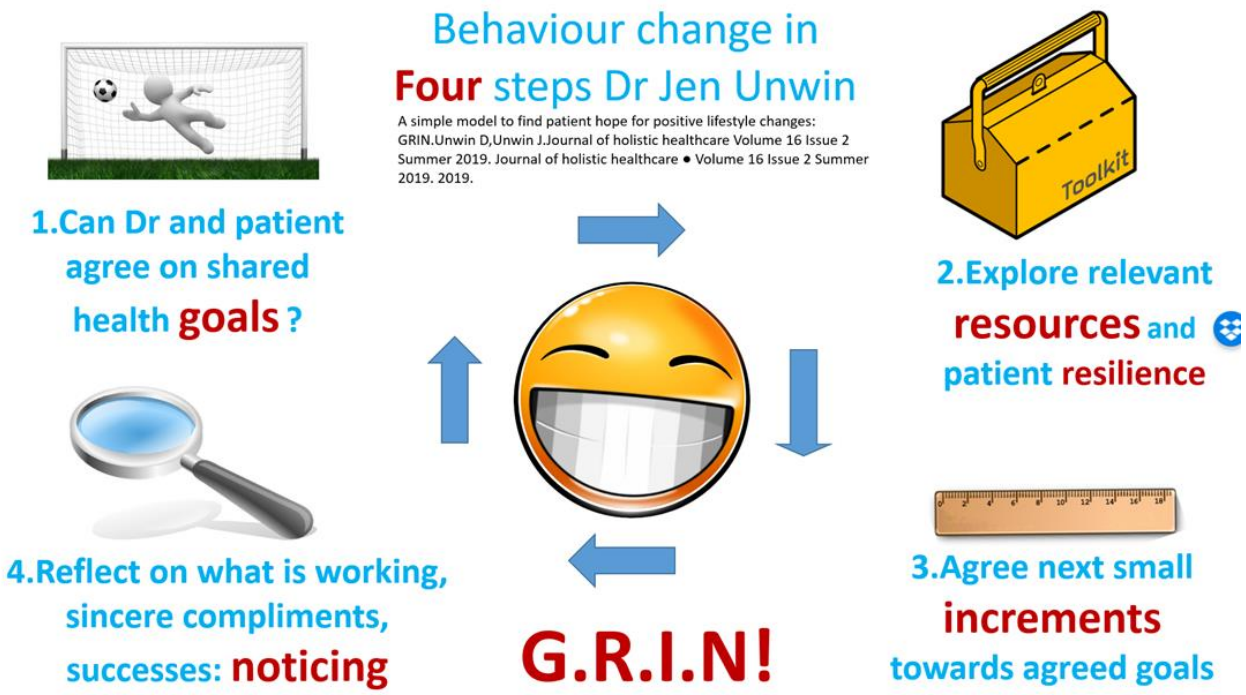
Sweeteners can trick you…

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)

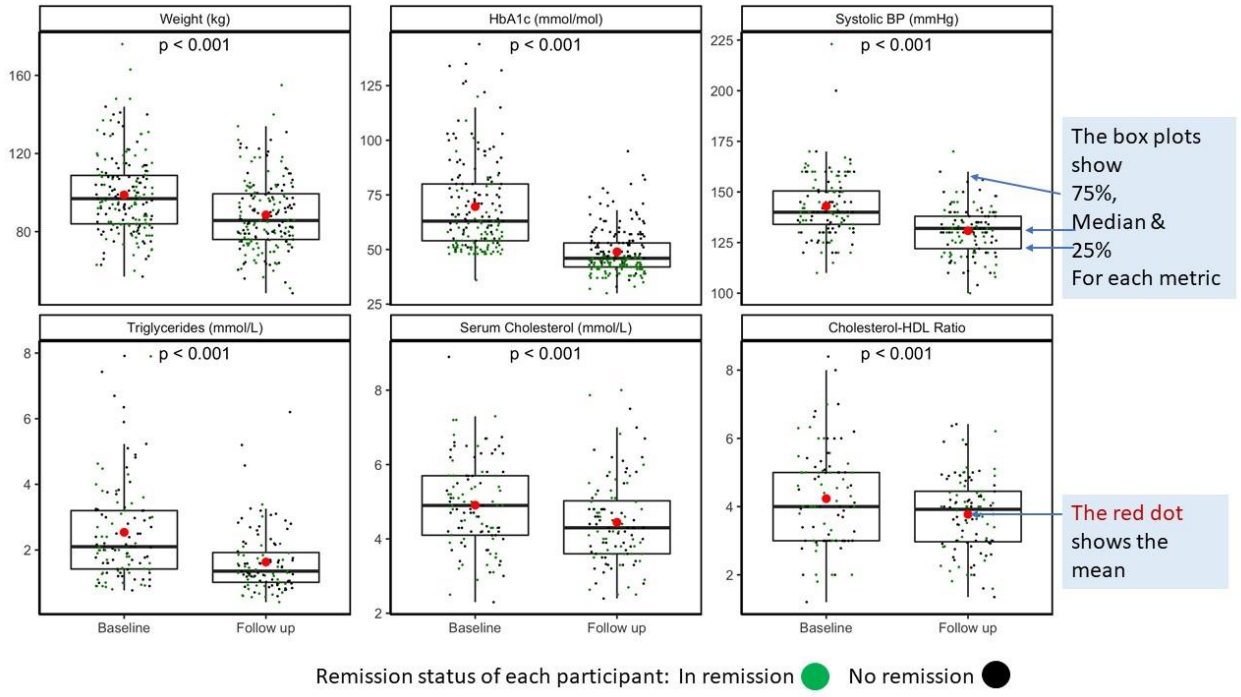
Typically, a low carb diet contains less than 130 grams of carb per day. How low to go depends on many factors. Discuss this with your health care practitioner

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.

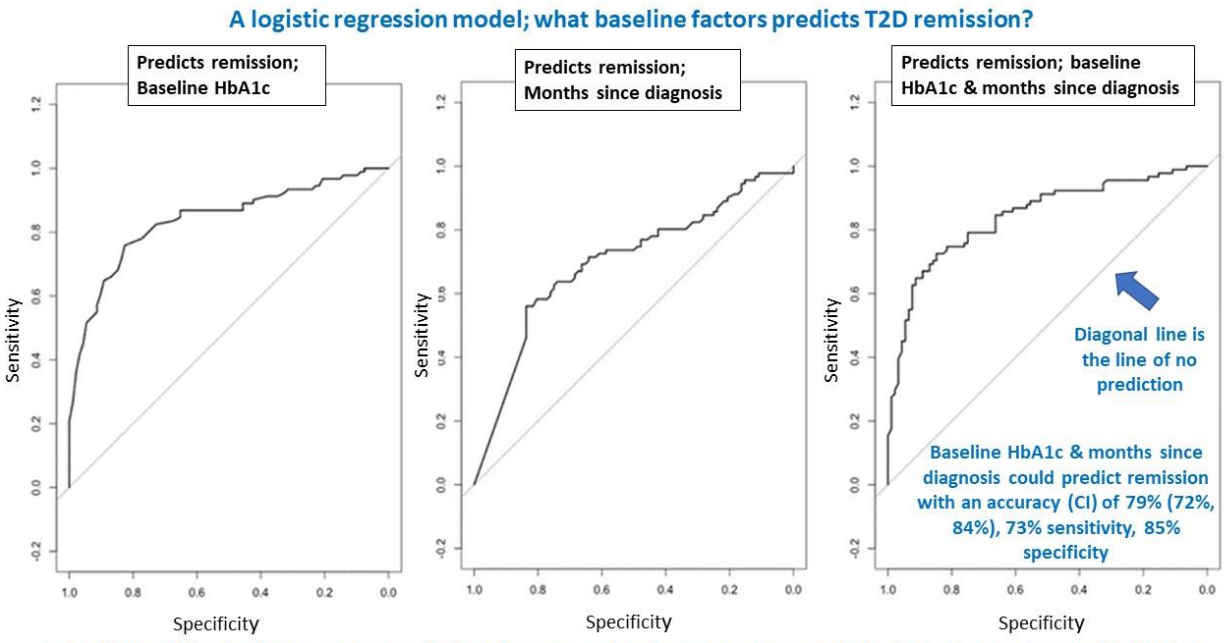
Statistical work is below

```
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.

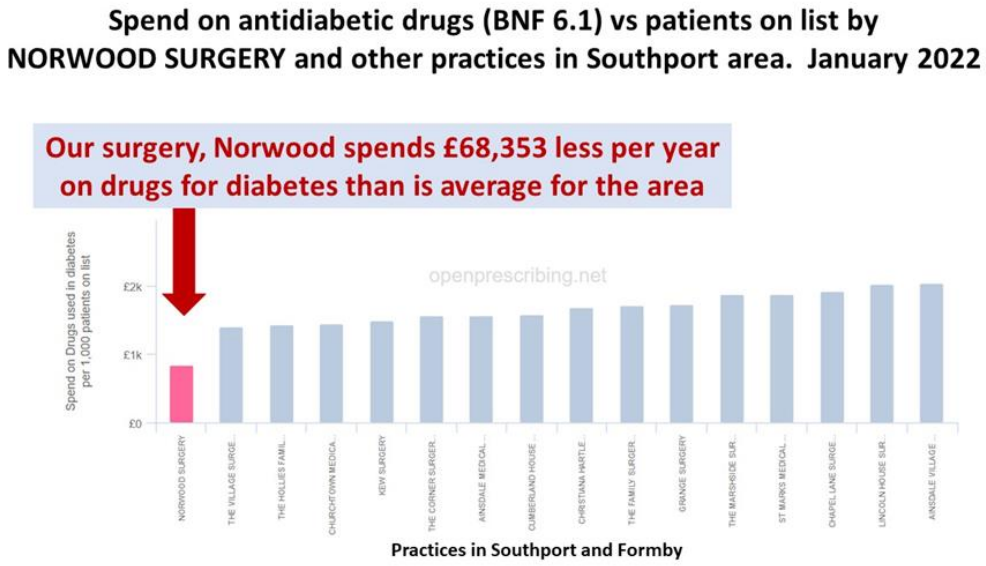
A logistic regression model predicting remission from both baseline HbA1c and baseline months since diagnosis (both continuous variables) could predict remission with an accuracy (CI) of 79% (72%, 84%), 73% sensitivity, 85% specificity and an f1 score of 0.77.

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



(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 encompasses 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.

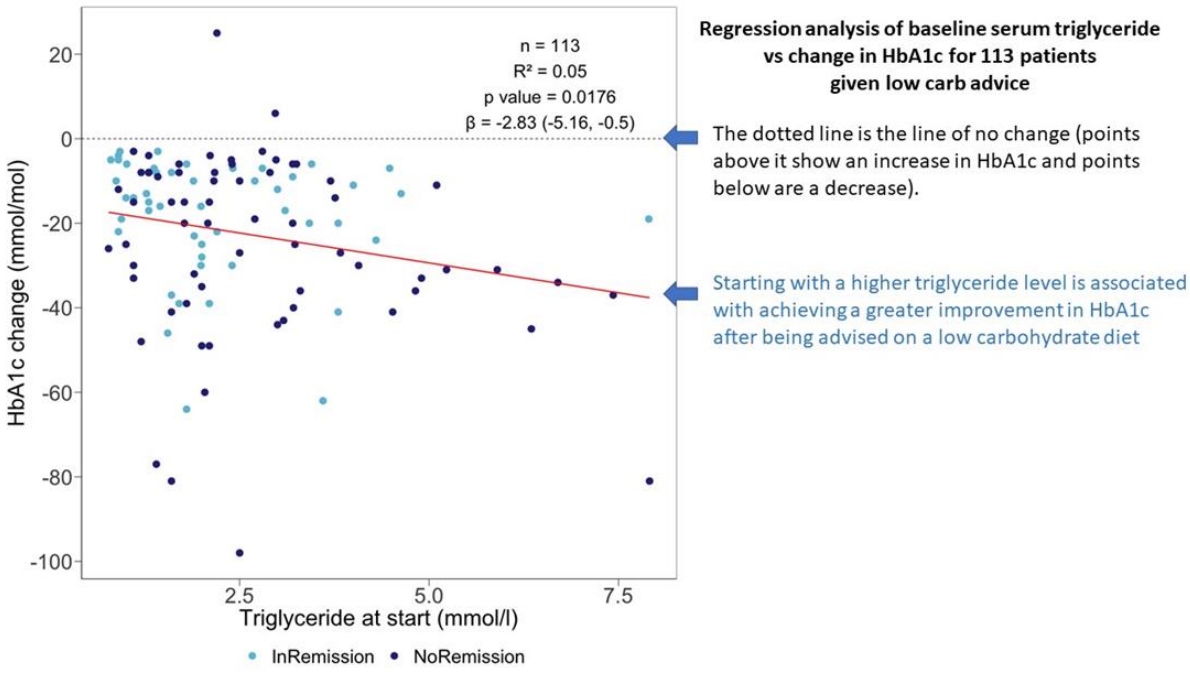
Any excess carbohydrate cannot be stored once the glycogen depots are full. If more glucose is ingested than can be oxidized for energy or stored as glycogen, it has to be turned into fat by the process of de novo *lipogenesis. This process only happens in the liver in humans, and triglyceride synthesized* 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.