Chapter

# Treating Type 2 Diabetes with Therapeutic Carbohydrate Restriction

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## Abstract

This chapter gives clinicians the tools to use therapeutic carbohydrate restriction as a dietary intervention for type 2 diabetes patients. The chapter is divided into three section, each addressing a different aspect of therapeutic carbohydrate restriction (TCR). Section 1 delves into the background of carbohydrate restriction, nutrition physiology, the three levels of therapeutic carbohydrate restriction physiological, and metabolic rationale for using TCR to treat the symptoms of type 2 diabetes. Section two explains how to start TCR in a patient population. It goes over which patients are good candidates for TCR and which ones should be approached with caution when implementing this dietary change and explains the importance of baseline assessments. Section three spells out how to administer and manage TCR in a clinical setting. It covers behavior change support, patient education on TCR principles, medication adjustments during the early stages of the intervention, and anticipating and treating common side effects.

**Keywords:** type 2 diabetes, obesity, therapeutic carbohydrate restriction, low carbohydrate diet, diabetes remission

## 1. Introduction

For the past 50 years, global rates of metabolic syndrome, diabetes, and obesity have been steadily rising [1]. While pharmaceutical interventions can assist patients in managing their conditions, and nutritional therapy is also important. Increased use of certain medications, such as insulin or sulfonylureas, can exacerbate the underlying insulin resistance, potentially leading to poorer glycaemic control over time [2]. Medications can help, but only to a certain extent. However, as we will see later in this course, nutritional therapy enhances their benefit and even helps lower the required dosage or allows for elimination. High quality evidence supports the efficacy of therapeutic carbohydrate restriction can be an important component for diabetes treatment, whether used alone or in combination with medications [3].

Therapeutic carbohydrate restriction is not a "cure-all, "and it's not the right treatment for everyone. It is, however, a successful clinical intervention that is tailored to specific conditions and patient groups.

In the early nineteenth century, therapeutic carbohydrate restriction for diabetes treatment was fairly common [4]. Its use in the treatment of epilepsy began in the early twentieth century. Physicians and nutritionists commonly recommended carbohydrate restriction for weight loss in the 1960s and 1970s [5].

### 1.1 The evidence of a low GI diet for type 2 diabetes

2021 systematic review and meta-analysis of published and unpublished randomized trial data

- A 2021 systematic review looked at 23 trials and found that those who followed a low carbohydrate diet achieved higher rates of diabetes remission (**Table 1**) compared to those who followed a low-fat diet without adverse events [7].
- Low-carbohydrate diets were also associated with a reduction in triglycerides, insulin sensitivity and weight loss at six months compared to the low-fat diets.

The Prospective Urban Rural Epidemiology (PURE) study.

- Epidemiological cohort study published in 2017 [8].
- 135,335 patients in high, medium and low-income countries with a median follow-up of 7.4 years.
- Recorded dietary intake using validated questionnaires; 52% were those whose carbohydrate calorie intake was over 60%.
- Patients with diabetes were not excluded from the study.
- 1230 patients (0.9%) dropped out, and 7369 (5.4%) were excluded from the final analysis due to pre-existing cardiovascular disease.
- Higher carbohydrate intake was associated with increased overall mortality (hazard ratio 1.28), and higher fat intake was associated with reduced overall

| Type 2 diabetes outcome | Criteria and cut-offs used |
|---|---|
| Reversal | HbA1c below 6.5% (7.8 mmol/L; 47.4 mmol/mol) without any diabetes medication, except metformin |
| Partial remission | Two HbA1c measurements 5.7–6.5%<br>(6.5–7.8 mmol/L; 38.8–47.4 mmol/mol)<br>Over the course of 1 year<br>No medications |
| Complete remission | Two HbA1c measurements below 5.7% (6.5 mmol/L; 38.8 mmol/mol)<br>Over the course of 1 year<br>No medications |

**Table 1.**
*Type 2 diabetes reversal and remission definition defined by the American diabetic association as follows [6].*

mortality (hazard ratio 0.77)- both of these were statistically significant. There was, however, no statistically significant link with cardiovascular disease.

- Saturated fat intake was associated with an increased risk of stroke, but monounsaturated fat intake was associated with reduced total mortality, and polyunsaturated fat intake was associated with reduced total mortality and reduced risk of stroke.
- There were some possible confounders in this study, for example, the fact that many who had a high carbohydrate diet lived in poorer areas, and it is difficult to separate the effects of the diet from the general impact of poverty on mortality. There was also no assessment of intake of trans fats and no analysis of the different types of carbohydrates that were eaten.

*1.1.1 Effect on lipids*

- A 2019 meta-analysis of 8 studies have shown improvements in HDL and triglyceride levels associated with a lowcarbohydrate diet [9].
- They conclude that 'dietary guidelines should consider carbohydrate restriction as an alternative dietary strategy for the prevention/management of dyslipidemia for populations with cardiometabolic risk'.

*1.1.2 American Diabetes Association*

- In 2019, the American Diabetes Association (ADA) published a consensus review regarding diet for patients with diabetes or pre-diabetes [3].
- This includes the statement that 'reducing overall carbohydrate intake for individuals with diabetes is associated with the most evidence for improving glycemia and may be applied in a variety of eating patterns.
- The review also states that 'a low-carbohydrate diet is a viable approach to a patient who is not meeting their diabetes targets or wants to reduce their diabetic medication'.

*1.1.3 2017 National Institute for health and care excellence (NICE) guidance*

The 2017 NICE guidance has several points which support a low GI diet. A low GI diet can be an effective way to consider, as many patients prefer to trial weight loss and lifestyle change before medication [10].

**1.2 Carbohydrate**

Unlike amino acids, fatty acids, and many micronutrients, dietary carbohydrate is not required for survival. Although some cells, such as red blood cells, white blood cells, and some parts of the kidney, require glucose, the body can produce enough glucose to meet those needs. Despite the widespread belief that the brain can only run on glucose, the brain can run on both glucose and ketones [11]. When we do not eat a lot of carbs, our bodies have three options for getting energy:

- We synthesize glucose from the liver through glycogenolysis. When the body requires energy, this provides a quick source of glucose.

- Gluconeogenesis is a process that allows us to make glucose from proteins and fatty acids. "Gluconeogenesis" literally means "the production of new glucose." It's a demand-driven process in which our livers convert fatty acids and amino acids into glucose to keep blood sugar levels from dropping too low.

- Fatty acids can be converted to ketone bodies. The brain and all glucose-dependent tissues get enough fuel naturally on a TCR diet [12].

Carbohydrate-restricted diets usually include some carbohydrates, but even if we eat no carbohydrates, our bodies will provide us with all the glucose and energy we require as long as we eat enough fat and protein. As a result, a well-planned, carbohydrate-restricted diet will provide all the nutrients needed.

### 1.3 What is the difference between a glycemic index and a glycemic load?

The ability of dietary carbohydrates to raise blood glucose levels varies greatly [13]. However, the carbohydrate density of each food is also a factor [14]. The glycemic index (GI) and glycemic load (GL) are terms used to describe these concepts.

When 50 grams of carbohydrate in watermelon are compared to 50 grams of carbohydrate in bananas, the carbohydrate in watermelon metabolizes quickly, resulting in a higher blood glucose response. As you can see, this indicates that its GI is higher. On the other hand, a banana has a much higher carbohydrate density than a watermelon. When similar serving sizes (120 grams of watermelon vs. 120 grams of banana) are compared, the serving of watermelon has a lower impact on blood sugar and thus has a lower GL.

The glycemic index response to food varies from person to person. The glycemic index of any given food can be influenced by the glycemic index of other foods eaten simultaneously [15]. The glycemic index is a good general guide, but the essential information is understanding how people react to specific foods (**Figure 1**).

### 1.4 Different carbohydrate restriction levels

Any dietary intervention that uses less than 130 grams of dietary carbohydrate per day is referred to as therapeutic carbohydrate restriction. The Dietary Reference Intake for the United States recommends this as the "minimum" level [11]. There are, however, various levels of carbohydrate restriction. The following definitions are used for better understanding:

- Ketogenic diets that are very low in carbohydrate — or keto diets — recommend no more than 20 grams of net dietary carbohydrate per day. The principles outlined in Dr. Atkins' New Diet Revolution are usually followed [17]. Other studies and protocols, such as those conducted by Virta Health, which you may have heard of, limit total dietary carbohydrates to 30 grams per day [18]. These two approaches will end up being very similar in practice. Almost everyone will experience a metabolic shift into nutritional ketosis due to both. The majority of patients find these diets to be incredibly filling. We advise patients to eat until they are satisfied rather than restricting or counting calories.

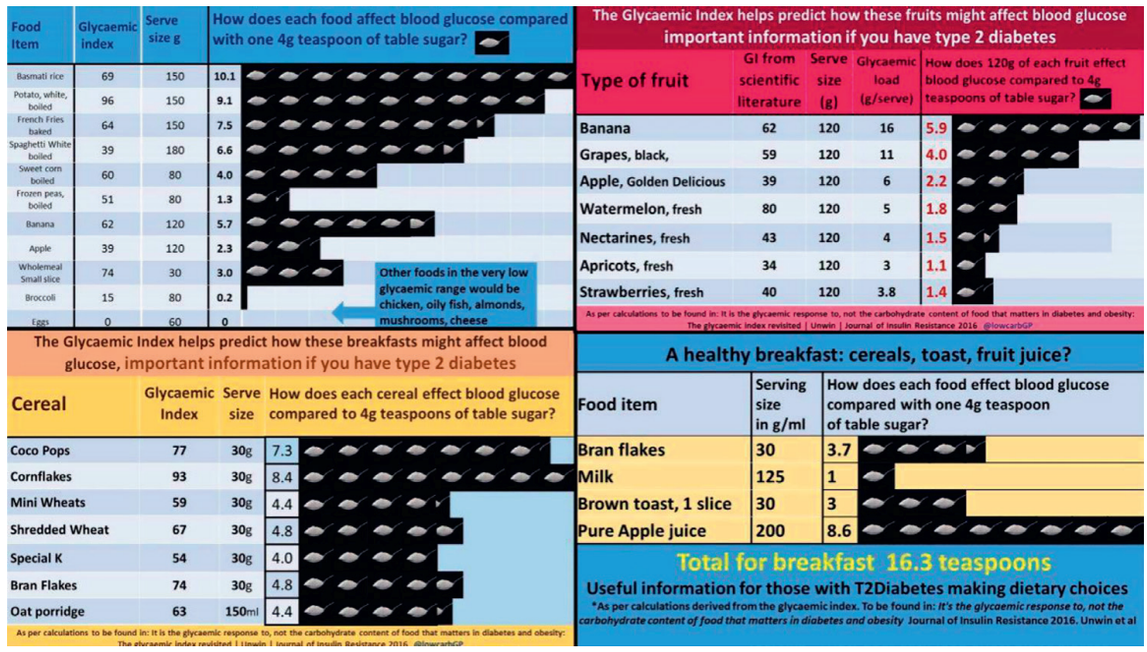


**Figure 1.**
*An infographic to show how the glycemic index helps inform dietary choices [16].*

- Low-carbohydrate diets with a moderate carbohydrate content recommend 20 to 50 grams of carbohydrate per day [19]. Nutritional ketosis may or may not occur at this carbohydrate restriction level. However, at this carbohydrate intake, most people will lose weight and improve their metabolic markers [19]. On a moderately low-carb diet, deliberate calorie restriction is not typically recommended, as it is on very low-carb ketogenic diets.

- Low-carbohydrate diets with a liberal carbohydrate intake typically recommend 50–100 grams per day. This carbohydrate intake is higher than most low-carb diets but lower than the US Daily Recommended Intake of 130 grams (DRI). Calorie and carbohydrate restrictions may or may not be used at this level. For some people, this level of carbohydrate restriction may not lead to nutritional ketosis or weight loss. However, studies have shown that even moderate carbohydrate restriction can improve metabolic markers such as blood sugar, HDL, and triglycerides [20].

## 2. Restricted carbohydrate diet and its physiological and metabolic effects

### 2.1 Therapeutic restricted carbohydrate

Therapeutic carbohydrate restriction lowers fasting and postprandial blood glucose and insulin levels while also reducing insulin resistance. All of these changes can improve metabolic syndrome markers [21]. In insulin resistance, it is harder for the body to maintain normal blood glucose leading to type 2 diabetes. Thus, it is counterproductive to consume carbohydrates that digest down into significant amounts of glucose [16].

As predicted by the glycemic index, restricting any foods that break down into glucose lowers blood glucose levels and insulin secretion. This includes whole-grain

starches and high-sugar fruits. A glucometer can easily track blood glucose levels at home or in a clinical setting. A glucometer is an essential tool for identifying foods that raise blood glucose levels, even for people who do not have diabetes. We recommend that patients monitor their glucose levels when starting TCR if possible.

### 2.2 Insulin

The main reason for monitoring blood glucose levels may have less to do with glucose and more with insulin. Carbohydrates in the diet raise blood sugar levels and stimulate insulin secretion. While this is a normal physiological response, it can negatively affect health. Insulin maintains homeostasis by transporting glucose into cells and inhibiting glucose production in the liver when blood glucose levels rise. This is a life-saving response because it prevents dangerously high glucose levels in the blood.

On the other hand, insulin has other functions that we, as clinicians, frequently overlook. Insulin, for example, prevents the body from burning fat for energy instead of encouraging fat storage [22]. As a result, higher insulin levels can be a problem for people trying to lose weight. Giving insulin to people with type 2 diabetes can set off a vicious cycle of weight gain and insulin resistance.

Genetics, environment, and lifestyle all play a role in how well someone manages their dietary carbohydrate intake. Insulin levels rise and can remain chronically elevated when people consume more carbohydrates than their bodies can handle, known as hyperinsulinemia [23]. When this happens, the body's response to insulin signals becomes ineffective. Insulin resistance is the term used to describe this condition [24].

The development of the metabolic syndrome and an increased risk of heart disease are strongly linked to hyperinsulinemia and insulin resistance [25]. Insulin resistance is thought to be a common underlying mechanism for various chronic diseases, including type 2 diabetes, hypertension, atherogenic dyslipidemia, and chronic inflammation [26].

We tend to use glucose levels as a proxy for insulin levels because point-of-care insulin meters are unavailable. However, it's important to note that just because glucose levels are normal does not mean insulin levels are as well. Glucose levels may be normal in the early stages of diabetes and metabolic syndrome because high insulin levels keep them there.

Restriction of carbohydrate intake, fortunately, is an effective way of addressing the root cause of hyperinsulinemia and insulin resistance.

## 3. Getting the intervention started for metabolic diseases

This section covers which patients are good candidates for TCR and which patients should be approached with caution when implementing this dietary change. It also explains the importance of baseline assessments and briefly covers pre-diet evaluation and counseling.

### 3.1 Selection of patients

Patients with any metabolic syndrome symptoms are ideal candidates for therapeutic carbohydrate restriction. Patients with hypertension, mixed dyslipidemia, hyperglycemia, including type 2 diabetes, or obesity, particularly abdominal obesity, fall into this category.

### 3.2 Exclusion criteria

- Acute, decompensated medical condition
- Advanced renal insufficiency not on hemodialysis
- Pyruvate carboxylase deficiency
- Hyperchylomicronemia

### 3.3 The necessity for caution

It's uncommon to come across someone completely against therapeutic carbohydrate restriction. You'll often come across a patient who will benefit from TCR but who will require more attention and caution from you.

### 3.4 Risks associated with a low carbohydrate diet

A study published in May 2018 followed over 2000 men for over 20 years and found that higher protein intake was slightly associated with a higher risk of heart failure [27]. However, not all associations reached statistical significance, and some confidence intervals crossed zero. The long-term effects of a low carbohydrate diet are largely unknown. There has been a concern raised by some studies about a high protein intake increasing the risk of renal stones. However, a low carbohydrate diet only needs to contain a normal amount of protein. Thus a low carbohydrate diet is not known to worsen renal function, and some studies have shown an association with an improvement in eGFR.

In August 2018, a paper was published suggesting an increase in mortality for those who ate a low carbohydrate diet, in which carbohydrates were replaced with animal proteins, in contrast to those who replaced carbohydrates with plant-derived protein [28]. Those who developed diabetes during the study were excluded from follow-up, which may limit the applicability of this study to the diabetic patients at whom this chapter is aimed. If patients ask about this study (which has been extensively covered in the media), it would be reasonable to suggest that their diet remains balanced even when carbohydrates are reduced with proteins coming from plant and animal sources.

#### *3.4.1 Diabetes type 2*

As evidence shows, therapeutic carbohydrate restriction is a valuable intervention for patients with type 2 diabetes. Patients with diabetes, particularly those taking glucose-lowering medications, must be able to use a blood glucose meter and communicate their results to their health care team quickly [29].

To avoid hypoglycemic episodes and ensure patient safety, you as a healthcare provider must be more vigilant with patients with type 2 diabetes.

#### *3.4.2 Hypertension*

For patients with hypertension, therapeutic carbohydrate restriction is also an effective intervention. On the other hand, these patients must be able to monitor their

blood pressure at home and communicate with their healthcare providers quickly to adjust antihypertensive medications appropriately. Remember that your team is critical in assisting the patient in avoiding symptomatic hypotension.

### *3.4.3 Gallbladder removal*

Therapeutic carbohydrate restriction may still be a promising intervention for patients with gallbladders removed. When teaching these patients what foods to eat, tell them to gradually increase the amount of fat in their diet to avoid diarrhea. However, most patients without a gallbladder can successfully follow TCR after a slow transition period.

### *3.4.4 Chronic kidney disease*

Due to the misconception that these diets are "high protein diets," there is often concern about using therapeutic carbohydrate reduction in patients with decreased kidney function. In reality, protein accounts for no more than 30% of calories in TCR diets. Except for those with pre-existing, advanced renal failure, this level is likely safe.

There is no evidence that protein intake at levels commonly consumed during TCR is harmful to people with mildly or moderately reduced kidney function [30], and plenty of evidence demonstrates its safety.

### *3.4.5 Kidney stones*

When starting TCR, patients predisposed to kidney stones may increase their risk. In particular, uric acid levels in the blood can rise, increasing the risk of uric acid kidney stones in susceptible people. Patients with kidney stones should stay hydrated by following general guidelines. Experienced clinicians have discovered that encouraging adequate amounts of sodium, potassium, and, most importantly, magnesium can help reduce the risk of kidney stones. We should advise patients who have had calcium oxalate stones, the most common type of kidney stone, to avoid high oxalate foods like spinach, almonds, and cashews. TCR is completely safe in patients who have had kidney stones.

### *3.4.6 Gout*

Patients prone to gout have the same concerns as those prone to uric acid kidney stones. As previously mentioned, uric acid levels can rise in the early stages of TCR. This can trigger a gout flare-up in susceptible individuals, though gout may improve over time on a carbohydrate-restricted diet [31]. These patients should drink plenty of water and get plenty of sodium, potassium, and magnesium. Another option for those prone to frequent attacks is to use prophylactic allopurinol during the early stages of the intervention.

### *3.4.7 Breastfeeding and pregnancy*

When it comes to TCR, pregnancy and breastfeeding must be considered. Although moderate carbohydrate restriction has long been used to treat pregnant women with gestational diabetes [32], carbohydrates are rarely restricted to the very low levels used for weight loss or type 2 diabetes treatment. The amount of

carbohydrate restriction should be individualized for the patient based on her medical history, but it should usually be at least 50 grams per day. According to a few case reports in the medical literature, more aggressive carbohydrate restriction during pregnancy or breastfeeding may increase the risk of ketoacidosis [33]. Fresh vegetables, meat, fish, eggs, dairy, nuts, seeds, and a small amount of fruit, on the other hand, provide adequate essential nutrition for both mother and baby.

### 3.5 Baseline tests

All TCR patients should have baseline and follow-up assessments to screen for potential harm and document successful progress.

To begin, keep track of each patient's starting weight. Even though it provides less detailed information, waist circumference is the simplest method. Furthermore, it is simple for patients to notice if their pants have suddenly become looser. Another critical vital sign, especially for those taking antihypertensives, is baseline blood pressure. Keep in mind that medications will almost certainly need to be adjusted once a patient begins TCR.

### 3.6 Lab tests

We recommend running the following baseline lab tests when starting a patient on TCR.

- **Comprehensive metabolic panel (CMP**): This test includes fasting glucose, kidney, and liver function, as well as basic electrolytes, which are all important to track on TCR. We must ensure that patients' baseline GFR is less than 30 ml/min because severe renal dysfunction is potentially contraindicated to TCR. Also, if the patient has fatty liver with elevated transaminases, we must document and monitor this, as it frequently improves with TCR.

- **HbA1c**: This is a three-month average glucose level measurement. This is critical to establish a baseline and track it over time as one of the main indicators of TCR success. HbA1c levels of 5.7 to 6.4% (6.5 to 7.6 mmol/L) are considered prediabetes, while 6.5% (7.8 mmol/L) or higher are considered diabetes.

- **Fasting insulin**: Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) can be calculated using fasting insulin and fasting glucose. We recommend checking insulin resistance at baseline because it is a major focus of TCR. On the other hand, fasting insulin is not a common test for most doctors. We recommend that you practice ordering and interpreting this test. While fasting insulin levels vary naturally [34], tracking the trend over time is an excellent way to track TCR progress.

Although there is no universally accepted reference range for fasting insulin, we can use the literature to help us develop useful ranges.

One study [35] found that levels above 25 micro IU/ml were associated with a very high risk of developing prediabetes, and levels above 12 were associated with a moderate risk, confirming an earlier study. In a later study, it was discovered that insulin levels above 8 micro IU/ml c orrectly predicted prediabetes in 80% of the people tested [35].

Furthermore, one study claimed that a HOMA-IR of less than 1.6 was a normal values [36].

- **Fasting lipid profile**: A baseline fasting lipid panel is recommended for everyone because mixed dyslipidemia is common in metabolic syndrome. We expect high-density lipids (HDL) to rise and triglycerides to fall due to TCR. We also need to keep an eye on LDL-C levels, as this is likely the first area of concern with TCR. While some guidelines recommend non-fasting panels to improve compliance, this makes interpreting triglycerides more difficult because their value is dependent on the content and timing of the most recent meal. As a result, fasting lipid panels are recommended for consistency.

### 3.7 Additional tests

- **Complete blood count**: Although significant changes in the CBC are uncommon, it's important to know that the patient does not have any baseline abnormalities like anemia or cytopenia.

- **Uric acid**: A baseline uric acid level is recommended for those prone to gout attacks or who have a history of uric acid kidney stones. The results may influence whether or not prophylactic allopurinol should be started for those with elevated levels.

- **TSH**: Because severe hypothyroidism affects weight loss, we recommend that everyone get a baseline TSH before starting TCR.

## 4. Carbohydrate restriction for therapeutic purposes

We'll go over the basics of patient education when starting TCR and how to support patients' lifestyle behavior changes in this section. We'll go over the initial medication adjustments that need to be made and potential side effects and how to deal with them.

### 4.1 Assisting with behavior change

A patient education and support component should be included in therapeutic carbohydrate restriction. Maintaining a simple initiation with as much support as possible will aid adherence and success.

The first step is to talk to patients about their current diet, diet history, and health goals to help them prepare for this nutritional change. If patients have a history of weight loss and regain, this is an opportunity to address their fears of failure and explain how this could be different.

Next, determine the patient's familiarity with carbohydrate restriction and provide education tailored to their level of understanding. Patients may be unsure if therapeutic carbohydrate restriction is the right treatment option. As discussed in previous sections, addressing these concerns is an opportunity to educate patients about the approach's safety and efficacy.

At the same time, the healthcare provider should inform patients about any possible side effects. Patients should be taught how to handle the most common problems and when to seek medical help.

### 4.2 Education of the patient

Therapeutic carbohydrate restriction usually entails eating a diet rich in whole foods that have been minimally or traditionally processed. Although meal replacement shakes or kits can be used to administer this diet, we will focus on using whole foods readily available in most grocery stores in this course.

The three principles of therapeutic carbohydrate restriction are as follows:

- To begin, keep carbs to a minimum.
- Second, make sure you are getting enough protein.
- Third, as needed, add or subtract fat to achieve satiety or weight loss goals.

Patients are encouraged to eat only when they are hungry and stop eating when they are satisfied. Because TCR makes patients feel fuller, they no longer need to eat on a regular 3-meal-per-day schedule and can instead rely on their hunger cues.

Based on their preference, your patients can be encouraged to eat meat, fish, poultry, eggs, above-ground vegetables, nuts, cheese, and fatty "fruits" like olives and avocados. They can also use olive oil, avocado oil, coconut oil, butter, and ghee as fat sources. Patients should avoid sugary foods that would be restricted on any weight-loss diet, including cake, cookies, ice cream, and other desserts, as well as pancakes, potato chips, fries, and soda and other sweetened beverages. You should also teach your patients why and how to avoid foods that are commonly portrayed as healthy, such as whole-grain bread and cereals, rice, beans, pasta, low-fat milk and dairy products with added sugar, and a variety of fruits. Because these foods are broken down into glucose, they may have unfavorable effects on blood sugar and insulin levels in those who are susceptible. These foods should be avoided when using therapeutic carbohydrate restriction to treat obesity, metabolic syndrome, or diabetes.

This usually results in a diet where carbohydrates account for less than 10% of total calories, protein accounts for 20–25% of total calories, and fat accounts for more than 65% of total calories. However, because we rarely ask patients to track their calories during TCR, data based on percentages of total calories is usually useless.

Furthermore, rather than a macronutrient ratio, the levels at which carbohydrates and protein exert metabolic effects appear to reflect absolute thresholds in grams consumed (Accurso et al., 2008; Layman, 2009). Instead of focusing on macronutrient percentages when educating your patients, you should focus on making food choices that limit carbohydrate intake, provide adequate-protein, and allow enough fat for satiety and flavor.

### 4.3 Low carbohydrate diet and medication changes

The issues that should be considered when patients taking diabetic medications decide to start a low GI diet. Particular care should be taken with sulfonylureas due to the risk of hypoglycaemia and SGL T-2 inhibitors due to the risk of euglycaemic ketoacidosis. Insulin requirements will often drop, and the healthcare provider should supervise this. The following are the points to consider while using diabetic medications in type 2 when on a low carbohydrate diet [37].

- Risk for hypoglycemia?

- Degree of adherence to carbohydrate restriction?

- Benefit of using the medication and/or any adverse effects or risks outweigh the benefits? (**Table 2**).

### 4.4 Medication for diabetes

The most important medications to reduce or eliminate first are those that lower blood glucose. The most serious concern we have with TCR in patients with blood sugar problems is that it will cause symptomatic hypoglycemia. As a result, the most important point to emphasize is the importance of blood glucose monitoring regularly. This means that insulin users must test several times throughout the day, including fasting and pre-meal tests. If you are only taking oral medications, you might have to test once or twice a day.

The degree to which we reduce or discontinue medications is determined by the wishes and concerns of our patients. For example, if avoiding hypoglycemia is more important, we can quickly lower drugs and temporarily allow higher blood glucose levels. We would adjust medications more slowly if the patient is more concerned about maintaining strict glucose control. The most important thing is to teach the patient about hypoglycemia symptoms and the importance of testing their blood glucose multiple times per day, especially in the first few weeks.

#### *4.4.1 Metformin*

We recommend continuing metformin with no dose adjustments when starting TCR because it does not cause hypoglycemia.

| **Class of antidiabetic medication#** | **Action** | **Hypo risk?** | **Suggested action (to continue/stop)** |
|---|---|---|---|
| Biguanides | Reduce hepatic gluconeogenesis, and reduce peripheral insulin resistance | No | Optional, consider clinical pros/cons. |
| Insulins | Exogenous insulin | Yes | Reduce/Stop (see under insulin section) |
| Sulfonylureas | Increase pancreatic insulin secretion | Yes | Stop (or if gradual carbohydrate restriction, then wean by e.g. halving dose successively) |
| DPP-4 inhibitors | Inhibit DPP-4 enzyme | No | Stop. No significant risk, but no benefit in most cases. |
| Thiazolidinediones | Reduce peripheral insulin resistance | No | Usually stop. Concern over risks usually outweighs benefits. |
| GLP-1 agonists | Slow gastric emptying. Glucose dependent pancreatic insulin secretion. | No | Optional, consider clinical pros/cons. |
| Alpha-glucosidase inhibitors | Delay digestion of starch and sucrose | No | Stop. No benefit on a low carbohydrate diet. |

*#Arranged as per Most Commonly Prescribed Diabetes Medications (data from 2020 [38]).*

**Table 2.**
*A summary of low carbohydrate diet and diabetic medication changes.*

### *4.4.2 Insulin*

Insulin, as the most potent glucose-lowering medication, should be adjusted first. When starting TCR, we should discontinue the use of short-acting insulin given before meals. The patients will likely not require the pre-meal, short-acting insulin because their meals are now much lower in carbohydrates. You can reintroduce short-acting insulin if their postprandial glucose levels are consistently above 200 mg/dL (11 mmol/L) despite TCR compliance.

Patients should also cut back on their long-acting insulin. If the patient is more concerned about hypoglycemic episodes, the long-acting insulin should be reduced by half when TCR begins. It should be reduced by one-third if they are more concerned with strict glucose control. This, however, assumes that their fasting blood glucose is less than 200 mg/dL (11 mmol/L) and that they have had adequate control. If their blood sugars are poorly controlled, and their lowest recent fasting glucose is greater than 200 mg/dL (11 mmol/L), hold off on lowering the long-acting insulin until their blood sugars improve. Finally, mixed insulins, which are a mix of long and short-acting insulins, are difficult to adjust accurately and should be avoided entirely. Only long-acting insulin should be given to the patient.

The one caveat to lowering insulin dosage is that we must be aware of adults with latent autoimmune diabetes (LADA). Although uncommon, these people are more insulin-dependent and will not be able to reduce or stop their dose as quickly or completely as others. TCR is still beneficial for them, but it should be done with caution and at a slower pace when reducing medication dosages. LADA should be considered if someone has a history of DKA or hospitalizations for severe hyperglycemia.

### *4.4.3 Sulfonylureas*

We recommend stopping sulfonylureas when starting TCR because they can cause significant hypoglycemia. Continue sulfonylureas until sugars are below 200 mg/dL (11 mmol/L) if someone has poorly controlled sugars at baseline, with fasting glucose above 200 mg/dL (11 mmol/L).

### *4.4.4 GLP-1 agonists and DPP-4 inhibitors*

These can also be continued until excellent glucose control is shown. We can then cut their doses in half to completely stop them once their blood sugars are under control.

### *4.4.5 Inhibitors of SGLT-2*

These medications are beneficial for people with diabetes because they have been shown to reduce cardiovascular mortality. However, they have been linked to an increased risk of DKA, which could be amplified if you are on a carbohydrate-restricted diet. SGLT-2 inhibitors, in particular, increase the risk of euglycemic ketoacidosis, which occurs when blood glucose remains normal despite significantly elevated ketones, to the point where the blood becomes dangerously acidic. As a result, if we aren't looking for it specifically, we may miss it. Check a beta-hydroxybutyrate level as well as a metabolic panel for acid–base status if you suspect euglycemic DKA. Because of this risk, we advise all patients starting TCR to stop taking SGLT-2 inhibitors one or two days before reducing carbohydrate intake.

*4.4.6 GLP-1 agonists and DPP-4 inhibitors*

These can also be continued until excellent glucose control is shown. We can then cut their doses in half to completely stop them once their blood sugars are under control.

### 4.5 Antihypertensive medications

Because TCR is an effective blood pressure (BP)-lowering treatment, many people taking antihypertensive medications may experience symptomatic hypotension. The first step is to inform your patients about low blood pressure symptoms such as dizziness, orthostasis, and fatigue. Ascertain that patients can monitor their blood pressure at home and quickly communicate the results to you or your healthcare team.

When starting TCR, we do not recommend stopping BP medications automatically unless the baseline BP is consistently below 110/70. However, if patients develop symptomatic hypotension, we advise discontinuing or reducing medicines as needed to alleviate symptoms.

### 4.6 Additional medications

Although this is not necessarily a TCR target, we have found that many people's gastroesophageal reflux disease (GERD) symptoms improve, allowing them to reduce or eliminate the use of proton pump inhibitors (PPIs) or H2 blockers. Patients may experience a rebound effect if treatment is abruptly stopped. Consider switching from a PPI to an H2 blocker for a few weeks before stopping or switching from every other day dosing to every other day dosing before stopping.

### 4.7 Treatment and side-effects

Preparing our patients for possible side effects is an integral part of increasing carbohydrate reduction compliance. Although TCR's side effects are usually mild and short-lived, they can be quite unpleasant when the patient is ready for them.

## 5. Conclusion

Physiological necessary glucose can be provided by gluconeogenesis. Starchy foods that are sometimes considered healthy, such as cereals, are broken down into glucose. It is possible to improve type 2 diabetes without drugs by following a low GI diet.

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