

Adapting Diabetes Medication for Low Carbohydrate Management of Type 2 Diabetes - A Practical Guide

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Introduction

The pathological changes associated with type 2 diabetes (T2D) can be reversed through lifestyle measures, in some cases leading to remission.(1) The low carbohydrate diet (LCD) is recognised as an effective option, that is clinically inexpensive with few side effects.(2) Many patients are achieving significant improvements in glycaemic control, with associated reduction in drug costs from cessation of hypoglycaemic agents.(3) Digital-technology behaviour change solutions for T2D remission are being delivered at scale.(4) Primary care clinicians need to be competent to adjust diabetes medications appropriately in individuals who follow a LCD.

The LCD in Type 2 Diabetes

A LCD comprises less than 130 grams of digestible carbohydrates per day.(5) Digestible carbohydrate refers to sugars and complex carbohydrates such as starch, which is digested to glucose. Aligned with national guidance, carbohydrate choices in a LCD will typically be higher fibre and low glycaemic index (GI).(6) Reduced total carbohydrate ingestion and low GI choices gives the LCD a low glycaemic load (GL). In T2D the GI and GL of food consumed is a determinant of blood glucose level and thus the requirement for hypoglycaemic medication.

Diabetes Medications and a LCD

Blood glucose levels typically fall substantially when an individual adopts a LCD. This article discusses key considerations regarding hypoglycaemic medications for a LCD and provides practical suggestions to prescribers. The recommendations are developed from the experience of the authors, discussion with experts, and the pharmacodynamics of the medications. Antihypertensive medications are not discussed in this article but clinicians need to be aware that a low carbohydrate diet can improve blood pressure, and antihypertensives may need to be adjusted.

When deciding the safety and appropriateness of T2D medications with a LCD there are three key clinical considerations:

- Is there a risk of the drug causing hypoglycaemia or other adverse event?
- What is the degree of carbohydrate restriction?
- Once carbohydrate is reduced does the drug continue to provide health benefit, and if so are the potential drug benefits greater than or less than possible risks and side effects?

Medications that create a risk of hypoglycaemia

Sulphonylureas (e.g. *gliclazide*) **and** ***Meglitinides*** (e.g. *repaglinide*): These medications should be reduced or stopped when a LCD is commenced. An initial dosage reduction of at least 50% is typically appropriate, with further reductions according to blood glucose response. There may be a period of short term hyperglycaemia while the individual adapts to a LCD.

Insulins: Practical expertise suggests a 50% reduction of daily insulin dose at initiation of the LCD is appropriate in most cases. In individuals whose HbA1c is markedly elevated a smaller reduction of perhaps 30% may be appropriate, with further reductions over time. For individuals on a basal-bolus regimen it is preferential to reduce or stop bolus insulin. In individuals on a mixed insulin or basal insulin alone each dose can be reduced by 30-50% at the start of LCD. Some patients can expect to

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come off insulin completely, over days or months, as insulin resistance resolves. Improving blood glucometer readings can guide the down titration of insulin.

It should be cautioned that some people may have an insulin insufficiency form of diabetes, such as latent autoimmune diabetes of adults. Whilst the LCD enables a reduction in insulin dosage it should not be completely stopped in this cohort of patients. Endogenous insulin insufficiency is more likely in patients who were not overweight at the time of diagnosis of diabetes, and it may be present in some with long standing T2D. Over-reduction in insulin dosage in these patients would lead to significant hyperglycaemia, and thus further dosage reduction would be avoided. It is recommended that additional investigation and expert advice is sought in cases of doubt as per good medical practice.

Medications that risk ketoacidosis

SGLT2 inhibitors (*'flozins'*): These carry a risk of causing ketoacidosis if a person has significant insulin insufficiency, with any diet. SGLT2i-induced ketoacidosis may occur with a normal blood glucose which heightens the risk of the life-threatening condition going unrecognised. Consider the possibility of insulin insufficiency, including in those who could have been misdiagnosed with T2D. In a community setting, for safety and simplicity, it may be appropriate for most patients to stop their SGLT2i when a LCD is initiated. This removes the SGLT2i-induced ketoacidosis risk, and additionally the effectiveness of the LCD means the benefit of a SGLT2i is diminished. (Note; a very LCD, typically <30-50g carbohydrate/day, can produce a physiologically normal state of ketosis, which should not be confused with the pathological state of ketoacidosis).

Medications that pose no excess risk with a LCD

Metformin: Safe to continue and in some patients continues to offer favourable benefits. Up to 25% of people experience gastrointestinal side effects from metformin.

GLP-1 agonists (*'-enatide', '-glutide'*): Safe to continue, with the beneficial actions of increased satiety and slowed gastric emptying, and possibly cardiovascular benefit. With a sustained LCD people may be able to stop their GLP-1 agonist.

Thiazolidinediones (*'glitazones'*): Safe to continue from a short term perspective. Concerns exist over their long term safety including; bladder cancer, heart failure, and bone mineral density. Thiazolidinediones are also known to cause weight gain. It is recommended to stop thiazolidinediones as soon as blood glucose levels allow.

DPP4 inhibitors (*'gliptins'*): Safe to continue, however clinical experience agreed these seem to have little blood glucose lowering effect in the context of a LCD.

Acarbose: Safe to continue, however on commencing a LCD the reduced starch ingestion means the patient can usually stop acarbose.

Blood glucose testing strips: Structured self-monitoring of blood glucose, such as paired pre and post meal testing, can be very helpful by providing rapid feedback on how foods affect blood glucose as a person adopts a LCD, and to inform whether medication doses can be reduced further. Patients on drugs that risk hypoglycaemia should have access to adequate testing strips.

Conclusion

The LCD is an increasingly popular option for managing T2D that can lead to; improvements in the condition, reduced medication burden, and (where needed) weight loss. Primary care clinicians need to be competent in adjusting diabetes medications to achieve safe and effective care.

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Three key clinical considerations:

- 4 ● Is there a risk of the drug causing hypoglycaemia or other adverse event?
- 5
- 6 ● What is the degree of carbohydrate restriction?
- 7 ● Once carbohydrate is reduced does the drug continue to provide health benefit, and if so are the potential drug benefits greater than or less
- 8 than possible risks and side effects?

10 Drug Group	11 Hypo risk?	12 Clinical suggestion
13 Sulfonylureas (e.g. <i>gliclazide</i>) and 14 Meglitinides (e.g. <i>repaglinide</i>)	Yes	Reduce/Stop (if gradual carbohydrate reduction then wean by halving dose successively)
15 Insulins	Yes	Reduce/Stop. Typically wean by 30-50% successively. Beware insulin insufficiency*
16 SGLT-2 inhibitors (<i>flozins</i>)	No	Ketoacidosis risk if insulin insufficiency. Usually stop in community setting.
17 Biguanides (<i>metformin</i>)	No	Optional, consider clinical pros/cons.
18 GLP-1 agonists (<i>-enatide/-glutide</i>)	No	Optional, consider clinical pros/cons.
19 Thiazolidinediones (<i>glitazones</i>)	No	Usually stop, concerns over long term risks usually outweigh benefit.
20 DPP-4 inhibitors (<i>glipitins</i>)	No	Usually stop, due to lack of benefit.
21 Alpha-glucosidase inhibitors (<i>acarbose</i>)	No	Usually stop, due to no benefit if low starch/sucrose ingestion.
22 Self-monitoring blood glucose	N/A	Ensure adequate testing supplies for people on drugs that risk hypoglycaemia. Testing can also support behaviour change (e.g. paired pre and post meal testing)

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* **Caution when reducing insulin if clinical suspicion of endogenous insulin insufficiency** (Patients with LADA misdiagnosed as T2D; a minority of T2D patients have endogenous insulin deficiency). Consider these possibilities if patient was not overweight at diagnosis. Exogenous insulin should not be completely stopped in these cases. Inappropriate over-reduction of exogenous insulin will lead to marked hyperglycaemia.