Managing Type 2 Diabetes with Therapeutic Carbohydrate Reduction (TCR)

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Purpose of this Document

Diabetes Australia, the American Diabetes Association, the European Association for the Study of Diabetes and Diabetes UK all now recognise therapeutic carbohydrate reduction (TCR) as one of a number of options for the management and potential remission of type 2 diabetes (T2D) [1-4]. This document is designed to aid medical management of individuals who have decided to undertake TCR. It is not designed to argue the relative merits of one dietary approach over another.

Executive Summary

1. Meaningful clinical benefits, including weight loss, improvement in glycaemic control and possible remission, reduction in the need for glucose lowering medications and reduction in blood pressure can be achieved by treating T2D with TCR.
2. People with T2D should be given realistic expectations of their chances of success with this approach and the education and support to keep them safe and help them achieve their goals.

3a. People with T2D should be monitored regularly while utilising TCR to assess the need for alteration to glucose and blood pressure lowering medications to avoid complications such as hypoglycaemia, hypotension and ketoacidosis.

3b. Management may include pre-emptive and step-wise reduction of glucose and blood pressure lowering medications but some therapies may need to be continued for their non-glycaemic effects.

INTRODUCTION

A low carbohydrate diet (LCD) is defined as one in which less than 26% of calories are derived from carbohydrate or has less than 130 grams per day of carbohydrates [1]. A very low carbohydrate ketogenic diet (VLCKD) is one in which less than 10% of its calories are derived from carbohydrates or has between 20 and 50 grams per day of carbohydrates [1]. Therapeutic Carbohydrate Reduction (TCR) is a term describing all interventions which reduce carbohydrate intake to less than 130 grams per day and includes both LCDs and VLCKDs.

Several systematic reviews and meta-analyses of well controlled trials suggest meaningful short term clinical benefits of TCR in T2D when compared to traditional higher carbohydrate diets. Relative benefits include improved satiety [5] more rapid weight loss, improvement in glycaemic control and a reduction in the need for diabetes medications [6-11]. Additionally, TCR is associated with significant reductions in both blood pressure and liver enzymes [12-14].

Goals of TCR in T2D may be improved glycaemic control, weight loss, reduction in glucose and blood pressure lowering therapies, T2D remission or a combination of the above. Diabetes remission is defined as a return of HbA1c to less than 6.5% that persists for at least three months in the absence of glucose-lowering pharmacotherapy [15]. TCR can be effective in producing T2D remission in the short to medium term. However, evidence of effectiveness from well controlled trials beyond 2 years is still limited [16].

TCR can most readily be achieved by the elimination of processed foods and sugary drinks, including fruit juice, and by focussing on the consumption of whole, natural, low carbohydrate foods.

Many of the issues covered in this document do not have evidence from high quality scientific studies on which to base recommendations. Where not specifically referenced, the recommendations are made on the basis of expert opinion.

CLINICAL CONSIDERATIONS

Absolute contraindications to TCR are end stage liver failure, generally with cirrhosis and risk of encephalopathy [17] and rare inborn errors of fat or ketone metabolism [18]. Relative contra-indications include type 1 diabetes (T1D), insulin deficient T2D, T3cD (primary pancreatic disease such as pancreatitis generally resulting in insulin deficiency), other forms of insulin deficient diabetes, sodium glucose cotransporter 2 inhibitor (SGLT2i) use, pregnancy, breastfeeding and eating disorders such as anorexia nervosa and bulimia.

TCR emphasises the optimal intake of dietary protein and healthy fat. This has prompted discussion about the use of this intervention in people with diabetes with pre-existing chronic kidney disease (CKD) [19]. The 2020 Kidney Disease Quality Outcomes Initiative (KDOQI) guidelines advise protein restriction for patients with CKD stage 3-5 with diabetes, not on dialysis, to 0.6-0.8 g/kg body weight to slow progression. This is opinion-level guidance (20) and has been called into question [21, 22]. In people with renal function ranging from normal to stage 3 CKD (i.e., eGFR ≥30 mL/min/1.73 m2), TCR is associated with stable or improved renal function [23-28]). Whilst the impact of this dietary approach on kidney function in those with advanced CKD (CKD Stages 4 and 5) has not been established [28], the risk of malnutrition characterised by protein energy wasting when following the current standard recommended dietary approach is potentially significant [29].

ENSURING THE CORRECT DIABETES CLASSIFICATION

It is important to ensure that a person with diabetes considering TCR has the correct classification of their diabetes. People initially labelled as having T2D may subsequently be found to have T1D or latent autoimmune diabetes in adults (LADA). Between five and ten percent of people initially diagnosed with T2D actually turn out to have T1D or LADA [30]. Although people with T1D and LADA can use TCR, remission is not possible and the risk/benefit ratio is potentially less advantageous. Screening for anti-GAD, IA2 and zinc transporter antibodies and measurement of paired C-peptide and glucose levels may be useful if there is uncertainty. C-peptide levels below or in the lower half of the "normal" range in the presence of hyperglycaemia indicate significant endogenous insulin deficiency. Some individuals with other forms of diabetes, particularly T3cD and

longstanding T2D may also be quite insulin deficient and paired glucose and C-peptide levels to establish this may be useful in decision-making and management.

MANAGEMENT OF PHARMACOTHERAPY

Healthcare professionals caring for a person with T2D who is significantly altering their diet must be competent in adjusting medications [31]. Pharmacotherapy adjustment may be required because the medication is no longer required , either at all or at the previous dose, or because it poses a significant safety risk in the context of TCR. A significant reduction in carbohydrate intake may lead to a reduction in the need for glucose lowering and possibly antihypertensive medication. Failure to appropriately adjust medication may lead to hypoglycaemia and/or hypotension. Furthermore, the combination of TCR with SGLT2i increases the risk of ketoacidosis which may be euglycaemic and not readily detected without specific ketone testing [32].

People with diabetes undertaking TCR should be made aware of the potential for either hyperglycaemia (if medications are reduced too aggressively or if dietary change is delayed or insufficiently strict) or hypoglycaemia (if medications, particularly insulin or sulphonylureas, are not reduced enough). People on insulin and/or SU require close blood glucose monitoring, either with finger prick capillary measurements 2-4 times/day or with continuous glucose monitoring (CGM). They should be reminded of the signs and symptoms of hypoglycaemia and should have an action plan in place to manage this if it does occur.

Biguanides

Metformin is generally safe to continue with TCR [31].

Sulphonylureas

SU medications carry a risk of hypoglycaemia [33] which is exacerbated in the context of reduced carbohydrate intake with TCR. SU should generally be ceased although this may not be possible immediately if baseline glycaemic control is suboptimal e.g. HbA1c >9% [31, 34].

Insulin

Insulin doses need to be carefully adjusted to avoid both hyper and hypoglycaemia and glucose monitoring with capillary fingerprick at least 2-4 times/day or CGM is strongly recommended for optimal safety. If baseline HbA1c is less than 9%, the total insulin dose can initially be reduced by 30 – 50%. This, ideally, should be given purely as basal insulin. Reduced doses of rapid acting insulin can be prescribed to be used before or after meals but are usually not required. If baseline HbA1c is 9.0% or greater, no change or smaller reductions in total insulin dose will be advisable, at least initially. Further changes in insulin dose can generally then be made on the basis of blood glucose monitoring [31, 34]. Reduction or cessation of insulin should take into account ketoacidosis risk, particularly if the individual is insulin deficient, taking SGLT2i, fasting or acutely unwell. Every person with diabetes should have a sick-day management plan.

Sodium-Glucose Co-Transport 2 Inhibitors (SGLT2i)

In people with T2D SGLT2i improve glycaemic control, reduce blood pressure and weight, non-fatal myocardial infarction, kidney failure, hospital admission for cardiac failure and may decrease cardiovascular and all-cause mortality [35]. It is thus important that the healthcare professional understands why SGLT2i therapy is being used and what risks may be incurred by its cessation. When used for glycaemic control alone the SGLT2i can generally be stopped pre-emptively with close monitoring of subsequent glucose control. However, in general, SGLT2i therapy should not be ceased if being used for established heart failure, atherosclerotic cardiovascular disease or CKD.

An approximate doubling in serum fasting ketone concentration has been observed after starting an SGLT2i, and this remains for several weeks at least [36]. For example, empagliflozin treatment increased fasting beta-hydroxybutyrate levels from 0.24 mmol/l to 0.56 mmol/l in people with T2D [37]. This compares to beta-hydroxybutyrate levels of 0.5 mmol/l to 3 mmol/l on a VLCKD [38].

The use of SGLT2i increases the risk of DKA which may be euglycaemic. This is a rare complication in T2D with an incidence of 0.6 to 2.2 per 1000 patient years [39]. SGLT2i are not approved for use in T1D in Australia but are being used by some practitioners, particularly if heart failure or CKD co-exists. The risk of DKA in a person with T1D on a SGLT2i is substantial with an incidence of 4-5 per 100 person-years [40]. DKA may be precipitated by intercurrent illness, dehydration or prolonged fasting [41, 42]. This risk may be increased by TCR particularly with VLCKDs [32]. It is therefore essential that T1D and LADA is recognised in people taking SGLT2i prior to commencing TCR.

In spite of the relatively low risk of DKA, both American and Australian guidelines have recommended that VLCKD diets not be used in T2D in combination with SGLT2i [1, 43]. However, in view of the potential benefits of both TCR and SGLT2i there may be individuals who would benefit from concurrent use of both.

People taking an SGLT2i must be made aware of the risks of ketoacidosis and have a sick day action plan regardless of dietary approach. The SGLT2i should be withheld for at least two days prior to and on the day of surgery or if the patient has an intercurrent illness, vomiting or diarrhoea or is dehydrated [44].

In people with diabetes considering TCR, DKA risk may be mitigated by using less extreme carbohydrate restriction and with regular ketone monitoring. When combining an SGLT2i with TCR, capillary ketone levels should initially be checked daily with the aim of keeping them less than 1.5 mmol/l. If ketone levels reach 1.5 mmol/l they should be advised to temporarily cease the SGLT2i and to seek medical advice prior to potential recommencement of the drug. If the person feels unwell, particularly if they have symptoms that might be consistent with ketoacidosis such as abdominal pain, nausea or vomiting, irrespective of measured ketone level, they should seek urgent medical attention [45].

The decision to commence, continue or cease an SGLT2i when managing a person with T2D utilising TCR is a decision which should be made by close consultation between the person with diabetes and their health care team.

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 agonists)

GLP-1 agonists are generally safe to continue in combination with TCR. Beyond glycaemic control, they provide the additional benefits of a reduction in appetite, weight loss [46] and improvement in cardiovascular and kidney outcomes [47].

Dipeptidyl peptidase 4 inhibitors (DPP4 Inhibitors)

DPP4 inhibitors are safe to continue if needed for glycaemic control in combination with TCR.

Alpha glucosidase inhibitors (AGI)

AGIs are safe to continue with TCR. However, as their mechanism of action is to modify the intestinal absorption of carbohydrates, they may be no longer effective or necessary.

Thiazolidinediones (TZD)

TZDs are safe to continue if needed for glycaemic control with TCR.

Frequency of review

People taking insulin or SU should initially be reviewed at least weekly whereas those not at risk of significant hypoglycaemia or hypotension could be reviewed every 2-3 weeks.

Antihypertensive Medication

More than fifty percent of people with T2D have hypertension [48]. LCDs [49] and VLCKDs [50] significantly reduce systolic and diastolic blood pressure and may decrease the need for antihypertensive medication.

People on anti-hypertensive medication should be advised that their blood pressure may drop and should be aware of symptoms of hypotension such as postural dizziness and fatigue. If blood pressure control is good, a pre-emptive reduction in antihypertensive medication should be considered. Ideally, people should self-monitor their blood pressure at home. A systolic blood pressure of less than 120 mmHg or symptoms consistent

with hypotension should prompt a reduction in blood pressure medication [31]. Antihypertensive medication reduction should occur in a step wise manner with diuretics and calcium channel blockers or therapies causing side-effects the first to be reduced. Generally an ACEi or ARB should be continued in individuals with established CV disease or CKD unless all other antihypertensives have been ceased and symptomatic hypotension persists.

Lipid Management

A common desire of people with T2D undertaking TCR is to minimise medications including lipid lowering agents. The effect of TCR on risk factors for atherosclerotic cardiovascular disease (ASCVD) is mixed. On the one hand TCR may improve glycaemic control, reduce blood pressure, increase HDLc and large buoyant LDL, reduce TG and small dense LDL [51-57] but on the other hand it may result in an increase in LDLc [52,58-69]. The net effect of these changes is unclear. There are no long-term published trials on the impact of TCR on major adverse cardiovascular events (MACE) including myocardial infarction, stroke and cardiovascular death [51] and no published guidelines specifically devoted to this issue.

In summary:

1. TCR has complex effects on lipid metabolism with the net effect on cardiovascular disease (CV) still uncertain.
2. Lipid lowering drug therapy has no increased toxicity in an individual utilising TCR
3. If the person with diabetes has established CV disease (secondary prevention) he or she is at high risk of further CV events and should be strongly encouraged to start or remain on aggressive LDLc lowering therapy, irrespective of TCR effects on other parameters.
4. For those without established CV disease (primary prevention) individual risk stratification, potentially utilising traditional risk factors but also considering newer parameters such as small dense LDL levels and coronary artery calcium scoring [70-74], would be appropriate, particularly if they do not wish to take lipid lowering therapy.

Managing Side Effects

Symptoms of carbohydrate withdrawal may include constipation, headache, halitosis, muscle cramps, bloating, diarrhoea, general weakness, and rash [5]. Collectively, these symptoms are known as the "keto flu" and occur during the first one or two weeks of a low carbohydrate diet, especially on days 3-5 [5]. These symptoms are believed to be caused by increased loss of sodium, potassium and water [75-77] from the kidney as a result of decreased insulin production [78]. Recommended management is to increase fluid intake to a minimum of 2.1 litres daily for women and 2.6 litres per day for men [79]. Extra salt may need to be temporarily added to the diet targeting a sodium intake of 3-5 grams per day [80]. People with hypertension, cardiac failure or CKD will need to have a daily salt target calculated on a case-by-case basis and be carefully monitored.

SUMMARY

People with T2D should be monitored carefully while utilising TCR to assess the need for alteration to glucose and blood pressure lowering medications to avoid complications such as hypoglycaemia, hypotension and ketoacidosis.

Management may include a pre-emptive reduction of medication. Education, careful monitoring, clear written instructions and action plans and judicious stepwise reduction in medication are all essential.

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