Therapeutic Carbohydrate Restriction – General Intervention

1. Introduction

These guidelines provide clinicians with a general protocol for implementing therapeutic carbohydrate restriction as a dietary intervention in hospitals or clinics. These guidelines are meant to be applied as a dietary intervention for specific conditions for which carbohydrate reduction has been shown to offer therapeutic benefits. In providing a clinical protocol for using therapeutic carbohydrate restriction, these guidelines offer the foundations for a shared language for clinicians to use in discussing and comparing interventions, improving protocols, and managing shared concerns.

The following text is based on biomedical literature as well as expert opinion. These guidelines are intended to inform and supplement a clinician's own expertise and experience in providing evidence based therapeutic nutrition

1.1 First principles

Carbohydrate restriction is an effective clinical intervention that clinicians may use to help patients achieve therapeutic goals for specific conditions.

Carbohydrate restriction targets specific conditions and patient populations. Carbohydrate reduction is not a "cure all," nor it is an appropriate intervention for all individuals.

Carbohydrate restriction should be tailored to the individual patient. It is not a "one-size-fits-all" approach to care. Clinicians should adapt carbohydrate restricted dietary interventions to the specific needs and health goals of their patients, in keeping with their own expertise, experience, and clinical judgment.

When patients choose carbohydrate restriction as a therapeutic intervention, it is the responsibility of clinicians to provide the support needed to do so safely. Rapid physiologic changes can be expected and medication management must be timely to avoid predictable interactions between these changes and common medications.

2. Background and definitions

2.1 Essential nutrition

A well-formulated carbohydrate restricted diet includes adequate energy, protein, fat, vitamins, and minerals.

With adequate protein and fat, the dietary requirement for carbohydrate is zero (Institute of Medicine [U.S.], 2005; Westman, 2002). Even when no dietary carbohydrate is consumed, glucose dependent tissues are able to utilize glucose produced through gluconeogenesis and glycogenolysis (Westman et al., 2007). Because dietary carbohydrate is not essential, it need not be a primary focus for certain therapeutic nutritional interventions.

	2.2 Different levels of carbohydrate reduction
	Dietary carbohydrate restriction can take many forms. The term "low-carbohydrate diet" lacks specificity and has been used to refer to carbohydrate intake levels that are low only in relation to population averages and/or measured as a percentage of kcals, but do not reach the therapeutic levels of restriction referred to here. Therapeutic carbohydrate restriction refers to dietary interventions measured in absolute amounts (grams/day) that fall below 130g of dietary carbohydrate per day, which is the U.S. Dietary Reference Intake (DRI) for carbohydrate (see Institute of Medicine [U.S.], 2005). The following definitions for levels of carbohydrate restriction are based on protocols currently in use or on definitions found in the literature: ● VLCK (very low-carbohydrate ketogenic) diets recommend 30g or less of net dietary carbohydrate per day (Hallberg et al., 2018). Deliberate restriction of kilocalories (kcals) is not typically recommended. ● LCK (low-carbohydrate ketogenic) diets recommend 30-50g of dietary carbohydrate per day (Saslow et al., 2017). Deliberate restriction of kcals is not typically recommended. ● RC (reduced-carbohydrate) diets recommend 50-130g of dietary carbohydrate per day, a level that is higher than levels listed above and lower than the U.S. DRI for carbohydrate. Deliberate restriction of kcals may or may not be recommended at this level. ● MC-CR (moderate-carbohydrate, calorie-restricted) diets recommend more than 130g of dietary carbohydrate per day with a range of 45-65% of daily kcals coming from carbohydrate ("Carbohydrate Counting & Diabetes | NIDDK," n.d.). In most cases, kcals are also restricted to maintain energy balance or to achieve a deficit for weight loss. This dietary intervention reflects the amount of dietary carbohydrate typically found in the "carbohydrate counting" dietary intervention that is given to many people with type 2 diabetes.
	2.3 Fiber
	Definitions of carbohydrate levels referred to above typically refer to non-fiber grams of carbohydrate, as fiber is not typically metabolized to glucose. Using food labels or nutrition data, the calculation of total carbohydrate minus fiber will result in "net carbohydrate."
	2.4 Glycemic index and glycemic load
	Dietary carbohydrates may vary considerably in their ability to raise blood glucose. However, the density of carbohydrate in each food is also a factor. For example, the carbohydrate in watermelon is more 'sugary' gram for gram than an equivalent weight of carbohydrate to be

	found in a banana, but the banana has a far greater density of carbohydrate than the watermelon, as the latter is mainly water. Despite its lower glycemic index, an equal size portion of banana has a greater effect on blood glucose than watermelon (Atkinson, Foster-Powell, Brand-Miller 2008; Unwin, Haslam, Livesey 2016)
	2.5 Protein
	In contrast to carbohydrate, protein is an essential macronutrient because essential amino acids are unable to be made by the body and need to be provided byby ingested protein. Patients may choose an omnivorous or plant-based approach in order to acquire adequate protein intake. It is important to note that most animal-sourced proteins have a much higher biological value than plant-sourced proteins, indicating that animal-sourced proteins are much more readily converted into body protein (Byrd-Bredbenner et al. 2009). The Recommended Dietary Allowance (RDA) intake for adults is 0.8 g protein per kilogram of body weight per day; however, this may be an underestimate of actual protein needs for many individuals (Layman et al. 2015; Phillips et al. 2016). When carbohydrate is restricted, dietary sources of protein and fat provide kcals in addition to providing the structural components of cells and tissue, therefore additional protein intake may be necessary.
	2.6 Fat and saturated fat
	Therapeutic carbohydrate restriction creates a metabolic milieu in which the body uses fat as a primary source of energy (see also 3.1). Dietary fat provides essential fatty acids and is needed for the absorption of certain micronutrients (vitamins A,D,E and K). Foods that contain monounsaturated, polyunsaturated (with a focus on omega 3s) and saturated fats are recommended. As it has not been clearly determined that saturated fats in foods contribute to adverse health outcomes (Forouhi et al., 2018), foods considered to be significant sources of dietary saturated fat are not usually restricted for this intervention.
	2.7 Calories
	Monitoring calorie intake and expenditure may or may not be necessary when implementing therapeutic carbohydrate restriction. If caloric expenditure exceeds caloric intake, fat stores may be utilized for energy, and weight loss is more likely to occur; however, weight loss may not be a specific goal of the intervention. Clinicians should note that other therapeutic dietary interventions, such as very low-calorie diets or intermittent fasting, effectively reduce carbohydrate intake as part of overall kcal reduction. Conversely, reducing carbohydrate intake in practice often serves to reduce overall kcal intake. Recommendations for deliberate kcal restriction are not typically part of VLCK and LCK clinical interventions, but may be used in research protocols. Deliberate kcal restriction may need to be part of the overall dietary guidance consideration, depending on the goal of the patient. However, patients often spontaneously reduce kcal intake with VLCK and LCK diets, even though they are not specifically directed to do so (Boden et al. 2005).

It is recommended that when therapeutic carbohydrate restriction is studied or used clinically in conjunction with calorie restriction that those diets be designated as such: VLCK-CR (very low-carbohydrate ketogenic diet-calorie restricted); LCK-CR (low-carbohydrate ketogenic diet-calorie restricted); and RC-CR (reduced-carbohydrate diet-calorie restricted).

2.8 Background - For further discussion and investigation

How the various approaches to therapeutic carbohydrate restriction should be defined is a matter of ongoing discussion. As the therapeutic benefits of carbohydrate restriction may be related to absolute amounts of carbohydrate consumed, designating this amount in grams/day consumption is preferable to designating carbohydrate amounts as a percentage of total kcals/day. Because much confusion may arise from lack of specificity in identifying levels of carbohydrate restriction in research settings, it is recommended that the level of carbohydrate restriction be designated in grams/day consumption in the name of the diet itself (i.e. carb30-diet) in order to quantify what level of carbohydrate restriction is being studied. Further, source of carbohydrate may be a consideration (refined vs. unrefined, for example). Alternately, an "intention-to-treat" approach may be taken. Due to the difficulty of accurately assessing long-term dietary intake, measuring designated outcomes in relation to information or advice given may be a more practical method of determining the effectiveness of an intervention.

3. Therapeutic potential

Therapeutic carbohydrate restriction can assist in improving all aspects of the metabolic syndrome, in part by reducing blood glucose levels, which in turn reduces fasting and postprandial insulin levels and improves insulin resistance (Volek & Feinman 2005). This is accomplished by restricting any foods that digest down into glucose, including starch from whole grains, as predicted by the glycemic index. In some cases, therapeutic levels of ketones are also produced.

3.1 Effect of carbohydrate-restricted diets on energy metabolism

The appropriate level of carbohydrate restriction to meet therapeutic goals will differ among patients. An amount of less than 50 g of carbohydrate per day frequently leads to a general change in metabolism from "glucocentric" (where glucose is relied on as a primary energy source) to "adipocentric" (where ketone bodies and fatty acids are primary energy sources), although this level varies across individuals (Westman et al., 2007).

At lower levels of carbohydrate restriction, most adults will enter into nutritional ketosis. During this state, the body relies primarily on fatty acids and a small amount of ketones can be detected in blood, urine or breath.

Ketones are molecules produced by the liver from fatty acids that can be used as a fuel source by extrahepatic tissues. Nutritional ketosis refers to the presence of ketones in the blood when insulin is low and the metabolism of fatty acids from adipose tissue is accelerated (Veech et al., 2001). Most people develop low levels of nutritional ketosis after an overnight fast, and ketones increase further with longer fasts or carbohydrate restriction. Ketone levels induced by carbohydrate restriction do not approach the levels induced by frank insulin deficiency as in diabetic ketoacidosis. This low-level nutritional ketosis is not harmful and may even be therapeutic (Veech et al., 2001).

	3.2 Nutritional ketosis versus ketoacidosis
	Nutritional ketosis: ● Natural physiological state allowing utilization of ketones as a supplemental fuel (Salway, 2004). ● Can occur in anyone during fasting or carbohydrate restriction ● Ketones generally remain below 3 mmol/L, and do not change blood pH ● Blood glucose remains below 270 g/dl (15mmol/L) ● Asymptomatic besides "fruity" breath due to acetone production (Anderson, 2015) Diabetic ketoacidosis ● Medical emergency requiring urgent intervention ● Occurs with frank insulin deficiency in people with type I diabetes or sometimes insulin-dependent type II diabetes. Insulin deficiency leads to unregulated lipolysis and high levels of fatty acids and ketone production. Patients on SGLT2i may be at increased risk of DKA. ● High levels of ketones (>3mmol/L), high glucose (>270g/dl) and metabolic acidosis (pH <7.3) ● Symptoms such as fatigue, confusion, vision changes, dehydration, polyuria, and rapid breathing.
	3.3 Other effects of therapeutic carbohydrate restriction
	Other physiological and metabolic changes are related to carbohydrate restriction. These may be directly related to changes in serum glucose levels or to changes in insulin levels and insulin resistance. The mechanisms for a number of cardiometabolic risk factors have been linked to underlying insulin resistance, including T2DM, hypertension, dyslipidemia, and chronic inflammation (Reaven, 1988; Festa et al. 2000; Roberts 2013). With regard to hypertension, high circulating levels of insulin that accompany insulin resistance have been associated with sodium retention, proliferation of vascular smooth muscle, increased sympathetic nervous system activity, and diminished release of nitric oxide from the endothelium (Hsueh 1991; Yancy et al. 2010). Reducing carbohydrate intake may be expected to improve blood pressure and to have an effect on fluid and electrolyte balance. With regard to dyslipidemia, high circulating levels of insulin have been associated with increased plasma triglyceride concentration, decreased high-density lipoprotein (HDL) cholesterol concentration, and increased levels of atherogenic small dense particles of low-density lipoprotein (LDL) cholesterol (Ferrannini et al. 1991; Reaven 1993). Reducing carbohydrate may improve the TAG/HDL ratio and certain markers of inflammation (Forsythe et al. 2008) .
	3.4 Effects on appetite and satiety
	Many therapeutic interventions that restrict carbohydrate are not deliberately limited in calories, although carbohydrate restriction frequently induces a spontaneous decrease in overall

	energy intake. The mechanisms behind this effect are not clearly understood. The emphasis on adequate protein intake during therapeutic carbohydrate restriction may play a part, as protein is generally considered to generate the most potent satiety signals (Blundell & Stubbs 1999). Because hunger has been shown to predict failure to comply with energy-restricted diets (Nickols-Richardson et al. 2005), where energy restriction is considered an important factor in a dietary intervention, carbohydrate restriction may be one way to achieve this.
	3.5 Therapeutic potential - For further discussion and investigation
	4. Initiating the intervention
	Interventions that involve therapeutic carbohydrate restriction should be set in a framework that includes the patient's own health goals and level of understanding. It should be offered alongside other evidence-based lifestyle interventions that could be synergistic, such as exercise or smoking cessation. The initiation of therapeutic carbohydrate restriction should also be made within the context of other relevant evidence-based pharmacologic therapies for the disease being targeted. Particular caution should be exercised with pharmacotherapies, with emphasis on knowledgeable de-prescribing when appropriate to avoid complications such as hypoglycemia.
	4.1 Pre-diet evaluation and counseling
	Initial assessment prior to initiation of therapeutic carbohydrate restriction should include evaluation of patient's current symptoms, past medical history, comorbidities, contraindications, and current medications. An exploration of the patients' health goals and how therapeutic carbohydrate restriction can assist the patient in meeting those goals may enhance the patient's understanding of how to implement the diet. It may also help to discuss how progress towards those goals will be assessed. The intervention should be individualized with regard to the patient's existing nutrition habits, resources, and living arrangements and roles (i.e. who does the cooking and food purchasing). Laboratory tests as indicated for presenting condition should be completed to rule out acute pathology and establish baseline metrics. Other considerations for implementation that should be discussed are psychosocial issues, such as but not limited to economic, cultural, or personal factors that may present challenges to successful administration of the diet.
	4.2 Defining the "ideal" patient for therapeutic carbohydrate restriction
	This was a suggestion by Brian Lenzkes. Perhaps we could get a sense from him about what he would be looking for with this information?
	4.3 Initial tests
	Clinical tests: Weight Height Waist circumference Hip Circumference Blood pressure Blood tests: Complete Blood Count (CBC)

	Comprehensive Metabolic Panel (CMP) Lipid panel TSH HbA1c Liver function tests to include GGT Optional Tests: Fasting insulin level Postprandial insulin assay/ Kraft protocol (if available and affordable) C-Peptide (for patients who are insulin-dependent, as the patient gets close to low doses of insulin [should this be in follow up section then?]) – To ensure that the patient is still making insulin Urine Albumin:Creatinine ratio Full thyroid panel, including TSH, fT3, fT4, RT3 and antibodies
	4.3 Other tests that may be considered
	Peak flow test Cardiac C-reactive protein ESR Uric acid Coronary calcium score(for risk stratification and ongoing monitoring)
	4.4 Personalization/individualization of dietary intervention
	4.5 Complicating co-morbidities
	Chronic kidney disease Type 1 diabetes mellitus Type 2 diabetes mellitus Hypertension There are also rare diseases where carbohydrate restriction could be a problem: glycogen storage disease type I (von Gierke disease), carnitine deficiency, carnitine palmitoyltransferase (CPT) deficiency, carnitine translocase deficiency, pyruvate carboxylase deficiency, acyl-CoA dehydrogenase deficiency (long, medium, and short chain), and 3-hydroxyacyl-CoA deficiency, acute intermittent porphyria.
	4.6 Considerations for initiation and delivery of intervention
	Inpatient, outpatient, digitally assisted modes of delivery
	4.6.1 Inpatient
	4.6.2 Outpatient
	This can be one-to one or in groups

	4.6.3 Technology and tools
	4.7 Initiating the intervention - For further discussion and investigation
5. Intervention	
Brief discussion of patient selection, personalization, safety, and effectiveness?	
	5.1. Objectives of intervention
	This will depend on targeted condition.
	5.2 Medication nutrition therapy
	A low-carbohydrate diet typically emphasizes real foods, but can be administered using a meal-replacements. Food-based low-carbohydrate diets include whole food sources such as meats, low-starch vegetables, full fat dairy, nuts and seeds, and small amounts of fruit and legumes, where appropriate. Although this can be done as a vegetarian diet, the diet encourages animal products and seafood. In counseling, the emphasis should be on foods and general carbohydrate restriction, rather than monitoring macronutrient content. Adequate protein,fat and fiber intake at each meal to give a sense of satiety and satisfaction should be emphasized. Protein intake recommendations are generally set at 0.8 -1.0 grams of protein per kilogram of estimated lean body mass for non-therapeutic diets; however, protein intake at 1.2 g - 2 g/kg/estimated lean body mass may better reflect protein metabolism in the context of therapeutic carbohydrate restriction (Phinney et al. 1983; Davis & Phinney 1990). Protein intake above levels set for the general population may be particularly important during the first few weeks of carbohydrate restriction (Phinney et al. 1983). Protein intake can vary based on individual needs and energy expenditure; very active or athletic individuals may require higher protein intake. Meat, fish, poultry, and non-meat sources such as eggs, full fat dairy, and low-carbohydrate nuts (such as pecans and macadamias) are examples of foods rich in protein. A low-carbohydrate diet will often include the liberal use of non-starchy vegetables, particularly leafy greens and sources of natural plant fats such as avocados and olives. However, for some patients, these may need to be more limited in quantity as they contribute to total and net dietary carbohydrate. Fiber from a variety of plant sources is thought to be beneficial for the gut microbiome (Valdes et al., 2018), but this emerging area of interest is beyond the scope of these guidelines. A low-carbohydrate diet allows intake of natural fats to satiety. These include any non-*trans* fats, such as olive oil, coconut oil, avocado oil, full-fat dairy, and butter, along with the fats naturally associated with whole food protein sources. Carbohydrate restriction strongly limits the intake of grains (rice, wheat, corn, oats) and grain-based products (cereals, bread, biscuits, oatmeal, pastas, crackers), sweetened dairy products (fruit yogurts, flavored milk products), and sweetened desserts (gelatins, puddings,

	cakes). Small amounts of starchy vegetables, legumes and fruit can be used at less restrictive levels of carbohydrate reduction, if amounts are within the daily carbohydrate intake. Non-starchy vegetables, seeds, and nuts are recommended in conjunction with or instead of fruit as sources of both soluble and insoluble fiber, and micronutrients.
	5.2.1 Nutrition education, counseling, care management
	Therapeutic carbohydrate restriction should include the foundational elements of any medical nutrition therapy, namely an educational component and a support component. Adherence, satiety, and simplicity are critical to early success.
	5.2.2 Facilitating behavior change
	A patient's readiness to change and support are essential for proper initiation of this therapy.
	5.2.3 Patient resources
	There are a variety of ways to educate the patient and his or her family regarding this diet. Clinicians should tailor educational materials to their patient population and needs. Please see this resource for a variety of patient education materials.
	5.3 Side effects, adverse outcomes, and treatment
	5.3.1 Electrolyte imbalance
	Some side effects of a low-carb diet such as lightheadedness , fatigue, and headache are due to low body salt and hypotension, especially in patients on blood pressure lowering therapy. High levels of insulin may cause the kidneys to retain salt and water (Brands and Manhiani, 2012). Lowering insulin with a low-carb diet can cause a diuresis and symptomatic hypotension. Patients should not restrict sodium on low-carb diets and will likely need additional sodium and hydration, especially in the first several weeks. For most patients, 2-3 grams per day is appropriate. This can be accomplished through salting food liberally, or sodium can be supplemented by advising patients to sip on a broth made with regular-sodium bouillon cubes (Steelman and Westman, 2016). Extra attention should be paid to sodium and hydration status for patients on multiple medications (Steelman and Westman, 2016). Patients with heart failure or chronic kidney disease will need more careful monitoring. Sodium intake should be kept at baseline until edema resolves, then increased if the patient has orthostatic symptoms (Steelman and Westman, 2016). Potassium can also become depleted, especially with potassium-wasting diuretics (thiazides and loop) or inadequate sodium intake. Attention should be given to adequate dietary potassium and sodium intake, especially in patients at high risk such as those on digoxin therapy (Sävendahl and Underwood, 1999). Supplementation should be considered if hypokalemia is persistent (Steelman and Westman, 2016; Westman et al. 2007).

	5.3.2 Constipation
	Constipation may also result from changes in fluid and electrolyte imbalance. To address this, begin by increasing fluid intake to minimum of 2 liters per day. Encourage the consumption of broccoli, cauliflower and greens. If not resolved, try 1 teaspoon of milk of magnesia or magnesium citrate at bedtime, bouillon supplements, or sugar-free fiber supplement.
	5.3.3 Muscle cramps
	Muscle cramps usually respond to magnesium supplementation. This can be delivered via milk of magnesia or 192 mg/day slow-release magnesium chloride (Slow-Mag), with the recommended dosage from to 400 mg daily. Magnesium glycinate up to 600 mg/day for symptomatic cramps is also well absorbed and causes minimal gastrointestinal symptoms. Magnesium glycinate can be decreased to 200 mg/day for maintenance. Supplementation should continue for as long as required to treat muscle cramps. Yellow mustard? (Ask Will Yancy)
	5.3.4 LDL increase
	There is widespread concern about the impact of high dietary fat intake with low-carbohydrate diets on cholesterol. However, low-carbohydrate diets have shown to be effective at increasing HDL and decreasing triglycerides with minimal change in LDL or total cholesterol (Westman et al., 2007). During weight loss, serum total cholesterol may rise. This small increase is usually temporary and is not an indication to increase or begin lipid lowering medications (Sävendahl & Underwood, 1999). Recheck lipid panel after weight loss has stabilized. A clinical trial has demonstrated no LDL rise using a low saturated fat/low carb diet. This could be an option if LDL rises and remains elevated at weight stability in patient population for whom this is a concern (Tay et al. 2014).
	5.3.5. Other potential side effects
	Other side effects to be aware of include heart palpitations, insomnia, temporary hair loss, temporary reduced physical performance, bad breath (from acetone), and low alcohol tolerance. Side effects are usually most severe during transition to the diet and improve with adequate electrolytes and fluids. Are there any other side effects/recommendations for treatment?
	5.4 Adjunct therapies
	5.4.1 Supplements
	Historical examples of low-carbohydrate diets have greatly restricted the intake of a variety of foods, requiring supplementation with a multivitamin. A well-formulated

	low-carbohydrate diet emphasizes a wide variety of plant and animal foods with high nutrient density. Although this diet will provide good nutrition for the majority of individuals, the recommendation of multivitamin supplementation should be on a personalized basis for the patient and is left to the healthcare practitioner's and patient's discretion. Individual testing of Vitamin D, B12, folate, and red cell magnesium can guide supplementation. Magnesium is commonly inadequate in modern diets (He et al., 2006). Electrolyte changes induced by a low-carb diet may increase magnesium losses. Most clinical trials of low-carb diets have included a daily multivitamin and mineral supplement (Westman et al., 2007). Magnesium supplementation may be warranted, especially if the patient experiences side effects. The consumption of magnesium-rich, low-carbohydrate foods should also be encouraged; these include foods such as, almonds, spinach, fatty fish, and avocados.
	5.4.2 Exercise
	Aerobic Endurance Strength-training
	5.4.3 Other
	5.5 Intervention - For further discussion and investigation
	6. Medication adjustment
	Understanding the impact of diet on common medications is important to keep patients safe. The diet itself is not dangerous but it does induce significant changes to metabolism and electrolyte balance that may cause patients to become over-medicated.
	6.1 Diabetes medications
	If patients are on insulin or sulfonylureas when beginning a low-carbohydrate diet, it is likely that does will need to be reduced immediately to prevent hypoglycemia. Thiazolidinediones are may be stopped because they contribute to weight gain but are unlikely to cause hypoglycemia. DPP-4 inhibitors and GLP-1 analogues are safe to use, however SGLT-2 inhibitors can be a problem because they can exacerbate dehydration and have been associated with DKA episodes. Metformin can be used effectively in conjunction with a low-carb diet (Steelman and Westman, 2016). Metformin does not present the same risks of hypoglycemia as insulin or sulfonylureas. See accompanying "medication deprescribing" materials (IPTN, Murdoch). Many patients can completely discontinue insulin on a low-carbohydrate diet. However, it is important to verify the diagnosis of type 2 diabetes over type I or Late Onset Adult Diabetes (LADA) before complete discontinuation. Consider the following factors suspicious for LADA before complete discontinuation of insulin: ● Young age at diagnosis ● Rapid transition from new diagnosis diabetes to requiring insulin (<5 years)

	• Continued requirement of insulin during periods of weight loss or bariatric surgery • Labile blood glucose (standard deviation of 50 is suspicious) • Low body weight, BMI <30 • Normal triglycerides and high HDL • Personal or family history of autoimmunity • History of DKA
	6.2 Anti-hypertensive medications
	Review medication list for anti-hypertensives. Blood pressure may need to be monitored (need additional details for this: how often to measure? What levels are concerning? Self-care & contact medical team?) Hyponatremia may be exacerbated by SGLT2 inhibitors, thiazide, and loop diuretics and many other medications. Other medications that can cause hyponatremia include cyclosporine and cisplatin, oxcarbazepine, trimethoprim, antipsychotics, antidepressants, NSAIDs, cyclophosphamide, carbamazepine, vincristine and vinblastine, thiothixene, thioridazine, other phenothiazines, haloperidol, amitriptyline, other tricyclic antidepressants, monoamine oxidase inhibitors, bromocriptine, clofibrate, general anesthesia, narcotics, opiates, ecstasy, sulfonylureas, and amiodarone.
	6.3 Other
	Warfarin doses may need to be adjusted and INR should be monitored more frequently during the diet transition (Steelman and Westman, 2016). Medications that have a narrow therapeutic range such as valproic acid should be monitored for potential dosing changes. Medications that interfere with lipolysis should be replaced or discontinued if possible: niacin, beta blockers, antidepressants, antipsychotics.
	6.4 Medication adjustment - For further discussion and investigation
	7. Follow-up care
	7.1 Monitoring and evaluation
	7.2 Maintenance and discontinuation of intervention

	Although the benefits of carbohydrate restriction for many conditions may be recognized, many experts have raised concerns about whether patients can adhere to such a diet indefinitely. Because dietary carbohydrate is not an essential nutrient, a well-formulated low-carbohydrate diet that includes a variety of vegetables presents no health risks from nutritional deficits. However, other considerations, such as traditional or celebratory foods, should be taken into account when discussing long-term adherence to a low-carbohydrate dietary intervention. Whether and in what manner to allow additional dietary carbohydrate to the diet will be an individual decision. It is unlikely that a return to previous levels of carbohydrate consumption would be recommended; to do so would likely lead to a return of previous health conditions that reduction of dietary carbohydrate ameliorated. However, as with other dietary components that are non-essential such as alcohol, limited amounts may be tolerated. For some individuals, increased dietary carbohydrate may be offset by deliberately restricting calories in a way that prevents weight gain. Other individuals may prefer to forgo calorie counting in favor of continued carbohydrate restriction.
	7.3 Follow-up care - For further discussion and investigation
8. Specific populations	
	8.1 Patients with a history of gout
	Patients with history of gout are at a higher risk of flare when transitioning to the diet, although long-term gout flares may improve on low-carb diets (Steelman and Westman, 2016).Consider prophylactic allopurinol during transition.
	8.? Specific populations – For further discussion and investigation
9. Additional resources for clinicians	
10. References	
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