

Therapeutic Carbohydrate Reduction: General Intervention	
1. Introduction	
	<p>This article provides clinicians with a general guide for implementing therapeutic carbohydrate reduction as a dietary intervention in hospitals or clinics. This guide is meant to be applied as a dietary intervention for specific conditions for which carbohydrate reduction has been shown to offer therapeutic benefits. In providing an implementation guide for using therapeutic carbohydrate reduction, this article offers the foundations for a shared language for clinicians to use in discussing and comparing interventions, improving guides, and managing shared concerns.</p> <p>The following text is based on biomedical literature as well as expert opinion. This guide is intended to inform and supplement a clinician’s own expertise and experience in providing evidence-based therapeutic nutrition.</p>
1.1 First principles	
	<p>Carbohydrate reduction is an effective clinical intervention that clinicians may use to help patients achieve therapeutic goals for specific conditions to be designated in “condition-specific guides.”</p> <p>Carbohydrate reduction targets specific conditions and patient populations. Carbohydrate reduction is not a “cure all,” nor is it an appropriate intervention for all individuals.</p> <p>Carbohydrate reduction 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.</p> <p>When patients choose carbohydrate reduction as a therapeutic intervention, it is the responsibility of clinicians to provide the close monitoring and 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.</p>
2. Background and definitions	
	<p>The historical origins of carbohydrate reduction date back to 1825, when Jean Anthelme Brillat-Savarin published <i>The Physiology of Taste</i>. In this book, Brillat-Savarin recommended a solution to obesity, which involved a “more or less rigid abstinence” from flours and starches. It is assumed that this would mean abstinence from sugar as well, as sugar was not yet readily available in large quantities in foods or beverages.</p> <p>The modern era of therapeutic carbohydrate reduction is typically identified as beginning with William Banting’s (1864) “Letter on Corpulence.” Banting had tried unsuccessfully to lose weight and was beginning to exhibit symptoms of metabolic disease when he met Dr. William Harvey, who prescribed a diet that restricted starches, sugar, and some dairy. Banting’s letter describes his nearly 50-pound weight loss, improvement of symptoms, and the diet itself.</p>

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In the early 20th century interest in therapeutic carbohydrate reduction resurfaced in the context of two chronic diseases: diabetes mellitus and epilepsy. Dr. Elliott Proctor Joslin and Dr. Frederick Madison Allen studied the effects of carbohydrate and calorie reduction in the management of diabetes, but interest in carbohydrate reduction in diabetes management waned with widespread use of exogenous insulin. (Westman, Yancy, & Humphreys, 2006)

In 1921, Dr. Russell M. Wilder of the Mayo Clinic introduced the ketogenic diet, a strict version of a carbohydrate-restricted diet, for the treatment of epilepsy. Reports from the time indicated a 50% success rate in treating epilepsy without drugs. However, as with diabetes, the dietary intervention fell out of favor with the advent of pharmacological treatments. (Freeman, 2013)

Carbohydrate reduction for weight loss was revived in the 1960s and 1970s. Although Dr. Robert Atkins (1972) is probably the best-known advocate of low-carbohydrate diets for weight loss, other physicians and other versions of low-carbohydrate diets were also in circulation at the time (Mackarness, 1975; Stillman & Baker, 1970). Frequently, these clinicians referred to the research of Dr. Alfred W. Pennington, who had successfully treated obese subjects with low-carbohydrate diets in the 1940s. Another “wave” of low-carbohydrate diet books arrived in the 1990s, including a re-release of Dr. Atkin’s diet. Despite the fact that the advice in most low-carbohydrate, weight-loss diet books contradicts advice given by the American Heart Association and the Dietary Guidelines for Americans, these books far outsell other weight loss books (Blackburn, Phillips, & Morreale, 2001). The positioning of these diets in the media as “fad diets” for “quick weight loss” has overshadowed their utility in clinical settings as interventions for specific conditions.

More recently, there has been a revival of interest in low-carbohydrate diets as clinical interventions for specific conditions. Ketogenic diets have been re-established as an effective nonpharmacologic treatment for intractable childhood epilepsy (Kossoff et al., 2018). In addition, varying degrees of carbohydrate reduction have been found to be one of the most effective dietary interventions for treatment of type 2 diabetes. In the U.K., the National Health Service (NHS) has approved a digital application that helps people with type 2 diabetes follow a low-carbohydrate dietary intervention. U.K. general practitioner Dr. David Unwin has demonstrated to the NHS how a low-carbohydrate diet can save money by offering patients an alternative to medications. In recognition of his work, Dr. Unwin has been named a Royal College of General Practitioners Clinical Expert in Diabetes and NHS Innovator of the Year 2016.

A recent Western Australian government report states that remission, rather than just management, should be the goal of interventions for type 2 diabetes and that a low-carbohydrate diet should be one of the options formally offered to patients with this diagnosis (Freeman et al., 2019). Finally, a 2019 consensus statement from the American Diabetes Association indicates that low-carbohydrate diets should be included as one of the nutrition therapy options offered to people with type 2 diabetes. The report also notes that “Reducing overall carbohydrate intake for individuals with diabetes has demonstrated the most evidence for improving glycemia and may be applied in a variety of eating patterns that meet individual needs and preferences” (Evert et al., 2019)

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

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	<p>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.</p>
<p>2.2 Different levels of carbohydrate reduction</p>	
	<p>Dietary carbohydrate reduction 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 reduction referred to here.</p> <p>Therapeutic carbohydrate reduction 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 reduction are based on protocols currently in use or on definitions found in the literature:</p> <ul style="list-style-type: none"> ● VLCK (very low-carbohydrate ketogenic) diets recommend 30g or less of 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 “carbohydrate counting” interventions given to many people with type 2 diabetes.
<p>2.3 Fiber</p>	
	<p>Definitions of carbohydrate levels referred to above may refer to either total carbohydrate content or 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 is referred to as “net carbohydrate.” As no comparative studies of “total” vs. “net” carbohydrate have been done, clinical experience may inform which approach is best for patients.</p>
<p>2.4 Glycemic index and glycemic load</p>	
	<p>Dietary carbohydrates may vary considerably in their ability to raise blood glucose (Atkinson, Foster-Powell, & Brand-Miller, 2008). However, the density of carbohydrate in each food is also a factor (Unwin, Haslam, & Livesey, 2016).</p>

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	<p>For example, when comparing the 50 grams of carbohydrate in watermelon to the 50 grams of carbohydrate in bananas, the sugar in watermelon metabolizes quickly to produce a higher blood glucose response, meaning its “glycemic index” is high. However, banana has a far greater density of carbohydrate than watermelon, as the latter is mainly water. When comparing similar serving sizes (120 grams of watermelon to 120 grams of banana), the serving of watermelon has a lower impact on blood sugar and thus its “glycemic load” is low.</p> <p>Glycemic index can vary from one individual to another, and the glycemic index of any given food can be affected by other foods consumed during the same meal (Meng, Matthan, Ausman, & Lichtenstein, 2017). Glycemic load is based on glycemic index, and thus both may vary considerably in practice.</p>
	<p>2.5 Protein</p>
	<p>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 by 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, Berning, Beshgetoor, & Moe, 2008).</p> <p>The Recommended Dietary Allowance (RDA) intake for adults is 0.8g protein per kilogram of ideal body weight per day; however, this may be an underestimate of actual protein needs for many individuals (Layman et al., 2015; Phillips, Chevalier, & Leidy, 2016). When carbohydrate is restricted, dietary sources of protein and fat provide kcal in addition to providing the structural components of cells and tissue, therefore additional protein intake may be necessary, up to 2.0g protein per kilogram of ideal body weight. Even at levels above the RDA, protein intake on a low-carbohydrate diets typically remains within the acceptable macronutrient distribution range (AMDR) of 10-35% of kcals.</p>
	<p>2.6 Fat and saturated fat</p>
	<p>Therapeutic carbohydrate reduction creates a metabolic milieu in which the body can use 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 (fat-soluble vitamins A,D, E and K). Foods that contain a combination of fatty acids—including monounsaturated, polyunsaturated and saturated fats—are recommended. As it has not been clearly determined that saturated fats in foods contribute to adverse health outcomes (Forouhi, Krauss, Taubes, & Willett, 2018), foods considered to be significant sources of dietary saturated fat are not usually restricted for this intervention. However, <i>trans</i> fats should be avoided. <i>Trans</i> fats are thought to contribute to disease through a number of potential mechanisms (Remig et al., 2010)</p>
	<p>2.7 Calories</p>
	<p>Monitoring caloric intake and expenditure may or may not be necessary when implementing therapeutic carbohydrate reduction. 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.</p>

	<p>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. In practice, reducing carbohydrate intake may also serve to reduce overall kcal intake in some cases.</p> <p>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, Sargrad, Homko, Mozzoli, & Stein, 2005).</p>
<p>2.8 Background - For further discussion and investigation</p>	
	<p>How the various approaches to therapeutic carbohydrate reduction should be defined is a matter of ongoing discussion. As the therapeutic benefits of carbohydrate reduction may be related to absolute amounts of carbohydrate consumed, designating this amount in grams/day consumption may be 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 reduction in research settings, the level of carbohydrate reduction could 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 reduction 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 than attempting to assess “compliance.”</p> <p>Another matter of ongoing discussion is the use of “net carbohydrate” versus “total carbohydrate.” Some practitioners assert that advice regarding “net carbohydrate” levels does not work as well as advice about “total carbohydrate” intake. Trials that compare these two approaches would provide some insight as to which approach may be preferable.</p> <p>Because reduced-carbohydrate therapeutic interventions vary in their requirement for kcal restriction, it is recommended that when these diets are studied or used clinically in conjunction with kcal 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).</p>
<p>3. Therapeutic potential</p>	
	<p>Therapeutic carbohydrate reduction can assist in improving all aspects of the metabolic syndrome, in part by helping to reduce blood glucose levels, which in turn can reduce fasting and postprandial insulin levels and improve insulin resistance (Volek & Feinman, 2005). This is accomplished by restricting any foods, including starch from whole grains, that digest down into glucose as predicted by the glycemic index. In some cases, therapeutic levels of ketones are also produced.</p>

	<p>3.1 Effect of carbohydrate-reduced diets on energy metabolism</p>
	<p>The appropriate level of carbohydrate reduction to meet therapeutic goals will differ among patients. An amount of less than 50g of carbohydrate per day frequently leads to a general change in metabolism from “gluco-centric” (where glucose is relied on as a primary energy source) to “adipo-centric” (where ketone bodies and fatty acids are primary energy sources), although this level varies across individuals (Westman et al., 2007).</p> <p>At lower levels of carbohydrate reduction, most adults will enter into nutritional ketosis. During this state, the body relies primarily on fatty acids for energy, and a small amount of ketones can usually be detected in blood, urine or breath.</p> <p>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 glucose is normal, insulin is low, and the metabolism of fatty acids from adipose tissue is accelerated (Veech, Chance, Kashiwaya, Lardy, & Cahill, 2001). Most people develop low levels of nutritional ketosis after an overnight fast, and ketone levels can increase further with longer fasts or carbohydrate reduction. Ketone levels induced by carbohydrate reduction 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).</p>
	<p>3.2 Nutritional ketosis versus ketoacidosis</p>
	<p>Nutritional ketosis:</p> <ul style="list-style-type: none"> ● Is a natural physiological state allowing utilization of ketones as fuel (Salway, 2004). ● Can occur in anyone during fasting or carbohydrate reduction. ● Typically results in ketone levels that remain below 3 mmol/L and do not change blood pH. ● Typically results in blood glucose levels that, in the absence of diabetes, remain normal, eg. <110mg/dl. ● Is asymptomatic besides "fruity" breath due to acetone production (Anderson, 2015). <p>Diabetic ketoacidosis (DKA)</p> <ul style="list-style-type: none"> ● Is a medical emergency requiring urgent intervention ● Occurs with frank insulin deficiency in people with type 1 diabetes or sometimes insulin-dependent type 2 diabetes. Insulin deficiency leads to unregulated lipolysis and high levels of fatty acids and ketone production. Patients on SGLT2 inhibitors may be at increased risk of DKA. ● Results in high levels of ketones (>3mmol/L), dehydration, and metabolic acidosis (pH <7.3). ● Usually, but not always, results in high glucose (>270mg/dl),

	<ul style="list-style-type: none"> • Is typically accompanied by symptoms such as fatigue, confusion, vision changes, dehydration, polyuria, and rapid breathing.
<p>3.3 Other effects of therapeutic carbohydrate reduction</p>	
	<p>Other physiological and metabolic changes are related to carbohydrate reduction. 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 type 2 diabetes, hypertension, dyslipidemia, and chronic inflammation (Festa et al., 2000; Reaven, 1986; Roberts, Hevener, & Barnard, 2013).</p> <p>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). By reducing insulin levels, reducing carbohydrate intake may be expected to improve blood pressure and to have an effect on fluid and electrolyte balance.</p> <p>With regard to dyslipidemia, high circulating levels of insulin have been associated with increased plasma triglyceride (TAG) concentration, decreased high-density lipoprotein (HDL) cholesterol concentration, and increased levels of atherogenic small dense particles of low-density lipoprotein (LDL) cholesterol (Ferrannini, Haffner, Mitchell, & Stern, 1991; Reaven, Chen, Jeppesen, Maheux, & Krauss, 1993). Reducing carbohydrate may improve the TAG/HDL ratio and certain markers of inflammation (Forsythe et al., 2008).</p>
<p>3.4 Effects on appetite and satiety</p>	
	<p>Many therapeutic interventions that restrict carbohydrate are not deliberately limited in kcal, although carbohydrate reduction frequently induces a spontaneous decrease in overall energy intake. The mechanisms behind this effect are not clearly understood, although it is possible that the state of nutritional ketosis may be a contributing factor in reducing appetite (Gibson et al., 2015). The emphasis on adequate protein intake during therapeutic carbohydrate reduction may also play a part, as protein is generally considered to generate the most potent satiety signals (Blundell & Stubbs, 1999). In addition, it has also been shown that high insulin levels contribute to increased appetite, therefore dietary strategies with the potential to lower insulin levels, including low-carbohydrate diets, have the potential to help regulate appetite (Rodin, Wack, Ferrannini, & DeFronzo, 1985).</p> <p>Because hunger has been shown to predict failure to comply with energy-restricted diets (Nickols-Richardson, Coleman, Volpe, & Hosig, 2005), where energy restriction is considered an important factor in a dietary intervention, carbohydrate reduction may be one way to achieve this with reduced hunger.</p>
<p>3.5 Therapeutic potential - For further discussion and investigation</p>	

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	<p>Ongoing matters of discussion include the level of carbohydrate reduction needed to achieve therapeutic benefits. A related matter is whether it is necessary to achieve a measurable level of nutritional ketosis to achieve therapeutic benefits and, if so, what that level is.</p>
<p>4. Initiating the intervention</p>	
	<p>Interventions that involve therapeutic carbohydrate reduction 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 an exercise program or smoking cessation plan. The initiation of therapeutic carbohydrate reduction 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.</p>
<p>4.1 Patient selection</p>	
	<p>Patients who may be a good candidate for some type of carbohydrate-restricted dietary intervention are those who have a health concern for which there is some evidence that this kind of diet can provide therapeutic benefit, such as weight loss, type 2 diabetes, cardiovascular disease, and non-alcoholic fatty liver disease (see Paoli, Rubini, Volek, & Grimaldi, 2013; Mardinoglu et al., 2018).</p> <p>Patients should also be able and prepared to use a blood glucometer to check serum glucose if on insulin or insulin secretagogues (sulfonylureas and meglitinides) and to communicate with the health care team during the diet intervention (Cucuzzella, Hite, Patterson, & Heath, 2019).</p> <p>In most cases, patients with an acute, unstable medical condition are not candidates for this dietary intervention.</p>
<p>4.2 Pre-diet evaluation and counseling</p>	
	<p>Initial assessment prior to initiation of therapeutic carbohydrate reduction should include evaluation of patient’s current symptoms, past medical history, comorbidities, contraindications, and current medications. An exploration of the patient’s health goals and how therapeutic carbohydrate reduction 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, living arrangements, and roles (i.e. who does the cooking and food purchasing). Laboratory tests as indicated for the presenting condition should be completed to rule out acute pathology and establish baseline metrics.</p> <p>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.</p>

4.3 Initial tests	
	<p>Clinical tests:</p> <ul style="list-style-type: none"> ● Weight ● Height ● Waist circumference ● Blood pressure <p>Blood tests:</p> <ul style="list-style-type: none"> ● Complete blood count (CBC) ● Fasting comprehensive metabolic panel (CMP), including: <ul style="list-style-type: none"> ○ glucose ○ electrolytes ○ kidney function ○ acid-base balance ● Fasting lipid panel, including HDL cholesterol and triglycerides ● Thyroid-stimulating hormone (TSH) ● Hemoglobin A1c (HbA1c) ● Liver function (including gamma-glutamyl transferase [GGT]) <p>Urine tests:</p> <ul style="list-style-type: none"> ● Urine albumin: creatinine ratio
4.3.1 Other tests that may be considered	
	<p>Fasting total insulin, homeostatic model of insulin resistance (HOMA-IR), or postprandial insulin assay/Kraft protocol (if available and affordable)</p> <p>Full thyroid function panel, including TSH, fT3, fT4, RT3 and antibodies</p> <p>Vitamin D</p> <p>High-sensitivity C-reactive protein (hsCRP)</p>

	<p>Advanced lipid panel</p> <p>Glucose tolerance testing (GTT)</p> <p>Peak flow test</p> <p>Erythrocyte sedimentation rate (ESR)</p> <p>Serum uric acid</p> <p>Coronary calcium score - for risk stratification and ongoing monitoring</p> <p>C-peptide levels - for patients who are on insulin, to ensure that the patient is still making insulin (see Section 6.1 below).</p> <p>Clinicians may also want to measure blood levels of certain medications that can be affected by the water loss that accompanies the initiation of therapeutic carbohydrate reduction, such as lithium and valproic acid (Depakote).</p>
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	4.4 Complicating co-morbidities
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	<p>Because of concerns regarding de-prescribing pharmacological therapies, the following conditions require close, frequent medication review when therapeutic carbohydrate reduction is used:</p> <ul style="list-style-type: none"> ● Type 1 diabetes mellitus ● Type 2 diabetes mellitus ● Hypertension ● Chronic kidney disease <p>There is little agreement as to whether the levels of protein typically consumed on a low-carbohydrate diet are harmful to patients with chronic kidney disease (Paoli et al., 2013). The concern is that “high” protein levels may impair renal function, but there is little evidence to suggest that protein intakes at the levels consumed on a low-carbohydrate diet are harmful for people with moderately decreased kidney function. For patients with advanced kidney disease, the recommendation for therapeutic carbohydrate reduction must be made on a case by case basis, as the standard “renal diet” may conflict with a low-carbohydrate diet in some regards.</p> <p>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 & Westman, 2016). Consider prophylactic allopurinol during transition.</p> <p>There are also rare diseases where carbohydrate reduction could theoretically 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), 3-hydroxyacyl-CoA deficiency, and acute intermittent porphyria.</p>
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4.5 Considerations for initiation and delivery of intervention	
	Therapeutic carbohydrate reduction may be initiated in an inpatient or outpatient setting. In addition, digitally assisted modes of delivery are available to help support patients as they transition to a low-carbohydrate diet. Clinicians can take advantage of digital technologies available to communicate with patients and monitor patient progress. These can be particularly useful in managing the deprescription of medications during the transition to a low-carbohydrate diet.
4.5.1 Inpatient	
	Cucuzzella et al. (2019) provides an overview of how a low-carbohydrate diet may be implemented in an inpatient setting. The full article may be accessed here .
4.5.2 Outpatient	
	Westman et al. (2018) provides an overview of how a low-carbohydrate diet may be implemented in an outpatient setting. The full article may be accessed here .
4.5.3 Technology and tools	
	Digital technology can provide opportunities for patient education and monitoring not previously available to clinicians. Hallberg et al. (2018) recently demonstrated that technology-enabled support could assist patients in transitioning successfully to a low-carbohydrate diet. Patient progress could be tracked remotely, and one-on-one health coaching was available to patients via text. This allowed the dietary intervention to be fully personalized to the patient's needs. The full article detailing this intervention may be accessed here .
5. Intervention	
	<p>In order to help patients adhere to the dietary intervention, simplicity in delivery of information is of primary importance. Clinicians may provide their own patient education material and may also take advantage of the numerous online resources that can assist patients in making the transition to a low-carbohydrate diet.</p> <p>Ideally, the level of carbohydrate reduction prescribed for a patient will be individualized to that patient's health needs. An initial target for carbohydrate reduction may be set based on the individual and adjusted as necessary to increase efficacy of and compliance with the intervention.</p>
5.1. Objectives of intervention	
	Objectives of therapeutic carbohydrate reduction will depend on targeted condition.

	<p>5.2 Medical nutrition therapy</p>
	<p>A low-carbohydrate diet typically emphasizes real foods but can be administered using meal replacement shakes or kits.</p> <p>Food-based, low-carbohydrate diets include whole food sources such as meats, low-starch vegetables, full-fat dairy, nuts, and seeds. They may also include small amounts of fruit and legumes when appropriate. Although therapeutic carbohydrate reduction can be done as a vegetarian diet, typically animal products and seafood are encouraged. In counseling, the emphasis should be on foods and general carbohydrate reduction, rather than monitoring macronutrient content.</p> <p>In educating the patient about therapeutic carbohydrate reduction, it should be emphasized that adequate protein, fat, and fiber intake at each meal will tend to provide a sense of satiety and satisfaction. 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 reduction (Davis & Phinney, 1990; Phinney, Bistran, Evans, Gervino, & Blackburn, 1983). Protein intake above levels set for the general population may be particularly important during the first few weeks of carbohydrate reduction (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.</p> <p>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 very low carbohydrate diets, these may need to be more limited in quantity as they contribute to total and net dietary carbohydrate.</p> <p>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.</p> <p>A low-carbohydrate diet allows intake of natural fats to satiety. These include any non-<i>trans</i> fats, such as olive oil, coconut oil, avocado oil, full-fat dairy, and butter, along with the fats naturally present in whole food protein sources.</p> <p>Carbohydrate reduction 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.</p>
	<p>5.2.1 Nutrition education, counseling, care management</p>
	<p>Therapeutic carbohydrate reduction should include the foundational elements of any medical nutrition therapy, namely an educational component and a support component.</p>

	<p>Adherence, satiety, and simplicity are critical to early success.</p> <ul style="list-style-type: none"> ● Assess patient’s familiarity with carbohydrate reduction and provide education appropriate to his/her knowledge or prior experience with this approach. ● Provide simple low-carbohydrate meal planning resources, including sample menus, recipes, and lists of prepared foods. ● Work together with patient to devise a personalized plan based on food preferences, lifestyle, and health conditions. It can be helpful to suggest specific low-carbohydrate alternatives to a patient’s favorite foods. ● Schedule routine follow up (in person, phone/Skype, and/or email) 1-4 times per month, per patient preference and need.
<p>5.2.2 Facilitating behavior change</p>	
	<p>A patient’s readiness to change and support are essential for proper initiation of this therapy. To help a patient prepare for this dietary change:</p> <ul style="list-style-type: none"> ● Discuss diet history and current health goals. ● Address fears about failure related to prior unsuccessful diet attempts. ● Address concerns regarding carbohydrate reduction. ● Assess readiness to change and provide guidance, reassurance, and support, as needed.
<p>5.2.3 Patient resources</p>	
	<p>There are many ways to educate the patient and the patient’s family regarding this diet. Clinicians should tailor educational materials to their patient population and needs.</p> <p>Please see this resource for a variety of patient education materials.</p>
<p>5.3 Side effects, adverse outcomes, and treatment</p>	
<p>5.3.1 Electrolyte imbalance</p>	
	<p>Some side effects of a low-carbohydrate 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 & Manhiani, 2012). When insulin levels are lowered due to either reduced insulin dose or reduced insulin secretion because of reduced carbohydrate consumption, this can cause diuresis and symptomatic hypotension.</p>

	<p>Unless there is a history of heart failure or salt-sensitive hypertension, patients should not restrict sodium on low-carbohydrate diets and will likely need additional sodium and hydration, especially in the first several weeks. For most patients, 2-3g of sodium (or 5-7g of salt) per day is appropriate. This can be accomplished by salting food liberally, or sodium can be supplemented by advising patients to sip on a broth made with regular-sodium bouillon cubes (Steelman & Westman, 2016).</p> <p>Extra attention should be paid to sodium and hydration status for patients on multiple medications (Steelman & 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 & Westman, 2016).</p> <p>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 & Underwood, 1999). Supplementation should be considered if hypokalemia is persistent (Steelman & Westman, 2016; Westman et al., 2007).</p>
	<p><i>5.3.2 Constipation</i></p>
	<p>Constipation may also result from changes in fluid and electrolyte imbalance. To address this, begin by increasing fluid intake to a minimum of 2 liters per day.</p> <p>Encourage the consumption of low-carbohydrate vegetables that are high in fiber, such as broccoli, cauliflower and greens.</p> <p>If not resolved, clinicians may recommend 1 teaspoon of milk of magnesia or magnesium citrate at bedtime, bouillon supplements, or a sugar-free fiber supplement.</p> <p>If constipation persists, this may be due to an increase in consumption of certain foods to which a patient may be sensitive, such as nuts or cheese. Individualized dietary counseling will assist in identifying how to proceed.</p>
	<p><i>5.3.3 Muscle cramps</i></p>
	<p>Muscle cramps are a common side effect when beginning a low-carbohydrate diet. They usually respond to magnesium supplementation.</p> <p>This can be delivered via milk of magnesia or slow-release magnesium chloride (Slow-Mag or generic equivalent), with the recommended dosage from 192 mg to 400 mg daily. Magnesium glycinate up to 600 mg per 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.</p>

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	<p>Another possible intervention for acute treatment of muscle cramps, with a low potential for adverse side effects is a spoonful of pickle juice or yellow mustard. The mechanism is not fully understood but is thought to occur via an inhibitory oropharyngeal reflex (Miller et al., 2010).</p>
	<p>5.3.4 LDL increase</p>
	<p>There is widespread concern about the effects that higher dietary fat intakes typical of low-carbohydrate diets will have on serum cholesterol levels. However, low-carbohydrate diets have been shown to be effective at increasing HDL and decreasing TAG with minimal change in LDL or total cholesterol (Westman et al., 2007).</p> <p>During weight loss, total serum cholesterol may rise. This small increase is usually temporary and is not an indication to increase or begin lipid-lowering medications (Sävendahl & Underwood, 1999). Clinicians are advised to recheck lipid panel after weight loss has stabilized.</p> <p>A small subsection of individuals may experience marked elevations in LDL cholesterol on transition to a reduced carbohydrate diet. They are referred to in the literature as lean mass hyper-responders (LMHR) and are generally lean and metabolically healthy with low triglycerides and high HDL-c. Cardiac imaging can help stratify risk in this population as LDL is not a good predictor of CVD risk when considered as an isolated metric. You can read more about the LMHR phenotype and the various studies here.</p>
	<p>5.3.5. Other potential side effects</p>
	<p>Other potential side effects of which clinicians should be aware are: heart palpitations, insomnia, temporary hair loss, temporary reduced physical performance or exercise tolerance, bad breath (from acetone), irritability, anxiety, temporary increase in appetite, fatigue and low alcohol tolerance. Side effects are usually most severe during transition to the diet and improve with adequate electrolytes and fluids.</p>
	<p>5.4 Adjunct therapies</p>
	<p>5.4.1 Supplements</p>
	<p>Historical examples of low-carbohydrate diets have greatly restricted the intake of a variety of foods, requiring supplementation with a multivitamin, and most clinical trials of low-carbohydrate diets have included a daily multivitamin and mineral supplement (Westman et al., 2007). However, a well-formulated low-carbohydrate diet emphasizes a wide variety of plant and animal foods with high nutrient density and will provide good nutrition for the majority of individuals.</p> <p>A recommendation of multivitamin supplementation should be on a personalized basis for the patient. Individual testing of Vitamin D, folate, and red cell magnesium can guide supplementation. B12 testing may also be warranted; however, it alone may not be sufficient. Methylmalonic acid and total homocysteine may be important to accurately diagnose a B12 deficiency (Stabler, 2013).</p>

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	<p>Magnesium is commonly inadequate in modern diets (He et al., 2006). Electrolyte changes induced by a low-carbohydrate diet may increase magnesium losses. 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.</p>
<p>5.5 Intervention - For further discussion and investigation</p>	
	<p>For the dietary intervention, some clinicians prefer to limit intake of omega-6 fatty acids, found primarily in processed vegetable oils from corn, soy, and canola. The concern is that an imbalance of high levels of omega-6 relative to lower levels of omega-3 fatty acids can contribute to inflammation and exacerbate conditions that therapeutic carbohydrate reduction is meant to treat (Simopoulos, 2008). Other clinicians feel the evidence of limiting food sources of omega-6 fatty acids is still inconclusive and that patients should focus on carbohydrate reduction alone.</p>
<p>6. Medication adjustment</p>	
	<p>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.</p>
<p>6.1 Diabetes medications</p>	
	<p>If patients are on insulin or sulfonylureas when beginning a low-carbohydrate diet, it is recommended that doses be reduced immediately to prevent hypoglycemia. Thiazolidinediones 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 should be use with caution because they can exacerbate dehydration and have been associated with diabetic ketoacidosis (DKA) episodes. It is recommended that SGLT2-i be stopped if a very low-carbohydrate diet is to be followed. Metformin can be used effectively in conjunction with a low-carb diet (Steelman & Westman, 2016). Metformin does not present the same risks of hypoglycemia as insulin or sulfonylureas.</p> <p>See accompanying “Medication de-prescribing” materials.</p> <p>Many patients on a low-carbohydrate diet can eventually completely discontinue insulin. However, it is important to verify the diagnosis of type 2 diabetes over type 1 or Latent Autoimmune Diabetes of Adulthood (LADA) before complete discontinuation.</p> <p>For patients who are on insulin, as the dose of insulin is lowered, C-peptide levels should be measured to ensure that the patient is still making insulin.</p> <p>Also consider the following factors suspicious for LADA before complete discontinuation of insulin:</p> <ul style="list-style-type: none"> ● Young age at diagnosis

	<ul style="list-style-type: none"> • Rapid transition from new diagnosis of diabetes to requiring insulin (<5 years) • Continued requirement for insulin during periods of weight loss or bariatric surgery • Labile blood glucose (standard deviation of 50 is suspicious) • Low body weight, BMI <30 and/or not overweight at diagnosis (BMI <25) • Normal TAG and high HDL • Personal or family history of autoimmunity • History of DKA
<p>6.2 Anti-hypertensive medications</p>	
	<p>Review medication list for anti-hypertensives. Blood pressure will need to be monitored in the clinic, ideally every 2-4 weeks during initiation of the dietary intervention. In addition, patients should be shown how to self-monitor blood pressure and be made aware of symptoms of low blood pressure, such as light-headedness upon standing or severe fatigue. These symptoms and/or systolic blood pressure below 120 should prompt reduction of anti-hypertensive medication.</p> <p>Hyponatremia may be exacerbated by SGLT2 inhibitors, thiazides, loop diuretics, and many other medications, including: 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.</p>
<p>6.3 Other</p>	
	<p>Warfarin doses may need to be adjusted and INR should be monitored more frequently during the diet transition (Steelman & Westman, 2016).</p> <p>Medications that have a narrow therapeutic range such as valproic acid (Depakote) and lithium should be monitored for potential dosing changes.</p> <p>Medications that interfere with lipolysis should be replaced or discontinued if possible, including: niacin, beta blockers, antidepressants, and antipsychotics.</p>
<p>7. Follow-up care</p>	
<p>7.1 Monitoring and evaluation</p>	
	<p>Clinicians should work with patients to empower them to take charge of their own health. Setting health goals together and providing patients with the resources and support to reach those goals is an important part of patient care.</p>

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After the initiation of therapeutic carbohydrate reduction, the patient should be advised to check blood pressure and, if applicable, blood glucose daily, including some post-prandial readings 1-2 hours after a meal. Having tools available so that patients can track medication, blood pressure, and glucose is indispensable to providing a safe transition to a low-carbohydrate diet. Paper or digital tools for logging daily readings are available (find an example of patient self-monitor glucose log [here](#)). Having the patient record weekly waist circumference and body weight measurements may also be helpful in monitoring progress, if changes in those markers is a goal.

A team approach to patient care may be helpful in supporting patients as they transition to a new way of eating. Clinicians and allied health professionals should be in close contact with the patient until a new medication regimen is optimized, and the patient can confidently apply the concept of carbohydrate reduction to dietary habits in general.

Ongoing support delivered in a group setting or one-on-one can help patients adapt to their new lifestyle. This support can be delivered by a health coach, a dietitian, nurse, or other allied health professional. Pharmacists trained in therapeutic carbohydrate reduction can be a valuable asset in terms of monitoring and educating patients with complex pharmaceutical regimens. A dietitian trained in therapeutic carbohydrate reduction can assist patients with identifying and overcoming barriers to adhering to this intervention, including limited financial or time resources, “trigger foods,” food addiction, and eating out (Cucuzzella et al., 2018).

7.2 Maintenance and discontinuation of intervention

Although the benefits of carbohydrate reduction 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. It is also worth noting that high-carbohydrate foods are heavily promoted and widely available; individuals trying to maintain a low-carbohydrate diet for health reasons may face significant challenges in such an environment.

Whether and in what manner to allow additional dietary carbohydrate into 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 using low-carbohydrate diets for therapeutic weight loss, increased dietary carbohydrate may be offset by deliberately restricting kcal in a way that prevents weight gain. Other individuals may prefer to forgo calorie counting in favor of continued carbohydrate reduction.

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	<p>9. Physician resources</p>
	<p>Additional references: Diabetes</p> <p>Additional references: Obesity</p> <p>Medication de-prescribing</p> <p>Patient education materials</p> <p>Patient self-monitoring glucose log</p> <p>Clinician guide – Inpatient (Cucuzzella et al., 2019)</p> <p>Clinician guide – Outpatient (Westman et al., 2018)</p>

Acknowledgements, Roles and Responsibilities

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