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Carbohydrate reduction for metabolic disease is distinct from the ketogenic diet for epilepsy

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Recent reviews of using therapeutic carbohydrate reduction to treat metabolic disease in paediatric patients have consistently made errors in the form of bias against recommending this nutrient-dense eating pattern despite strong evidence for its use in adults and emerging evidence in paediatric patients. The purpose of this perspective is to review these errors, which include conflating 4:1 ketogenic diets with well-formulated ketogenic diets and the needless medicalisation of using therapeutic carbohydrate reduction in paediatric populations.

Keywords: type 1 diabetes; type 2 diabetes; obesity; paediatrics; low carbohydrate; ketogenic.

Introduction

The American Academy of Paediatrics' (AAP) 2023 report on 'Low-carbohydrate diets in children and adolescents with or at risk for diabetes' endorsed low or very low carbohydrate diets, also known as therapeutic carbohydrate reduction (TCR), under close medical supervision for children with type 1 diabetes (T1D), type 2 diabetes (T2D), or at risk of T2D.[1] It is important to ensure that medical nutritional therapy (MNT) remains as flexible as possible in the battle against chronic metabolic disease as support for a wide variety of eating patterns is needed to address the increasing burden of disease. From 2001 to 2017, the prevalence of paediatric T1D increased by 45.1% and the prevalence of paediatric T2DM increased by 95.3%.[2] As of 2020, the prevalence of paediatric obesity had risen to 21.5%.[3] The status quo still leads to significant morbidity as men and women diagnosed with T1D before the age of 10 see their expected lifespans reduced by 18 and 14 years, respectively.[4] Approximately 13 years after a diagnosis of T1D, the prevalence of neuropathy, retinopathy and nephropathy is 59%, 27% and 5%, respectively.[5] Children with T1D exhibit abnormal brain development with lower white matter and gray matter even if their glycaemia is 'at goal'.[6] The current standard of care is at fault for these poor outcomes.

In this report, we expected – *but did not find* – information that would highlight the unique benefits of using MNT generally and TCR specifically to treat metabolic conditions. We believe the AAP missed a crucial opportunity to help curb bias against TCR, which has demonstrated efficacy and safety in multiple settings for adults and paediatric populations in long-term studies.[7,8,9] Unfortunately, even though the AAP endorses TCR for paediatric metabolic disease, they needlessly medicalise this eating pattern by recommending numerous blood draws and trending of 14 different laboratory measurements. This recommendation is despite TCR being a nutrient-dense pattern of eating that exceeds the minimum nutrient reference value thresholds for all micronutrients in children and adolescents.[10,11] Our concerns regarding the report relate to four key topic areas: (1) the conflation of 4:1 ketogenic diets (KDs) with well-formulated TCR, (2) the effects of TCR on nutrition, (3) growth and (4) disordered eating.

Bias created by conflation of 4:1 ketogenic diets with well-formulated therapeutic carbohydrate reduction

Firstly, the AAP authors conflated 4:1 or 3:1 KDs that are used to treat epilepsy with well-formulated TCR that are used to improve metabolic health. Therapeutic KDs for epilepsy are generally 4:1 or 3:1, where there are 4 g or 3 g of fat for every 1 g of protein and carbohydrate, respectively. For a 4:1 KD, this equates to 80% – 90% of calories from fat.[12] This high-fat level ensures adequate production of ketones, which can be lifesaving for children with refractory treatment-resistant epilepsy who would have breakthrough seizures should their ketone levels fall below a critical threshold.[12] These 4:1 KDs have never been recommended for the treatment of metabolic disease, which is the topic of this report. The TCR used to treat metabolic disease is

based on a modified Atkins diet.[12] This eating pattern contains 70% of calories from fat, which is far less than the 90% seen in a 4:1 KD. Indeed, one of the most popular well-formulated TCR allows for two cups of leafy vegetables and one cup of nonstarchy vegetables, which fulfils the AAP's recommended five servings of vegetables per day through age 18.[13]

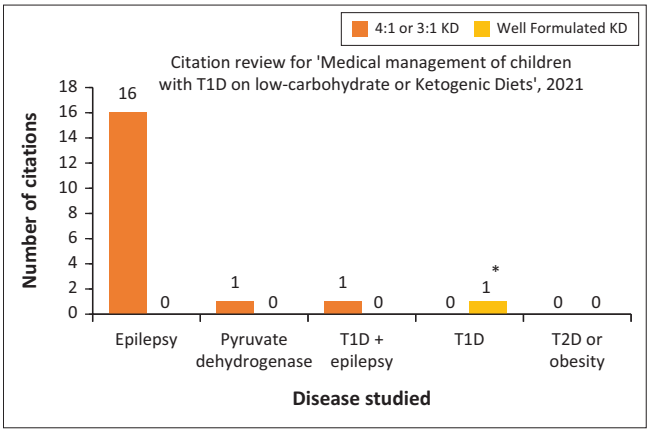
Bias created by fear mongering nutritional deficiencies not seen in therapeutic carbohydrate reduction

The report recommends 14 different laboratory measurements with five different blood draws over the first year for children following TCR regardless of whether their underlying diagnosis is T1D, T2D or even if they are only *deemed to be at risk* of developing metabolic disease. Tests include magnesium, zinc, selenium, vitamin D, comprehensive metabolic panel, urinalysis, beta-hydroxybutyrate, free and total carnitine, complete blood count, fasting lipid panel, calcium, phosphorous, urine calcium and a DEXA scan if the patient has been on TCR for greater than 2 years. These recommendations are from a 2021 review of studies on the management of paediatric T1D subjects on a low-carbohydrate or KD.[14] This review again conflates 4:1 or 3:1 KDs with well-formulated TCR. Out of 34 references, one study is an online survey of 316 respondents who support the use of TCR in paediatric T1D, one study is a six subject case series on the negative outcomes of using a KD to treat paediatric T1D and 18 studies are on 4:1 or 3:1 KD to treat epilepsy or rare congenital metabolic diseases (Figure 1). Therefore, following the lineage of data, the current 2023 AAP report cites concerns about using a KD for T1D, T2D and obesity from this 2021 review that itself is largely based on data from using a 4:1 or 3:1 KD for epilepsy.

This misinterpretation of the data becomes apparent when these concerns are investigated further. For example, regarding the concern for carnitine deficiency on a KD, the 2023 AAP report cites this 2021 review, which then cites a 2002 article in which all subjects were inducted on a 4:1 KDs for epilepsy. There are no cases of carnitine deficiency in the literature on well-formulated TCR. Indeed, meat is the most common source of carnitine, and a well-formulated TCR allows for meat consumption ad libitum. This mistake is repeated for magnesium, zinc, selenium and vitamin D deficiencies; anaemia and bleeding risk because of platelet dysfunction; disturbances in acid-based status; liver and kidney function and calcium, phosphorus and urine calcium derangements.

Biases created by conflating growth issues of children with epilepsy and therapeutic carbohydrate reduction

This conflation of the risks of a 4:1 KDs is repeated in the citations for growth, bone health and nephrolithiasis. Regarding growth, the largest study of TCR in people with



KD, ketogenic diets; T1D, type 1 diabetes; T2D, type 2 diabetes.
*, 6 subject case series

FIGURE 1: The subject matter of citations in 'Medical management of children with type1 diabetes on low-carbohydrate or ketogenic diets'.

Type 1 diabetes showed no associated growth reduction.[15] The AAP report correctly points out that insulin is required for proper growth and development but omits the fact that people with T1D following TCR must use exogenous insulin to cover protein. Thus, TCR does not fully alleviate the requirement of exogenous insulin for people with T1D, and it is in the context of protein and insulin that growth occurs normally and normoglycaemia is possible.[15] It is also worth noting the unprecedented efficacy with an average a1c of 5.67% in the participants who adopted TCR. We know from numerous studies that elevated A1cs that are typical of children with T1D following the standard carbohydrate emphasised diet are responsible for stunting growth and causing damage to a child's developing brain.[16,17,18]

Biases created by implying therapeutic carbohydrate reduction causes eating disorders when no such data exist

Finally, the authors cite concerns regarding eating disorders (EDs) and KDs. There is no evidence that clinician-recommended MNTs promote EDs. The authors cite a study on diet culture, which is nonspecific and would imply any MNT including Mediterranean diets are at risk for causing EDs.[19] Another citation on the dangers of carbohydrate reduction inducing EDs states 'the role of low carbohydrate diets per se has not been clearly established as a predictor of an eating disorder'.[20] Indeed, the published literature shows that elevated A1cs typical of the standard approach to paediatric T1D is correlated with EDs and low diet quality.[21] A critical feature of well-formulated TCR is improving diet quality through the reduction of ultra-processed, high-glycaemic foods, which are implicated in disordered eating.

Conclusion

There is a reoccurring theme in the clinical report where the lack of evidence for well-formulated TCR in children is

magnified while the lack of evidence for other dietary patterns, such as the Dietary Guidelines for Americans or the Mediterranean diet in children with metabolic disease is minimised. In adults, the AHA and ADA both recommend the use of low carbohydrate eating patterns to treat T2DM, with the ADA reporting that:

> [*R*]educing 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.[22,23]

There have been many large randomised and controlled studies on well-formulated TCR in adults and every point made in the clinical report that is salient to adults has been found to not be of concern. In adults, there is minimal to no risk of deficiencies of carnitine, magnesium, zinc, selenium, vitamin D deficiencies, anaemia, bleeding, poor bone health, nephrolithiasis or eating disorders. We must look to adult literature to temporarily answer these concerns in children as research in these areas is currently lacking for all eating patterns in paediatric subjects. For example, a 2009 Cochrane review found only six randomised controlled trials on dietary change alone in paediatric subjects with obesity.[24] This absence of evidence does not indicate harm. These theoretical risks must be weighed against the possible benefits of improving glycaemia, especially when the current standard of care has such poor outcomes. Furthermore, as discussed earlier, a TCR meal plan can be created that exceeds the nutrient reference value thresholds for children and adolescents.[11] Professional organisations have a remarkable opportunity to follow in the ADA's footsteps and be innovative with MNT for diabetes and obesity in children. For that to happen, we need to have common ground with the correct terminology and stop conflating 4:1 KDs that are used to treat epilepsy with well-formulated TCR that is used to treat metabolic disease. Future reports on TCR should include practitioners and researchers who utilise TCR in their practice or research to avoid inaccuracies and confusion regarding the use of TCR for metabolic disease.

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Authors' contributions

Each author independently read and evaluated the existing literature. M.C. conceptualised a perspective paper based on the body of evidence. All authors assisted with the original manuscript and subsequent drafts.

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