Supplement Article

Low-carbohydrate diets and cardiometabolic health: the importance of carbohydrate quality over quantity

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Carbohydrates are increasingly being implicated in the epidemics of obesity, diabetes, and their downstream cardiometabolic diseases. The "carbohydrate-insulin model" has been proposed to explain this role of carbohydrates. It posits that a high intake of carbohydrate induces endocrine deregulation marked by hyperinsulinemia, leading to energy partitioning with increased storage of energy in adipose tissue resulting in adaptive increases in food intake and decreases in energy expenditure. Whether all carbohydrate foods under real-world feeding conditions directly contribute to weight gain and its complications or whether this model can explain these clinical phenomena requires close inspection. The aim of this review is to assess the evidence for the role of carbohydrate quantity vs quality in cardiometabolic health. Although the clinical investigations of the "carbohydrate-insulin model" have shown the requisite decreases in insulin secretion and increases in fat oxidation, there has been a failure to achieve the expected fat loss under low-carbohydrate feeding. Systematic reviews with pairwise and network meta-analyses of the best available evidence have failed to show the superiority of low-carbohydrate diets on long-term clinical weight loss outcomes or that all sources of carbohydrate behave equally. High-carbohydrate diets that emphasize foods containing important nutrients and substances, including high-quality carbohydrate such as whole grains (especially oats and barley), pulses, or fruit; low glycemic index and load; or high fiber (especially viscous fiber sources) decrease intermediate cardiometabolic risk factors in randomized trials and are associated with weight loss and decreased incidence of diabetes, cardiovascular disease, and cardiovascular mortality in prospective cohort studies. The evidence for sugars as a marker of carbohydrate quality appears to be highly dependent on energy control (comparator) and food source (matrix), with sugar-sweetened beverages providing excess energy showing evidence of harm, and with high-quality carbohydrate food sources containing sugars such as fruit, 100% fruit juice, yogurt, and breakfast cereals showing evidence of benefit in energy-matched substitutions for refined starches (low-quality carbohydrate food sources). These data reflect the current shift in dietary guidance that allows for flexibility in the proportion of macronutrients (including carbohydrates) in the diet, with a focus on quality over quantity and dietary patterns over single nutrients.

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INTRODUCTION

As the concern about dietary fat has begun to abate, carbohydrates are increasingly coming under attack for their role in the epidemic of obesity and its downstream cardiometabolic complications, including diabetes and cardiovascular disease. Much of the attention has focused on the quantity of carbohydrates in the diet, with traditional carbohydrate staples such as cereal grains, pulses, and pasta coming under attack in the mainstream media, popular books, and social media.[1–10] This negative messaging has coincided with a surge in the popularity of low-carbohydrate diets and their variants such as the ketogenic diet.[11] This review explores the evidence for the role of carbohydrate quantity vs quality in cardiometabolic health, making the case for the importance of carbohydrate quality.

CARBOHYDRATE QUANTITY

"Carbohydrate-insulin model"

To explain how carbohydrate may lead to obesity and its downstream cardiometabolic complications, the "carbohydrate-insulin model" has been proposed.[12–15] The basis of this model is that an overabundance of carbohydrate or a high ratio of carbohydrate to fat or protein leads to endocrine dysregulation marked by hyperinsulinemia, which drives fuel partitioning, with carbohydrate directed away from metabolically active tissue (heart, lung, liver, etc.) to adipose tissue, resulting in a state of "cellular internal starvation" with adaptive increases in intake and decreases in energy expenditure resulting in weight gain. Although clinical investigations of the model have shown that low-carbohydrate diets produce the predicted metabolic and endocrine responses (that is, the requisite decreases in insulin and increases in fat oxidation to test the model), these diets have failed to achieve the expected weight loss benefit. A series of carefully controlled, randomized, inpatient feeding trials at the National Institutes of Health did not achieve the predicted increases in total energy expenditure and body fat loss when a low-carbohydrate diet or low-carbohydrate ketogenic diet was compared with a high-carbohydrate diet.[16,17] Although another carefully conducted longer-term randomized trial did show the expected increase in total energy expenditure with a low-carbohydrate diet compared with a high-carbohydrate diet during a weight loss maintenance phase following a period of weight loss,[18] there was instability in the effect. Using a prespecified analysis plan in which the comparisons were based on the baseline pre–weight loss anchor (the conditions under which the doubly labelled water measurement was validated and for which the statistical power was calculated) rather than the immediate post–weight loss anchor, Hall and Guo[19] showed that the effect disappeared. All of the clinical investigations to date have also failed to show the expected decrease in the most relevant clinical marker, body fat.[16,17] While these data collectively have been taken as evidence of experimental falsification of the model, it can be argued that the principal mechanism by which low-carbohydrate diets induce weight loss is not through an increase in energy expenditure but rather through alterations in food intake regulation that lead to reduced energy intake and/or spontaneous increases in physical activity over the long term, neither of which was assessed in these carefully controlled clinical investigations (as both variables were tightly clamped).

Low-carbohydrate diets in practice

A large database of long-term randomized controlled trials of dietary advice, conducted under free-living conditions, has provided an opportunity to test whether low-carbohydrate diets are able to induce weight loss through the above and/or other mechanisms in the "real world." These trials have failed to show a meaningful advantage of low- over high-carbohydrate diets. A network meta-analysis of 48 randomized trials – involving 7286 participants – of diets of varying macronutrient distributions showed no differences in weight loss at follow-up at 6 and 12 months.[20] A subsequent large randomized trial, the DIETFITS (Diet Intervention Examining the Factors Interacting With Treatment Success) trial, confirmed these findings, revealing that no differences were found between a "healthy" low-carbohydrate diet and a "healthy" high-carbohydrate diet in 609 overweight or obese participants over 12 months.[21] The lack of superiority of low-carbohydrate diets over high-carbohydrate diets extends to cardiometabolic risk factors. In systematic reviews and meta-analyses of randomized trials, the early improvements in glycemic control seen at 6 months were not found to be sustained at 12 months in people with diabetes.[22] Improvements seen in triglycerides and high-density lipoprotein cholesterol have also been shown to come at the expense of increases in the more atherogenic and established lipid targets for cardiovascular risk reductions, low-density lipoprotein cholesterol (LDL-C), non–high-density lipoprotein cholesterol (non-HDL-C), and apolipoprotein B (apo B), in people with and without diabetes.[22,23] The quality of the protein and fat substituting for the carbohydrate in low-carbohydrate diets, however, is an important consideration: the "Eco-Atkins" randomized trial revealed that a low-carbohydrate diet comprising higher quality unsaturated fat

from nuts and canola oil and plant protein reduced low-density lipoprotein cholesterol compared with a high-carbohydrate diet in 47 overweight hyperlipidemic participants over 4 weeks during which foods were provided, and the reduction extended out to 6 months during which foods were self-selected.[24,25] Irrespective of the carbohydrate content and outcome, the most important determinant of success in the available randomized trials over the long term has consistently been adherence to any one diet and clinic attendance irrespective of the macronutrient distribution.[20,26,27]

Low-carbohydrate diets and population health

The evidence from large prospective cohort studies that allow one to assess the relationship between carbohydrate exposures and downstream clinical outcomes of cardiometabolic diseases of public health and clinical importance has observed harm at the extremes of intake. In a systematic review and meta-analysis of 5 prospective cohort studies involving 432 179 participants over a median follow-up of 25 years, there was a U-shaped relationship between carbohydrate and mortality, with low-carbohydrate (<40% energy) and high-carbohydrate (>70% energy) diets associated with increased mortality and the wide range in between (40%–70% energy) associated with lower mortality.[28] An analysis of the Prospective Urban and Rural Epidemiological cohort study involving 135 335 participants free of cardiovascular disease from 18 low-income, middle-income, and high-income countries revealed no adverse association with low-carbohydrate diets, showing only high-carbohydrate diets (>70% energy) to be associated with increased cardiovascular and all-cause mortality over 10 years of follow-up.[29] The quality of the macronutrients substituting for the carbohydrate was again an important consideration. Whereas the substitution of animal fat or animal protein for carbohydrate was associated with an increase in mortality, the substitution of plant-based unsaturated fats and protein for carbohydrate was associated with a reduction in mortality.[28] The source of carbohydrate was also found to be important. A simultaneous publication of the Prospective Urban and Rural Epidemiological study suggested that the quality of carbohydrate may modify the association, with the highest intake of carbohydrate from sources such as legumes and fruit associated with lower, rather than higher, cardiovascular mortality and all-cause mortality.[30] Overall, these data suggest there is a wide range of acceptable carbohydrate intakes and that carbohydrate quality may be a more important focus than quantity in evaluating the relationship between carbohydrate intake and cardiometabolic outcomes.

Carbohydrate quality

A number of markers of carbohydrate quality have been described. These can generally be divided into 4 main markers: high-quality food sources of carbohydrate (whole grains, pulses, or fruit), low glycemic index (GI) and glycemic load (GL), high dietary fiber, and low sugars. The best available evidence from randomized controlled trials of intermediate cardiometabolic risk factors and prospective cohort studies of clinical cardiometabolic disease outcomes has highlighted that dietary patterns of high-carbohydrate intake that emphasize these carbohydrate quality markers show evidence of advantages for the prevention and management of cardiometabolic diseases.

High-quality food sources of carbohydrate

Systematic reviews and meta-analyses of randomized controlled trials have shown that dietary patterns emphasizing dietary pulses (involving >50 trials in >1000 participants with up to 1 year of follow-up)[31–36] or fruit (involving >20 trials in >1000 participants with up to 6 months' follow-up)[37,38] result in weight loss/maintenance as well as improved glycemic control, blood lipids, and blood pressure. The systematic reviews and meta-analyses of whole grains (involving >25 trials in >2000 participants with up to 16 weeks' follow-up), however, suggest that the improvements are restricted to whole grain sources from oats and barley.[39–42] This evidence from randomized trials of intermediate cardiometabolic risk factors has been found to be consistent with evidence from prospective cohort studies of clinical cardiometabolic disease outcomes. Systematic reviews and meta-analyses of prospective cohort studies have shown that high intakes of whole grains (involving >15 studies in >400 000 participants with up to 25 years' follow-up),[43–45] dietary pulses (involving 8 studies in >200 000 participants with up to 29 years' follow-up),[31,45] and fruit (involving >10 studies in >500 000 participants with up to 23 years' follow-up)[45,46] are associated with decreases in cardiovascular disease incidence, as well as diabetes incidence and cardiovascular mortality and all-cause mortality in the case of whole grains and fruit.

Low glycemic index and glycemic load

Systematic reviews and meta-analyses of >50 randomized controlled trials conducted in >4000 participants showed that low GI and GL dietary patterns lead to weight loss/maintenance and clinically meaningful improvements in glycemic control, as assessed by a reduction in glycated hemoglobin of ~0.5% (a level that

is at the lower limit of efficacy of the available antihyperglycemic agents and exceeds the threshold set by the US Food and Drug Administration for new drug development[47]), as well as improvements in blood lipids and blood pressure, compared with high GI and GL dietary patterns.[48–55] This evidence is in agreement with the available evidence from prospective cohort studies concerning the relation between low GI and GL of the diet and clinical cardiometabolic disease outcomes. Systematic reviews and meta-analyses of >20 prospective cohort studies in >600 000 participants have shown that low GI and GL dietary patterns are associated with decreased incidence of diabetes and cardiovascular disease with up to 25 years' follow-up.[43,48,56–62] Evidence of a causal relationship with clinical cardiometabolic disease outcomes is further supported by an important biological analogy with the oral prandial agent acarbose, an alpha-glucosidase inhibitor that effectively converts the diet to a low GI/GL dietary pattern. Systematic reviews and meta-analyses of clinical outcomes trials in subjects with type 2 diabetes and large individual clinical outcome trials in subjects at risk for type 2 diabetes with impaired glucose tolerance have shown that acarbose results in similar reductions in glycated hemoglobin and, concomitantly, reductions in type 2 diabetes,[63] hypertension,[64] and cardiovascular events,[64,65] with one exception – the Cardiovascular Evaluation (ACE) trial. Despite showing a reduction in type 2 diabetes, this trial failed to show a reduction in cardiovascular events with a lower dose of acarbose in Chinese adults with impaired glucose tolerance and pre-existing coronary heart disease.[118]

High dietary fiber

Systematic reviews and meta-analyses of >100 randomized controlled trials involving >5000 participants show that high viscous soluble fiber intake from oats, barley, psyllium, and konjac mannan lead to improvements in blood lipids, including the established therapeutic targets low-density lipoprotein cholesterol, non–high-density lipoprotein cholesterol, and apolipoprotein B (for which there are approved health claims in the United States [https://www.fda.gov/food/labelingnutrition/ucm2006876.htm], Europe [https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2011.2207], and Canada [https://www.canada.ca/en/health-canada/services/food-nutrition/food-labelling/health-claims/assessments.html]); glycemic control (for which there is an approved health claim in Canada for the reduction of postprandial glycemia [https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/fn-an/alt_formats/pdf/label-etiquet/claims-reclam/assess-evalu/glucose-complex-polysaccharides-complexe-glycemique-eng.pdf]); and blood pressure.[42,67–71] The same has not been shown for sources of insoluble fiber.[72] Although this evidence from randomized controlled trials suggests that the improvements in intermediate cardiometabolic risk factors is most reliably linked to sources of viscous soluble fiber, there is no such distinction in the available prospective cohort studies. Systematic reviews and meta-analyses of ≥10 prospective cohort studies in >1 000 000 participants have shown that high total fiber, independent of source (cereals, vegetables, or fruit) or type (insoluble vs soluble), is associated with decreased incidence of diabetes and cardiovascular disease over follow-up of up to 19 years.[43,73,74]

Low sugars

Most of the evidence supporting public health recommendations to limit sugars derives from sugar-sweetened beverages providing excess energy. This observation is seen clearly in the available randomized controlled trials of fructose, the moiety of sugars to which harm has been attributed owing to its unique set of metabolic and endocrine responses. Systematic reviews and meta-analyses of >50 randomized controlled trials in >1000 participants have shown that fructose, in energy-matched substitutions with other carbohydrates (predominantly starch), does not show harmful effects on intermediate cardiometabolic risk factors and even shows beneficial effects (especially for fruit) for glycemic control and blood pressure.[38,74–88] Signals for harm are restricted to conditions whereby fructose is added to diets as a source of excess energy (derived almost exclusively from sugar-sweetened beverages in the available trials) compared to the same diets without the fructose and subsequent excess energy.[38,75–89] These conditional effects are supported by the evidence from prospective cohort studies of clinical cardiometabolic disease outcomes. Although systematic reviews and meta-analyses of >15 prospective cohort studies in >400 000 participants have shown an adverse association of sugar-sweetened beverages with incident obesity, diabetes, heart disease, and stroke,[90–95] these adverse associations are markedly attenuated with adjustment for energy (thus many models do not adjust for energy as it is considered to be on the causal pathway between the exposure [sugars] and the outcome [cardiometabolic diseases]) and do not hold when modeling the total, added, or free sugars they contain (all sugars, sucrose, fructose) alone.[75–77,96–98] Other important food sources of sugars from grains and grain products, dairy and dairy products, and fruit and fruit products have also failed to show harmful associations and have even shown protective associations in the case of fruit, 100% fruit juice, yogurt, and breakfast cereals.[75–77,96] Taken together, the evidence suggests that any benefit of low-sugar dietary patterns appears to

be mediated by energy control (comparator) and the food source (matrix) rather than any special metabolic or endocrine mechanisms attributed to the fructose-containing sugars they contain. Whereas sugar-sweetened beverages providing excess energy show evidence of cardiometabolic harm, many high-quality carbohydrate food sources that often contain fructose-containing sugars show evidence of net benefit (fruit, 100% fruit juice, yogurt, and breakfast cereals [especially whole grain and high-fiber breakfast cereals]) in energy-matched substitution for refined starches (low-quality carbohydrate food sources) in balanced weight-maintaining diets.

IMPLICATIONS FOR PUBLIC HEALTH

A narrow focus on carbohydrate quantity over quality has important implications. One of the greatest concerns is a replay of the "low-fat" paradigm. It follows from this paradigm that manufacturers will produce "low-carbohydrate" foods that, like their "low-fat" predecessors, are of no or even less nutritional value yet share a similar energy content. Should these products be marketed or perceived as "healthier," the unintended consequence may be overconsumption of these products with no benefit, or even harm to, public health. The public may also not follow the intended recommendations. The available long-term randomized controlled trials did not test the notion that eating low-fat diets would reduce obesity and its complications. The notion tested was whether the dietary advice to eat low-fat diets would have this effect. There is abundant evidence suggesting that despite the ubiquity of low-fat dietary advice, the absolute amount of dietary fat consumed has declined little, while the absolute amount of carbohydrate and protein increased up until the mid-2000s. Although these changes drove a decrease in the percentage of energy from fat, overall energy intake increased.[99] The difference between what the public is told to do and actually does needs to be understood. Another concern is that a focus on "low-carbohydrate" foods may distract one from more important dietary risk factors. The Global Burden of Disease Project, a massive analysis allowing the burden of premature morbidity and mortality attributable to the leading 79 risk factors to be compared directly using population-attributable risk fraction modeling techniques, provides important evidence that making a reduction in carbohydrate quantity a public health priority may lead to unintended harm.[100] The most recent 2017 update does not identify high-carbohydrate intake from foods (with the exception of sugar-sweetened beverages) as a dietary risk factor. In contrast, low intakes of the various markers of carbohydrate quality are identified as important dietary risk factors, with low intakes of whole grains, fruit, vegetables, fiber, and legumes (pulses) among the leading contributors to disability-adjusted life years and mortality out of 15 dietary risk factors globally.[101] High intake of processed meat or red meat, which are often used to replace carbohydrate in low-carbohydrate dietary patterns, are also identified as dietary risk factors that increase disability-adjusted life years and mortality.

MODERNIZATION OF NUTRITION RECOMMENDATIONS

Dietary guidelines and clinical practice guidelines for nutrition therapy for obesity, diabetes, and cardiovascular disease have undergone an important modernization over the last decade. Historically, these guidelines focused on a narrow acceptable macronutrient distribution range (eg, acceptable macronutrient distribution range of 55% energy from carbohydrate and 30% energy from fat). As more emphasis was placed on quality over quantity of carbohydrate, fat, and protein, this focus became progressively broader (45%–65% energy from carbohydrate, <35% energy from fat, and 15%–20% energy from protein).[102] The progression has continued with a further shift away from a focus on single macronutrients to more food- and dietary pattern–based recommendations. The most recent clinical practice guidelines for nutrition therapy in diabetes and cardiovascular disease in the United States,[103,104] Europe,[105] and Canada[106,107] have taken this approach. Other clinical practice guidelines have also begun to adopt food and dietary pattern–based recommendations, including those drawn up by Obesity Canada, which will release its updated clinical practice guidelines in 2019 (https://obesitycanada.ca/resources/clinical-guidelines/), and the European Association for the Study of Diabetes, which has commissioned a series of systematic reviews and meta-analyses of dietary patterns for diabetes to inform the update of their clinical practice guidelines.[108–112] It is recognized by guidelines developers and public health policy makers that a focus on single nutrients does not represent how people eat and misses important interactions between different nutrients (nutrient-nutrient interactions), the nutrients and the food form (nutrient-matrix interactions), and the foods and the dietary patterns in which they are contained (food-diet interactions).

Individuals may also respond differently to different dietary patterns and their components. There is evidence that people with pretreatment dysglycemia, marked by a high fasting blood glucose (prediabetes) and low fasting blood insulin, may benefit more from dietary patterns that target carbohydrate quantity or

quality. Retrospective analyses of several randomized controlled trials have shown that people with this phenotype achieve greater weight loss when randomized to low-carbohydrate (low-GL), low-GI, high-fiber, or high whole grain interventions.[113–115] This finding, however, has not held across all trials, with fasting insulin modifying the association differentially.[116] A macronutrient intake–associated FGF21 genotype has also been shown to modify the effect of weight loss diets varying in the distribution of macronutrients, with a carbohydrate intake–decreasing allele resulting in greater reductions in waist circumference and body fat in response to a high-carbohydrate diet.[117] A PPM1K genetic variant resulted in a greater reduction in insulin and beta-cell function (homeostasis model assessment B score) in response to a low-carbohydrate diet.[118] Other genotypes (3 single-nucleotide polymorphism multilocus genotype responsiveness patterns involving PPARG, ADRB2, and FABP2) and phenotypes (high insulin secretion 30 minutes after an oral glucose tolerance test), however, have not been shown to modify the effect of weight loss diets varying in the distribution of macronutrients.[21] There remains a need for further research to better define the responses of these different phenotypes/genotypes to different macronutrient distributions and dietary patterns. Ultimately, adherence is the most important determinant of achieving the benefits of any one dietary pattern, so the success in identifying responsive phenotypes/genotypes that predict success may be in using this information as a tool to drive adherence.

As nutrition recommendations become more inclusive of a broader macronutrient distribution and shift to a focus on more food- and dietary pattern–based recommendations, the overarching approach to nutrition therapy is to consider the advantages and disadvantages of all dietary patterns for which evidence is available and the responsiveness patterns of different phenotypes/genotypes, with the acknowledgement that no one diet fits all. The goal is to align this evidence with the values, preferences, and treatment goals of the individual to enable the individual to select a dietary pattern that provides the greatest adherence over the long term and so allows them to achieve the intended benefits of the dietary pattern.[105,106] As the evidence for different dietary patterns accumulates, an even greater emphasis on individualization is expected.

CONCLUSION

A focus on carbohydrate quantity appears to be less useful and provides fewer options than a focus on carbohydrate quality. Based on values and preferences, some people will benefit from low-carbohydrate dietary patterns, especially those that substitute high-quality unsaturated fats and plant-protein for carbohydrate. Others will benefit from high-carbohydrate dietary patterns that emphasize high-quality carbohydrate foods such as whole grains (especially oats and barley), pulses, or fruit; low GI and GL; or high fiber (especially viscous fiber sources). Systematic reviews and meta-analyses of the best available evidence show that these markers of carbohydrate quality in the context of high-carbohydrate intakes decrease intermediate cardiometabolic risk factors in randomized controlled trials and are associated with weight loss and decreased incidence of diabetes, cardiovascular disease, and cardiovascular mortality in prospective cohort studies. The evidence for sugars as a marker of carbohydrate quality appears to be highly dependent on energy control and food source, with sugar-sweetened beverages providing excess energy showing evidence of harm but high-quality carbohydrate food sources that contain sugars – such as fruit, 100% fruit juice, yogurt, and breakfast cereals (especially whole grain and high-fiber breakfast cereals) – showing evidence of benefit in energy-matched substitutions for low-quality carbohydrate food sources. These data highlight the limitations of a reductionist "one-size-fits-all" nutrient-centric approach and the necessity of the current shift in dietary guidance from a focus on single nutrients such as carbohydrate ("high carb" vs "low carb") toward food- and dietary pattern–based recommendations that allow for flexibility in the proportion of carbohydrates in the diet, with a focus on quality over quantity and dietary patterns over single nutrients.

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