The 117th Abbott Nutrition Research Conference
June 21, 2018 • Columbus, Ohio, USA

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# CARBOHYDRATES

## THROUGH THE LIFE CYCLE AND ACROSS TISSUES

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# Welcome

Aiming to better understand how dietary carbohydrates can optimally support health and recovery from disease, Abbott Nutrition convened an expert interdisciplinary group of scientists from nutrition, molecular genetics, physiology, and pediatrics to present their scientific contributions.

Topics included the role of carbohydrates through the life cycle, from infants to older adults; latest research and guidelines around management of gestational diabetes; metabolic flexibility in energy substrate oxidation across key tissues; and next generation, food challenge responsive biomarkers for health status. Researchers also discussed the role of dietary patterns and snacking in health and disease.

Obesity and diabetes have reached epidemic proportions and are projected to increase over the next decade with important consequences for cardiometabolic complications. The epidemiology clearly shows that sugar alone is not the dietary culprit of cardiometabolic disorders. Rather it is the quantity of sugar and related eating occasions, and perhaps even the food form and accompanying dietary quality (eg, fruit vs sweetened fruit beverage) that contribute to cardiometabolic risk. The clinician's focus should be aimed at incremental change to optimize carbohydrate intake, with appreciation for the individual's dietary pattern. Indeed, not all carbohydrates are equal, and new research suggests that slowly digested carbohydrates help optimize blood glucose response and fueling of key metabolic tissues such as skeletal muscle, liver, and adipose. And with rising rates of gestational diabetes, it is especially important that we understand how best to promote the metabolic health of infants and future resilience in adults.

We offer the proceedings from this research conference to present the most recent global research on carbohydrates that may benefit clinical practice to improve health and prevent chronic diseases.

Manager Area Scientific Affairs..... Sean M. Garvey, PhD
Global Mobility and Metabolism Platform Leader.....Ricardo Rueda, MD, PhD, MSc
Divisional Vice President, Scientific and Medical Affairs..... Snigdha Mishra, PhD
Divisional Vice President, Global Research and Development ..... Hakim Bouzamondo, MD, MSc, MBA
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# Carbohydrates Through the Life Cycle & Across Tissues

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November 2018

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**117th Abbott Nutrition Research Conference Faculty**
Left to right, front: Dr Joel Cramer, Dr Suzan Wopereis, Prof Helen Murphy, Dr Robert Murray
Left to right, middle: Dr Richard Mattes, Prof David Benton
Left to right, back: Dr John Sievenpiper, Prof Rafael Salto

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# Carbohydrates Through the Life Cycle & Across Tissues

The 117th Abbott Nutrition Research Conference was held at Ross Park, headquarters of Abbott Nutrition Research & Development in Columbus, Ohio, USA on June 21, 2018. This report contains summaries of presentations given by the following contributors.

## Keynote Address

***Carbohydrate Quality: What Do I Tell My Patients?***

John L. Sievenpiper, MD, MSc, PhD, FRCPC
University of Toronto
Li Ka Shing Knowledge Institute at St Michael's Hospital
Toronto, Ontario, Canada

Obesity and diabetes have reached epidemic proportions and are projected to increase over the next decade with important consequences for cardiometabolic complications. As the ultimate role of fat in this dual epidemic has been questioned, carbohydrates are increasingly being indicted as the main culprit. Much of the concern has focused on sugars, but traditional carbohydrate staples like cereal grains, pulses, and pasta are also under scrutiny.

Dr Sievenpiper reviews the available evidence suggesting that not all sources of carbohydrates behave similarly. High quality systematic reviews and meta-analyses show that high carbohydrate diets that are low in glycemic index, high in fiber, or emphasize specific foods (eg, whole grains, pulses, fruit) decrease cardiometabolic risk factors in randomized controlled trials, and are associated with decreased weight gain, diabetes incidence, and cardiovascular disease incidence and mortality in prospective cohort studies. These data reflect the current shifts in dietary guidance that focus on quality over quantity, and dietary patterns over single nutrients.

## Carbohydrates Through the Life Cycle

***Carbohydrates for Performance Across Adolescence and Adulthood***

Joel T. Cramer, PhD, FACSM, FNSCA, FISSN
University of Nebraska-Lincoln
Lincoln, Nebraska, USA

Dr Cramer reviews the biochemistry of carbohydrate metabolism and discusses the importance of carbohydrate quality and timing in sports nutrition. Sports nutrition principles can translate to performance nutrition, which applies more broadly beyond sport to all human performance. Of particular interest is the use of performance nutrition, sometimes through reverse engineering of sports nutrition, to support metabolic health and quality of life in older adults, in whom carbohydrate storage and blood glucose fluctuations may best be limited.





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***Gestational Diabetes Mellitus: Latest Research and Guidelines***

Prof Helen R. Murphy, MBBChBAO, FRACP, MD
University of East Anglia, Norwich
King's College London
London, England, United Kingdom

One in six live births occur in women with diabetes, of which, by far the most common type accounting for approximately 85% of all diabetes cases, is gestational diabetes mellitus (GDM). Prof Murphy explains the maternal risk factors, epidemiology, screening methods and controversial diagnostic criteria for GDM; and reviews dietary guidelines for the management of GDM. Prof Murphy also explains how new technologies such as continuous glucose monitoring may pave the way for improved risk assessment, personalized treatment, better management, and improved health outcomes for both mother and baby.

***Savoring Sweet: Carbohydrates in Infant, Toddler, and Child Nutrition***

Robert Murray, MD
The Ohio State University
Columbus, Ohio, USA

Nutrition supports the remarkable rate of growth of infants and toddlers: weight gain, linear growth, and continued development and refinement of organs and physiological systems. Dr Murray reviews the benefits and organoleptics of human milk, in part due to carbohydrates, that contribute to infant feeding and growth. Importantly, between 6 and 24 months of age, the infant/toddler will evolve a stable set of food preferences and eating habits. Complementary feeding (CF) should repeatedly offer the infant/toddler every flavor, taste, and texture of nutrient-rich foods in each of the five food groups. Dr. Murray reviews areas for improvement in parent/caregiver CF food selection, with appreciation for added sugar content and diet quality.

## Metabolic Flexibility and Carbohydrates Across Tissues

***Role of Dietary Carbohydrates on Metabolic Flexibility in Key Target Tissues: Liver, Adipose Tissue and Skeletal Muscle***

Prof Rafael Salto, PhD
University of Granada
Granada, Spain

Dietary carbohydrates, depending on their glycemic index, have differential effects on metabolic flexibility. Prof Salto explains that metabolic flexibility is the capability of a tissue to select fuel substrate use in response to specific nutrient availability. An example is the capability of skeletal muscle to switch between primary fat and glucose metabolism in response to an insulin stimulus. This flexibility takes place in healthy lean individuals and is hampered in individuals with diabetes and obesity. Prof Salto further discusses the role of diet in metabolic flexibility.





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***Phenotypic Flexibility as a Measure of Health Through the Life Cycle***

Suzan Wopereis, PhD
Netherlands Organisation for Applied Scientific Research (TNO)
Zeist, The Netherlands

Often we underestimate nutrition's impact on human biology. Eating is one of the top physiological stressors throughout a typical day in modern society. No tissue is spared, and the stomach, brain, intestines, circulatory system, and pancreas spearhead the food response. So great is the response that researchers at TNO are evaluating key aspects of the physiological response to food as a biomarker for health status. Dr Wopereis shares details and preliminary evaluation of this PhenFlex food challenge test.

***Carbohydrates, Mood and Cognition***

Prof David Benton, PhD, DSc
Swansea University
Swansea, Wales, United Kingdom

Does carbohydrate consumption influence how we think and feel? Can a sugary drink improve mood and memory? Do the effects of aging and dementia reflect changes in glucose metabolism? Prof Benton discusses the clinical evidence and reviews several studies suggesting that carbohydrates play an important role in brain function beyond basal metabolism. Prof Benton also reviews the evidence showing that better glucose tolerance is associated with positive impacts to memory.

## Closing Keynote

***Snacking and Energy Balance***

Richard D. Mattes, MPH, PhD, RD
Purdue University
West Lafayette, Indiana, USA

Snacking is prevalent, increasing in frequency and accounts for approximately 20-25% of daily energy intake. Dr Mattes reviews the health effects of snacking and mechanisms by which snacking can promote positive energy balance and weight gain. He identifies nuts as highly satiating, and part of a healthful diet without posing a risk for weight gain.





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# Keynote Address:

***Carbohydrate Quality: What Do I Tell My Patients?***

John L. Sievenpiper, MD, MSc, PhD, FRCPC



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# Carbohydrate Quality: What Do I Tell My Patients?

John L. Sievenpiper, MD, MSc, PhD, FRCPC

**Introduction** Obesity and diabetes have reached epidemic proportions and are projected to increase over the next decade with important consequences for their downstream cardiometabolic complications. As the role of fat in this dual epidemic has been placed in doubt, carbohydrates are increasingly being indicted as the main culprit. Much of the concern has focused on the absolute amount and proportion of carbohydrates in the diet with all sources including traditional carbohydrate staples like cereal grains, pulses, and pasta coming under attack in the mainstream media, popular books, social media, the medical literature, and statements of prominent advocacy groups.

The "carbohydrate-insulin model" has been proposed to explain the ability of carbohydrate to contribute to obesity and its downstream cardiometabolic complications. This model posits that an overabundance of carbohydrate leads to endocrine dysregulation marked by hyperinsulinemia, which drives fuel partitioning with carbohydrate directed away from metabolically active tissue (eg, skeletal muscle, heart, lung, liver, etc.) to adipose tissue, resulting in a state of "cellular internal starvation" with compensatory increases in dietary intake and decreases in energy expenditure leading to weight gain. Although the model has confirmed that low carbohydrate diets produce the requisite decrease in insulin, these diets have failed to achieve the predicted weight loss benefit. A series of very carefully controlled, randomized, inpatient feeding trials at the National Institutes of Health (NIH), were unable to achieve the predicted increases in energy expenditure and body fat loss comparing low carbohydrate diets with high carbohydrate diets.[1,2] While it can be argued that the ability of low carbohydrate diets to induce decreases in energy intake through alterations in food intake regulation or to stimulate spontaneous increases in physical activity were not assessed (as both variables were tightly clamped), a large database of long-term randomized controlled trials conducted under free-living conditions (in which these mechanisms could manifest) have not shown any advantages of low carbohydrate diets over high carbohydrate diets. A network meta-analysis of 48 unique randomized trials involving 7,286 participants of diets of varying macronutrient profiles, and subsequent randomized trials, have not shown differences in weight loss at 6-months and 12-months of follow-up. Irrespective of the carbohydrate content, the most important determinant of success in these trials has been adherence to any one diet or macronutrient distribution, and clinic attendance.[3]

Although the evidence from randomized trials has failed to show the predicted advantages of low carbohydrate diets for weight loss and the downstream cardiometabolic improvements, large prospective cohort studies suggest that high carbohydrate diets may still have an adverse association with important cardiometabolic disease outcomes. An analysis of the Prospective Urban and Rural Epidemiological (PURE) cohort study in 135,335 participants free of cardiovascular disease from 18 low-income, middle-income, and high-income countries showed increased cardiovascular and all-cause mortality comparing the highest with the lowest quantiles of carbohydrate exposure, independent of the type of carbohydrate over 10 years of follow-up. Another simultaneously published analysis of the PURE study, however, suggested that the type of carbohydrate may modify the association with carbohydrate sources from legumes and fruit showing the opposite association: a cardiovascular mortality and all-cause mortality benefit.[4]

A more important focus may be on carbohydrate quality rather than quantity for cardiometabolic health. Carbohydrate quality can be defined broadly across 4 main domains: low glycemic index/load (GI/GL), high fiber, food-based approaches emphasizing specific carbohydrate-containing foods (whole grains, pulses, and fruit), and low sugars (Fig 1). A careful review of the best available evidence from prospective cohort studies of clinical outcomes and



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randomized controlled trials of intermediate endpoints follows for each domain of carbohydrate quality.

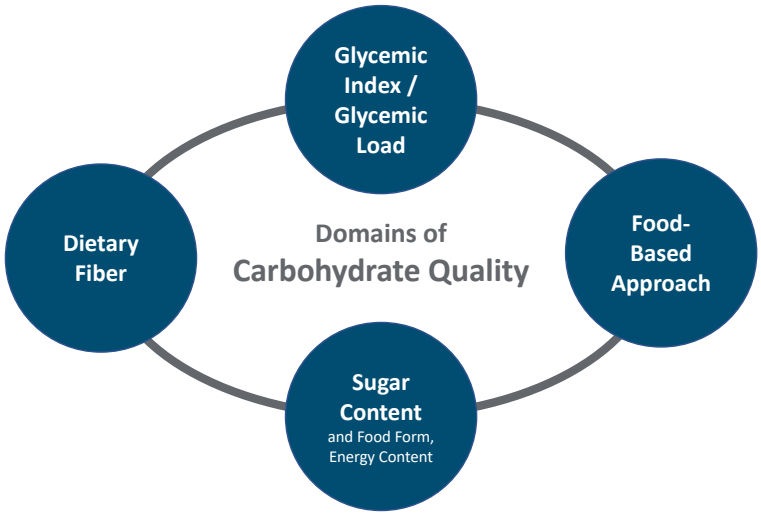


**Fig 1. Four domains of carbohydrate quality.**
Food-based approach includes whole grains, pulses (beans, peas, chickpeas, and lentils), and fruit.

**Glycemic Index/Load (GI/GL)** Low GI or GL dietary patterns have shown evidence of advantages for the prevention and management of cardiometabolic diseases in the context of moderate to high carbohydrate intakes. 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 decreases in diabetes and cardiovascular disease incidence compared with high GI and GL dietary patterns up to 25 years of follow-up.[5] This line of evidence agrees with the available evidence from randomized controlled trials of the effect of GI and GL on intermediate cardiometabolic risk factors. Systematic reviews and meta-analyses of >50 randomized controlled trials in >4000 participants show that low GI and GL dietary patterns lead to weight loss/maintenance, and a clinically meaningful improvement in glycemic control by HbA1c of ~0.5% (a level that is at the lower limit of efficacy of most antihyperglycemic agents, and exceeds the minimally meaningful threshold for new drug development set by the FDA), as well as improvements in blood lipids, and blood pressure compared with higher GI and GL dietary patterns.[5]

**Dietary Fiber** High fiber dietary patterns have shown evidence of advantages for the prevention and management of cardiometabolic diseases in the context of high carbohydrate intakes. Systematic reviews and meta-analyses of ≥10 prospective cohort studies in >1,000,000 participants have shown that total fiber, independent of source (cereals, vegetables, or fruit) or type (insoluble versus soluble), is associated with decreased incidence of diabetes and cardiovascular disease when comparing the highest with the lowest levels of fiber intake up to 19 years of follow-up.[6] The evidence from randomized controlled trials, however, suggests that improvements in intermediate cardiometabolic risk factors is most reliably linked to sources of viscous soluble fiber. Systematic reviews and meta-analyses of >100 randomized controlled trials in >5,000 participants show that high viscous soluble fiber intake from oats, barley, psyllium, and konjac mannan result in improvements in blood lipids (for which there are approved health claims in Canada, US, and Europe), glycemic control, and blood pressure.[7]

**Food-Based Approaches** Dietary patterns emphasizing specific carbohydrate-containing foods that include whole grains, dietary pulses (beans, peas, chickpeas, and lentils), and fruit have shown evidence of advantages for the prevention and management of cardiometabolic diseases in the context of high carbohydrate intakes. Systematic reviews and meta-analyses of prospective cohort studies have shown that high intakes of whole grains (>15 studies in >400,000 participants with follow-up to 25 years), dietary pulses (8 studies in >200,000 participants with follow-up to 29 years), and fruit (>10 studies in >500,000 participants with follow-up to 23 years) are associated with decreases in cardiovascular disease and diabetes incidence, and cardiovascular and all-cause mortality in the case of whole grains and fruit.[8-10] This line of evidence is generally concordant with evidence from randomized controlled trials of the effect of whole grains, dietary pulses, and fruit on intermediate cardiometabolic risk factors. Systematic reviews and meta-



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analyses of randomized controlled trials show that dietary patterns emphasizing dietary pulses (>50 trials in >1,000 participants with follow-up to 1 year) or fruit (>20 trials in >1,000 participants with follow-up to 6 months) result in weight loss/maintenance; and improved glycemic control, blood lipids, and blood pressure.[9,11] The systematic reviews and meta-analyses of whole grains (>25 trials in >2,000 participants with follow-up to 16 weeks), however, suggest that the improvements are restricted to whole grain sources from oats and barley.[12]

**Sugars** Any benefit of low sugar dietary patterns appears to be dependent on food form and energy control. Most of the evidence supporting public health recommendations to limit sugars derives from sugar-sweetened beverages (SSBs). Although systematic reviews and meta-analyses of >15 prospective cohort studies in >400,000 participants have shown an adverse association of SSBs with incidence of obesity, diabetes, heart disease, and stroke, these adverse associations are markedly attenuated with adjustment for energy (hence, many investigators 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 independent of food form.[13] 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.[13] These conditional associations are supported by the evidence from randomized controlled trials of fructose, the sugar moiety 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 >1,000 participants have shown that fructose, in energy matched substitutions with other carbohydrates (mainly starch), does not show adverse effects on intermediate cardiometabolic risk factors, and even shows advantages for glycemic control and blood pressure. Adverse effects are only seen when fructose supplemented diets with excess energy compared to the same diets without the excess energy, suggesting that any harm relates to the excess energy rather than any special mechanisms attributed to fructose-containing sugars.[13]

**Unintended Consequences of a Focus on Carbohydrate Quantity** A singular focus on carbohydrate quantity over quality may have important unintended consequences. One concern is that we may get a repeat of the "low fat" paradigm, in which manufacturers produce "low carbohydrate" foods that, like their "low fat" predecessors, are of no or less nutritional value and similar caloric content. If the consumer believes that they are "healthier", then the response may be overconsumption with no benefit or even harm to public health. Another concern is that a focus on "low carbohydrate" foods may take attention away from more important dietary risk factors. The Global Burden of Disease Project, a massive pooling project that allows for a comparative analysis of the global burden of disease attributable to the leading 79 risk factors using population attributable risk fraction modeling, provides important evidence that making carbohydrate quantity a public health priority would be misleading.[14] The most recent update does not identify high carbohydrate intake from foods (with the exception of SSBs) as a dietary risk factor. On the contrary, low intakes of various domains of carbohydrate quality are identified as dietary risk factors that increase premature morbidity and mortality, with low intakes of whole grains (1st), fruit (2nd), and fiber (6th) explaining ~1/3 of the burden of disease attributable to 14 dietary risk factors in North America. Some maneuvers used to achieve low carbohydrate diets, such as high intake of processed meat or red meat, are also identified as dietary risk factors that increase premature morbidity and mortality.

**The Path Forward: What Do I Tell My Patients?** Dietary guidelines are already moving away from a focus on single nutrients, such as carbohydrates, to more food and dietary pattern based recommendations. This shift recognizes that a focus on single nutrients misses important interactions between different nutrients, the nutrients and the food form/matrix, and the foods and the dietary patterns in which they are contained. There is also recognition that no one diet "fits all", and adherence is one of the most important determinants of the success of any



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dietary approach. One must consider that there are a number of dietary patterns with evidence of advantages and disadvantages, and this evidence must be aligned with the values, preferences and treatment goals of the individual to achieve the greatest adherence over the long term.[15]

**Conclusions** Carbohydrate quality appears to be a more important consideration than carbohydrate quantity. Although some people may benefit from a low carbohydrate dietary pattern, others may benefit from high carbohydrate dietary patterns that are low in GI, high in fiber (especially viscous fiber sources), or emphasize specific foods such as whole grains (especially oat or barley sources), pulses, or fruit. The best evidence from systematic reviews and meta-analyses of the available evidence shows that these domains of carbohydrate quality are associated with decreased weight gain, diabetes incidence, and cardiovascular disease incidence and mortality in prospective cohort studies, and decrease intermediate cardiometabolic risk factors in randomized controlled trials. The evidence for sugars as a domain of carbohydrate quality appears to be highly dependent on food form and energy. These data reflect the current shift in dietary guidance away from reductionist "one-size-fits-all" nutrient-centric recommendations (eg, "low fat", "low carb"), to 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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# Carbohydrates Through the Life Cycle:

***Carbohydrates for Performance Across Adolescence and Adulthood***

Joel T. Cramer, PhD, FACSM, FNSCA, FISSN

***Gestational Diabetes Mellitus: Latest Research and Guidelines***

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# Carbohydrates for Performance Across Adolescence and Adulthood

Joel T. Cramer, PhD, FACSM, FNSCA, FISSN

What is the difference between *sports nutrition* and *performance nutrition*? *Sports nutrition* specifically focuses on improving sports performance in athletes, ranging from marathon runners to gymnasts. When strategically fueled, athletes can perform better. Therefore, *sports nutrition* can be considered finite, focusing on acute, short-term performance improvements structured around individual sport events, seasons, athletes, and teams. In contrast, *performance nutrition* broadly encompasses performance of the human body. Specifically, the performance of skeletal muscle, which impacts nearly all facets of life. Obvious examples of muscle performance include force production and movement that keep our bodies moving during physical activities like walking, playing, swimming, or gardening. Less obvious examples include the preeminent roles of skeletal muscle performance in resting metabolism, posture, balance, low back pain, activities of daily living, and glucose homeostasis. Therefore, *performance nutrition* can be considered infinite, encompassing chronic health improvement structured around life and longevity. We have acquired critical knowledge of skeletal muscle performance through applied science and research originating in *sports nutrition*. This knowledge can be translated and applied to our broader goals of *performance nutrition*, albeit sometimes through opposing mechanisms and reverse engineering. The translation of our knowledge from *sports nutrition* science and research holds the potential to influence long-term skeletal muscle health by improving the quality of carbohydrate consumption from a *performance nutrition* perspective.

The ultimate purpose of carbohydrates in *sports nutrition* is to serve as fuel for energy during sports performance, which demands high levels of immediate and sustained energy.[1] Energy transfer in skeletal muscles occurs through the breakdown and replenishment of adenosine triphosphate (ATP), often described as the body's energy currency. For muscles to contract and produce force and/or movement, ATP is hydrolyzed to adenosine diphosphate (ADP) + inorganic phosphate (Pi) + energy transfer. Ultimately, the ADP is eventually rephosphorylated to ATP to facilitate the cyclic process of energy transfer. Our muscles have the capability to catabolize carbohydrate, fat, and/or protein to replenish ATP stores. However, the quickest and most efficient metabolic pathway that our skeletal muscles rely on for rapid resynthesis of ATP is glycolysis, which is defined as the breakdown (oxidation) of the carbohydrates, glucose or glycogen.[2] In addition to energy storage (ATP), the other basic end byproducts of glycolysis, carbon dioxide and water, are eventually eliminated or recycled by the body via cellular respiration. For the glycolytic metabolic pathway to operate most efficiently, carbohydrate must be consumed and glycogen must be stored, which emphasizes the importance of carbohydrate intake. Therefore, using glycolysis as the primary metabolic pathway by which our muscles quickly and efficiently use carbohydrates as fuel for energy, is heavily reliant on carbohydrate intake.

The rate and magnitude of carbohydrate utilization for energy during sports-related activities is dependent on the intensity and duration of the activity.[1] For the marathoner and high endurance athletes, research in *sports nutrition* indicates that optimal loading strategies can increase carbohydrate stores in the body (ie, endogenous carbohydrates) by nearly 100%.[3] Thus, not only are we capable of substantially manipulating carbohydrate storage in our bodies for sports events, there is a strong implication for evidence-based recommendations in *sports nutrition* to optimize the carbohydrate loading strategy.[1] Ultimately, scenarios like this identify three specific goals for carbohydrate recommendations from sports nutritionists, which include providing exogenous carbohydrates to (1) serve as a fuel source; (2) alter substrate utilization to preserve endogenous carbohydrates as a fuel source; and (3) resynthesize lost or depleted endogenous carbohydrates for fuel sustainability.[1]



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During overnight fast, there is an 80% reduction in liver glycogen stores, which is likely present when beginning exercise in a fasted state.[4] However, following a mixed meal, 20% of carbohydrate intake is stored as liver glycogen.[1] Similarly, a 42% increase in muscle glycogen has been reported after carbohydrate ingestion.[5] The recommendations for carbohydrate intake timing prior to exercise or sports performance events suggest that high glycemic carbohydrates consumed ≤60 minutes prior to exercise will likely induce hypoglycemia, which may be lessened by including protein.[1] In contrast, complex carbohydrate consumption 2-3 hours prior to exercise allows blood glucose and insulin concentrations to return to baseline, and improves performance without the risk of hypoglycemia during the activity.[1] Incidentally, the phenomenon of exercise-induced hypoglycemia occurs via the same mechanisms responsible for treatment of type 2 diabetes with exercise. Exercise stimulates the uptake of blood glucose into skeletal muscles, which is independent of insulin,[6] thereby demonstrating the translation of reciprocal knowledge obtained through *sports nutrition* research to the health benefits of exercise for the management of carbohydrate-related metabolic health and disease.

The influence of the glycemic index of the carbohydrate ingested, specifically for exercise and athletic performance, appears to have the greatest impact on the timing of energy availability. High glycemic carbohydrate intake rapidly increases blood glucose and insulin concentrations, which can induce hypoglycemia when timed close to the initiation of exercise, but does not seem to impact overall performance compared to low glycemic carbohydrate intake.[7] However, when the goal is a rapid resynthesis of glycogen stores during recovery after exercise, a high glycemic carbohydrate intake may be valuable, but only when there are repeated exercise or athletic performance events in one day, such as a double header in baseball/softball or multiple soccer matches.[8] Subsequently, the recommendation is to consume a high glycemic carbohydrate during recovery after exercise at a rate of 1.0-1.2 $g \cdot kg^{-1} \cdot hour^{-1}$ within 4 hours of recovery, particularly, if the next exercise bout or athletic performance event is 3-6 hours later. Otherwise, the glycemic index or amount of carbohydrate intake during recovery is much less important.[8] Research shows that when low glycemic resistant starches are consumed prior to exercise, performance is not substantially impacted, yet the rate of glycogen recovery is reduced.[9] When translating this *sports nutrition* knowledge to a *performance nutrition* perspective, rapid spikes in blood glucose and insulin concentrations are potentially harmful to long-term skeletal muscle health.

Carbohydrate intake recommendations during long-term endurance athletic events is influenced by the need for high rates of gastric emptying and monosaccharide absorption.[9] During exercise, blood is shunted from the digestive system to the working muscles. Gastrointestinal distress is therefore increased when undigested food and unabsorbed nutrients remain in the digestive system and jostle during exercise bouts. Thus, rapid gastric emptying and rapid carbohydrate absorption are desirable during an athletic event lasting 2 or more hours when carbohydrate intake is usually necessary.[10] Since glucose and fructose are absorbed by two separate transporter mechanisms, carbohydrate absorption can be accelerated when a combination of glucose and fructose are ingested simultaneously. This concept is often referred to as multiple transportable carbohydrates in the *sports nutrition* literature. The effects of consuming multiple transportable carbohydrates is very rapid, large spikes in blood glucose and insulin concentrations, as well as enhanced utilization of exogenous carbohydrates as the immediate source of energy.[11] Although this is desirable during specific *sports nutrition* applications, it is possible that the widespread consequences of consuming large amounts of multiple transportable carbohydrates with high glycemic responses in the general population is damaging to long-term skeletal muscle health from a *performance nutrition* perspective.

The metabolism and substrate utilization in children and adolescents are different from adults. Children have a lower overall glycolytic capacity as evident by (1) lower blood lactate concentrations; (2) lower glycolytic enzyme turnover; (3) lower muscle glycogen; and (4) a greater reliance on slow-twitch, type I fiber mechanisms for energy transfer.[12] Although children quickly adapt to changes in carbohydrate and fat intake, children metabolize fat at a greater rate



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than adults, which results in more glycogen sparing. Furthermore, adolescents during puberty exhibit transient decreases in glucose tolerance and insulin sensitivity, which promote the storage of excess carbohydrates and display temporary risk factors for type 2 diabetes that return to normal shortly after puberty. Previously malnourished children who are fed for catch-up growth are particularly susceptible to storing excess carbohydrate as fat.[13] The use of low glycemic carbohydrates for children shows potential benefit in decreasing early obesity rates.

The translation of *performance nutrition* by inverting or reverse engineering our knowledge of *sports nutrition* may serve as an effective tool for long-term skeletal muscle health. To invert our *sports nutrition* principles, the reversed goal would be to encourage endogenous carbohydrates as the primary source of fuel for skeletal muscles, and limit the immediate use of exogenous carbohydrates. The new focus would be to force the body to displace and cycle carbohydrates from intake → blood glucose → muscle glycogen → energy utilization, rather than intake → blood glucose → energy utilization. This focus would de-emphasize the necessity of rapid glycogen repletion, yet still accomplish the task of glycogen resynthesis, just over a longer period. The hypothesis would be that cycling carbohydrates through the additional step of storage prior to utilization would reduce the excess amount of circulating carbohydrates, thereby reducing the likelihood of glucose storage as adipose tissue. The concept is depicted in Fig 1 below of the skeletal muscle, adipose tissue (clouds), and liver.

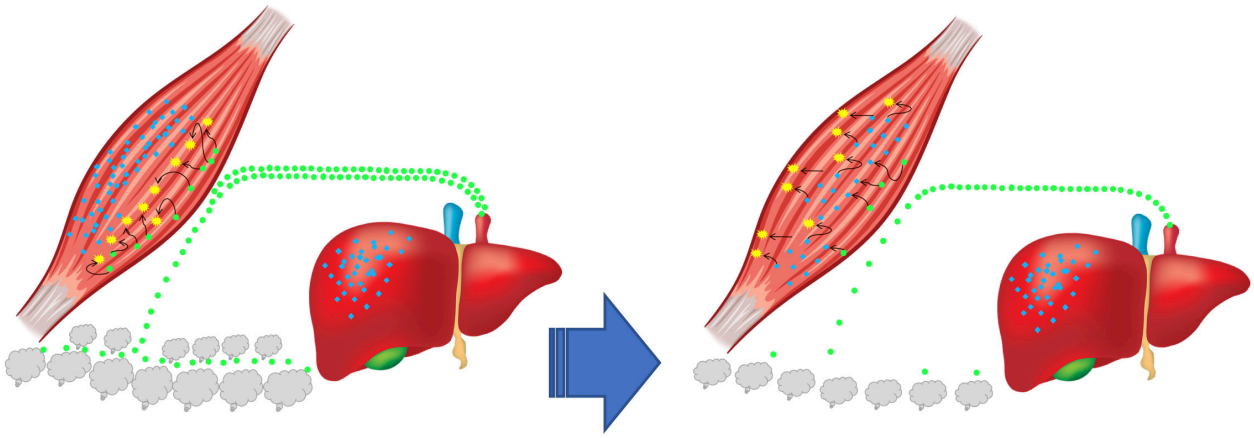

**Fig 1. Carbohydrate cycling concept: cycle carbohydrates through muscle glycogen storage prior to energy utilization.** Illustrated: skeletal muscle, adipose tissue (clouds), liver. Green dots represent glucose, blue diamonds represent stored glycogen, and yellow bursts represent energy utilization.

The concept of reverse engineering our *sports nutrition* recommendations for long-term health might best start with replacing high glycemic, rapidly absorbed carbohydrates, that are currently available in popular beverages, with low glycemic, slowly absorbed carbohydrates. This reconceptualization of the carbohydrate quality widely consumed in popular beverages to reduce the glycemic response, and promote endogenous carbohydrate use for energy, may be a good first step in promoting long-term skeletal muscle health, reducing obesity, and lowering metabolic disease risk factors.



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# Gestational Diabetes Mellitus: Latest Research and Guidelines

Prof Helen R. Murphy, MBBChBAO, FRACP, MD

One in six live births occur in women with diabetes, of which, by far the most common type, accounting for approximately 85% of all diabetes cases, is gestational diabetes mellitus (GDM).[1] GDM is a serious pregnancy-related condition, which increases the risk of pregnancy complications for both mother and child. It is of particular concern in low- and middle-income countries, which experience 85% of the annual global diabetes deliveries, and 90% of the most serious pregnancy complications. As women are increasingly entering pregnancy overweight and obese, the rates of GDM will likely rise further. Eight priority countries (India, Pakistan, Bangladesh, China, Indonesia, Nigeria, Brazil and Mexico) account for more than half of the global live births and global diabetes burden.

The maternal risks of GDM include pre-eclampsia, and increased obstetrical intervention including induction of labor and caesarean delivery. GDM often recurs in subsequent pregnancies, with recurrence rates of at least 40%-60% reported.[2] Women with a GDM pregnancy have a 70% increased risk of progression to type 2 diabetes (T2D) within 5-10 years. Women with higher pre-pregnancy body mass index (BMI) or higher gestational weight gain are most at risk. Every 1 kg increase in maternal pre-pregnancy weight is associated with a 40% increased risk of T2D. Women with excessive gestational weight gain also retain approximately 3 kg more up to 15 years after pregnancy. Data from our own clinic highlight the cumulative impact both of gestational and of inter-pregnancy weight gain across successive pregnancies (Fig 1).[3]

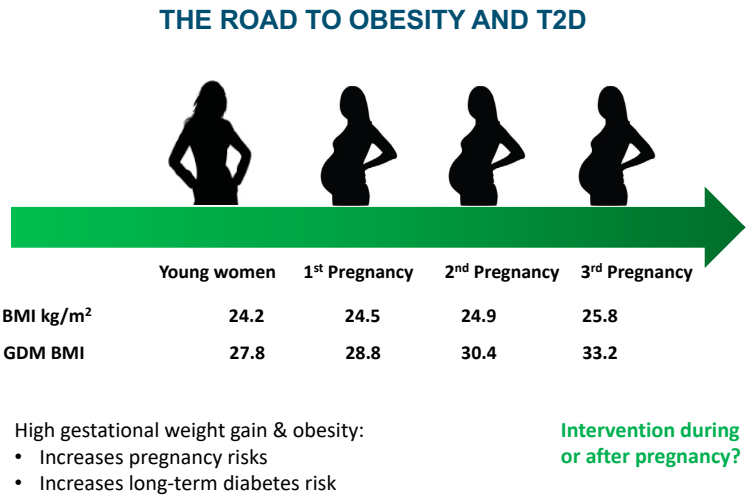


**Fig 1. Excessive gestational weight gain in women with GDM is associated with retained weight after pregnancy.[3]**
GDM=gestational diabetes mellitus

Maternal hyperglycaemia stimulates fetal pancreatic insulin secretion leading to (1) increased fetal growth acceleration; (2) increased fetal fat accumulation; (3) large for gestational age (LGA), defined as birthweight >90th percentile; and (4) macrosomia, defined as birthweight >4000 g. LGA increases the risk of preterm and instrumental and/or operative delivery and stillbirth.[4] These delivery complications can lead to more permanent disabilities, including hypoxic brain damage, shoulder dystocia and Erb's palsy. Furthermore, LGA infants are themselves predisposed to developing insulin resistance, obesity and T2D perpetuating an intergenerational cycle of cardiometabolic disease.[5] Optimising maternal glucose control during pregnancy is therefore important both for a successful pregnancy outcome, and for longer-term health of both mother and child.



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**GDM Screening** GDM screening can be either a one- or two-step process. In the two-step process, all women receive a 50 g one-hour glucose challenge test (GCT), and those who screen positive (typically defined as post GCT glucose of ≥140 mg/dL or 7.8 mmol/L) proceed to a formal 75 g oral glucose tolerance test (OGTT) diagnostic test. The GCT is a lower cost and less burdensome test, and can therefore be applied to all pregnant women. However, the benefits of a universal test have to be weighed against the potential delays (typically 10 days) before the formal diagnosis and initiation of treatment. The one-step approach involves a single 75 g OGTT, which is offered only to women who belong to a recognised high-risk group:

- Prior diagnosis of impaired glucose tolerance or previous GDM pregnancy
- Maternal age >30 years
- Pre-pregnancy BMI >30 kg/m$^2$
- Multiple gestation
- Family history of diabetes (particularly in first-degree relative)
- Previous LGA infant or infant over 4.5 kg
- Ethnic origin with high prevalence of T2D (eg, Indian, Pakistani, Bangladeshi, Middle-Eastern, Caribbean)

The challenge with risk factor-based screening is that many women with GDM (in some populations up to 50%) have no recognised risk factors. In addition, risk factor screening is variably implemented with different cut-offs in maternal BMI applicable for different ethnic groups. Currently, the International Association of the Diabetes and Pregnancy Study Groups (IADPSG), World Health Organization (WHO), American Diabetes Association (ADA), UK National Institute for Health and Care Excellence (NICE), and Australasian Diabetes In Pregnancy Society (ADIPS) recommend the one-step screening approach. The UK NICE guidelines also advise that women with previous GDM have a 75 g 2-hour OGTT or self-monitoring of blood glucose in early pregnancy. The United States Preventive Services Task Force supports screening after 24 weeks, but not earlier.

**GDM Diagnosis** The recognition that the relationship between glycaemia and maternal-fetal outcomes is a continuum, as described in the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study, has created controversy regarding appropriate diagnostic thresholds.[6] Based on these findings, the IADPSG recommend that any of the following glucose cut-offs be considered diagnostic for GDM: (1) fasting ≥5.1 mmol/L; (2) 1-hour ≥10.0 mmol/L; or (3) 2-hour ≥8.5 mmol/L (92, 180 and 153 mg/dL respectively).[7] WHO and the ADA support the IADPSG diagnostic criteria. Different populations manifest different proportions of hyperglycaemia at each OGTT time point. For example, the proportion of women with GDM whose fasting glucose cut-off exceeds 5.1 mmol/L (92 mg/dL) is very context-specific and varies from 25%-75%. The UK (NICE) has recommended a higher fasting ≥5.6 mmol/L, but lower 2-hour cut-off ≥7.8 mmol/L (101 and 140 mg/dL, respectively). Data from our GDM clinic showed that the women missed by the higher fasting glucose proposed by NICE, were at higher risk than the additional women detected by the lower 2-hour cut-off.[8]

**GDM Treatment** Treatment of GDM is less controversial. An Australian trial confirmed that treatment of women with more severe hyperglycaemia reduced serious pregnancy complications, albeit with increased obstetrical intervention.[9] A subsequent trial also demonstrated improvements in obstetric and perinatal outcomes associated with treatment, mainly diet and lifestyle, in women with less severe hyperglycaemia.[10] All professional organisations therefore advise self-monitoring of blood glucose (SMBG) with diet and lifestyle modification as first line therapy. The recommended glucose control targets are typically (1) fasting glucose <5.3 mmol/L (95 mg/dL); (2) 1-hour <7.8 mmol/L (140 mg/dL); and (3) 2-hour <6.7 mmol/L (120 mg/dL). This pragmatic clinical approach achieves satisfactory glucose control in approximately two thirds of women with GDM.



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We have recently performed a systematic review and meta-analysis demonstrating that dietary interventions (in addition to routine clinical advice) can further optimise maternal glycaemia and reduce newborn adiposity.[11] However, the quality of the published trials do not support any particular diet (Mediterranean, low fat, low carbohydrate, low glycemic index, or total energy restriction) as being more or less effective. The take-home message is that any culturally acceptable dietary intervention is likely to be effective. Many professional organisations also recommend 30 minutes of moderate daily exercise throughout pregnancy. Up to one third of women require supplementary treatment to achieve their glycemic targets. The use of oral agents which cross the placenta (including both metformin and/or glyburide) remains controversial, leading the ADA and American College of Obstetricians and Gynecologists (ACOG) to recommend insulin as the preferred treatment option.

**Future Directions** Particular attention should be paid to the prevention of GDM in obese women who may already have accelerated fetal growth at an earlier gestational age. Randomised clinical trials of diet and lifestyle interventions and of metformin have failed to prevent development of GDM in obese women. As not all overweight and obese women develop GDM, more research is needed to develop better tools for the earlier detection (and treatment) of GDM in high-risk groups. More research is also needed regarding the most effective screening and diagnostic programmes for GDM in low- and middle-income countries. These may include biomarkers and/or direct assessment of maternal glucose using novel continuous glucose monitoring (CGM) systems. As CGM becomes an increasingly accessible and affordable treatment option for GDM, this may pave the way for improved risk assessment, personalised treatment, better management, and improved health outcomes for both mother and baby.

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# Savoring Sweet: Carbohydrates in Infant, Toddler, and Child Nutrition

Robert Murray, MD

Nutrition supports the remarkable rate of growth of infants and toddlers: weight gain, linear growth, and continued development and refinement of organs and physiological systems.[1] Human milk is sweet and fragrant to stimulate avid sucking. Human milk is a complex bioactive fluid with a broad array of components, including indigestible human milk oligosaccharides that support the developing immune system, and factors that promote digestion, regulate hormonal signaling, stimulate tissue development, and modulate inflammation to ensure a stable transition from *in utero* to *ex utero* life.[2,3] Gastrointestinal motility, which is rudimentary at birth, coordinates over time, paralleling changes in the gut nervous system. Similarly, gastric, intestinal and pancreatic digestive functions develop gradually in response to daily exposure to swallowed material, including nutrients, allergens, microbes, and chemicals. An entire secondary digestive system is established through bacterial colonization, which begins a dialogue with the host's metabolism.[4,5]

From birth, the infant/toddler engages in intense sensory-motor exploration that results in extremely rapid brain expansion.[6] By 12 months the infant brain will double and by 36 months triple in volume, due to synaptogenesis and myelination of axons. During this period, the brain accounts for 50-60% of the infant's basal metabolic rate.[1]

Initial food choices have consequences beyond growth. Human milk provides complete nutrition until around 6 months of age when the infant's needs for energy, iron, and zinc require complementary foods (CFs). The sensory and motor experiences associated with first foods, the type, variety and timing, including the many colors, flavors, smells, and textures contribute to life-long food preferences. CFs are a critical contributor to cognitive, social, and emotional maturation. Attention, affect, learning capacity, memory, and motivation all are affected by diet quality.[7] Although individual nutrients are important (eg, iron, omega-3 fatty acids, choline), it is the synergy between nutrients that matters. A deficiency in one nutrient affects how other nutrients function. This makes dietary diversity and balance a crucial target, in alignment with the 2015 Dietary Guidelines for Americans (DGA).[8,9] If the 20th century was the era of the individual nutrient, the 21st century will be the era of the dietary pattern.

A dietary pattern is the totality of foods and beverages an individual consumes regularly over time. The DGA states that "these dietary components act synergistically in relation to health."[8] The health benefits of nutrition, as well as the mitigation of chronic disease risk, arises from the quality of foods consumed. Every individual has a personal dietary pattern, based on their exposures, food preferences, family eating style, and cultural norms. Improvements occur from substitution of more nutrient-rich items for ones of lesser nutritional value. Changes that occur incrementally are sustained longer.

Between 6 and 24 months of age, the infant/toddler will evolve a stable set of food preferences and eating habits.[9] Formerly, individual solid foods were introduced in a sequence meant to prevent allergic reactions. Recent research showed that, contrary to conventional teaching, withholding allergenic proteins increased, not decreased, the risk of allergic symptoms. Instead, the aim of CFs should be to repeatedly offer the infant/ toddler every flavor, taste, and texture of nutrient-rich foods in each of the five food groups (ie, fruits, vegetables, whole grains, dairy, quality proteins). First foods differ world-wide. But offering small tastes of a wide variety of foods will be more advantageous for the infant than large servings of a few foods.



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Although nutrient consumption among 6-12 months old in the US is generally good, there remain problems with parental/caregiver food selection.[9] Breast milk and/or infant formula provide a strong nutritional framework. At 6 months, a modest 20% additional energy is needed; by 12 months an additional 50%. The infant's need for iron and zinc is tantamount. Formerly, introduction of beef and iron-fortified cereals covered both well. Discouragement of red meat throughout the 20th century led to a dramatic fall in beef consumption. National Health and Nutrition Examination Survey (NHANES) data show that only 11.3% of infants are offered beef on any given day. Nearly as many infants are given deli meats and hot dogs, low in iron but high in sodium. Use of infant cereals has fallen with time too, creating the need for other sources of iron and zinc among CFs.[10, 11] Choices made by US caregivers could be strengthened for each of the 5 food groups. Inappropriate early introduction of cow's milk before 12 months is still found in 14-20% of infants. Powerful protein sources such as fish, eggs, and yogurt are not commonly utilized, yet snack type foods and desserts and soft drinks are often fed in over half the infants in the US. One-half of fruit servings are consumed as 100% juice. If juice is withheld until 12 months, as recommended, then caregivers must compensate with more whole fruit. Unfortunately, green vegetables are only offered to 6% and 7% of infants and toddlers, respectively, a percentage that changes little as the child ages.[10,11]

Assuring a strong initial dietary pattern represents a new goal for parents/caregivers.[9] The social and emotional exchange between infant and caregiver during meals is a factor in food enjoyment. Birth-to-24-month dietary guidance will need to emphasize parent/caregiver feeding style to ensure that the quality of CFs matches the extraordinary needs of early childhood. Parents/caregivers who encourage "play" with new foods can capitalize on the natural sensory and motor exploratory skills of the infant/toddler to increase new food acceptance.

Nutrient and energy needs are high between 12 and 24 months, and taste preferences and eating habits are being established. Fluid milk assumes a similar, but narrower role in the diet of toddlers once breast milk and infant formula are withdrawn. Our Western dietary pattern—high in saturated fats, sugars, starches, sodium and kilocalories, but low in nutrients—takes root during this period. Fifty percent of toddlers consume sweetened drinks and 90% consume added sugars daily, while nearly half consume potatoes and one-third consume sweetened cereals.[11,12] Toddlers eat every 3-4 hours due to energy needs. Generally, toddlers consume 3 meals and 3 smaller eating sessions daily. Unfortunately, the term "snack" is applied to what should be considered mini-meals. Toddler snacks account for 288 kcal/day and many nutrients, such as fiber, Vitamins C, D, E, and B12, along with calcium, iron, zinc, and potassium.[12,13] But the snacks also contain many foods high in energy but low in nutrients. Over 90% of US toddlers consume daily sweet-salty snack foods, and over 80% consume desserts. These foods lower diet quality scores among children and teens 2-5 years old (59.9), 6-11 years old (53.7), and 12-17 years old (52.3) (Healthy Eating Index, HEI, a global assessment of dietary pattern using 12 component categories and scoring a maximum of 100 points).[14] Nearly ubiquitous among school age children, snack type foods account for 40% of daily calories.[13]

Approximately 8-10% of calories consumed by infants/toddlers are added sugars.[12,15] There is no guidance for an acceptable amount in early life. Infants do not derive any benefit from added sugars. Toddlers may benefit from small amounts of added sugars used to promote new or high-quality food items.[7] Added sugar consumption in the US has fallen more than 20% since 2000 to levels below those of the late 1970s. Despite that, obesity continues to rise.[7] The DGA, the American Heart Association, and the World Health Organization have all promoted added sugar intake at less than 10% of total calories. This level was not based on data showing harm above the 10% level. Rather, the value was modeled: if a person consumes the recommended servings per day from each of the 5 food groups, then less than 10% of calories are available for added sugars.[8] Currently, no nation in the world has a per capita added sugar intake below the 10% level. Systematic reviews and meta-analyses fail to show a correlation between added sugar consumption and obesity or between sugar intake and nutrient insufficiency until sugar intake exceeds 20-25% of total calories.[16,17]



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Five foods/beverages account for 75% added sugar intake in children: soft drinks, fruit-flavored drinks, grain desserts, other desserts, and candy (Fig. 1).[8,18] Nutrient-rich foods that contain added sugars, such as yogurt, flavored milks, sweetened cereals, and 100% fruit juice, contribute little to total added sugar intake. But they do contribute substantially to diet quality.[19] Nutrition advice in the 21st century should seek to improve diet quality. It's not the sugar as much as the nutrient contribution of the food containing sugar that matters.

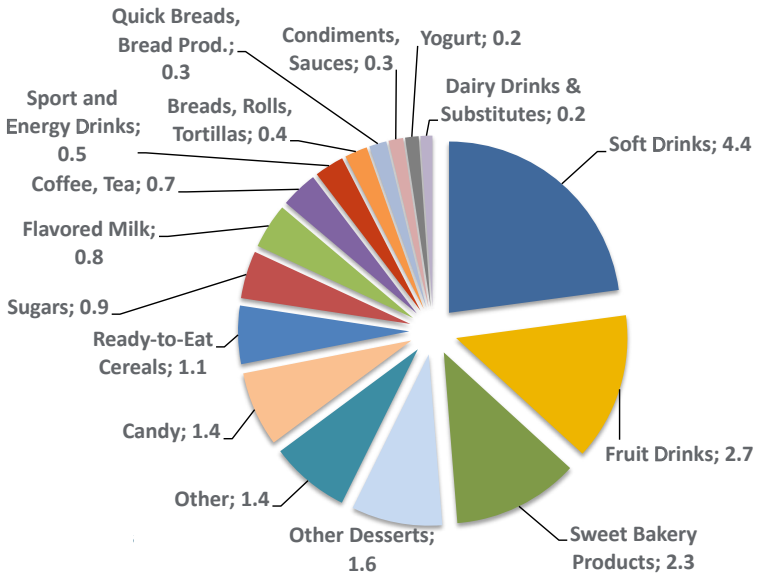


**Fig 1. Added sugars in children's diets.**
**National Health and Nutrition Examination Survey (NHANES) 2007-2010, 2-18 years of age.**
Values are teaspoons per day equivalents.

IMPORTANT NOTICE: Breastfeeding is best for babies and is recommended for as long as possible during infancy.

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# Metabolic Flexibility and Carbohydrates Across Tissues:

***Role of Dietary Carbohydrates on Metabolic Flexibility in Key Target Tissues: Liver, Adipose Tissue and Skeletal Muscle***

Prof Rafael Salto, PhD

***Phenotypic Flexibility as a Measure of Health Through the Life Cycle***

Suzan Wopereis, PhD

***Carbohydrates, Mood and Cognition***

Prof David Benton, PhD, DSc



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# Role of Dietary Carbohydrates on Metabolic Flexibility in Key Target Tissues: Liver, Adipose Tissue and Skeletal Muscle

Prof Rafael Salto, PhD

Humans have acquired metabolic adaptations, including enhanced energy storage, to mitigate the effects of famine and starvation. Despite little use in developed, food-rich countries, this adaptive process to a deficit in energy intake persists, at least in part, during weight gain upon refeeding. Energy is directed at accelerating specifically the recovery of the body's adipose tissues rather than other tissues. This preferential 'catch-up' fat is commonly observed in both children and adults after malnutrition, anorexia nervosa, cancer cachexia, diabetes and intentional weight loss.

Carbohydrates help promote these metabolic adaptations in a coordinated way, involving short-term regulatory processes (ie, changes in hormone secretion and signaling pathways), and long-term adaptations (ie, changes in gene expression that sustain the channeling of glucose to fat). The effects of carbohydrates on metabolism, glycemia, insulin and glucagon secretion depend on their glycemic index (GI), saccharide composition, and rates of digestion and absorption in the intestinal tract. Non-digestible carbohydrates can also modulate metabolism following fermentation by the intestinal microbiota to generate short-chain fatty acids and other signaling molecules.

Dietary carbohydrates, depending on their GI, have a strong effect on metabolic flexibility. Metabolic flexibility is the capability of the organism to select fuel oxidation in response to specific nutrient availability.[1] For example, muscle can switch between predominant fat or glucose catabolism to generate energy, depending on the stimulus. This flexibility takes place in normal healthy lean individuals and is hampered in individuals with diabetes and obesity, leading to metabolic inflexibility.

A high glycemic index (HGI) diet leads to increases in serum glucose, insulin, cholesterol and triacylglycerol (TG) levels. These alterations reflect changes in fuel metabolism across key organs and tissues such as liver, muscle and adipose tissue. In liver, a HGI diet increases glycogen and fat deposits, too, since energy is preferentially stored as fat in humans. Fuel selection in muscles of individuals fed HGI diets is biased to glucose consumption instead of fatty acids (FA), which impacts muscle performance during exercise. Finally, a HGI diet increases white adipose tissue mass, which can promote a proinflammatory state in the organism. All these effects are normalized by a low glycemic index (LGI) diet (Fig 1).

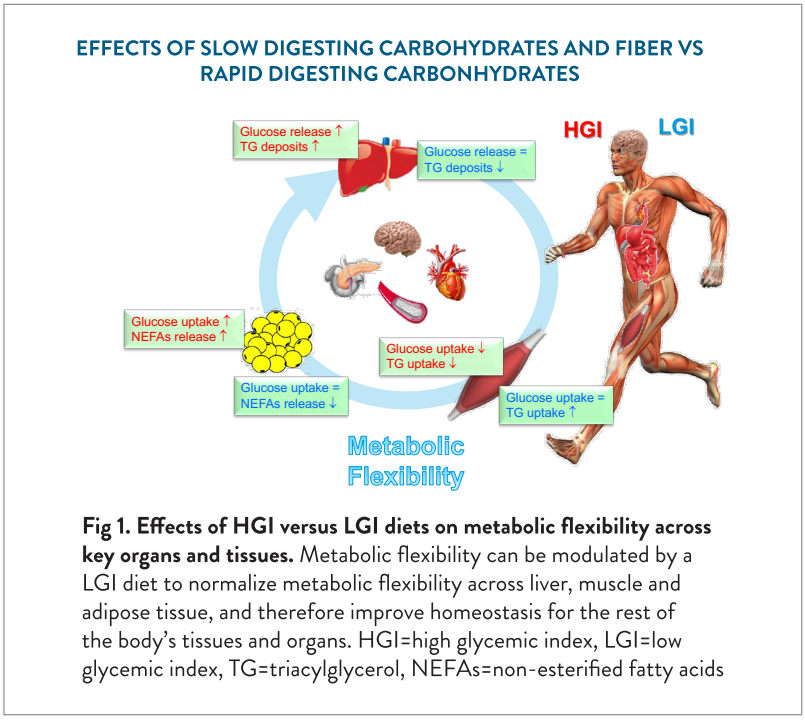


**Fig 1. Effects of HGI versus LGI diets on metabolic flexibility across key organs and tissues.** Metabolic flexibility can be modulated by a LGI diet to normalize metabolic flexibility across liver, muscle and adipose tissue, and therefore improve homeostasis for the rest of the body's tissues and organs. HGI=high glycemic index, LGI=low glycemic index, TG=triacylglycerol, NEFAs=non-esterified fatty acids



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The liver contributes to homeostasis and metabolic flexibility by helping control the distribution of energy to the rest of the body. Liver has a central role in metabolic flexibility since it can both efficiently use and produce glucose and TG. At the plasma membrane, liver expresses transporters for glucose and FA. Glucose transporter type 2, liver (GLUT2; SLC2A2) is a specialized transporter involved not only in the uptake but also in the export of glucose. Furthermore, GLUT2 can mediate the internalization of other monosaccharides such as fructose, which enter the glycolytic pathway at an unregulated point and thus serves as a quick energy supply when needed (eg, hypercatabolic hospitalized patients, sprinters, weightlifters). However, in a situation of overfeeding, excess of unregulated energy supply such as fructose can promote metabolic inflexibility. In a fasted state, while glycolysis and glycogen synthesis are inhibited in the liver, gluconeogenesis from non-carbohydrate precursors and glycogen breakdown work together in the maintenance of glycemia. Obviously, in a fasted state liver takes advantage of the TG uptake to produce FA and to promote its import by mitochondria through the carnitine palmitoyltransferase 1 (CPT1) transporter. Once FAs are inside the mitochondria, ß-oxidation, Krebs cycle and respiratory chain provide the ATP needed for the liver.

A HGI diet has remarkable effects on liver carbohydrate and lipid metabolism. First, it increases glucose uptake, glycolysis and alters glycogen metabolism. At the same time, it inhibits gluconeogenesis. Under these circumstances, liver is a net glucose consumer rather than a glucose exporter. Regarding lipid metabolism, a HGI diet blocks FA use and enhances the conversion of glucose to TG, promoting a hepatic lipogenic program that leads to an increase in blood TG and cholesterol, enhanced TG transport to adipose tissue, and even worse, hepatic steatosis. Further, a HGI diet raises insulin levels acutely, leading to short-term regulation of liver carbohydrate metabolism. Glycogen synthesis increases, followed by pyruvate dehydrogenase complex (PDC) activation, thus facilitating the synthesis of Krebs cycle intermediates. Nevertheless, a HGI diet exerts its long-term effects in liver through upregulation of several key enzymes. A HGI diet induces the expression of GLUT2 transporter, glycolytic enzymes such as pyruvate kinase (PK), represses expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase 2, mitochondrial (PCK2; PEPCK), and importantly, enhances the amount of lipogenic enzymes such as acetyl-CoA carboxylase (ACAC) and fatty acid synthase (FASN). In parallel, a number of signaling molecules are generated: glucose-6-phosphate (G6P) and xylulose-5-phosphate (X5P).

The long-term regulation of metabolism induced by HGI diets is mediated by specific transcription factors that upregulate expression of genes that encode lipogenic enzymes. For example, carbohydrate-responsive element-binding protein (ChREBP; MLXIPL) contains several phosphorylation sites and a glucose-sensing domain that is activated by G6P.[2] During administration of a LGI diet or fasting, ChREBP is phosphorylated and inactive in the cytosol. A HGI diet increases levels of X5P, which activates protein phosphatase 2A (PP2A; PPP2CA) and promotes de-phosphorylation of ChREBP and its translocation to the nucleus. When G6P binds to the glucose-sensing domain, ChREBP now upregulates expression of genes involved in the conversion of glucose to fat. The effects of a HGI diet can be reverted by the administration of LGI diets that normalize glycemia and insulinemia, and furthermore, decrease liver fat and glycogen levels.[3-4]

Muscle is the main energy consumer of the body. It has the capability to use glucose or FA as metabolic fuels and the potential to switch fuels. This capability to switch fuels is tightly regulated by insulin and insulin sensitivity as well as exercise and training. In a healthy individual, during fasting and low exercise conditions muscle is mainly consuming FA from circulating TG. In a moderate exercise (70% $VO_2$ max), carbohydrate metabolism supports up to 50% of the muscle energy demand. High intensity exercise makes muscle even more dependent on glucose metabolism.

In muscle, FA are taken up through an inducible fatty acid translocase (FAT; CD36), activated as acyl-CoAs and then transported to the mitochondria by CPT1. After a HGI diet, the enhanced insulin levels promote the translocation of a specific insulin-dependent glucose transporter, GLUT4, to the plasma membrane as well as to block FA transport



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through FAT.[3] This metabolic fuel selection is further conditioned by upregulated glycolysis, induction of PK levels, and even more importantly, by activation of PDC.

PDC constitutes one of the main decision points in muscle fuel selection. PDC is inhibited by phosphorylation by pyruvate dehydrogenase kinases (PDK).[5] In muscle, PDK4 can be regulated acutely and in the long term. It is activated by the FA catabolites ATP, acetyl-CoA and nicotinamide adenine dinucleotide hydrogen (NADH), while pyruvate from glucose metabolism inhibits PDK4. Moreover, HGI diets regulate PDK4 expression through specific transcription factors. In a healthy individual with a LGI diet, and, therefore, low insulin levels, PDK4 amount increases, consequently inhibiting PDC and facilitating the use of FA as fuels. On the contrary, in a healthy individual, a HGI diet enhances insulinemia and lowers PDK4 synthesis. This translates to PDC activation, a preferential use of glucose as the main fuel, and an inhibition in the use of FA.

In a LGI diet, long-term regulation of PDK4 expression is controlled by several transcription factors that include forkhead box O1 (FOXO1) and peroxisome proliferator activated receptors (PPARs). PPARs are activated by FAs and a positive cycle promotes FA as energy source. The switch to a HGI diet blocks FOXO1 in the cytosol by insulin-mediated phosphorylation, and therefore at the nucleus PDK4 transcription is blocked. Furthermore, insulin increases glucose uptake through GLUT4 translocation to the plasma membrane and raises pyruvate levels that depress PDK4 activity, promoting glucose use. This long-term regulation is dependent on insulin-mediated AKT serine/threonine kinase (Akt) intracellular signaling, a key pathway affected by insulin resistance that leads to metabolic inflexibility.[6]

Albeit in the past, adipose tissue has been considered a fat storage organ, this tissue has far more complex metabolism. In a healthy individual, adipose tissue obtains its energy from FA, while glucose is mainly reserved to produce glycerol phosphate needed to re-esterify FA to TG. When the energy provided by the diet is high and the GI is also elevated, a channeling of glucose to TG takes place. The effects of high-energy intake or a HGI diet go beyond the increase in adipose mass. These diets can produce hyperplasia and hypertrophy of adipocytes that lead to inflammation, decrease in insulin sensitivity, increase in non-esterified FA (NEFAs), and altogether diminish muscle glucose uptake and use, as well as promote peripheral insulin resistance.

In a fasted state, adipose tissue mainly uses FA as metabolic fuel. FA from liver are used to provide energy, and the remainder undergoes a re-esterification process that is essential to prevent the generation of circulating NEFAs. Therefore, the control of this TG cycle is important for regulation of metabolic flexibility throughout the body. High fat, HGI diets can promote channeling of glucose to TG, first increasing glucose uptake through a stimulation of GLUT4. Nevertheless, if the situation persists, insulin insensitivity occurs, with a decreased response to beta-adrenergic stimuli and a failure to regulate circulating NEFAs.

The channeling of glucose to TG is also a long-term adaptive process where transcription of lipogenic genes is clearly enhanced. In this process a specific isoform of ChREBP, termed beta, is essential.[2] This isoform is active, permanently located at the nucleus, therefore making and amplifying the effects of a HGI diet in the adipose tissue. A LGI diet can modulate adipose tissue metabolic inflexibility by the activation of PPAR signaling that, together with beta-adrenergic signaling through mitogen-activated protein kinase (MAPK) or 5'-AMP-activated protein kinase (AMPK) pathways, stimulates PDK4 activity, decreases glucose to FA conversion and enhances NEFA esterification.[7] A LGI diet, combined with fiber, also promotes the browning of the adipose tissue, evidenced by the increase of uncoupling mitochondrial proteins (mainly UCP1), which would likely lead to higher basal metabolism.

In conclusion, humans have a program of metabolic adaptations to promote efficient storage and use of fuels that relies on hormonal and transcriptional regulation allowing long- and short-term control of metabolism. Furthermore,



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liver, muscle and adipose tissues crosstalk to finely promote homeostasis. HGI diets might induce long lasting changes in metabolism leading to metabolic inflexibility. These negative effects are enhanced when combined with high fat diets, diabetes or obesity. Current investigations highlight the utility of carefully designed mixtures of slow digesting carbohydrates and fiber for ameliorating metabolic alterations in different physio- and pathological situations.[8]

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# Phenotypic Flexibility as a Measure of Health Through the Life Cycle

Suzan Wopereis, PhD

A healthy diet, within an overall healthy lifestyle, may maintain or improve cardiometabolic health and help prevent chronic diseases. However, showing that a specific dietary product, dietary pattern, or even a positive change such as losing weight, has a beneficial effect on cardiometabolic health in the general population is not easy. A next generation of biomarkers is needed that reflects optimal health rather than disease. Based on a proposed improved definition of health,[1] in which health is regarded as the resilience of the body to deal with daily stressors, Netherlands Organisation for applied scientific research (TNO) established new methodology, including biomarkers, which relates to the body's ability to adapt as a measure for health, which is referred to as phenotypic flexibility. In the literature, several human nutrition intervention studies indicated the added value of evaluating phenotypic flexibility in showing health modulation.[2–5] However, there was a need for a generic holistic standardized challenge test that would be able to identify the early signs of individual homeostatic disturbances as well as assessing individual health benefits from nutrition, by showing an optimized response to the challenge test.

Based on an extensive literature review,[6] the so called PhenFlex challenge test was developed. The PhenFlex challenge consists of a 400 mL oral dietary formulation (60 g palm olein, 75 g glucose, and 20 g casein). The idea was to collect a multitude of biomarker response profiles, reflecting defined and accepted biological processes followed by sophisticated multivariate statistical analyses, to more powerfully detect early changes than the limited set of individual biomarkers that is used traditionally by evaluating single blood markers after an overnight fast (Fig 1). In the example of vascular health, such a composite biomarker could be composed of flow-mediated dilation, a functional marker of endothelial function and blood pressure, resilience markers for endothelial damage after a metabolic challenge test such as vascular cell adhesion molecule (VCAM), intercellular adhesion molecule (ICAM), and selectin E (SELE) responses, and total cholesterol or specific single nucleotide polymorphisms related to an increased risk for cardiometabolic disease development.[7] By combining this information into an integrated readout called "health space,"[8] a next generation flexibility marker for vascular health can be extrapolated.

To investigate if this phenotypic flexibility approach had potential, a number of human volunteer studies have been performed in patients with type 2 diabetes as well as in healthy individuals.[8,9] These studies showed that clear differences in individual health status could be determined in response to the PhenFlex challenge test. Lean younger active people processed the challenge test faster, and showed a better ability to adapt as compared to sedentary elderly. Furthermore, in the general population (age 30-60) it was shown that with increasing adiposity the individual's metabolic age increased, where subjects with high adiposity reacted similarly to the challenge test as compared to elderly subjects.[8] In addition, the PhenFlex response of patients with type 2 diabetes was clearly different from the healthy response.[9] These data indicate the ability of the PhenFlex challenge test to assess personal health.

As the PhenFlex challenge approach has been standardized it can now be used to scientifically demonstrate individual health effects and the effect of single food products on health. Following review of the relative contribution of each of the biomarkers in the initially broad panel in the previous studies, now a subset of biomarker responses can be used which are most important in measuring health in a certain domain of health or for a certain food product. Importantly, this indicates the possibility that recovery of homeostasis (eg, resilience) could be regarded as a new measure of individual health. In a first proof of concept case with whole grain wheat products, we showed a positive effect on



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resilience, as subjects' biomarkers moved toward the range of the younger group after 12 weeks of exchanging refined grains for whole grain wheat (Hoevenaars et al, submitted). Furthermore, the PhenFlex challenge test was able to discriminate between subjects that had a health benefit from 20% caloric restriction and those who did not (ie, responders vs non-responders). It appeared that only subjects with reduced phenotypic flexibility at baseline—indicated by multiple metabolites that showed a disturbed response to the PhenFlex challenge—could improve health, whereas subjects with already good flexibility, and therefore a good health status, could not further improve.[10] Finally, based on assessing flexibility in glucose metabolism by applying an oral glucose tolerance test (OGTT) in a cardiovascular patient population, we demonstrated that different insulin resistance (IR) subgroups could be distinguished (no IR, muscle IR, liver IR, or liver and muscle IR), and that these subgroups responded differently to two healthy diets. Patients with muscle IR benefit most from a Mediterranean diet, evidenced by increased beta-cell function (Disposition Index); patients with liver IR benefit most from a low fat diet; whereas, patients with combined liver and muscle IR benefit most from a Mediterranean diet, but to a lesser extent than patients with only muscle IR.[11] These data exemplify the potential for personalized nutrition.

**Future perspectives** It is envisioned that nutrition in the future will be personal. Nutrition intervention or dietary advice will be based on a diagnosis, by using personal health data including biological (eg, phenotypic flexibility) as well as behavioral measures. A science based model will be used to translate these data into personalized nutritional goals and foods. This model is then tailored to specific personal preferences and goals, to gain better adherence to diet. In addition, in the near future, information from large numbers of personal health databases will be available, which can be used to link diet, lifestyle and environment with health outcomes to fine-tune personalized lifestyle advice. Regular or even daily data from people will be available, which reflect long-term phenotypic flexibility; this has already been demonstrated by Snyder and colleagues.[12] Therefore, phenotypic flexibility may be a future standard measure of health through the life cycle. It is possible that a digital life companion will provide people with personalized lifestyle advice throughout life; starting even before conception, updated with the latest scientific evidence, tailored to your preferences, goals, culture, social and economic environment, thereby preventing even the developing fetus from chronic lifestyle related diseases.

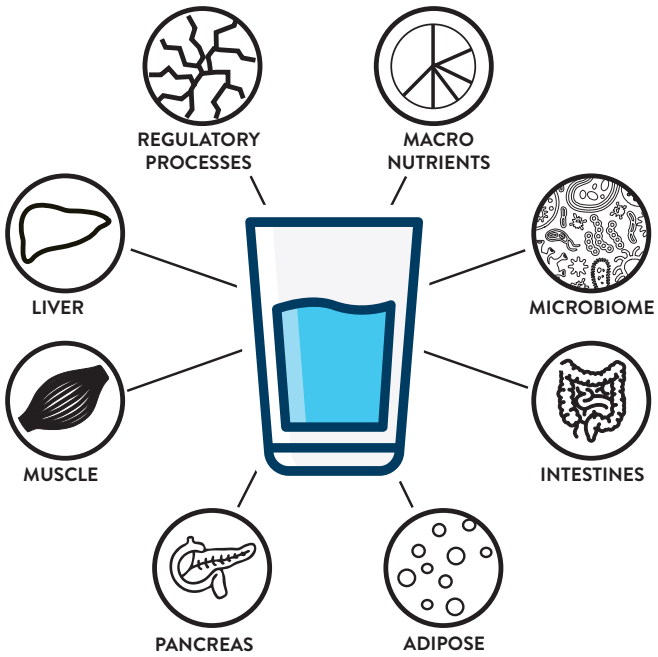


**Fig 1. The PhenFlex challenge test.**
The PhenFlex challenge test aspires to be a holistic standardized test that can measure health-related biological processes from key tissues and organs in the body impacted by nutrition and lifestyle.



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# Carbohydrates, Mood and Cognition

Prof David Benton, PhD, DSc

**The brain:** The brain is the command center of the body, yet it lacks the ability of other organs to run on a range of fuels, and has only limited energy reserves. The brain is about two percent of body weight, and has been calculated to have about 86 billion neurons that consume 20% to 25% of basal metabolic rate, resulting in the consumption of 120 grams of glucose a day. The brain runs primarily on glucose, a source of energy that needs to be continually replenished as stores will be exhausted in five to ten minutes. A graphic illustration is offered by the occasions when patients with diabetes inject themselves with too much insulin and blood glucose falls to low values. Rapidly the brain, starved of glucose, is unable to function normally; vision may be blurred, speech slurred and cognitive functioning is generally disrupted. In the 1940s and 1950s insulin was used to starve the brain of glucose to induce a coma, in the belief it was a treatment for psychiatric disorders, in particular schizophrenia. As such, the level of glucose in the blood, largely a reflection of short and longer-term responses to carbohydrate consumption, plays an important role in neural functioning. Does carbohydrate consumption therefore influence how we think and feel? Do the effects of aging and dementia reflect changes in glucose metabolism and is carbohydrate supplementation beneficial?

**Carbohydrate consumption:** In fasted young and older adults, simply giving a drink containing glucose has been found to improve episodic memory.[1] Episodic memory is the recall of events associated with time, place and context, and contrasts with semantic memory that reflects factual information that lacks context. It is episodic memory that is particularly disrupted in dementia. Although various aspects of cognition have been studied, and on occasions a benefit from a sugary drink reported, the overwhelming impression is memory and mood improve most consistently.

**Glucose tolerance:** Glucose tolerance is an indication of how well, after the ingestion of carbohydrate, the body absorbs glucose from the blood. In those with good tolerance, after a meal blood glucose peaks after about half an hour, and returns to baseline values after about two hours. If levels initially rise to higher values, and stay at higher values for a longer period, this is described as impaired glucose tolerance or prediabetes. If the levels stay raised for even longer, then diabetes may be the reason. There are many reports that those with better glucose tolerance have a better memory. This phenomenon is found even in healthy young adults, where glucose tolerance is in the normal accepted range.[2] As we age, glucose tolerance tends to become impaired, and those with poorer glucose tolerance have a poorer memory.[3]

**Glycemic load:** If the pattern of changes in blood glucose level after a meal is associated with better memory, can foods enhance memory? Depending on the amount and type of the carbohydrate, foods differ in the extent to which they increase blood glucose levels. We often do not eat a single food, but rather several items that cumulatively produce the glycemic load (GL), the overall impact on blood glucose. There is increasing evidence that meals with a lower GL are beneficial, wherein blood glucose rises more slowly and

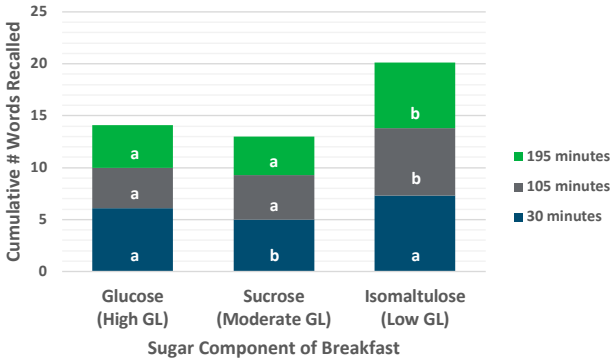


**Fig 1. The influence of type of meal on memory.**[3]
Groups with different letters show significant differences (P<0.03)
GL=glycemic load



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is released over a longer period. For example, a study of identical breakfasts, that varied only in the sugar chosen as a sweetener and hence differed in GL, reported that children at the end of the morning had better memories and mood after a low glycemic meal.[4] In older adults, without diabetes, it has been found that the memory and mood of those with good glucose tolerance were better after eating a meal with a low rather than high GL (Fig 1).[3] However, this effect was not observed in those with poorer glucose tolerance, albeit they did not have diabetes.

**Children – a high risk group?:** In children, basal metabolic rate, per unit of body mass, is higher than adults; in fact, from infancy to adulthood it declines to less than half its initial value. More specifically, a given amount of a child's brain tissue uses twice as much energy as a similar amount from an adult.[5] As such, we must consider whether children are particularly susceptible to the level of blood glucose and hence the consumption of carbohydrate. A study in the afternoon gave 9 to 10-year old children, on different days, a glucose-containing drink or a placebo.[6] On the days they received the glucose drink, they spent more time on task attending to their school work and had a better memory. Such a finding may be familiar to parents that find that the bad temper and poor attitude of their child can change for the better when the child has eaten at the end of the school day. Giving foods that slowly release glucose is likely a better choice over a sugary drink. Given the high metabolic requirements of children, a working hypothesis is that children need to regularly maintain blood glucose levels by consuming carbohydrate. The worry is that the advice to eat little and often, can become too much and too often, resulting in early obesity.

**Blood glucose and dementia:** Older adults are another high risk group, and may be more susceptible to the effect of blood glucose levels. Lower rates of brain glycolysis (glucose metabolism) are associated with the severity of the brain changes that are characteristic of Alzheimer's disease with its associated problems of memory.[7] As the hippocampus is the brain area responsible for memory, an interesting finding is that those, who some years before had higher levels of blood glucose, some years later had a greater reduction in the volume of this brain area.[8] Similarly, those who years before had higher levels of blood glucose, at post mortem had higher levels of brain glucose, that in turn were associated with the severity of dementia.[9] Although at present these relationships are only correlations, the question arises as to whether high levels of blood glucose, and hence carbohydrate consumption, predispose to dementia? In fact, persons with type 2 diabetes have a 60% greater chance of developing dementia, and some even call dementia "type 3 diabetes."[7]

**What dietary advice should we give?:** The association between high levels of blood glucose and the later development of dementia led to widespread media coverage with headlines such as "Sugar causes Alzheimer's disease." The more accurate but less sensational headline should have been "High blood glucose is associated with Alzheimer's disease." Similarly, throughout the lifespan, a low GL meal has been found to benefit mood and memory. Thus, the advice is to consume a low GL meal with a selection of low glycemic index (GI) foods to help maintain a healthy blood glucose level. The GI involves ranking foods on a scale from 0 to 100 according to the extent to which blood glucose increases after eating. A drink of pure glucose has a GI score of 100.

We need to shift our focus from sucrose as the major problem contributing to impaired glucose tolerance and high blood glucose levels. Sucrose is a disaccharide, that is only half glucose, with a moderate GI of 65. There are many more problematic foods with higher GI scores, eg, cornflakes, white bread, and baked potato. Adding fiber, protein and fat to a meal will help reduce the meal GL and slow the glycemic response.[10]



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# Closing Keynote:

***Snacking and Energy Balance***

Richard D. Mattes, MPH, PhD, RD



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# Snacking and Energy Balance

Richard D. Mattes, MPH, PhD, RD

The high prevalence and severe consequences of overweight and obesity are now well established. The less well-understood issue is what is driving this energy imbalance. Though some have argued decreased physical activity is largely responsible, findings from the gold standard method to measure energy expenditure—doubly-labeled water—clearly indicate this is not the case. There has been no substantive change of energy expenditure over the past forty years, and absolute expenditure matches predictions based on cross-species analyses.[1] The decreased expenditure due to lower physical activity is offset by the increased energy required to support the increasing fat mass. Thus, attention is focused on energy intake. Intake is determined by how much energy is consumed in each eating event and how frequently eating occurs. Theoretically, there is reciprocity between the two actions so that it is possible to eat large portions infrequently or small portions frequently, and maintain body weight equally well under each scenario. However, the rising prevalence of overweight/obesity documents that such reciprocity is not precise. Much attention has centered on increasing portion sizes and insensitivity and/or disregard for physiological cues to moderate intake. Considerable evidence supports this view. However, the role of increased eating frequency has not received comparable consideration and may be the larger problem.[2] Snacking is not synonymous with eating frequency as meals may be skipped, but it is a very close proxy. This review will focus on the health effects of snacking.

The first issue related to the study of snacking is to define the term. This has proven to be highly problematic. Common definitions are based on when an eating event occurs (eg, mid-morning, mid-afternoon, evening), type of food consumed (eg, salty and sweet single-serve convenience items), energy content (eg, researcher defined-fixed amount, less than a meal), some combination of these, or consumer defined (eg, consumer identifies an eating event as a "snack"). The latter is used most commonly in epidemiological studies. No definition is both tightly defined and ecologically valid. Snacks can provide more energy than meals (also not well defined), occur at any time of day and at any interval relative to "meals," and may be comprised of any type of food. So, clinical interventionists tend to define snacks by energy content and timing of consumption with known questionable ecological validity while epidemiologists base decisions on consumer self-report, with poor precision as a consequence. Nevertheless, there is unequivocal evidence that by any definition, the prevalence of snack and eating frequency has been increasing. It is now estimated that there is a mean of approximately 2.25 snacking events per day per person in the US population.[3]

The energy contributed by snacks is less well characterized. National Health and Nutrition Examination Survey (NHANES) data indicate snacks contribute approximately 600 kcal/d for males and 450 kcal/d for females, and the trend dating back to the 1971-1974 survey is steadily increasing for both sexes. Indeed, the increment in snacking energy has outpaced the energy contributed by meals (Fig 1).[3] So, in summary, snacking is prevalent, increasing in frequency and accounts for approximately 20-25% of daily energy intake.

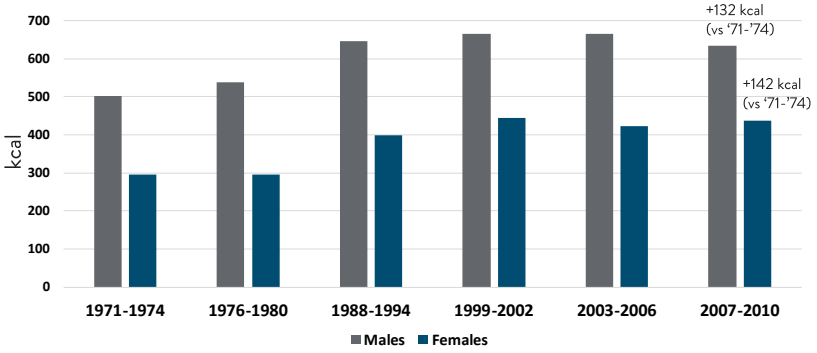


**Fig 1. Trends in snack energy intake among US adults. National Health and Nutrition Examination Survey (NHANES) data.[3]**
NHANES energy from snacks (among all population average; 1971-2010, Ptrend all <0.0001)



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Given this high contribution of energy, it would be expected that snacking would be clearly associated with weight gain and overweight/obesity. There are data demonstrating this,[4] but NHANES data are equivocal. How can this be reconciled? Under-reporting is a well-known shortcoming of collecting dietary intake data in free-living individuals. In NHANES data, the lack of association between snacking and body weight reported with the full sample shifts to a strong positive association when implausible reporters are excluded.[5] This holds for males and females across the life cycle. The clinical trials are similarly not straight-forward. However, in a recent narrative review, it was noted that in 16 of the 18 published clinical trials, the study duration was less than or equal to only 8 weeks.[6] This is an inadequate timeframe to measure body weight as an outcome. Additionally, in randomized clinical trials exploring the association between eating frequency and appetite, none had a sample size greater than 20 and for 9/12 trials, the duration was less than one day.[6] For an outcome of known high variability (appetite), this again is an inadequate basis to draw conclusions. So, in summary, the epidemiologic evidence supports an association between eating frequency and body weight when plausible reports are assessed and the clinical literature is not sufficiently robust to evaluate this association.

A full understanding of the contribution of snacking to health requires identification of mechanisms that could account for such a relationship. A large number of options have been tested. First, it is uncontested that the food industry has made the food supply highly palatable, convenient, reasonably priced and readily available. Moreover, social norms have shifted making it acceptable to eat in diverse locations and at almost any time of day. Thus, snacking has been enabled. Second, snacks may paradoxically augment hunger. Eating small amounts in the absence of hunger can increase the conscious desire to eat for any number of reasons (eg, boredom, sensory stimulation) and the generally smaller energy load of snacks fails to exert a strong effect on hunger. Third, the timing of snacks leads to short-term shifts in appetite that are no longer relevant when planned eating events occur.[7] Thus, snacks tend to add to the energy content of the diet rather than displace other energy sources (eg, smaller meals). Fourth, it is possible that by increasing eating frequency through snacking, the normal endocrine signaling systems that modulate intake are desensitized.[8] That is, they fail to show clear increases and decreases and this flux may be the functional dimension of the signaling system. Some have argued that snacking later in the evening is especially problematic for weight gain, but this has not proven robust. If this were the case, one might expect European nations with a cuisine that entails late night eating (eg, Spain) should have the highest prevalence of overweight/obesity, but this is not the case.[9] Fifth, though the literature is mixed, multiple trials have demonstrated that eating fewer times per day is associated with reduced postprandial thermogenesis (energy dissipation as heat). Thus, more energy is available for storage. This is especially true with irregular eating patterns.[10]

Snacks do not necessarily result in positive energy balance and weight gain. Some are energy neutral. Nuts are a good example. Because they are highly satiating, their energy is not efficiently extracted and they may lead to elevated energy expenditure when consumed chronically. The literature shows nuts can be incorporated in a healthful diet without posing a risk for weight gain.[11] Other foods may behave similarly, but this must be documented.

Having argued snacks pose a threat for weight gain and increased health risk, it should be acknowledged that sub-groups of the population (eg, patients with cancer, some elderly) would benefit from this outcome. For these individuals, snacks comprised largely of beverages are likely to be the most effective and they lead to the weakest compensatory response. High protein foods may hold some greater satiety value than the other macronutrients, but the differences between them are small and of short duration.

The issue of snacking and energy balance aside, snacks may present opportunities to improve nutrient intake and overall health. The nutrient density and effects on other outcomes such as postprandial glycemia or lipemia should be evaluated before judging the impact of snacks on health.



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