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AUTISM

## Autism! Back to School Updates

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### A CURRENT UNDERSTANDING OF AUTISM

The story of autism spectrum disorders (ASD) is unique compared to other disorders in that few have seen such an unexplained increase over time, strain on personal and health care resources, rise of social activism and advocacy organizations, and controversial treatment approaches. First reported in 1943, autism poses particular challenges for researchers given the numerous potential contributing factors. Although treatable, it is considered an incurable, multifactorial disorder that is influenced by genetic, neurological, environmental, and immunological aspects.[1] That being said, recent developments have helped create a better understanding of the heterogeneity of ASD and its variable phenotypes.[2]

Autism itself is a biologically based disorder of brain development. This neurodevelopmental disorder is characterized by variable degrees of social and language deficits. Children with ASD demonstrate stereotypically restricted and repetitive behavior. Variants of ASD include conditions such as pervasive developmental delay (PDD) and Asperger disorder (AD). A 2012 Centers for Disease Control and Prevention (CDC) report estimates that of all autism diagnoses in the United States, 47% were PDD and 9% were AD.[3] Comorbid conditions — such as ADHD on the other hand — are separate but appear to have a higher prevalence in ASD.

The incidence of ASD has increased 10-fold in the last 25 years. In 1990, the estimated prevalence was 5 per 10,000 children. A report published by the U.S. Department of Health and Human Services indicates that among children aged 6-17, prevalence of autism increased from 1.16% in 2007 to 2.00% in 2012,[4] although the CDC estimates that one in 110 children now born in the United States has ASD.[5]

Although there is controversy regarding the various factors that may contribute to ASD prevalence and severity, perhaps the most frustrating aspect of ASD for both parents and health care professionals is that its cause(s) remain unknown. That being said, most experts agree that ASD is a genetically predisposed

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disorder that seems to require an inciting environmental trigger (or triggers). For most cases of ASD, no single gene or group of genes has been definitively shown to significantly impact its development. However, there is a 90% concordance between identical twins vs 30% in fraternal twins.[6]

The pathophysiology of autism is — without surprise — not well understood. A genetic cause can be identified in only 20% of ASD cases, involving genes that converge on common pathways that alter synaptic homeostasis.[7] There is good evidence to support the understanding that autism is characterized by inflammatory and abnormal neural connections, particularly underconnectivity of cortical systems leading to abnormal interhemispheric communication. With corroborating advanced imaging from fMRI, this abnormal brain function correlates well with many of the stereotypical behaviors seen in ASD.[8]

## DYSFUNCTIONAL GUT

One of the most widely debated aspects of ASD is gastrointestinal (GI) dysregulation — specifically conditions known as dysbiosis and increased intestinal permeability. However, the exact cause for increased prevalence of GI abnormalities in ASD is unknown. Up to one-third of children with autism exhibit some form of GI disorder clinically (e.g., constipation, abdominal pain, diarrhea, gastroesophageal reflux disease). The human gut is home to a dynamic and complex community of microbes that can profoundly influence nervous system growth and development.[9] Many of the behavioral challenges associated with autism likely can be explained by gut dysfunction, noting that many autistic children have communication barriers and have challenges expressing their discomfort.

One study found that ASD children treated with vancomycin saw an improvement in both abnormal gut bacteria and GI symptoms, while also seeing improvements in autistic behavior.[10] Lactulose-mannitol testing reveals that the majority of these children exhibit abnormal intestinal permeability, which is thought to indicate atrophy of the intestinal mucosa and injury to intercellular junctions. This altered intestinal permeability is thought to allow absorption of incompletely digested peptides that behave as receptor agonists leading to abnormal brain-gut neuroactivity that result in behavior changes.[11]

Along these lines, duodenal biopsies from 25 autistic children show increased lymphocytic proliferation and other immune abnormalities, indicating a possible autoimmune etiology.[12] A separate study of 36 autistic children reported significantly higher levels of IgG, IgM, and IgA to food proteins such as casein and lactoglobulin compared to controls.[13] An autoimmune etiology in ASD is supported by an epidemiological study showing that families affected by autism had 1.87 relatives with autoimmune disorders, which is significantly more common when compared to the general population, and surprisingly even more common than families affected by other common autoimmune diseases such as lupus and rheumatoid arthritis.[14] Another study even found that 36.7% of autistic patients and 21.2% of their direct relatives demonstrated active "leaky gut" syndrome as compared to 5% of controls.[15] These findings suggest an inheritable predisposition for ASD that, when triggered by environmental events, may play a key role in prevalence and severity.

## GLUTEN-FREE/CASEIN-FREE DIET

The majority of published studies show a statistically significant benefit of a gluten-free/casein-free (GFCF) diet in ASD. However, specific characteristics of best and non-responders to GFCF intervention have not yet been elucidated. That some children benefit from this dietary intervention and others do not is likely due to variable ASD phenotypes.[16] One striking case report in the literature reported significant benefits in a child with severe ASD, morbid obesity, and epilepsy, who after limited response to other interventions, was placed on a GFCF-ketogenic diet that used medium-chained triglycerides and a high intake of vegetables. Over the course of a few years, the child's Autism Rating Score

## Summary Points

- Autism is a biologically based disorder of brain development characterized by variable degrees of social and language deficits with stereotypically restricted and repetitive behavior.
- Autism spectrum disorder is considered an incurable, multifactorial disorder that is influenced by genetic, neurological, environmental, and immunological aspects.
- Autism is a treatable condition that starts with early diagnosis and initiation of early intensive behavioral intervention.

went from severe to non-autistic, her intelligence quotient increased 70 points, and she became seizure-free with normal follow-up EEGs.[17] Needless to say, in keeping with the favorable benefit-harm ratio, it is entirely reasonable for families affected by ASD to implement a GFCF diet.

In addition, many studies demonstrate the need to supplement the diet of autistic patients with omega-3 fatty acids, probiotics, vitamins, and minerals in combination with other medical and psychological interventions.[18] However, good data showing conclusive clinical benefit of these additions largely are lacking and there have been calls to investigate the likely beneficial role of probiotics in ASD.[19]

### MERCURY AND ENVIRONMENTAL TOXINS

Another popular ASD suspect is thimerisol (ethylmercury), which was previously contained in childhood vaccinations. This, perhaps more than any other aspect of the autism story, has been hotly debated. A review by the FDA found that prior to 1999, the additive sum of childhood vaccinations exceeded EPA limits for safe exposure of methylmercury. Although epidemiological studies have failed to find a connection between the small amounts of mercury in vaccines and incidence of ASD,[20] one study demonstrated a 61% associated increase in the rate of autism incidence for every 1000 pounds of mercury released from industrial pollution.[21]

There is ongoing concern about the growing chemical milieu that children are exposed to early in life. A well-known source of mercury exposure comes from amalgam fillings. However, whether there are any adverse health effects from this remains a subject of debate.[22] While mercury is a well-known neurotoxin with no acceptable level of exposure, it is unproven as a significant cause of autism by itself. However, mercury may just be the tip of the iceberg. Children today are exposed to thousands of synthetic chemicals, with at least 200 being known neurotoxins and another 1000 demonstrating neurotoxicity in laboratory tests. According to the CDC's biomonitoring program, there are more than 100,000 chemicals commonly used every day in household cleaners, solvents, pesticides, food additives, lawn care, and other products. Every year another 1000 chemicals are introduced that do not take into account the mixtures and various combinations of commercial and consumer products to which people are exposed.[23]

Another alarming study found nearly 300 environmental toxins in the umbilical blood of neonates.[24] Animal models show that even low levels of these toxins can negatively affect neurodevelopment. Indirect human evidence points to the sensitivity of the developing brain to lead, mercury, and other toxins. The strongest proof-of-concept evidence comes from research linking ASD to various chemical exposures in early pregnancy.[25] Given this information, it is reasonable for parents and practitioners alike to follow the precautionary principle that states, "When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically."[26]

That being said, it has been postulated that previously undetected inherited metabolic defects predispose those who would eventually be diagnosed with ASD due to impaired detoxification systems that are not adequately able to handle the same low level of toxic exposure as normally developing children. For example, in a study of more than 200 autistic children treated with the chelating agent DMSA, urinary levels of mercury were significantly higher compared to neuro-typical controls.[27] Additional studies lend support to the hypothesis that even though children with autism and neuro-typical children both have similar exposures,[28] those with ASD exhibit abnormal urinary porphyrin levels, which indicates abnormal mercury metabolism and elimination.[29]

Although children with ASD may be susceptible to even "normal" levels of mercury exposure, and although there are some data showing increased urinary output of toxic metals with use of chelating agents,[30] evidence showing clinically beneficial outcomes from the use of chelating agents such as EDTA and DMSA is lacking.[31] What's more, NIH-funded trials were halted prematurely due to ethical concerns.[32] However, there are reasonable lifestyle approaches to help reduce toxic body burden for

would-be-mothers and families with young children (see EWG link in resources).

### TO VACCINATE OR NOT TO VACCINATE: THE CASE OF MMR

The MMR vaccine has been implicated by many parents as a triggering event for autism. Although there were early concerns, no link between the MMR vaccination and autism has been found.[33] In fact, a recent study found that children with ASD have similar levels of antibodies against the MMR vaccine as same-age neuro-typical controls.[34] An infamous study published in the *Lancet* in 1998 that suggested a link in ASD with colitis and MMR vaccination[35] was retracted in 2010 by the journal due to serious irregularities.[36] An 8-year U.S. federal court process that finally ended in 2010 concluded that ASD was not caused by an adverse reaction to vaccination.[37] To the contrary, it is now estimated that MMR vaccinations administered in the United States from 2001-2010 helped prevent more than 16,000 cases of congenital rubella syndrome — a known cause of ASD — which in turn helped prevent more than 6000 new cases of ASD during that 10-year period.[38]

Study retractions and court rulings have hardly transformed the thinking of many antivaccine advocacy groups. A recent CNN story reported that measles infections, once considered eradicated in the United States, have increased.[39] For example, another story by NPR reported that 21 vaccine-skeptical parishioners of a North Texas Church who had not been adequately immunized with MMR were infected in a measles outbreak.[40] For reference, it is estimated that 1 of 1000 children ultimately die from measles infections, even with the best of care.[39] As a result, there have been calls to set aside philosophical quarrels and instead respond with empathy and open family-centered dialogue to address misinformation and concerns about vaccinations.[41]

Alternative childhood immunization schedules (ACIS) are one approach for families that refuse standard CDC vaccine schedules. Despite controversy of a well-known ACIS (the Sears alternative vaccine schedule[42]), a recent survey of 517 families in Washington found that this approach did not predominate, with only 9.4% of parents reporting use of ACIS.[43] The real advantage of offering ACIS to concerned parents is not about efficacy or promoting a "better or worse" vaccination schedule, but rather in establishing a trusting relationship while ensuring eventual full immunization and protection for children.

### BEHAVIORAL AND SPEECH THERAPIES FOR ASD

Although the cause(s) of autism are unknown, there are reasonable and effective treatments for ASD. The most common, and arguably the most effective approaches address behavioral, communication, and social deficits. Early screening during routine well-child exams can identify signs of ASD, which in turn should lead to initiation of speech-language therapy (see NICHCY link in resources). Effective services should vary with individual children, depending on the child's age, cognitive level, language skills, behavioral needs, and family priorities. With some children, it is appropriate to incorporate augmentative and alternative communication (AAC), such as the Picture Exchange Communication System, other high- and low-tech assistive technology tools, and/or sign language. A meta-analysis of single-case research studies indicates strong effects for the use of AAC on communication skills. Although effect sizes should be interpreted cautiously due to the small number of studies, social skills, challenging behaviors, and spelling also appear to be positively affected.[44]

Although behavioral intervention methods appear to have a positive impact on learning, communication, and behavior in children with ASD, intervention studies suffer from methodological problems that make it difficult to form definitive conclusions regarding efficacy. That being said, there is evidence to support the use of applied behavioral analysis for functional skills development, and there are

#### Autism Resources

- University of Wisconsin Integrative Medicine autism module for clinicians and families: www.fammed.wisc.edu/integrative/modules/autism-spectrum-disorders
- Talk about Curing Autism: www.TACAnow.org
- Autism Research Institute: www.autism.com
- UC Davis Mind Institute: www.ucdmc.ucdavis.edu/mindinstitute
- Sears Alternative Vaccine Schedule: http://childrenshealthchoices.org/schedules.html
- Gluten-free/Casein-free Diet: www.tacanow.org/tag/gfcf
- M-CHAT early clinical childhood screening tool: www.firstsigns.org/screening/tools/rec.htm#asd_screens
- Environmental Working Group resources for lowering toxic body burden: www.ewg.org
- Early intervention behavioral therapy resources: http://nichcy.org
- Current ASHA research reviews of most treatment options: www.ncepmaps.org/Autism-Spectrum-Disorders-Evidence-Map.php

## Treatment Suggestions for Autism

- Gluten-free/casein-free diet trial is low risk and has evidence to support its use.
- Reasonable body burden reduction strategies can be considered.
- In addition to a healthy anti-inflammatory diet, a sensible approach to supplements includes a good daily multivitamin with minerals, omega-3 fatty acids, vitamin D, and a probiotic.
- For families that refuse the standard CDC vaccination schedule, it is reasonable to offer alternative vaccine schedules with the aim of strengthening the family-physician relationship and ensuring eventual full immunization protection.
- When making a decision about which therapies to implement, the family should consider what is best for their child, what is available in the community, what are the monetary costs, and what life/work and scheduling changes will be needed.
- An experienced multidisciplinary team should provide a formal evaluation of social behavior, language and nonverbal communication, adaptive behavior, motor skills, atypical behaviors, and cognitive status.
- Follow-up diagnostic and educational assessments should be performed every 1-2 years.

clear benefits of Lovaas therapy compared to no treatment. Furthermore, increased therapy intensity is known to be more effective than no- or low-intensity therapy. The National Research Council suggests that young children with ASD should receive at least 25 hours of individualized and structured intervention per week, 12 months a year.[45] In general though, as no definitive behavioral or developmental intervention improves all symptoms for every child, it is recommended that therapy management be guided by each child's needs and availability of resources.[46]

Other common and effective behavioral therapies include Greenspan's Floortime and Developmental Individual Difference Relationship Model, which incorporates play activities with an emphasis on emotional development. Relationship Development Intervention is a parent-based treatment approach that works to improve social skills, adaptability, and self-awareness skills. Social Communication/ Emotional Regulation/Transactional Support uses practices from a variety of other approaches in order to promote child-initiated communication and skills in a variety of settings.

Although there are anecdotal reports of benefits from sensory motor interventions, such as sensory integration therapy or use of a sensory diet, results are limited and inconsistent. A review of auditory integration therapy by the American Speech-Language and Hearing Association concluded that efficacy standards for use by audiologists and speech-language pathologists are not yet available. At this time, families should pursue these therapies with some skepticism until further research can be conducted.[47] ■


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**OBESITY**

# Artificial Sweeteners and High-fructose Corn Syrup: Effects on Diabetes and Weight

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Americans are addicted to sugar. The U.S. Department of Agriculture estimates consumption of sugars and sweeteners to be 150 pounds per year per person. There are more processed food and beverage choices than ever, and many of them contain processed sweeteners such as high fructose corn syrup or artificial sweeteners. In addition, rates of obesity and type 2 diabetes are at epidemic levels in the United States. The concern is that consumption of these fake sugars may be to blame for weight gain and increased rates of type 2 diabetes. There are convincing mechanisms to support this as a feasible hypothesis, but the evidence is inconclusive based on the research studies completed to date.

In 2003-2004, Americans consumed an estimated 585 grams (20.6 ounces) of beverages with added sugar and 381 grams (13.4 ounces) of food with added sugar per day.[1] At the same time, sugar substitutes have become a staple in the American diet. Artificial sweeteners have been around since the 1800s, with saccharin being the first synthesized in 1879.[2] High-fructose corn syrup (HFCS) was discovered in 1957, and in recent years it has become a cheaper substitute for sugar in a variety of

## Summary Points

- Artificial sweeteners have been engineered to be hundreds to thousands times sweeter than table sugar, which allows small amounts to be used in food and drinks and allows them to be low calorie and sugar-free.
- High fructose corn syrup alters the effects of leptin and ghrelin, which decrease satiety and lead to increased food intake that can cause weight gain.
- Studies suggest that sugar-sweetened beverages and artificial sweeteners both can contribute to the development of type 2 diabetes, but more studies are needed to confirm that there is a more direct relationship.

beverages and food products. Artificial sweeteners were developed to provide sugar-free alternatives for those needing less sugar in their diets or those trying to lose weight; use has risen over the last 30 years.[1] However, many questions linger. What are the risks of these manmade substances used in place of sugar? Is it a coincidence that there is more obesity and diabetes as these products have gained popularity? Is moderation the key and has consumption of these substances become excessive? This article will try to answer some of these questions and provide guidance for talking to patients about artificial sweeteners.

### HIGH-FRUCTOSE CORN SYRUP

HFCS represents 40% of sweeteners added to food in the United States.[3] In 1957, Marshall and Kooi published a paper about the synthesis of fructose from glucose.[4] Their process was not conducive to mass production so it was not adopted at that time. Between 1965-1970, a Japanese scientist developed a way to commercially manufacture fructose. In the United States between 1975 and 1985, sucrose use in processed foods and soft drinks started, because the cost of importing sugar (also known as sucrose) became more expensive. HFCS became a cheaper, sweeter, sweetening alternative, as well as a way for the United States to make use of an overproduction of corn. The U.S. government saw this as an opportunity to subsidize its use.

Fructose does not require insulin to enter the cells. It is primarily taken up by the liver to become glucose, glycogen, and acetyl CoA, which becomes triglycerides. HFCS is a fructose made from corn starch. The corn starch becomes a syrup that is mixed with enzymes to change glucose to fructose. By chromatography HFCS is 42% fructose, but commercially used HCFS is 55% fructose so its sweetness is equivalent to sugar in taste and sweetness. This preparation also has fewer calories than sugar.[5] The syrup is a mixture of HFCS 55, which is 55% fructose, 40% glucose, and 5% higher saccharide. Crystalline fructose and HFCS, which are two different forms of fructose, have similar effects on blood glucose levels, but HFCS causes more dramatic increases in blood glucose as compared to crystalline fructose.[6]

Some argue that there is no difference between fructose and HFCS. Fructose is a naturally occurring monosaccharide found in fruit. So what is the difference between fructose and HFCS? HFCS is consumed in higher concentrations and in liquid, so it is absorbed more readily into the bloodstream, whereas the fructose in a piece of fruit is mixed with fiber at a lower concentration, thus leading to a slower absorption. Another point to consider is that HFCS has been engineered to have a higher concentration of fructose than the concentration of fructose in sucrose when the same amount of sweetener is used in food.[5] The higher fructose load from HFCS may lead to high triglycerides with recurrent exposure as explained below. The connection between HFCS and pancreatic insulin secretion or insulin resistance is complicated, though the consumption of HFCS has not itself been directly linked to the development of diabetes.

Fructose enters the glycolytic pathway through fructose-1-phosphate, which bypasses the rate-controlling step of glycolysis (*see Figure 1*). This leads to unregulated amounts of lipogenic substrates and increased triglycerides.[7] Postprandial hypertriglyceridemia is promoted by fructose-containing foods. This has been shown to occur within 24 hours of fructose consumption, but effects on de novo lipogenesis and whether triglyceride levels remain high with prolonged consumption of HFCS are not known.[3] The effect of fructose vs a high glucose diet was studied, and by day 42 of the trial elevated low density lipoprotein cholesterol (LDL) disappeared in subjects receiving fructose.[5] In this same study, fasting triglycerides were elevated in males but not in females in the fructose group.[5] Another study comparing groups consuming fructose, sucrose (half glucose and half fructose), and glucose found that LDL cholesterol was elevated in the fructose and sucrose groups but not in the glucose group.[8] Postprandial triacylglycerol levels were comparable in HFCS, sucrose, and 100% fructose, all of which are fructose-containing substances.[7]

Fructose can cause weight gain because it does not stimulate insulin secretion or leptin production in the adipose tissue. Stanhope and Havel demonstrated that fructose-sweetened beverage consumption led to lowered circulating concentrations of leptin, insulin, and glucose. The decreased circulating leptin levels led to less postprandial suppression of ghrelin.[7,9] Ghrelin is orexigenic, which means that it promotes appetite. Secretion of ghrelin occurs in a pulsatile manner, where it is highest before eating and then decreases with food intake.[10] Insulin, leptin, and ghrelin signal to the central nervous system to provide signals of satiety. This means that the effects of fructose on ghrelin through the suppression of leptin can lead to a lack of satiety and increased caloric intake. Increased caloric intake can lead to weight gain and obesity (*see Figure 2*).

The relationship between the development of diabetes and fructose or high fructose consumption is not well established. One study showed that hepatic insulin sensitivity decreased with small amounts of daily fructose consumption.[8] This may indicate that there is a relationship to insulin resistance and fructose that could potentially lead to the development of type 2 diabetes. It is well known that weight gain and insulin resistance are risk factors for the development of diabetes. So it appears that between the effects of fructose on ghrelin and its influence on weight gain and the effects of fructose on insulin resistance that fructose may contribute to the development of type 2 diabetes.

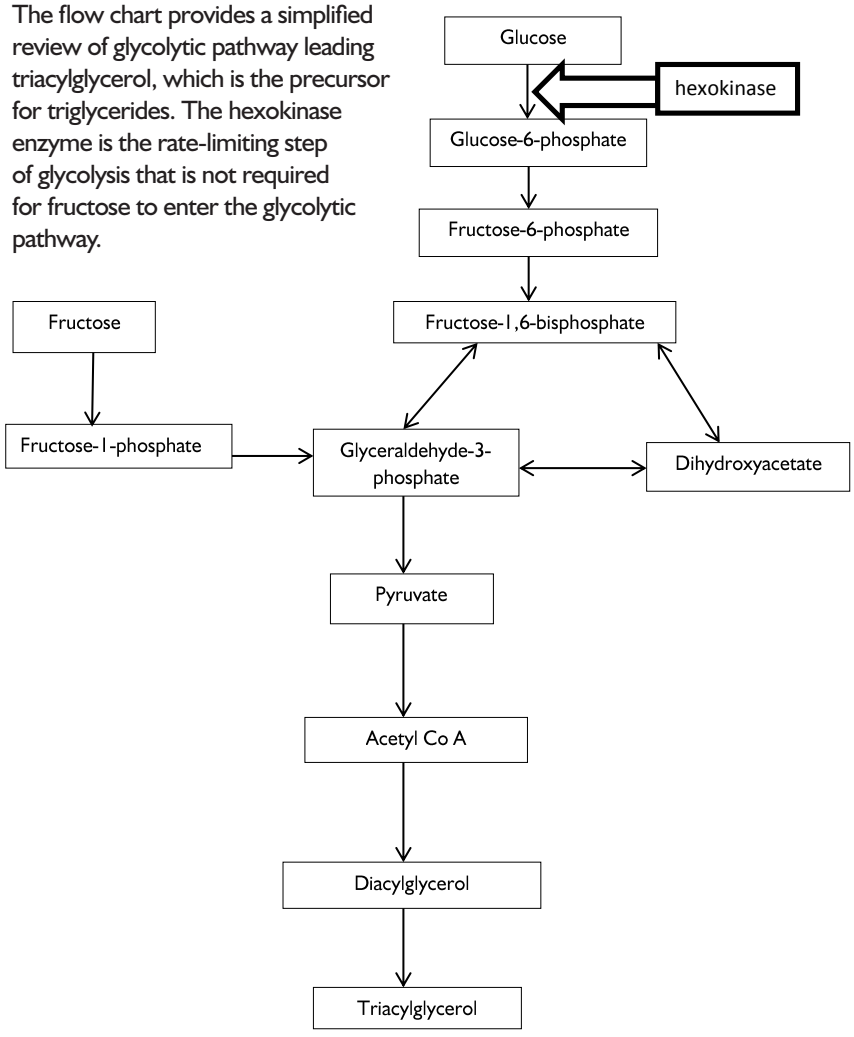
## ARTIFICIAL SWEETENERS

Americans are eating more sugar than ever, especially added sugar in sweetened beverages. A way to decrease this consumption has been to consume non-nutritive sweetened beverages. There are multiple different formulations of artificial sweeteners with new ones being approved in recent years. Aspartame was the first to be approved by the FDA in 1981. Other approved non-nutritive sweeteners include saccharin, sucralose, acesulfame K, and neotame. Each of these artificial sweeteners is much sweeter than table sugar (*see Table*).

One thing that most artificial sweeteners have in common is that they were accidental discoveries, later being approved by the FDA. Saccharin was discovered in 1879 when Constantin Fahlberg was analyzing components of coal tar. He went to dinner one night and picked up a roll to find that it was very sweet. Earlier in the day he had spilled his experiment on his hands. He went back to the lab to find the substance.[11] In 1965, James Schlatter was recrystalizing aspartame in ethanol and licked his fingers to turn a page, discovering that aspartame was sweet.[12] In 1967, acesulfame K was also discovered by the licking of fingers after touching the substance.[12] Sucralose was discovered in 1976 when two scientists were asked to test a chlorinated sugar but misunderstood and thought that they were supposed to taste it instead of test it.[13]

### Figure 1: Glycolytic Pathway Leading Triacylglycerol

The flow chart provides a simplified review of glycolytic pathway leading triacylglycerol, which is the precursor for triglycerides. The hexokinase enzyme is the rate-limiting step of glycolysis that is not required for fructose to enter the glycolytic pathway.



In general, many people believe consuming non-caloric or non-nutritive sweeteners promotes weight loss. But is this really the case? The consensus appears to be that non-caloric sweeteners do not lead to weight loss nor do they prevent weight gain.[1,14] Non-caloric sweeteners do not seem to promote the same satiety as caloric sweeteners. Artificial sweeteners have been shown to affect glucagon like peptide-1 (GLP-1) secretion. GLP-1 secretion from the L cells in the intestine is dependent on the presence of carbohydrates, lipids, and proteins. It slows stomach emptying, promoting satiety (*see Figure 3*). One study in adolescents and young adults tested the effects of 75 gram glucose loads after drinking a diet soda or unflavored carbonated water.[15] Three hours after the glucose load the glucose, GLP-1, and insulin were measured; the insulin levels between the two groups were not that different and the GLP-1 was elevated in the diet soda group.[15] Different studies have been done to look at GLP-1 with different sweeteners. Sucralose has been shown to elicit a GLP-1 response whereas aspartame has not.[1] Another study looking at individuals with a body mass index (BMI) of 42 demonstrated that when given sucralose prior to an oral glucose tolerance test, blood sugars peaked at higher levels and insulin levels were 20% higher compared to receiving water prior to an oral glucose tolerance test.[16] This suggests that artificial sweeteners affect blood sugar level and insulin secretion. The mechanism behind this is not known. The influence of artificial sweeteners on appetite, energy balance, and body weight have not been fully characterized.

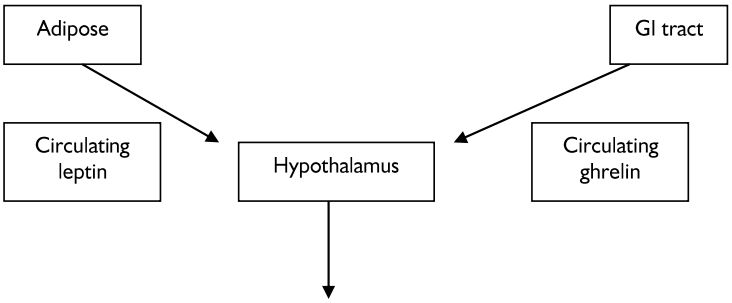
Table: Sweetness Comparison Between Artificial Sweeteners and Sucrose

| Artificial sweeteners | Sweetness relative to sucrose |
|---|---|
| Acesulfame K | 200 |
| Aspartame | 180 |
| Neotame | 8000 |
| Saccharin | 300-500 |
| Sucralose | 600 |
| HFCS | ~1 |
| Glucose | 0.5-1 |
| Fructose | 1-2 |
| Honey | 1 |
| Stevia | 300 |

Another study examined 224 adolescents over a 2-year period. Both groups had their BMIs measured at the beginning of the study. The experimental group was provided with noncaloric beverages every 2 weeks and three phone calls were made to parents as motivation. The control group did not get this attention.[17] At the end of 2 years, there was no difference in the two groups with respect to BMI.[17] One might conclude that artificially sweetened beverages do not help with weight loss, but we could also say that they do not cause weight gain. Another study compared the effects of ad libitum food intake in a group consuming sucrose-sweetened beverages to a group consuming artificially sweetened beverages over a 10-week period.[18] Results showed that those consuming sucrose-sweetened beverages had a 28% increase in calorie intake in the form of carbohydrates and a decrease in protein and fat intake. They also gained weight and increased their fat mass.[18] The MESA study followed patients for 3 years to look for the development of type 2 diabetes and metabolic syndrome. The incidence of diabetes was assessed in three follow-up exams where participants self-reported type 2 diabetes diagnosis based on blood sugar, self-reported diagnosis, or the use

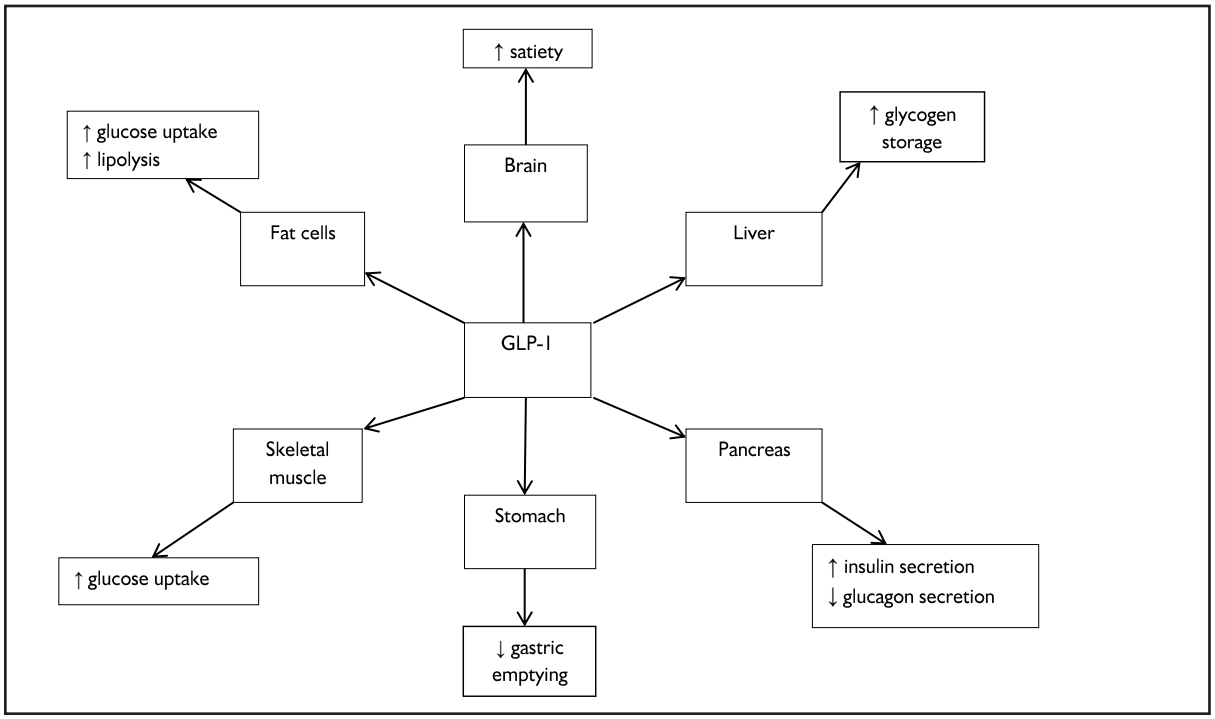
Figure 2: Hormone Effects on Hypothalamus that Affect Satiety

Leptin suppression occurs with fructose because ghrelin doesn't decrease the way it does with glucose.




| Leptin Effects | | Ghrelin Effects |
|---|---|---|
| Decreases | Food intake | Increases |
| Increases | Energy expenditure | Decreases |
| Increases | Fat catabolism | Decreases |
| Decreases | Plasma glucose | Increases |
| Decreases | Body weight | Increases |

Figure 3: Glucagon-like Peptide-1 Effects on the Body that Lead to Decreased Glucose Levels and Decreased Caloric Consumption




of diabetes medications.[19] Participants were asked about consumption of diet soda and regular soda; 14% of participants consumed at least one diet soda daily. Follow-up of the participants revealed a 67% higher rate of type 2 diabetes in those who consumed diet soda compared to those who did not consume diet soda.[19] This association was reported to be independent of baseline measurements.[19] Another study looked at men and their risk of type 2 diabetes, and an association of sugar-sweetened and artificially sweetened beverages.[20] Results showed that sugar-sweetened beverages were associated more with the diagnosis of type 2 diabetes.[20] The results of this study, however, are not unexpected. Some of the sugar-sweetened beverages in this study contained HFCS. The artificially sweetened beverage consumption in the San Antonio Heart Study cohort was analyzed and a dose response effect was found.[21] Those individuals who consumed more artificially sweetened beverages gained more weight.[21] Individuals of normal weight who consumed more than 21 artificially sweetened beverages a week doubled their risk of becoming obese. The change in BMI in those individuals who consumed artificially sweetened beverages increased by 47% compared to those who did not consume artificially sweetened beverages.[21] Other risk factors such as gender, ethnicity, diet, diabetes, and exercise were considered and consistently showed higher weight gain in the individuals consuming more artificially sweetened beverages.[21]

These studies have shown a spectrum of possible effects of artificial sweeteners. They affect appetite by decreasing satiety. Although artificial sweeteners did not affect weight in teens or adults, there was an increased incidence of type 2 diabetes demonstrated in a consumption survey. One study showed that increased consumption of artificially sweetened beverages led to increased BMI. Another study did not show this same result in men; however, the food frequency questionnaire also showed that those who consumed the sugar-sweetened beverages also had poorer diets compared to those who consumed artificially sweetened beverages.[20]

## DISCUSSION

Sugar is an unhealthy addiction in the United States and is increasing worldwide. Consumption of HFCS peaked in 1998 at 54 gallons per person, but by 2011 it had decreased to 21 gallons.[16] A Bloomberg Report found a decreased fondness for corn sugar and soft drinks in general, and cited that more people are choosing to drink water, juice, and tea.[16] Although it is a promising sign that the nation is becoming more health conscious, there has been an increasing popularity of artificial sweeteners. The thought behind artificial sweeteners is that the feeling of deprivation from sugar will be less without increasing blood glucose levels or leading to weight gain. However, there is evidence that artificial sweeteners are not necessarily the healthy alternatives that they were once thought to be. A

position paper by Gardner et al concluded that there is not enough evidence to confirm that artificial sweeteners should be recommended to replace caloric sweeteners, but that the better approach is to decrease the amount of added sugar in one's diet. [22]

Novel sweeteners, such as stevia, tagalose, and trehalose, will be another category to observe as more research is done. Stevia is extracted from *Stevia rebuadiana*, a perennial shrub species. Extracts from this plant have been used for the treatment of diabetes in South America. One study demonstrated that the polyphenol component extracted from the plant was beneficial in treating hyperglycemia, improving glomerular filtration rate, and improving hepatic injury in rats with diabetes.[23] Stevia may be a safer option as a sweetener; however, more studies will need to be done. The commercially available brand Truvia® is a blend of erythritol and stevia. Tagalose and trehalose are also naturally occurring substances that are not as well researched. Another type of sweetener is erythritol, which is a sugar alcohol. Other sugar alcohols include mannitol, xylitol, and sorbitol. Sugar alcohols are added to many "sugar-free" items like candy, gum, and other sweets and are meant to enhance the sweetness of the artificial sweetener. Blood sugar is affected by sugar alcohols and, when consumed in large quantities, can cause diarrhea and bloating.

How do we counsel our patients who are confused about food labels and believe that reduced sugar or no added sugar automatically means a better choice? Discuss the facts: "Sugar-free" or "no sugar added" do not mean that a food product does not contain sugar. Many products contain sugar alcohols that will raise blood sugar. More natural alternatives — including honey, maple syrup, agave nectar, and fruit juice — may be better choices. Some argue that these substances also contain fructose, but smaller amounts of naturally occurring fructose are likely to be better choices than HFCS. These natural choices may also raise blood sugar, so moderation is important. Detrimental health effects also can occur with the overconsumption of these more natural sweetening agents. When it comes to beverages, water and unsweetened tea are best, and, if some sweetness is desired, seltzer water with some real fruit juice could provide an alternative. Providing patients with education about the various sweeteners and substances containing sugar, sugar alcohols, and HFCS and encouraging moderation is beneficial to their overall health given the lack of a strong conclusion about the consumption of these products in general. ■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SHORT REPORT

# Osteopathy for Children

*By David Kiefer, MD, Editor*

SOURCE: Posadzki P, et al. Osteopathic manipulative treatment for pediatric conditions: A systematic review. *Pediatrics* 2013;132:140-152.

This analysis lumped together results from 17 randomized, controlled trials evaluating osteopathic manipulative treatment (OMT) for pediatric conditions. The authors point out that only five of the trials were of high methodological quality, and, of those five, only one showed efficacy of OMT over placebo. The symptoms that may have been improved were associated with congenital nasolacrimal duct obstruction, daily weight gain, length of hospital stay, dysfunctional voiding, infantile colic, or postural asymmetry, whereas those that did not seem to benefit from OMT were cerebral palsy, idiopathic scoliosis, obstructive apnea, or temporomandibular disorders. Mixed results were seen for otitis media and asthma. Only eight of the 17 studies had adequate statistics available to calculate effect sizes; the mean effect size for these eight studies was 0.20, or small. The wide variety of OMT techniques used, as well as the spectrum of medical conditions included, varying sizes of study populations, and statistical deficiencies all limit the clinical applicability of the results from this systemic review. As stated by the authors, the evidence for OMT's efficacy in pediatric conditions is "weak, limited, and contradictory." However, it does serve as a starting point of a discussion for researchers (hopefully, future well-designed projects will address the literature gaps) and it provides a few hints for when to consider OMT in children. ■

## Summary points

- A summary of research results from 17 randomized trials failed to find convincing evidence for the effect of osteopathic manipulative treatment (OMT) for pediatric conditions.
- There was a large range in methodological quality, OMT techniques used, and medical conditions treated, which limits drawing any firm conclusions.

## CME QUESTIONS

**1. All of the following treatments in ASD are shown to be effective *except*:**
a. at least 25 hours/week of individualized behavioral and speech-language therapy.
b. chelation therapy with DMSA and EDTA.
c. gluten-free/casein-free diet in some children with ASD.
d. prevention of congenital rubella syndrome by vaccinating with MMR.

**2. A 45-year-old female with type 2 diabetes presents to the office for follow-up. She mentions that she has been trying to cut down on her sugar and has been trying to buy things that are "sugar free" and have "no added sugar." What advice would you give her?**
a. That's a good dietary change so you can eat what you want.
b. That stuff is bad; you should just eat the regular versions of the food.
c. That's good but you still need to watch your portions since high intake can still raise your blood sugar when consumed in large quantities.
d. That stuff is bad you should only try to eat foods that don't have labels.

**3. The most convincing evidence for the use of osteopathic manipulative treatment in children is for which medical condition?**
a. Infantile colic
b. Asthma
c. Otitis media
d. Cerebral palsy

## [IN FUTURE ISSUES]

Acupuncture and infertility

Telomere length and supplements

Spirituality and cancer