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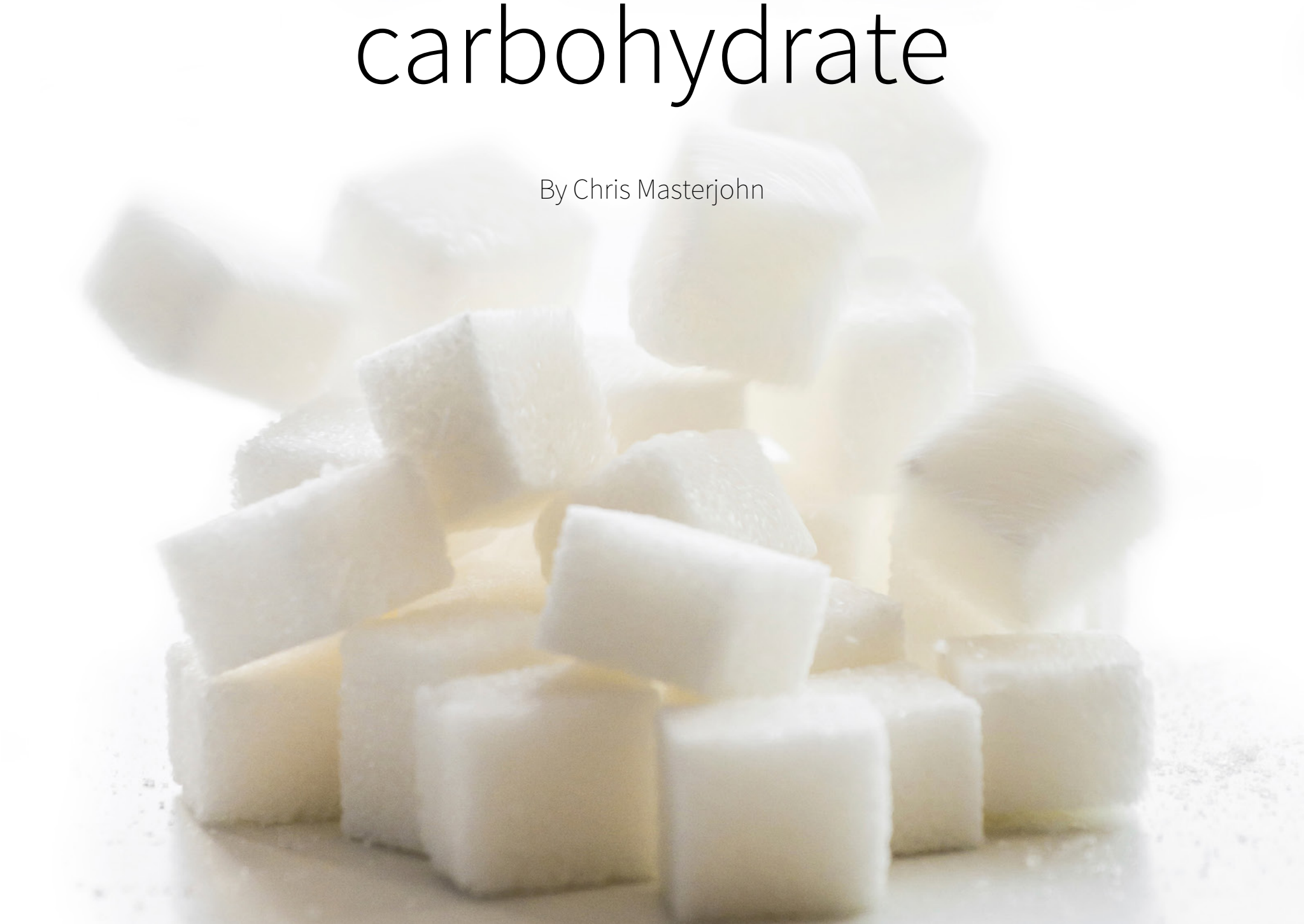
Sugar is the ultimate antioxidant and insulin will make you younger: Appreciating a few poorly recognized but critical contributions of carbohydrate

By Chris Masterjohn



To be clear, when I use the term "sugar" in the title of this editorial I am not advocating a diet rich in refined carbohydrate and washed down with sugar-sweetened soft drinks. I am, instead, using the word in a less colloquial sense to refer to glucose, the primary sugar in biological energy metabolism. And now that I am 34, I don't expect insulin or any other hormone to make me 33 again, but I do expect insulin to make me age more gracefully and to protect me against many facets of degenerative disease that tend to accumulate with age in Westernized populations.

As the stance against saturated fat begins to soften, we need to exercise caution that we do not replace the demonization of saturated fat with the demonization of sugar. Toward that end, I would like to use this space to highlight some of the positive roles of glucose and insulin.

Glucose is the ultimate antioxidant. We tend to think of antioxidants as compounds that will directly neutralize reactive oxygen species in a test tube, but we actually have a complex endogenous antioxidant system that is ultimately fueled by glucose. Through the pentose phosphate pathway, glucose supplies hydrogen ions and electrons – which we could call "reducing power" – to NADPH, which is derived from niacin, also known as vitamin B_3. The enzyme glutathione reductase uses riboflavin, also known as vitamin B_2, to pass this reducing power on to glutathione. Glutathione, the master endogenous antioxidant, then uses this reducing power to neutralize hydrogen peroxide to water, to neutralize lipid peroxides to less harmful hydroxy-fatty acids, and to recycle vitamin C. Vitamin C recycles vitamin E, the principal bulwark against lipid peroxidation in cellular membranes. Thus, the multiple roles of glutathione within the antioxidant defense system – mitigating the accumulation of reactive oxygen species, protecting vulnerable fatty acids within cellular membranes, and cleaning up any damage that has slipped through the system – are all ultimately supported by the reducing power derived from glucose.

Insulin signaling is also important to the antioxidant defense system because it increases the synthesis of glutathione. One small but fascinating study published in the journal *Metabolism* in 2006 demonstrated the relevance of this point in type 2 diabetes. Compared to healthy controls, diabetic patients had poor glutathione status. In fact, their ratio of reduced to oxidized glutathione was cut in half. The investigators then exposed the diabetic patients to a euglycemic hyperinsulinemic clamp. In this approach, both sugar and insulin are infused into the patients' blood at concentrations that keep blood sugar normal and insulin elevated. After

"As the stance against saturated fat begins to soften, we need to exercise caution that we do not replace the demonization of saturated fat with the demonization of sugar."

being exposed to this condition for two hours, the glutathione status of the diabetics normalized to the level of healthy controls.

Pumping patients' veins full of glucose and insulin is wildly impractical as a treatment for diabetes. Nevertheless, the study provides proof of principle that – at least with respect to the antioxidant defense system – type 2 diabetes is a condition of inadequate insulin signaling, not excess insulin signaling.

> "[...] at least with respect to the antioxidant defense system – type 2 diabetes is a condition of inadequate insulin signaling, not excess insulin signaling."

Poor glutathione status is most likely a major contributor to the accumulation of advanced glycation endproducts (AGEs) in diabetes, which are, in turn, major contributors to the development of diabetes itself as well as its cardiovascular complications. But the contribution of insulin to glutathione synthesis is only one of several ways that insulin protects against AGEs.

Quantitatively, the two main contributors to AGEs within human plasma are methylglyoxal and 3-deoxyglucosone. Let us first consider how insulin would affect the accumulation of methylglyoxal, and then we will move on to 3-deoxyglucosone.

Methylglyoxal can be derived from glycolysis when intermediates within the pathway known as triose phosphates accumulate. Insulin clears these intermediates by stimulating the enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH). It can also be derived from ketogenesis: acetone, one of the major ketone bodies, is converted in a two-step process first to acetol and then to methylglyoxal by the enzyme CYP2E1. Insulin suppresses ketogenesis and also suppresses CYP2E1. Once formed, methylglyoxal is detoxified to pyruvate, which can then enter energy metabolism in a variety of ways. This pathway requires glutathione and two enzymes known as glyoxalase-1 and -2. Insulin stimulates the synthesis of glutathione as well as the expression of glyoxylase-1. Thus, insulin suppresses the generation of methylglyoxal from all sources and stimulates its detoxification. This makes insulin central to the defense against AGEs.

The only study I know of that has looked at how this plays out in living humans found that methylglyoxal levels rise on the Atkins diet. The study was small and had no control group, so it should not be taken as the final word. But when we consider the biochemistry involved, the findings are strongly consistent with what we would expect from the falling insulin levels that occur during carbohydrate restriction.

AGEs derived from 3-deoxyglucosone are greater in concentration than those derived from methylglyoxal in the plasma and blood cells of healthy controls. Both classes of AGEs increase in diabetes, but the increase in

methylglyoxal-derived AGEs is greater, making them more numerous than those derived from 3-deoxyglucosone in diabetic plasma. If the findings from diabetic rats can be generalized to humans, AGEs in tissues besides blood are likely to be overwhelmingly derived from methylglyoxal rather than 3-deoxylglucosone. Nevertheless, for a more complete picture, I will briefly discuss the metabolism of 3-deoxyglucosone.

3-deoxyglucosone is primarily derived from enzymatic metabolism of fructosamines, which form from the direct interaction of sugar with protein. The most notable fructosamine is Hba1c, the glycated form of hemoglobin that is used in diagnosing and monitoring diabetes. Although the metabolism of 3-deoxyglucosone is poorly understood compared to that of methylglyoxal, it appears to be primarily metabolized to 3-deoxyfructose by a group of enzymes known as aldoketo reductases. These enzymes are under the control of Nrf2, a transcription factor that regulates a suite of genes involved in xenobiotic metabolism and antioxidant defense.

From a nutritional perspective, the polyphenol compounds found abundantly in unrefined plant foods are thought to be the principle dietary strategy to stimulate Nrf2. Insulin would protect against 3-deoxyglucosone accumulation by clearing glucose from the blood and stimulating its downstream intracellular metabolism. The reduction of 3-deoxyglucosone, moreover, requires NADPH, which derives its reducing power from glucose in the pentose phosphate pathway. Thus, although high blood glucose concentrations drive the formation of 3-deoxyglucosone, cytosolic glucose is critical to its detoxification.

In trying to make sense of why our bodies would coordinate protection against oxidative stress and glycation to be dependent on glucose and insulin, I use the following paradigm. Our ability to store carbohydrate is very limited because, compared to fat, glycogen is voluminous, wet, and heavy. A person of healthy bodyweight stores about 30 times as much fat as carbohydrate. Unlike the virtually unlimited supply of fat within the body, glycogen stores are easily depleted or repleted over the course of days. Thus, I believe our bodies are hardwired to regard leptin (influenced most strongly by total body fat) as a metric of long-term energy status and insulin (influenced most strongly by acute intake of carbohydrate) as a metric of short-term energy status. Protecting against oxidative stress and glycation requires energy-intensive processes that are critical over the long-term but can be sacrificed over the short-term with relative impunity if the body perceives its short-term energy supply as limited.

In principle, glucose is the ultimate antioxidant and insulin is central to the defense against oxidative stress and glycation. Nothing I have written here, however, implies that more glucose and more insulin is always better. It would be foolish to think there is no point of diminishing returns and no possibility of a U-shaped curve where excesses could pose problems as severe as inadequacies. If for no other reason, diminishing returns will be seen when carbohydrate-rich foods begin to displace protein- and fat-rich foods to the point where proteins, fats, or the micronutrient profiles that accompany them become the limiting factors for health.

What I am advocating here is a recognition of the positive contributions of carbohydrate itself to these systems. In popular writings, antioxidant defense is often reduced to vitamin E, vitamin C, and plant polyphenols, while glycation is misleadingly attributed to sugar. This could easily lead us to a diet rich in meat, vegetables, and fat, without considering positive roles for whole foods rich in natural sugars and starches. Recognizing positive benefits of glucose and insulin within these systems should cause us to open up our menu to whole foods whose central place in the diet is to provide carbohydrate.

Defining exactly how much carbohydrate is needed to optimize these systems would be difficult. Randomized trials testing the long-term effect of isocaloric substitutions of carbohydrate for other macronutrients on glutathione status and AGE accumulation would be useful, but to my knowledge have not been done. Even if we had such studies, the carbohydrate requirement would heavily depend on contextual factors such as physical activity. Additionally, in the context of a diet made from whole foods, shifting macronutrient profiles will lead to inadvertent shifts in micronutrient profiles, and the micronutrient profile of the diet could influence whether increases in carbohydrate supply show a clear benefit to antioxidant defense and glycation status.

In clinical use, I think titration of the carbohydrate supply should be one of the tools used to improve an oxidized or deficient glutathione pool. The European Laboratory of Nutrients Health Diagnostics and Research Institute offers a methylation panel that includes measurements of glutathione in its reduced and oxidized forms. This kind of test could be used to determine the need for such a titration and to assess the efficacy of such a titration.

As we move forward, we need to frame our discussions of glucose as a nutrient and insulin as a protective hormone whose protective functions are being lost in obesity and diabetes. With this framework, we may be able to shake off the old rhetoric about fats without redirecting it toward carbohydrate as the new nutritional boogeyman. Then we can look freely at the buffet of dietary tools at our disposal and study with a clearer collective mind how to maximally reap their benefits in a way that is tailored to each of us as an individual. ◆

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Milk gone bad: A1 beta-casein and GI distress

Effects of milk containing only A2 beta casein versus milk containing both A1 and A2 beta casein proteins on gastrointestinal physiology, symptoms of discomfort, and cognitive behavior of people with self-reported intolerance to traditional cows' milk

Introduction

Milk is an important food for young infants and a common source of nutrition among adults. However, many humans stop producing the lactase enzyme responsible for digesting the milk sugar lactose after weaning, a condition called lactose intolerance. When individuals with lactose intolerance consume lactose through milk or other forms of dairy, they may experience varying forms of gastrointestinal (GI) distress, including abdominal pain, bloating, gas, nausea, and diarrhea. These symptoms are caused by the fermentation of lactose in the colon, since it was not absorbed in the small intestine.

Roughly 65% of the human population is considered to have a reduced ability to digest lactose after infancy. However, the prevalence of true lactose intolerance is difficult to discern because studies have varied in their interpretation of what constitutes this condition. Many surveys rely on self-reported lactose intolerance, but many individuals who self-report lactose intolerance show no evidence of lactose malabsorption.

An alternative explanation for the high levels of self-reported lactose intolerance may be the type of protein in milk. The two major protein groups in milk are whey and casein, with the latter accounting for about 80% of total protein. The most common genetic variants of casein protein in milk are A1 beta-casein and A2 beta-casein.

A2 beta-casein is recognized as the original form of beta-casein and is the only beta-casein found in the milk of purebred Asian and African cattle. The A1 beta-casein variant is found among cattle of European origin and is believed to have arisen more than 5,000 years ago. Accordingly, most milk sold commercially is a combination of A1 and A2 beta-caseins, as it is sourced from European cattle or other cattle that have been crossbred with European cattle. Examples include Guernsey cows, Holsteins, and Ayrshires. Human milk and milk from goats and sheep contains only A2 beta-casein.

The beta-casein proteins are degraded into beta-casomorphins (BCMs) during the digestive process. The main difference between A1 and A2 beta-casein is that A1 beta-casein produces BCM-7 upon digestion while A2 beta-casein does not. There is a growing body of evidence suggesting that BCM-7 is bioactive and is associated with inflammation and several disease states, such as diabetes and coronary heart disease. However, these associations are not without criticism.

Up until now, nearly all the evidence investigating health effects of BCM-7 and the beta-casein variants has been observational or conducted in test tubes and animals. The current study was designed to compare the human health effects of consuming milk containing only A2 beta-casein with milk containing A1 beta-casein type in terms of GI function, symptoms, and inflammation.

The two common forms of casein present in milk are A1 beta-casein and A2 beta-casein, which differ as a result of a genetic mutation in cattle over 5,000 years ago. There is observational, test tube, and animal evidence to suggest that A1 beta-casein may promote inflammation and be linked to inflammatory disease states. The study under review put this to the test in humans.

Who and what was studied?

This was a double-blind, randomized crossover trial in Shanghai, China in which 45 middle-aged men and women consumed 250 milliliters of milk after two meals per day for 14 days. All participants were of Han Chinese ancestry. They had a self-reported intolerance to commercial milk (moderate digestive discomfort) and did not regularly consume dairy, but none had irritable bowel syndrome or inflammatory bowel disease. A urinary galactose test confirmed that 23 of the 45 participants were lactose intolerant.

Figure 1: Study design

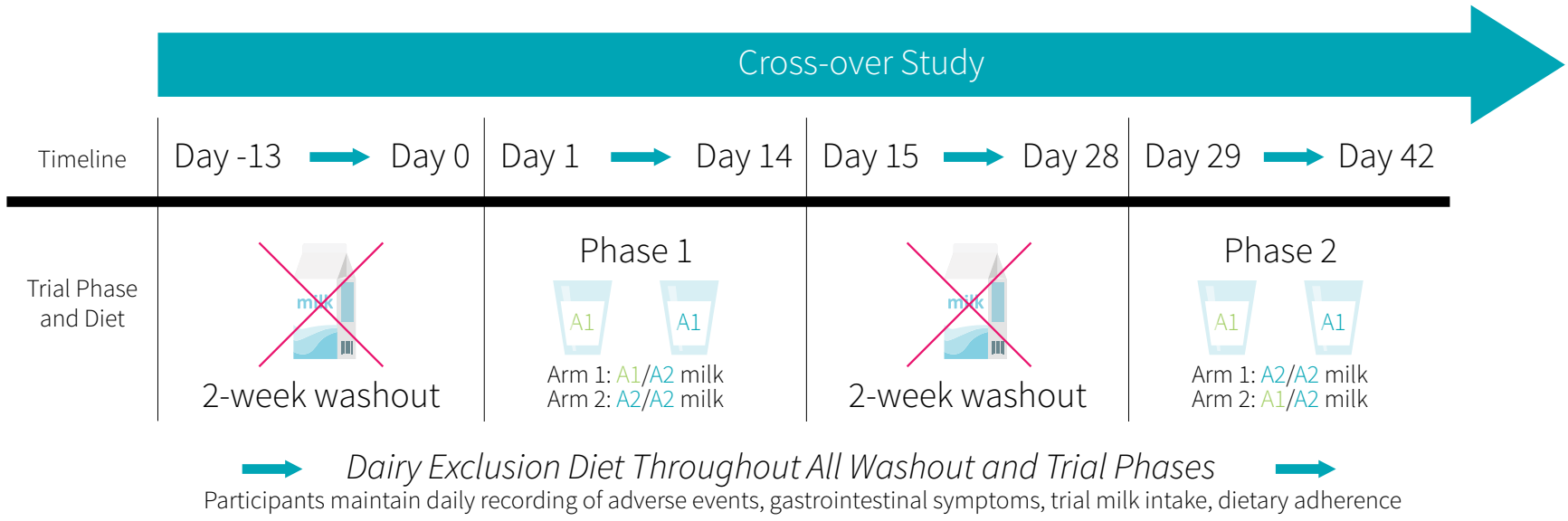
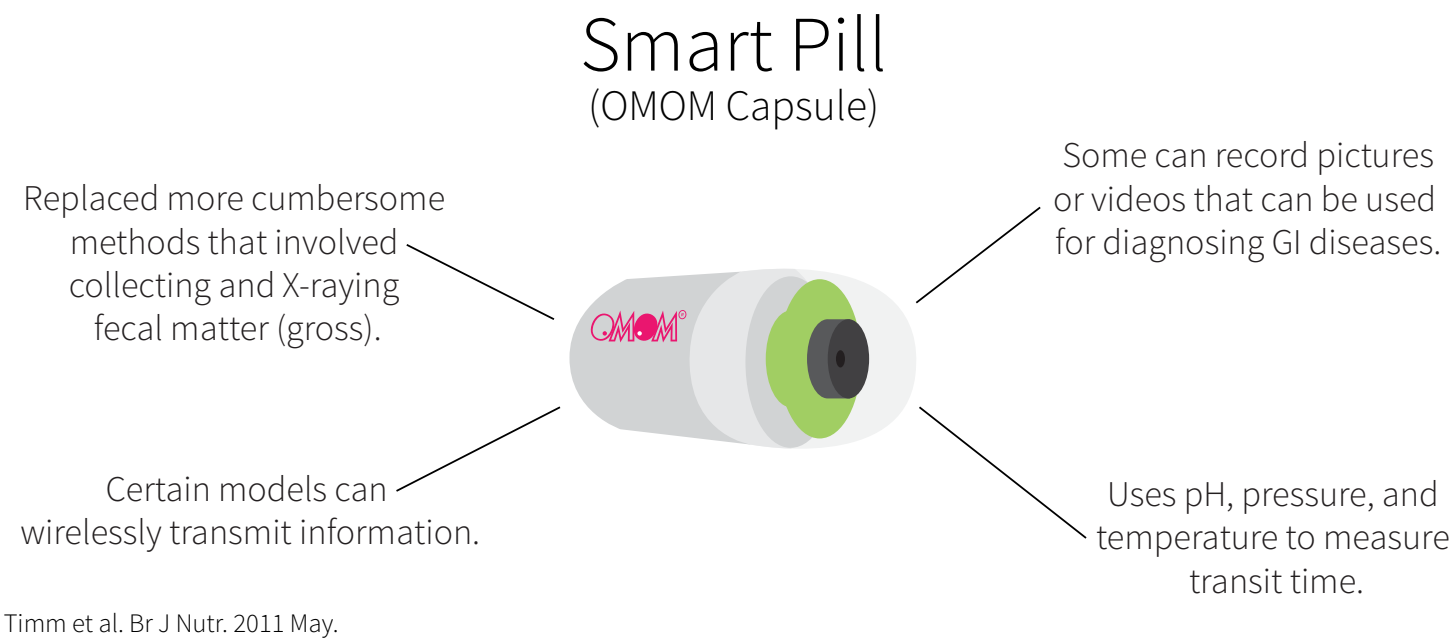


Figure 1 summarizes the study design. Over the course of eight weeks, each participant went through two two-week milk phases and two two-week washout phases. During the milk phases, the participants consumed either a milk containing only the A2 beta-casein (from cows confirmed to be A2-only producers) or a milk containing a combination of A1 and A2 beta-casein (milk containing only the A1 beta-casein is not commercially available and the A1/A2 combination is standard in consumer milk). All participants completed both milk phases, with half beginning with the A2-only intervention and half beginning with the A1/A2 intervention. Aside from the differences in casein type, the milk was identical. During the entire eight weeks, the consumption of dairy products other than those provided was prohibited.

Participants used daily diaries to record milk intake, GI symptoms using the Bristol Stool Chart (a medical aid that classifies faeces into seven groups), and adverse events. At the beginning and end of each two-week milk phase, the participants underwent a computer-based test that measured the speed and effectiveness of information processing (Subtle Cognitive Impairment Test; SCIT) and laboratory testing that included the use of a smart pill (depicted in Figure 2) to record stomach and intestinal inflammation and physiology. In addition to the self-reported milk intake diary, the counting of milk cartons was used to assess compliance.

Figure 2: Functions of a Smart Pill



Reference: Timm et al. Br J Nutr. 2011 May.

This double-blind, randomized crossover trial had 45 middle-aged, dairy-intolerant Chinese men and women consume 250 milliliters of milk twice daily after meals for two weeks. The milk contained either only A2 beta-casein or both A1 and A2 beta-casein. Measurements of GI function and inflammation, as well as cognitive function, were assessed before and after each intervention.

What were the findings?

Consumption of milk containing A1/A2 beta-casein led to significantly greater increases in interleukin-4 (IL-4), immunoglobulin (Ig) G, IgE, and IgG1 compared to the consumption of milk containing A2 beta-casein only. Additionally, A1/A2 milk significantly reduced fecal levels of total short-chained fatty acids (SCFAs), acetic acid, and butyric acid. The latter two are specific types of SCFAs.

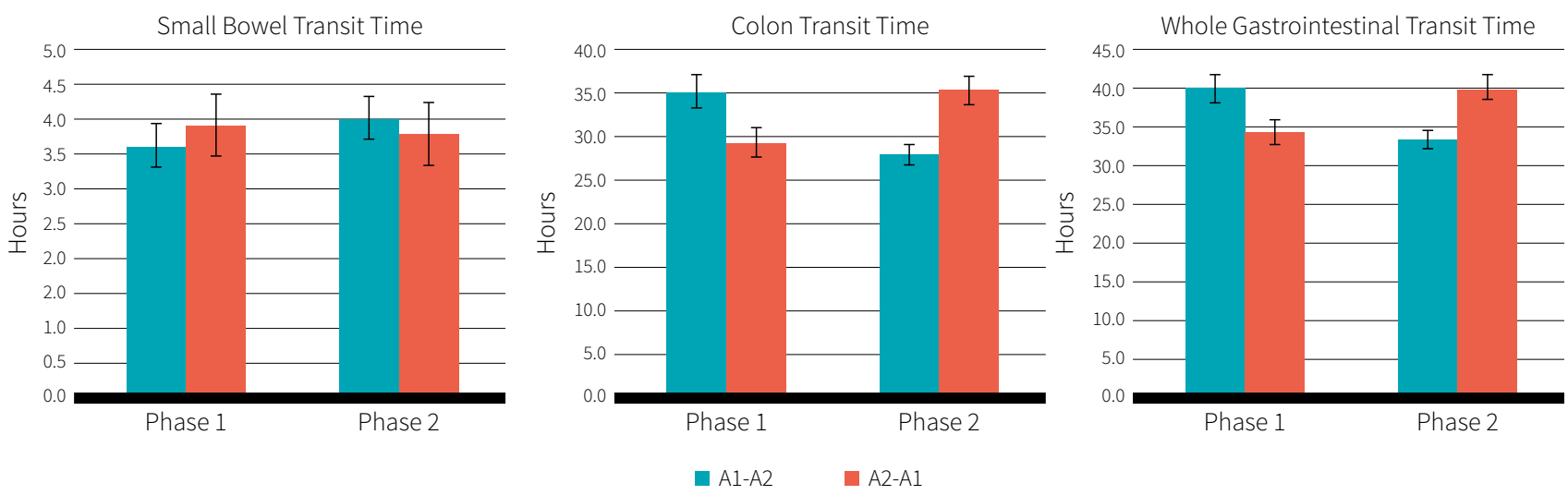
GI symptoms significantly worsened with A1/A2 milk only compared to baseline. Specifically, consuming A1/A2 milk resulted in more bloating, flatulence, and borborygmus (the rumbling or gurgling noise made by the movement of fluid and gas in the intestines). Stool frequency and stool consistency were also significantly increased compared to baseline with the consumption of A1/A2 milk, but not with the consumption of A2 only milk.

Using data from the smart pill, consumption of A1/A2 milk was associated with significantly longer GI transit time than consumption of A2 only milk, by about six hours (40 vs. 34 hours, respectively, as seen in Figure 3). This was due to a significantly longer transit time in the colon. Intestinal inflammation improved in 36% of participants and stomach inflammation improved in 23% of participants after switching from A1/A2 milk to A2 only milk. By contrast, intestinal and stomach inflammation both improved in 11% of participants when switching from A2 only milk to A1/A2 milk. Almost all other participants showed no difference between milk types.

Consuming A2 only milk was associated with significantly quicker response time and lower error rate on the SCIT than consuming A1/A2 milk.

Data was re-analyzed comparing individuals with confirmed lactose intolerance to those without. Consuming A1/A2 milk was associated with significant worsening of GI symptoms in both groups, with the lactose intolerant group exhibiting worse symptoms than the tolerant group. This was not observed with A2 only milk, as GI symptoms were comparable to those observed after the dairy-free washout period in both lactose tolerant and intolerant individuals. Moreover, the GI symptom scores between lactose tolerant and intolerant groups were not significantly different from one another when consuming A2 only milk.

Figure 3: A1/A2 gastrointestinal transit time



Both lactose tolerant and intolerant individuals showed similar increases in whole GI and colon-specific transit times with A1/A2 milk compared to A2 only milk. Both groups also showed significant increases in IL-4, IgE, and IgG1 and significant decreases in total SCFAs with A1/A2 milk vs A2 only milk.

The primary adverse event was diarrhea and was reported by 10 of 45 participants (22%). Of these, eight were owed to the consumption of A1/A2 milk, three related to A2 only milk, and three unrelated to either milk.

Consumption of milk containing only A2 beta-casein was associated with significantly less serum inflammation and GI symptoms than milk containing both A1 and A2 beta-caseins. A2 milk was also associated with significantly greater SCFA production and cognitive ability on the SCIT test. Individuals with lactose intolerance reported similar GI symptoms as those without lactose intolerance when consuming A2 only milk but reported worse symptoms with A1/A2 milk.

What does the study really tell us?

The study under review shows that consuming milk with only A2 beta-casein is associated with reduced GI symptoms, lower concentrations of inflammatory biomarkers, greater SCFA production in the colon, shorter GI transit time, and shorter response time and lower error rates on the SCIT compared with milk containing both A2 and A1 beta-caseins. The increased SCFA production, primarily butyrate and acetate, is especially notable considering that SCFAs play a prominent role in human health and mediate the beneficial health effects of fiber consumption. The shorter GI transit time is difficult to interpret, as whether this may aid with constipation or lead to diarrhea would depend on the baseline transit time of the individual.

This study also suggested that some GI symptoms ascribed to lactose intolerance were present only with the consumption of milk containing A1 beta-casein. Both milk products contained equal amounts of lactose, which reinforces the concept that the differences in outcomes were driven by the presence or absence of A1 beta-casein.

This study has notable limitations, such as the purely Han Chinese study sample group. It's also unclear how a longer time frame would have impacted the results, which future research will need to investigate, considering that milk consumption is often consistent and prolonged in real life. In addition, this study focused solely on GI symptoms, so any non-GI effects of A1 and A2 beta-caseins were not tested.

Finally, this study was funded by The a2 Milk Company Limited. One of the six authors was also an employee of this company, but he was not involved in performing the study or data analysis. Rather, he conceived and designed the study, selected variables of interest, and contributed to the manuscript.

This study tells us that consuming milk containing only A2 beta-casein may result in less GI distress and inflammation than consuming milk containing both A1 and A2 beta-caseins. This applies to individuals with and without lactose intolerance. More research is needed to determine if these effects are observed in populations other than the Han Chinese and if duration of consumption plays a mediating role.

The big picture

Studies using rats and mice have demonstrated that A1 beta-casein exhibits inflammatory properties mediated by opioid receptors in the gut. This supports the findings of the current study, but its implications remain unknown. It is notable that the rat study also found A1

beta-casein to increase the production of the enzyme dipeptidyl peptidase 4 (DPP4) in the small intestine. DPP4 degrades hormones that help regulate insulin secretion and blood glucose levels, and DPP4 inhibitors are widely used in the management of type 2 diabetes. It is therefore possible that long-term exposure to A1 beta-casein may have an effect on blood glucose management, although future research will need to investigate this.

The inflammatory opioid effects of the A1 beta-casein derivative, BCM-7, have also been postulated to affect the brain. This has been offered as one potential explanation for the delayed psychomotor development in cow milk formula-fed infants compared to breastfed infants, as human breast milk contains only A2 beta-casein. Additionally, some studies have associated A1 beta-casein and BCM-7 with neurological diseases like autism, schizophrenia, and psychosis.

The finding of increased response times and error rates on the SCIT in the current study support the above, as elevated levels of inflammatory markers have been shown to play a role in Alzheimer's disease and an impairment of executive function and processing speed in the elderly, even after controlling for age and other health-related factors. Cognitive impairment has also been observed in newly-diagnosed patients with celiac disease, which improves with adherence to a gluten-free diet. It is well-known that gluten elicits a powerful immune and inflammatory response in these individuals.

The reduction in SCFAs in the colon could be owed to an excessive production of mucus that normally provides a protective barrier and home to the microbiome. This is because the microbiome organisms are responsible for producing SCFAs as a byproduct of eating the fiber we cannot digest. The A1 beta-casein derivative, BCM-7, has been shown to increase mucus production in test tubes and in rats. Whether these changes occur in humans and whether they have a physiological effect remain unknown. However, SCFAs play a prominent

"The inflammatory opioid effects of the A1 beta-casein derivative, BCM-7, have also been postulated to affect the brain. This has been offered as one potential explanation for the delayed psychomotor development in cow milk formula-fed infants compared to breastfed infants"

role in human health, such as through improved blood glucose control and insulin sensitivity, and their reduction would be unfavorable.

Much of the evidence supporting the inflammatory role of A1 beta-casein is observational or stems from studies performed in test tubes and animal models. Any human evidence is largely anecdotal and unreliable. The only other human trial to investigate differences between A1 and A2 beta-casein was conducted in 41 men and women from Western Australia. Using an eight-week crossover design similar to the current study, this previous work showed that A2 milk was associated with less bloating, abdominal pain, flatulence, and voiding difficulty than A1 milk. The current study confirms and extends these findings. Notably, this previous trial used 750 milliliters of milk daily and an A1 beta-casein only milk as the comparator to the A2 milk. The current study used less milk (500 milliliters per day) and a commercially available combination milk (A1 plus A2), both of which make these results more applicable to the general population.

It is possible that the milk sugar lactose interacts with BCM-7 to mediate the observed effects. This is supported by the current study findings that individuals with lactose intolerance did not report a worsening of GI symptoms with the consumption of milk containing A2 beta-casein only. Perhaps the inflammatory properties of BCM-7 affect the production of the lactose-degrading enzyme, lactase, leading to malabsorption in normally lactose-tolerant individuals. Perhaps BCM-7 changes the microbiome in a manner that makes it more susceptible to lactose fermentation. These are plausible theories, but require further testing.

A1 beta-casein and its derivative, BCM-7, have shown a range of effects both in test tubes and in animal models. This includes promoting inflammation that has the potential to disrupt blood glucose management and cognitive function over the long-term. Data from human trials is limited but does support the inflammatory findings. However, more research is needed to investigate the long-term impact of A1 beta-casein consumption.

Frequently asked questions

Where can I buy milk that contains only A2 beta-casein?

A2 beta-casein is the only beta-casein found in human, goat, and sheep milk, making these forms of dairy a safe bet for reducing exposure to A1 beta-casein. The a2 Milk Company also produces a milk from selectively bred cattle that contains only A2 beta-casein, but this product is not commonplace in the U.S. It is sold as a premium product in Australia and New Zealand.

What should I know?

Although only two human trials have been published comparing milk that contains A1 beta-casein to A2 beta-casein, both have shown that A1 beta-casein results in greater GI distress. The current study adds to this by showing that it is also associated with increased intestinal inflammation and reduced cognitive functioning. These findings support test tube and animal research that has found similar effects. The current study also suggests that some individuals with self-reported lactose intolerance may be reacting to A1 beta-casein rather than lactose, as they do not show symptoms when consuming milk containing only A2 beta-casein. ◆

Given the massive amount of dairy consumed in the world, you'd think A1 and A2 milk would be more widely studied. Hopefully this trial spurs further research. Discuss it at the ERD private Facebook forum.