

The Second-Meal Effect: A Review

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Introduction

Consumption of low glycemic-index (LGI) foods has been shown to attenuate blood glucose response during the postprandial period immediately following a meal. In addition, positive metabolic effects can persist well beyond this period. One of these extended effects, known as the “second-meal effect,” is the positive effect of the bioavailability of glucose on the glucose tolerance of the subsequent meal.¹ This second-meal effect, initially observed in normal-weight, healthy adult subjects using glucose and guar,² has also been documented in patients with type 2 diabetes.³⁻⁵

Human Clinical Study Overview

Seventeen second-meal-effect human clinical studies have been published to date, most with statistically significant results. All studies share a common crossover design, but differ in the types of study populations, sample sizes, test meals, and timing between meals. A majority of the studies (14) examined healthy, normal-weight subjects; three involved patients with type 2 diabetes.³⁻⁵ Typical second-meal effect studies used relatively small sample sizes ($n = 6$ to 15)^{2,6,7}; however, some studies were conducted with larger sample sizes—the largest with 45 participants.⁵ While most studies (11) examined the time interval between breakfast and lunch (4 - 5 hr), approximately one-

third focused on the period between dinner, or evening snack, and breakfast (6 studies; 10 - 12 hr).

Finally, test-meal composition varied considerably from study to study. A few involved the feeding of single-food ingredients or individual foods, such as glucose with or without guar,^{2,7} uncooked cornstarch vs. nothing,⁴ or white bread.³ However, in most instances, study subjects were fed mixed meals primarily consisting of lentils, kidney beans, barley, amylose-enriched baked goods, or spaghetti as the primary LGI carbohydrate source, and wholemeal bread, white bread, potato, or farina as the primary high glycemic-index (HGI) carbohydrate source.

Mechanism of Action

Consumption of a LGI meal has often been shown to improve glucose tolerance at the subsequent meal. Originally, this effect was attributed solely to prolonged glucose absorption. However, according to a newer study, the improvement is a result of the physiological properties of the carbohydrates that are typically found in LGI foods, not simply a diminished glucose response.¹ Two major properties of carbohydrates affecting glucose tolerance after a second meal are presented below.

Prolonged Glucose Absorption

For many years, improved glucose tolerance following a second meal was assumed to result entirely from the prolonged absorption of glucose from the small intestine following the initial meal.^{2,6-8}

The mechanism by which slow absorption of carbohydrate following a meal improves second-meal glucose tolerance has not been established. A possible mode of action is that slower postprandial carbohydrate absorption minimizes postprandial glycemia, which, in turn, minimizes postprandial insulin levels. Reduced insulin levels should decrease the likelihood of glucose falling to below fasting levels and triggering the formation of ketone bodies and the release of nonesterified fatty acids (NEFAs). The net result is enhanced glucose uptake by peripheral tissues.

Colonic Fermentation

More recent data indicate that colonic fermentation, via short-chain fatty acids (SCFAs) can also play a major role in promoting the second-meal effect.⁹⁻¹¹ Perhaps the most convincing evidence supporting the role of SCFAs in improving second-meal glucose tolerance comes from Brighenti et al.¹ In this study, 10 normal-weight, healthy subjects were fed three test meals for breakfast in random order. The meals consisted of sponge cakes made with: 1) HGI: amylopectin, a completely and rapidly-digested starch, and 5 g of cellulose, a nonfermentable fiber; 2) HGI-Lac: amylopectin with 5 g of lactulose, a rapidly fermentable disaccharide; or 3) LGI: amylose, a slowly digestible, partly fermentable starch and 5 g of cellulose; and black tea. Five hours later, subjects consumed a standard lunch of pasta, white bread, ham, cheese, and mineral water. As expected, both the HGI and the HGI-Lac breakfasts led to significantly higher postprandial peak glucose ($P<0.03$ at 30 min) and peak insulin ($P<0.03$ at 1 hr) values after breakfast compared to LGI. However, the addition of lactulose to the HGI breakfast markedly reduced glucose levels after the standardized lunch, such that HGI-Lac was

significantly lower than HGI at 3 hr ($P<0.01$) and 4 hr ($P<0.05$) postprandially and very similar to levels following the LGI breakfast. The addition of lactulose to HGI also led to a dramatic increase in breath hydrogen ($P<0.001$ at all times after lunch), a large decrease in plasma NEFAs AUC ($P<0.05$), and slower gastric emptying after lunch ($P<0.05$). Based on these observations, the authors concluded that fermentable carbohydrates potentially contribute to improved second-meal glucose tolerance by reducing “NEFA competition for glucose disposal” and by affecting slowing gastric emptying.

Fermentable carbohydrates stimulate glucagon-like peptide-1 (GLP-1). Although a direct connection between colonic fermentation and carbohydrate metabolism has been established,¹² a detailed mechanism is not yet available. Likely, such a link is mediated through SCFAs that are produced as a result of colonic fermentation. A growing body of animal data indicates that SCFAs mediate GLP-1, an incretin hormone that is secreted by enteroendocrine L cells located in the distal small intestine and colon in response to food intake.¹³ According to Drucker et al,¹³ this hormone plays a key role in the regulation of carbohydrate metabolism in three ways: 1) It promotes increased beta-cell mass in the pancreas by stimulating beta-cell proliferation and by inhibiting apoptosis. 2) It helps to control glycemia by acting on glucose sensors, inhibiting gastric emptying, reducing food intake, and decreasing glucagon secretion. And, 3) it strongly stimulates insulin secretion in patients with type 2 diabetes.

Several studies in which rodents were fed indigestible, fermentable carbohydrates provide clear evidence that SCFAs promote increased endogenous GLP-1 production. For example, Gee and Johnson¹⁴ found that rats given a single meal containing 10% lactitol (wt/wt) as part of a semisynthetic diet showed significantly higher levels of

plasma GLP-1 10 hr after the start of the meal compared to those without lactitol. Furthermore, Reimer and McBurney¹⁵ fed rats either a fiber-free elemental diet or the same diet containing 30% fiber (cellulose, pea fiber, oat fiber, sugar beet fiber) for 14 days and found that supplementation with fiber resulted in elevated cecal and colonic SCFA, ileal proglucagon mRNA, and plasma GLP-1. Likewise, Cani et al¹⁶ obtained similar results after supplementing a standard diet with 10% oligofructose for 4 weeks. Oligofructose supplementation led to an increase in the number of enteroendocrine L cells, number of cells expressing GLP-1, and increases in proglucagon mRNA and peptide content in the proximal colon.

Short-chain fatty acids act directly on adipose tissue. According to the model proposed by Robertson,¹² SCFAs can also improve carbohydrate metabolism by acting directly on adipose tissue. Under this scheme, GPR43, a former orphan G-protein receptor that can bind to SCFAs, mediates the antilipolytic activity of SCFAs in adipose tissue by inactivating hormone-sensitive lipase, the enzyme responsible for cleaving triglycerides into free fatty acids and glycerol. The inactivation of hormone-sensitive lipase should lead to a subsequent reduction in plasma NEFAs. Lastly, lowering plasma NEFA levels would be expected reduce insulin resistance¹⁷ by decreasing the inhibitory effect of insulin on hepatic glucose production and by inhibiting the stimulatory effect of insulin on glucose uptake by peripheral glucose-dependent cells.¹²

Limitations to the Current Studies

Even though the current body of scientific literature regarding the second-meal effect shows largely positive results, the data suffer from several limitations:

- Sample sizes were usually small, and the studies were performed by a small handful of laboratories.
- To date, human clinical studies have only examined the meal intervals between breakfast and lunch and between dinner and breakfast. It is unknown whether the second-meal effect can be demonstrated between lunch and the evening meal.
- With the exception of one human clinical study,⁹ levels of GLP-1 have not been measured in any of the second-meal effect studies.
- No analytical methods are available that can accurately predict the rate and extent of fermentation of a particular food in the human colon, and there is still disagreement over appropriate analytical methods for measuring resistant starch.
- No published animal models are available to test the second-meal effect.

Conclusions

Thus, the benefits of incorporating LGI foods into a diet extends beyond the immediate post-prandial phase and as such may help prevent or delay the progression of type 2 diabetes. This phenomenon, known as the "second-meal effect," has been observed in both normal-weight non-diabetic subjects and in patients with type 2 diabetes. The mechanism of action behind the second meal effect has been assumed to be a direct consequence of prolonged glucose absorption leading to: stable insulin levels, decreased tendency for glucose to fall to sub-fasting levels, minimal release of NEFAs, and maintenance of glucose uptake by peripheral tissues . However, a growing body of animal data suggests that the effect may also be mediated by SCFA produced from colonic fermentation whereby SCFA attenuate postprandial blood

glucose levels of the subsequent meal by inactivating hormone-sensitive lipase in adipose tissue via the intestinal incretin GLP-1 or via the G-protein receptor GPR43.

References

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