

The Second Meal Effect and Its Influence on Glycemia

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Abstract

The study of factors that influence blood glucose homeostasis is becoming increasingly important as prevalence rates for insulin resistance and type 2 diabetes have increased. Diets with a low glycemic index (lowGI) have been shown to reduce the risk for diseases by limiting the increase of glucose in the blood. LowGI intake in one meal also has been shown to limit the postprandial glycemic response (PPGR) to a subsequent meal; a concept termed the “second meal effect”. Although there have been many theories for the mechanisms responsible for the second meal effect, the exact cause has yet to be elucidated. It is important for both research investigators as well as patients to consider food consumption prior to testing PPGR, as there is evidence that the GI of one meal not only affects the PPGR of that meal, but will also influence the PPGR of the following meal(s). Here we will review recent evidence regarding factors believed to contribute to the second meal effect and the magnitude of their impact.

Keywords: Glycemic index; Glycemic load; Postprandial glycemic response; Glycemia; Second meal effect; Glycogen

Introduction

It is vital for individuals with diabetes or other metabolic conditions to control blood glucose in order to prevent the development of cardiovascular disease and other pathological conditions. In fact, the first goal listed in the American Diabetes Association’s 2008 position statement is for those with diabetes to properly maintain blood glucose within a narrow range [1]. Careful attention to diet is essential for maintaining controlled blood glucose levels. Research has shown that eating meals containing high glycemic loads and low amounts of fiber can increase an individual’s risk for developing type 2 diabetes [2,3].

The increase in blood glucose levels after a meal is termed postprandial glycemic response (PPGR). PPGR is a measure that can be used to gauge the competency of the metabolic system. Essentially, postprandial blood glucose concentration is controlled by two components, glucose appearance and glucose clearance [1,4-6]. Glucose appearance and the magnitude of the glycemic response are affected by the speed at which a carbohydrate is digested and enters the blood stream. A healthy human body is able to minimize PPGR and maintain euglycemia. An important process in removing glucose from the blood after a meal is the activation of the insulin signaling pathway, and subsequent glucose transport into various peripheral tissues including skeletal muscle and adipose tissue. The most important tissue for glucose removal is skeletal muscle, which has been shown to be responsible for 85% of the body’s insulin-stimulated glucose clearance [7].

There have been attempts to create a method of measuring/predicting a food’s ability to impact glycemic response [8]. Jenkins et al. [9] developed a concept known as the glycemic index (GI) to classify a food based on a PPGR. Wolever and Bolognesi C [10] defines GI “as the incremental area under the glucose response curve for a 50-g carbohydrate portion of a food expressed as a percentage of that after 50g carbohydrate of white bread is taken by the same subject”. Although there are multiple ways to express area under the curve [11], the most common method at it relates to GI is the incremental area under the curve ignoring the area under the baseline [11]. Said another way, GI is determined by measuring the increase in blood glucose concentration above fasting levels over a two-hour period after consuming a food that usually contains 50 grams of carbohydrate [8]. This value is then

divided by the glycemic response to a reference food such as 50 grams of glucose or white bread and multiplied by 100 [1,4]. An additional measure is termed glycemic load (GL), which takes into account both the GI of the food and the amount of carbohydrate in the food. GL is calculated by first dividing the GI by 100 then multiplying this value by the carbohydrate content (grams) followed by multiplying by, the total weight of the food. In summary, the higher the GI value of a food, the more it is expected to increase blood glucose levels [8].

It is currently estimated that there are 26.8 million individuals in the United States with type 2 diabetes mellitus [12]. With diabetes becoming more prevalent, there is a need for studies on glycemic response to food items and GI. These systems of classifying foods based on their impact on PPGR can be very helpful to diabetics who need to carefully monitor their blood glucose concentrations [13].

One factor known to affect glycemia has been termed “the second meal effect”. The second meal effect is a phenomenon where the GI of one meal can influence the glycemic response to a subsequent meal [14,15]. This concept is illustrated in Figure 1. For instance, a low glycemic index (lowGI) breakfast has been shown to lower the PPGR to lunch [14]. This effect also has been shown to last overnight with the GI of an evening meal affecting the PPGR to a breakfast meal the following morning [16]. If not recognized and controlled for by the investigator, the second meal effect may influence the results of studies determining the effects of particular food items on glycemia. The purpose of this review is to investigate the influence of the second meal effect in studies researching PPGR and examine the factors that contribute to the second meal effect.

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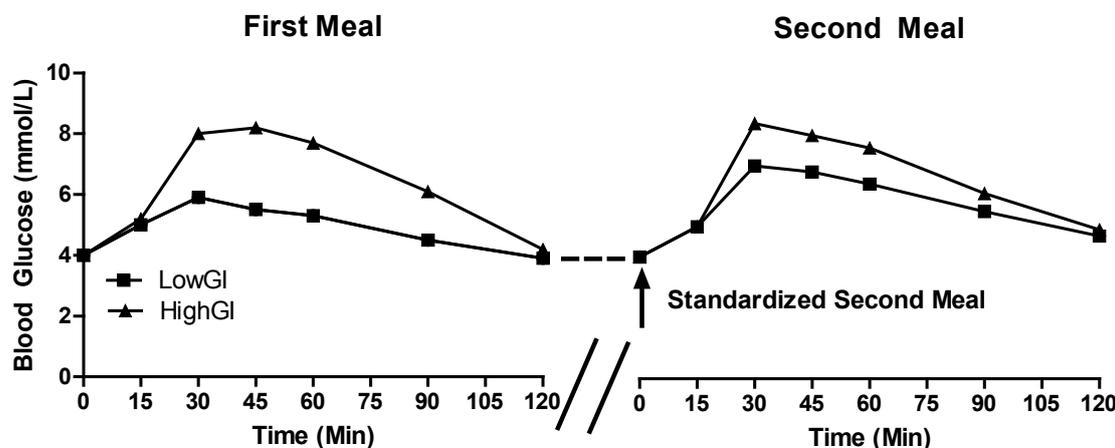


Figure 1: Example of blood glucose curves to a first and second meal in response to meals of high and low glycaemic indices. A meal with a low glycaemic index (lowGI) has a lower postprandial glycaemic response during the first meal compared with a high glycaemic index (highGI) meal and is capable of lowering the glycaemic response to a standardized second meal.

Glycemic index

The observation of a second meal effect was reportedly discovered in the early 20th century [17,18]. Research on the second meal effect has recently become more popular due to the fact that poor glycaemic control is linked to multiple health complications [19]. In 1988, Wolever et al. [15] studied the impact of meals with differing GIs on the second meal effect. The subjects consumed 2 different evening meals on separate occasions, with one of high (GI:105) and the other of low (GI:40.6) glycaemic index. Glycaemic response was then measured the next day following breakfast, to determine if the GI of an evening meal affected the glycaemic response of the subsequent morning meal. It was found that evening meals with a lowGI significantly lowered the mean PPGR to a breakfast meal the next morning compared to a meal with a highGI (6.36 vs. 6.91 respectively; $p < 0.05$).

Fiber

Recent research suggests that fiber may be a significant contributing factor that impacts PPGR, independent of the GI [20]. Fiber can help reduce the PPGR to a meal by slowing down the digestion rate or by reducing the amount of glucose that is absorbed in the small intestine [21]. Fiber and indigestible carbohydrates (resistant starch and dietary fiber) also have been shown to reduce the PPGR to a subsequent meal. This was examined by Granfeldt et al. [20] who compared three different evening meals with varying carbohydrate content (barley kernels, spaghetti, and white bread) to examine the effects of indigestible carbohydrates on GI and the influence each meal had on the PPGR to a breakfast meal the following morning. A spaghetti meal made of durum wheat was found to have a GI of 54, while the barley kernel meal had a GI of 53. The third meal, the reference white bread, had a GI of 100. The authors found that the barley meal, which contained high levels of indigestible carbohydrates, significantly reduced (-23%) the PPGR to the standardized breakfast meal compared to white bread or spaghetti, and concluded the reduction was due to the higher amounts of indigestible carbohydrates [20].

Indigestible carbohydrates have become a common explanation among researchers for the second meal effect. One mechanism by which indigestible carbohydrates is believed to be able to mitigate the glycaemic response to a subsequent meal (second meal effect) is through short chain fatty acids (SCFA) created by colonic fermentation

[14,22,23]. It has been shown that a spaghetti meal with a GI of 58 prior to 19.8 g of barley dietary fiber content being added resulted in a significantly lower glucose AUC during a second meal compared to the barley porridge meal (GI:97) [24]. In addition, the spaghetti with twice the barley dietary fiber content meal also led to significantly higher colonic fermentation as assessed by breath hydrogen, as well as butyrate (SCFA) levels compared to the barley porridge meal. The authors theorized that the SCFAs were responsible for the reduction in the PPGR to the standardized breakfast meal. Evidence supporting this theory includes a negative correlation between plasma butyrate and propionate with glycaemic measurements. However, there also was a positive correlation between fasting free fatty acid (FFA) levels and PPGR to the breakfast meal. The authors suggest that the FFAs influenced insulin sensitivity and therefore the glycaemic response to the breakfast meal. While this study did not provide evidence of a link between SCFAs and FFAs, other studies have suggested that SCFAs may suppress FFA concentration levels [22,25].

Brighenti et al. [22] also investigated the effects of indigestible carbohydrates on PPGR in a study that examined breakfast meals of lowGI, highGI, and highGI with lactulose sponge cakes. Lactulose was added to the third test meal due to the fact that it is indigestible yet highly fermentable. The authors found that PPGR in response to the breakfast meal was significantly lower for the lowGI meal compared to the other two treatments. The highGI with lactulose breakfast resulted in significantly lower PPGR at the 3 and 4 hour post-standardized lunch time periods compared to the highGI breakfast. The authors hypothesized that SCFAs may be responsible for delayed gastric emptying and that a delay in gastric emptying could cause the second meal effect. However, this effect was only significant in the lactulose group, while both the highGI with lactulose and lowGI breakfast resulted in colonic fermentation. In addition, the glycaemic measurements were not correlated with the rate of gastric emptying. Therefore, the delayed gastric emptying is believed to only play a secondary role in the influence on the second meal effect. Instead, it is believed that the SCFAs formed through colonic fermentation suppressed FFAs, therefore aiding in glucose disposal and the lowering of the PPGR to the lunch meal [22].

Liljeberg et al. [26] also observed a second meal effect on glycaemic control, but came to a different conclusion as to what was responsible

for the effect. The authors found that 2 of the 4 lowGI meals lowered blood glucose levels following a subsequent meal. Of those two meals one had a high indigestible carbohydrate content the other had a low content. It also was found that the spaghetti meal, which had the lowest PPGR to lunch, also had the fewest indigestible carbohydrates. In addition, two highGI meals that had higher levels of indigestible carbohydrates failed to cause a second meal effect. This led the authors to believe that fermentable carbohydrates are not responsible for the second meal effect. Instead, they suggest that the lowGI of the meal is responsible for the second meal effect, although it is evident that not all meals of lowGIs are equal in inducing the second meal effect.

In summary, while not all studies are in complete agreement, it appears that indigestible carbohydrates in lowGI foods are at least partially responsible for the second meal effect. Although the exact mechanism behind the second meal effect has yet to be elucidated, delayed gastric emptying caused by short chain fatty acids, and improved insulin sensitivity are two other possibilities that have been proposed.

Lactic acid

Lactic acid is produced during fermentation and has been shown to reduce PPGR to a single meal [27,28]. Najjar et al. [29] assessed the presence of organic acids (lactic acid) by measuring the pH of the bread and found that the sourdough bread had a lower pH than the white bread, indicating a greater amount of lactic acid. The authors also reported that the sourdough bread eaten as a breakfast meal resulted in a significantly lower PPGR to a lunch meal compared to the whole wheat and whole wheat barley breakfast meals. The sourdough bread breakfast also resulted in a significantly lower incretin (GLP-1 and GIP) response to the lunch meal compared to the other test breads. While insulin sensitivity has been shown to be increased by incretins (GLP-1) [30], this study did not find any significant difference in insulin response between the sourdough bread and the other test breads. Nor did they find any differences in insulin sensitivity index among the different test breads. Therefore, it is unlikely that changes in insulin sensitivity were responsible for the lower PPGR to the subsequent meal after a sourdough bread breakfast. Previous studies also have shown that organic acids may slow the rate of gastric emptying [28,31,32]. However, Najjar et al. [29] assessed gastric emptying through paracetamol absorption studies and found no significant difference between the sourdough bread and the other tests breads indicating a reduction in the rate of gastric emptying was not responsible for the reduced PPGR in these studies. In the end, the authors found a link between the sourdough bread and organic acids, and the second meal effect, but were unable to elucidate the exact mechanism behind the lower PPGR to a subsequent meal.

In another study examining the influence of lactic acid on the PPGR to a second meal, Ostman et al. [33] compared the impact of barley bread with and without lactic acid on the PPGR to a subsequent lunch meal. Consuming barley bread containing lactic acid at breakfast significantly reduced the glycemic response after breakfast and lunch when compared to the control breakfast. The authors suggested that prolonged starch digestion may have suppressed the concentration of FFAs in the plasma, which may aid insulin sensitivity as suggested by Wolever et al. [34]. Another possible explanation is that the lactic acid aided in the formation of SCFAs through colonic fermentation, which may impact gastric motility. However, due to the fact that there were only 4 hours between breakfast and lunch it is unlikely that this was enough time to ferment SCFAs [33]. Therefore, while there is evidence that consuming a meal containing lactic acid can aid in lowering the

PPGR to a subsequent meal the exact mechanism responsible for this effect is unclear.

Glycogen and insulin

Another possible explanation of the second meal effect is that it is caused by the suppression of FFAs and glucose being stored as glycogen. Jovanovic et al. [19] studied the postprandial glycemic and insulemic responses to a standard lunch meal on two separate occasions; with and without breakfast being consumed that same day. Glycogen was measured using ^{13}C magnetic resonance spectroscopy before lunch. Then 3 grams of [$U\text{-}^{13}\text{C}$] glucose was given at lunch and glycogen was measured again after lunch 2 and 5 hours later. It was found that eating breakfast suppressed FFAs and reduced the glycemic response (73%) to a standard lunch compared to not eating breakfast. It also was found that fasting glycogen levels were similar on days with and without breakfast. However, on days when breakfast was consumed, there was approximately 50% more glucose contributing to the formation of glycogen within 2 hours of eating lunch compared to days when no breakfast was eaten. Furthermore, this value was doubled within 5 hours of lunch on breakfast days. There also was an inverse correlation between FFA levels prior to lunch and glycogen signaling after lunch. The authors hypothesized that insulin release following a breakfast meal suppressed FFA concentrations, as well as increased insulin action, skeletal muscle glucose uptake, and glycogen storage.

Other blood markers

There is evidence that the second meal effect involves cytokines and hormones other than insulin. Nilsson et al. [23] reported that consuming an evening meal of ordinary barley kernel bread (GI:52) resulted in significantly lower concentrations of glucose, insulin, IL-6, and FFAs, as well as higher levels of GLP-1 and adiponectin compared to the white-wheat bread meal (GI:100). The authors speculated that a reduction in FFAs was responsible for the improvements seen in glucose tolerance the next morning, as FFAs are known to impair insulin sensitivity [35]. These improvements in glucose tolerance were thought to be in part through the insulin sensitizing effects of increased adiponectin and its ability to lower FFAs in circulation [36] and the reductions in IL-6, a known activator of adipose tissue lipolysis [37]. In addition, increases in GLP-1, which has been shown to reduce gastric emptying and increase insulin release [38], may also be a contributing factor in the second meal effect. Furthermore, breath hydrogen excretion revealed a potential role for colonic fermentation of indigestible carbohydrates and the accumulation of SCFAs. These all appear to be possible mechanisms that may have contributed to the lower FFA values and second meal effect seen in the ordinary barley kernel bread compared to the white wheat bread meals.

Second meal effect and type 2 diabetes

Although many of the studies presented in this review have utilized healthy subjects, the second meal effect has also been observed in subjects with insulin resistance and type 2 diabetes. Clark et al. [39] examined how high (GI:64) and lowGI (GI:56) breakfast meals influence the glycemic response to a standardized lunch in individuals diagnosed with type 2 diabetes. The lowGI meal, which contained psyllium soluble fiber, resulted in a significantly lower PPGR to the breakfast meal compared to the highGI breakfast meal but these differences did not persist after lunch. The same findings were observed for insulin and FFAs. While the lowGI breakfast meal containing psyllium fiber offered acute benefits in glucose, insulin, and FFA AUC values, it did not induce a second meal effect. These findings contradict those of Axelsen et al. [40] who found that carbohydrates in the form

of uncooked starch (slow digesting starch) consumed as an evening meal improved glycemic response in individuals with type 2 diabetes to a breakfast meal compared to white bread. Jovanovic et al. [41] also found that in individuals with type 2 diabetes, eating breakfast can lower PPGR to a lunch meal compared to not eating breakfast. They also reported that while eating breakfast did not influence insulin levels in individuals with type 2 diabetes, it did suppress FFA levels, which correlated with glucose AUC values. These findings suggest that FFAs may play a role in the second meal effect in this population.

Duration of the second meal effect

Knowing the duration of the second meal effect can be important, not only for individuals with type 2 diabetes, but also for healthy individuals trying to control their glucose excursions. Jenkins et al. [42] determined the Staub-Traugott effect, now called the second meal effect, lasted from breakfast to lunch (a 4 hour period) by showing that slow digesting carbohydrate breakfast meals improved glucose tolerance during a subsequent lunch. Others have shown that lowGI foods consumed in the evening can improve the glucose tolerance to a breakfast meal the following morning [15]. However, Nilsson et al. [14] found that the effect did not last from breakfast to dinner (9.5 hours). Therefore, additional information is still required to understand the dietary and population specific factors that may influence the duration of the second meal effect.

Summary and Conclusions

While the second meal effect is beginning to receive attention, it is likely that many health care providers and researchers are still unaware of this phenomenon. The second meal effect appears to be related to several mechanisms. Eating foods with lowGIs and indigestible carbohydrates have been shown to reduce postprandial glycemic responses, and can be a very useful tool for diabetes management. In addition, researchers conducting glycemic testing to meals or glucose challenges should understand the impact the second meal effect can have on their testing. Failure to carefully monitoring the GI and indigestible carbohydrate content of a subject's evening meals prior to morning testing may have profound effects on the results. As important and useful as the knowledge of the second meal effect is, it is important to continue research in this area and elucidate the exact mechanisms responsible.

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