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Jovanovic, A., Gerrard, J., & Taylor, R. The Second-Meal Phenomenon in Type 2 Diabetes. Diab Care. 2009;32:1199-1201.

What We Know, Think We Know, or Are Starting to Know

Of the things we "think we know", one that you may never have heard of is *the second meal phenomenon*. It takes the more official name of the 'Staub-Traugott effect', after the two researchers who replicated the initial finding, and was first described in the early 1920's. Despite the potential importance of this effect for metabolic health, a PubMed search of the Staub-Traugott effect yields only 19 results from a 100yr period, while searching the more colloquial 'second meal phenomenon' yields just 44 papers over the same period.

So what is this effect describing? And why could it be important?

The second meal phenomenon describes a physiological effect where glucose tolerance is significantly better after a prior exposure to rises in blood glucose [(1)]. The first descriptions of the effect were derived from research using sequential oral glucose tolerance tests [OGTT], where 75g glucose is ingested and blood glucose responses are monitored, all administered in the same day. What was noticed was that the rise in blood glucose in response to subsequent OGTT, despite the exact same amount of glucose being ingested, was much lower. Thus, the term 'second meal phenomenon', as it is the response to the second meal that is lower following the rise in blood glucose after a first meal.

While the second meal phenomenon has been consistently demonstrated in metabolically healthy humans [(1-4)], there have been questions over whether this effect is present as glucose tolerance diminishes, e.g., during the development and onset of type-2 diabetes [T2D]. If such a phenomenon is present, and daily postprandial glucose levels could be reduced, this could potentially have important implications of management of T2D.

The present study investigated whether the second meal phenomenon was present in participants with T2D.

The Study

8 participants with T2D completed 3 separate controlled test days. The 3 tests included:

- Day A: Standard breakfast followed by standard lunch
- Day B: No breakfast followed by standard lunch
- Day C: No breakfast followed by standard lunch + arginine infusion [administered 1hr before lunch]

The standard breakfast was comprised of milk, toast, orange juice, marmalade, and margarine, and consisted of the following macronutrients:

- 106g carbohydrate, 18g fat, 15g protein, 646kcal

The standard lunch was comprised of a cheese sandwich, orange juice, yogurt, and jellies, and consisted of the following:

- 103g carbohydrate, 30g fat, 40g protein, 858kcal

The test days were administered in random order, 2-4 weeks apart. Glucose, insulin, glucagon, and free fatty acids were the main outcomes of interest.

Results: Participants' mean age was 56yrs, BMI of 36, and average duration since diagnosis of T2D of 8.1yrs.

- ***Blood Glucose:*** During the 'Day A' condition [breakfast first], plasma glucose levels measured 2hr after lunch were 8.6mmol/L, compared to 10.9mmol/L at the same time during the 'Day B' [no breakfast condition]. The 'Day C' arginine infusion resulted in a 40% lower blood glucose response, compared to the lunch-only condition with no arginine. The overall area under the curve* for glucose after lunch when breakfast was consumed was ~95% lower compared to when lunch only was consumed [0.68mmol/L vs. 12.32mmol/L].

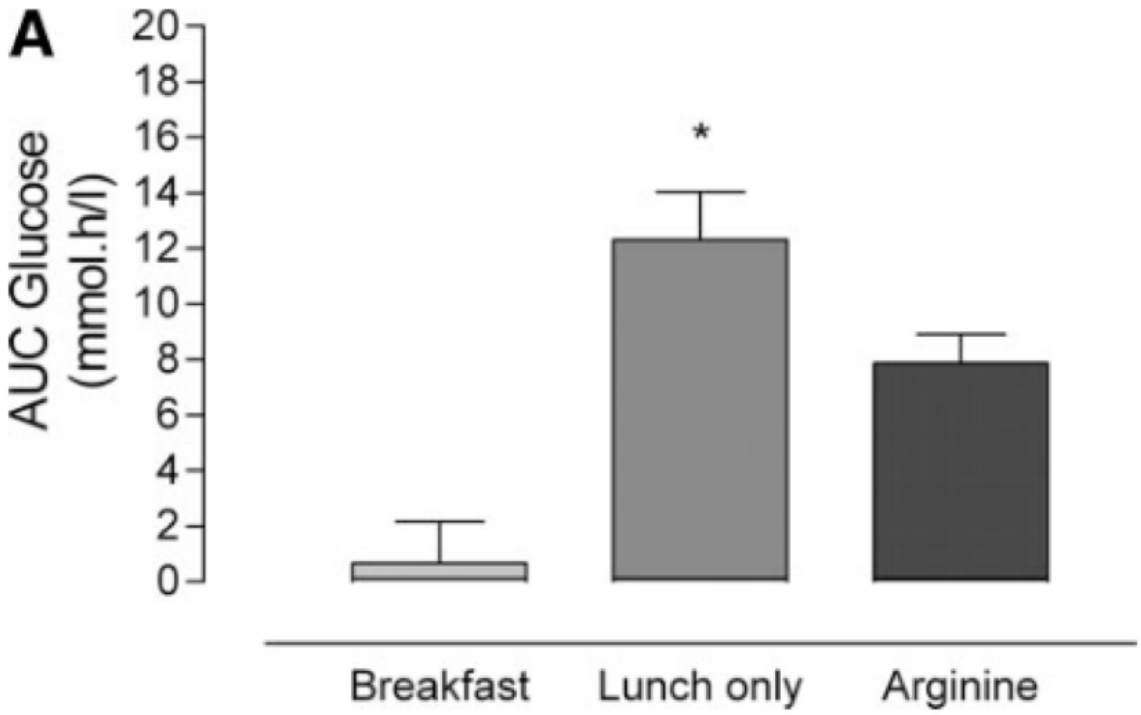
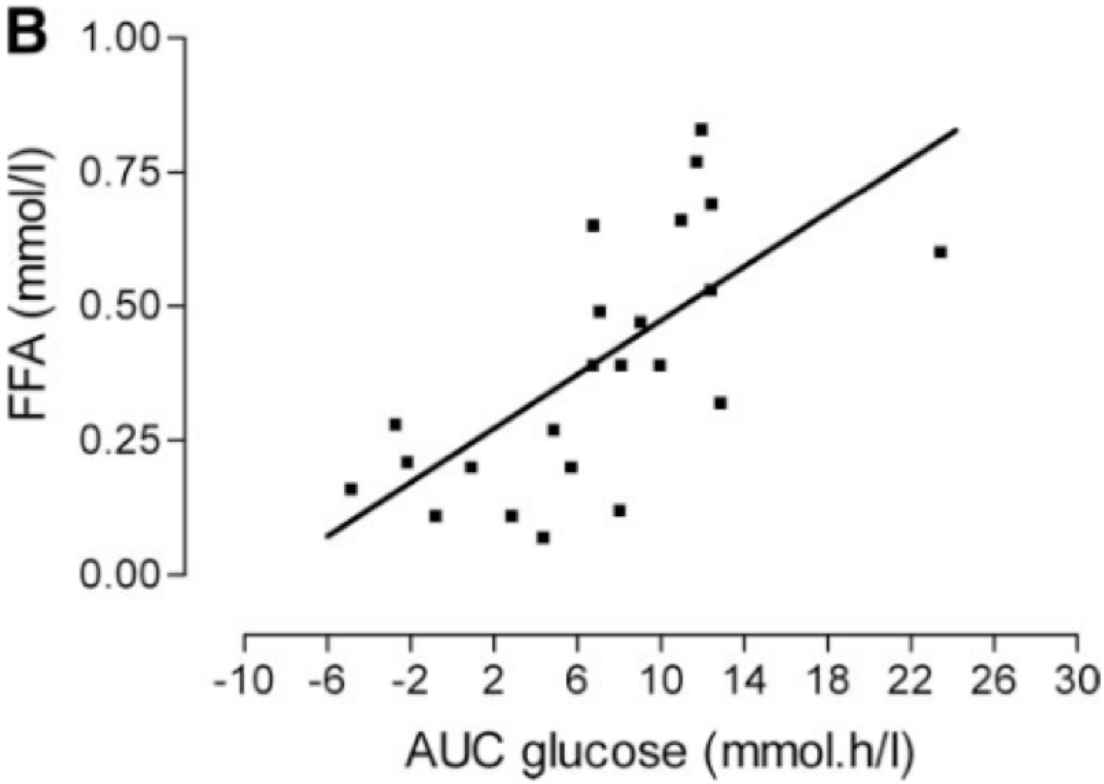


Figure *from paper illustrating the respective glucose area under the curve for the 3 test conditions, where 'Breakfast' indicates the AUC after lunch, following breakfast being consumed. The greatest magnitude of effect was observed in this condition, while the addition of an arginine infusion - arginine infusions have been shown to increase glucose disposal, potentially due to enhancing insulin secretion - resulted in a 40% lower glucose AUC after lunch, even though breakfast was omitted.*

- ***Insulin:*** There was no significant difference in fasting insulin level between test days, or in insulin levels following lunch.

- ***Free Fatty Acids:*** Fasting FFA levels were similar between days. Following breakfast on 'Day A', circulating FFA levels were significantly suppressed from 0.18mmol/L to 0.04mmol/L. However, on the 'Day B' [no breakfast] condition, FFA levels were 0.65mmol/L before lunch and 0.27mmol/L at 2hr after lunch. The 'Day C' arginine infusion 1hr before lunch led to a suppression of FFA before [0.35mmol/L] and after [0.18mmol/L] lunch. The pre-lunch concentration of circulating FFA strongly correlated to the blood glucose response after lunch [see ***Figure*** below].



*Geek Box: Area Under the Curve

If you read research, you'll come across the commonly used term 'area under the curve', or the 'AUC'. Imagine you had a 1-meter deep bucket, and you filled it with a slow tap. If you measured the level of water in the bucket at different time points, you would have the value for each time-point, e.g., 30cm, 60cm, 90cm. But the sides of the bucket in the first 10cm would be exposed to the water for longer, while the bucket is filling. So, if you wanted to calculate the total exposure of the bucket to water once it is full, you could use a mathematical formula to calculate this value. Rather than just have the concentration of water in the bucket at specific times, you now have the full concentration of the whole bucket over the time it took to fill. To convert this analogy, the AUC gives you a measure of the total exposure to a compound in circulation. For example, let's say you measure blood glucose in the 2-hours after a meal, every 30mins. This gives you 4 values. Each of those values alone doesn't give you a measure of the total exposure to blood glucose over that timeframe, because they are single values taken when in fact blood glucose was elevated and changing minute-to-minute. Therefore, to capture the full exposure over the entire 2-hour period, AUC calculations can be used for different measures, whether glucose, insulin, free-fatty acids, or perhaps a supplement. This provides a more informative picture of the level of exposure to a compound in circulation, whether a nutrient, hormone, or other metabolite or measure.

The Critical Breakdown

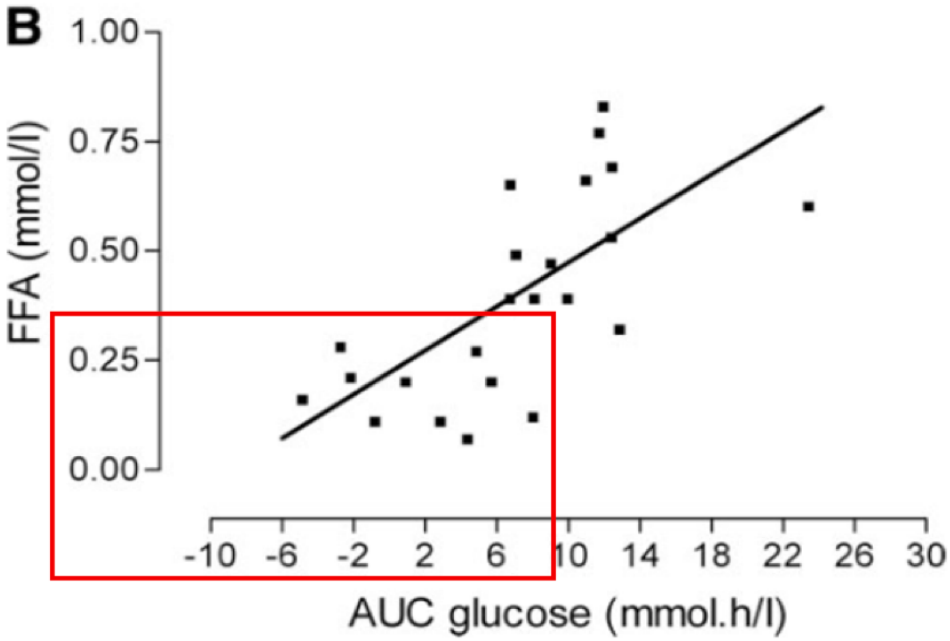
Pros: Previous studies examining the second meal phenomenon in T2D had used OGTT or venous infusions, however, the present study was a food-based intervention and examined blood glucose in response to food. The test days were tightly controlled for food and metabolic measures.

Cons: The test meals were similarly matched for carbohydrate, but not matched for protein and fat. Given that protein may exert effects on insulin secretion, this could have influenced the results. The higher fat content may also have reduced gastric emptying, thereby delaying the blood glucose response. The study had a very small sample size of n = 8. Oddly, the sex breakdown of the study participants was not provided.

Key Characteristic

It can be too common in nutrition papers for a number of outcomes to be reported as standalone statistical analysis. For example, let' s say blood glucose, insulin, cholesterol, and bodyweight are all measured. Each of these data sets will be analysed alone, generally with a paired t-test or an analysis of variance [ANOVA], depending on the study design. However, these measures may often correlate together: how strongly would, for example, blood glucose levels correlate with measured body fat? In this case, the required analysis is regression or correlation analysis. In a regression analysis, the value of one variable is predicted from the value of another variable, i.e., how much would Y be expected to change if we increased/decreased X by a given unit amount? Correlation analysis concerns finding whether there is an association between two variables.

The present study investigated the correlation between FFA levels before lunch and the blood glucose response after lunch. Below is the figure from the paper [as above], with the red square added for effect by myself.



On the bottom [X] axis is blood glucose area under the curve [AUC], which increases from left to right on the axis. On the left [Y] axis is circulating free fatty acid [FFA] levels, which increases from bottom to top on the axis. The solid black line that runs through the middle of the graph is the slope that represents the best 'fit' for the data, i.e., how the values on the Y-axis [in this case FFA] would best predict the values of the X-axis [blood glucose]. Each data point is then represented by a mark around the line, in this case black squares. The correlation is determined by an 'r number', which is a value between -1 to 1, with -1 being a perfect negative correlation, 0 being no correlation at all, and 1 being a perfect positive correlation. In this study, this analysis resulted in an r = 0.67, indicating a strong positive correlation between circulating FFA before lunch and the blood glucose response after lunch. If you focus on the box I have inserted in red, you' ll see the low FFA values of up to 0.25mmol/L within the triangle [on the left Y-axis], and you' ll see that each data point within the box which reflects this range of FFA also correlates [on the bottom X-axis] with a very low glucose AUC. If you then focus on the data points outside the red triangle, you' ll see that as FFA levels increase, the blood glucose AUC tends to increase. Now this is interesting because...

Interesting Finding

The relationship between the second meal phenomenon and circulating FFA levels provides an important insight into the relationship between fat and glucose metabolism. While we often tend to think of these exclusively, if we are thinking of relationships between blood glucose and another variable, that variable will tend to be insulin. However, this overlooks the relationship between circulating fat and glucose tolerance. Back in 1999 in an elegant metabolic ward study, Linda Morgan et al. [5] demonstrated that the change in insulin sensitivity over the course of the day, from higher in the morning to impaired in the evening, mirrored the variation in circulating FFA across the day. FFA levels tend to peak in the early hours of the day and morning as the body continues through an overnight fasted state, releasing stored fatty acids for energy. Thus, omitting breakfast leads to a continued elevation in circulating FFA levels, which has also been shown in participants with T2D [6,7]. As elevations in FFA induce insulin resistance, this provides a mechanistic explanation for the impaired glucose tolerance observed in participants in T2D following a lunch meal, when breakfast has been omitted [6,7]. The suppression of FFA in response to a morning meal appears to have a legacy effect over the remainder of the day, and lower FFA levels before lunch as a result of a prior meal are consistently associated with reduced blood glucose responses to the lunch meal [6,7].

Relevance

The study was the first to directly confirm the existence of the second meal phenomenon in T2D. However, a number of subsequent studies have shown the same relationship. For example, Lee et al. [6] found that breakfast consumption in participants with T2D resulted in a rapid suppression of circulating FFA levels, which remained low right up to lunch and rose only slightly in response to lunch, contributing to a significantly reduced post-lunch glucose response.

What is interesting is that this relationship does not appear to be mediated by insulin secretion, rather it appears to be enhanced by the suppression of FFA [as discussed above], and enhanced skeletal muscle glycogen uptake [3]. The research group behind the present study also conducted a tightly controlled study to investigate the second meal phenomenon and glycogen storage, and found a 50% greater rate of glycogen uptake into skeletal muscle in the 2hr period after lunch following a prior breakfast meal, compared to when lunch was consumed alone [3]. The post-lunch glucose response was also significantly attenuated, and both the reduced post-lunch glucose response and the enhanced skeletal muscle glycogen uptake correlated strongly with FFA levels before lunch, which had been significantly reduced following the prior breakfast meal [3].

Perhaps the most profound finding in this study is the difference in the glucose AUC after lunch following prior breakfast, compared to lunch alone: 0.68mmol/L vs. 12.32mmol/L. Often, percentage differences may be misleading and in this case the reported ~95% difference is obviously a huge percentage, but the absolute values are profoundly different, and of considerable relevance to blood glucose management in T2D. Although not quite the same percentage difference, substantial magnitude of effects have been observed in other studies testing this hypothesis: Jakubowicz et al. found that the 3hr glucose AUC was 36.8% and 26.6% higher after lunch and dinner, respectively, when breakfast was omitted compared to when breakfast was consumed, in participants with T2D [7].

Despite the potential explanation in suppressed FFA and enhanced glycogen uptake, there may be a role for insulin: Lee et al. [6] showed that the insulin response after lunch was enhanced following a prior breakfast. Ultimately, the mechanisms of the second meal phenomenon remain to be fully elucidated, and further research will be needed with larger sample sizes to fully determine the efficacy of this concept in diabetes management.

Application to Practice

While the management of T2D is within the remit of clinical nutrition, it is also important to remember that diabetes is spectrum from early impaired glucose tolerance all the way to diagnosis. While the merits of breakfast consumption are debatable for otherwise healthy individuals, there is a consistent body of evidence that suggests that in individuals with impaired glucose tolerance, greater morning energy intake may result in beneficial effects on acute blood glucose responses to subsequent meals and, as a result, better 24hr blood glucose regulation.

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