ALINEA

NUTRITION

DECEMBER 2020

www.alineanutrition.com

TABLE OF

CONTENTS

Jakubowicz D, Wainstein J, Ahren B, Landau Z, Bar-Dayan Y, Froy O. Fasting until noon triggers increased postprandial hyperglycemia and impaired insulin response after lunch and dinner in individuals with type 2 diabetes: a randomized clinical trial. Diabetes Care. 2015;38(10):1820–1826.

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

The variation in glucose tolerance and insulin action over the course of the day [referred to as 'diurnal variation' in research] is a well-established characteristic of human metabolism. Experimental research has shown that insulin responses are amplified during the early part of the day, and impaired at night [(1)]. Glucose tolerance is also amplified during the early part of the day, and these effects may be driven by circadian rhythms in peripheral tissues, i.e., the pancreas, liver, and skeletal muscle, being optimised for intake earlier in the day [(2,3)].

Interestingly, this diurnal variation in glucose tolerance may be independent of the daily fasting duration, i.e., it is more specific to the 'clock time' of the day [(4)]. Thus, whether extended fasting until the evening would still result in impaired glucose tolerance at that time of the day, while glucose tolerance in the morning would still be more sensitive, despite a shorter overnight fast. The improved glucose and insulin responses earlier in the day suggests that timing food intake to this period may be important for metabolic health.

Intervention studies have shown significant differences in glucose and insulin responses earlier vs. later in the day, and also improved responses to subsequent meals over the course of the day when a larger first meal is consumed [(5,6)]. These improved parameters of blood glucose regulation and insulin action may have important implications for diabetes management.

The present paper examined the effects of consuming breakfast compared to skipping breakfast and fasting until lunch, on glycemic control in participants with type-2 diabetes ['T2DM'].

The Study

The intervention was a randomised, open-label*, crossover, within-subject clinical trial. The 26 participants were included with the following criteria:

- Aged between 30-70yrs
- T2DM for <10yrs
- HbA1c of 7-9% [HbA1c provides a measure of blood glucose levels over the previous 2 months, rather than day-to-day fluctuations; >6.5% is considered diabetic]
- BMI of 22-35
- Habitual breakfast consumers

The participants had not worked shifts within 5-years preceding the study, and had not crossed time zones for a month prior [to minimise any residual impact of jet-lag on circadian rhythms]. Participants were not on insulin, but were included if they were taking metformin, and discontinued their metformin dose 2-days prior to the interventions.

*Geek Box: Open Label Trials and Within-Person Comparisons

'Open label' means that both the researchers and the participants know what intervention the participants are receiving. Consequently, it is completely unblinded, compared to a single-blind trial, where the researchers know what intervention the participants are receiving, or a double-blind trial, where neither researchers or participants know. Open-label trials are often used to compare treatments, or interventions. For example, comparing Drug A vs. Drug B, or comparing Diet A vs. Diet B. While blinding is desirable as a means to reduce bias being introduced into a study, it is not always feasible, particularly in nutrition research where participants are being asked to comply with a specific intervention. In the present study, the researchers wanted to compare the effects of consuming breakfast to skipping breakfast and fasting until lunch. It would have be unfeasible, given the testing protocols involved, to blind researchers and participants to this; hence the trial was conducted as an open-label study, with participants randomised to either the breakfast or breakfast skipping group first, before crossing over to the opposite of which intervention they started with. 'Within-subject' means that each subject was compared against themselves; their data from one intervention compared to the other. It means the results are less influenced by differences from person to person.

The participants underwent two intervention test days, separated by 2-4 weeks. The first intervention included breakfast ['**YesB**'], where participants consumed three isocaloric [i.e., having the same amount of calories] meals with:

- **breakfast at 0800hrs**
- **lunch at 1330hrs**
- **dinner at 1900hrs**

In the second intervention, participants skipped breakfast and fasted until lunch [' **NoB**']

- **fast until lunch**
- **lunch at 1330hrs**
- **dinner at 1900hrs**

All meals were matched for energy [701kcal] and macronutrients [26% protein, 54% carbohydrate [7% fibre], 20% fat].

For the two days preceding each test, participants were provided with meals and asked to follow the meal schedule of the forthcoming test day at home, i.e., before YesB, 3 meals at 0600-0830hrs, 1230-1430hrs, 1830-2030hrs; before NoB, 2 meals at 1230-1430hrs, 1830-2030hrs. Participants self-reported compliance to this in-home preschedule to the study dietitian on test days.

On test days, patients arrived fasted at 0700hrs; blood samples were taken at 0800hrs [before breakfast in the 'YesB' intervention], and then 15min, 30min, 60min, 90min, 120min, and 180min after eating commenced; these same sample time points were taken in the ' NoB' intervention, except participants were fasted for all samples. The sample schedule was repeated for both lunch and dinner meals.

The primary outcome was post-prandial* blood glucose responses after lunch and dinner comparing the 'YesB' to the ' NoB' interventions. Secondary outcomes included insulin, GLP-1, free-fatty acids [FFA], C-peptide, and glucagon levels.

*Geek Box: Post-Prandial Metabolism

'Post-prandial' refers to the period after eating a meal. Therefore, 'post-prandial glycaemia' refers to blood glucose levels after a meal, while 'post-prandial lipaemia' refers to blood fat [lipid] levels after a meal. Post-prandial responses to food intake have been recognised since the 1950's as a factor influencing metabolic health. As early as 1979, dietary influences on cardiovascular disease were described as a "post-prandial phenomenon". Recently, there is an increasing focus on post-prandial metabolism. Most assessments of health use fasted samples, for example fasted blood glucose or triglycerides. However, many people spend over 12hrs a day, and Satchin Panda's research has suggested up to 15hrs a day, in a post-prandial state. This means fasted samples may only reflect a small snapshot of the overall day, and may not capture how well individuals respond to meals over the course of the day. Post-prandial glucose and lipid levels may provide a more refined risk assessment for cardiovascular disease, and diabetes progression. What is emerging is the the post-prandial period is a crucial factor influencing metabolic health.

Results: 22 participants [12 male, 10 female] completed the study.

Compared to the 'YesB' breakfast-inclusive intervention, blood glucose peaks after lunch and dinner during the 'NoB' condition [i.e., following breakfast skipping] were 38.9% and 24.9% higher, respectively.

The glucose area-under-the-curve* ['AUC'] after lunch and dinner in the ' NoB' condition were 36.8% and 26.6% higher, respectively, compared to the 'YesB' condition.

On the 'NoB' day, insulin AUC was 17.9% and 7.9% lower after lunch and dinner, respectively. On the 'NoB' day, the peak in insulin levels was delayed by 30min and 60min, and the peak insulin value was 24.7% and 10.8% lower, after lunch and dinner, respectively.

On the ' NoB' day, the AUC for free-fatty acids [FFA] were 41.1% and 29.6% higher after lunch and dinner, respectively. FFA levels during the morning [0800-1100hrs] on the ' NoB' day were 1,787.1% higher compared to 'YesB' ; the AUC for blood glucose after lunch and dinner correlated significantly with the AUC for FFA during the morning fasted period [0800-1330hrs].

Compared to ' NoB' , glucose and insulin values were 35.7% and 68.6% higher after breakfast [further discussion under 'Interesting Finding' , below].

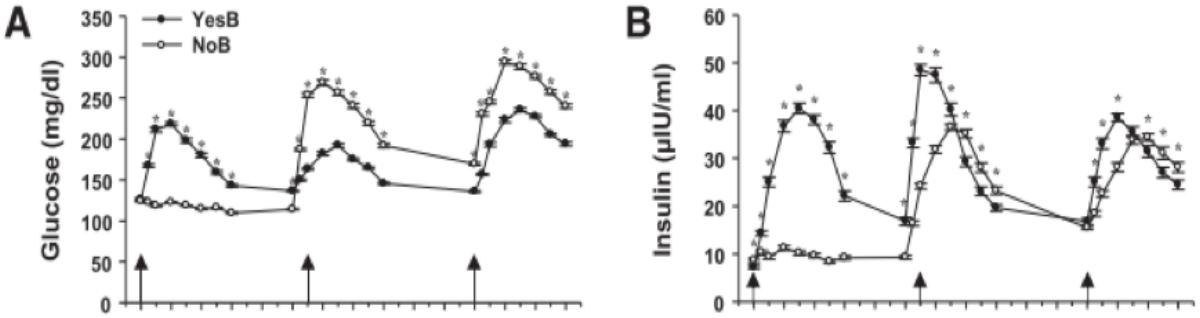

Figure *from paper illustrating the difference in blood glucose levels* ***(left)*** *and insulin* ***(right)*** *comparing breakfast consumption vs. breakfast omission; breakfast omission results in significantly greater increases in blood glucose levels following lunch and dinner, compared to the blood glucose increases following breakfast consumption. In addition, the insulin response is much lower in response to lunch. The combination of elevated glucose and lower insulin is indicative of impaired glucose tolerance and insulin sensitivity.*

*Geek Box: The 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 over the period it is filling, 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 rather crude 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 the levels of glucose in the blood 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. The simplest way of thinking about AUC is this: the total exposure over a certain timeframe.

The Critical Breakdown

Pros: The study had a good design; the crossover meant each participants served as their own control, minimising any between-person variations. Diets during the interventions were controlled, in particular providing the same energy content at lunch and dinner on both days, which allowed for the responses to those meals to be comparable against the same level of energy [see more under 'Key Characteristic']. The precise sampling schedule allowed the researchers to capture post-prandial responses over the course of the entire day. The study was conducted in a highly relevant clinical population, with onset T2DM, and was adequately powered in numbers of completing participants to detect differences between the groups.

Cons: The in-home schedule prior to the intervention days was quite wide in terms of food timing, with 2hr windows to consumed each meal. While participants were provided with their meals, and the cross-over design may have mitigated any differences, tightly controlled chrono-nutrition studies indicate that circadian rhythms in peripheral tissues important for metabolism, like the liver and pancreas, can shift quickly, particularly with delayed meal timing [7]. Thus, if certain participants ate all of their meals at 0830hrs, 1430hrs, and 2030hrs, and certain ate at 0600hrs, 1230hrs, and 1830hrs, these differences could influence responses.

Compliance during the in-home schedule was also self-reported, and although food was provided for these days, deviation from the protocol can never be fully ruled out.

Further, while tightly controlled nutrition interventions will always be shorter in duration, this study ultimately represents two-single day interventions. In this regard, it is difficult to extrapolate the results beyond the acute responses shown.

Finally, the open-label nature of the study means the potential for bias cannot be entirely ruled out, although the study does not give rise to any immediate concerns in this regard.

Key Characteristic

Maintaining the energy content of the lunch and dinner on the ' NoB' days allowed for a more refined test of the interaction between meal timing, and breakfast skipping vs. breakfast intake.

A previous study by Kobayashi et al. [8] with a similar design and two-single day interventions, evaluated the effects of breakfast skipping on blood glucose regulation and matched both diets for total energy [2190kcal]. .

In the current study under review, matching energy and carbohydrate content of the lunch and dinner, and not compensating for the energy missed at breakfast, allowed for a more

However, while the breakfast intervention in that study had three meals with even energy distribution per meal [circa.700kcal], the lunch and dinner meals on the breakfast skipping day contained circa.1100kcal each. The study found that breakfast skipping resulted in increased overall 24hr blood glucose levels, and the post-prandial glucose response after dinner was greater than after lunch. However, these effects could have reflected the greater energy content [700kcal] and carbohydrate content of the lunch and dinner [163g vs. 115g, respectively] on the breakfast skipping days.

In the current study under review, matching energy and carbohydrate content of the lunch and dinner, and not compensating for the energy missed at breakfast, allowed for a more accurate test of the effects of breakfast skipping for blood glucose regulation at subsequent meals, in diabetic participants.

Interesting Finding

Despite the higher glucose and insulin responses to breakfast, this would be entirely expected given the comparison was against a fasted morning state; what is very interesting is the fact that glycaemic responses to subsequent meals was greatly attenuated following breakfast consumption.

What may explain this is a term know as the "second meal phenomenon", which extends an observation first described 100yrs ago, known as the ' Staubb-Taugott Effect' : that the blood glucose response to a second meal is enhanced by a previous carbohydrate meal.

However, until recently the presence of a ' second meal phenomenon' in diabetics was controversial [9,10]. A number of factors may underpin this ' second meal phenomenon' . The first is that the insulin response to a second meal may be more rapid after consumption of a prior meal [10]. In a well-controlled meal tolerance test study, the peak insulin level after the second meal occurred 45min earlier after the second meal than after the first meal, which peaked at 90 min [10]. In the present study, skipping breakfast delayed the peak in insulin levels after lunch and dinner by 30min and 60min, respectively.

The second factor relates to the suppressing effect of insulin on circulating free-fatty acids, which was demonstrated by Roy Taylor' s diabetes research group at Newcastle University. Jovanovic et al. showed that the rise in blood glucose after lunch was 95% less when lunch was preceded by breakfast, and this effect related to the suppression of FFA following breakfast [9].

This is also consistent with the present study; breakfast consumption suppressed FFA levels, and skipping breakfast resulted in 41.1% and 29.6% higher levels of FFA after lunch and dinner, respectively. This is consistent with previous research showing that, from a circadian perspective, circulating FFA display diurnal rhythms that mirror glucose rhythms; glucose rhythms are amplified in the morning, while FFA are suppressed during the feeding/day phase in humans and peak during the biological night [11]. Hence, extending the morning fast results in significantly elevated FFA levels, which may contribute to impaired glucose and insulin responses to meals later in the day [9,11].

Finally, the benefit to this legacy effect of a first meal on subsequent meals may be dependent on the timing of that meal being early in the day, i.e., breakfast. This is due to the inherent circadian variation in glucose metabolism, and hormones under circadian control that are important factors for insulin release, i.e., GLP-1 and GIP, which is significantly greater in the morning than evening, and has been shown to enhance insulin responses in the morning vs. afternoon [12].

Relevance

While most research for both diabetes and cardiovascular disease has focused on fasting measures [i.e., blood glucose and blood lipid monitoring], recently there is a strong case emerging that post-prandial metabolism is an important determinant of metabolic risk. In diabetes, from 31% to up to 70% of HbA1c values, a marker of long-term blood glucose regulation, are explained by post-prandial blood glucose levels [13].

More particularly, post-prandial glucose levels are more predictive of poor 24-hrblood glucose regulation in diabetics with mild to moderate elevated blood glucose levels, whereas fasting levels contribute more to 24-hr blood glucose levels in severe diabetes [13]. Further, post-prandial glucose levels are associated with increased cardiovascular and diabetic complications in persons with impaired glucose tolerance or mild-moderate diabetic control [14]. Thus, interventions with the potential to improve overall 24hr blood glucose levels may be important in the clinical picture of diabetes management.

In the present study, there was a clear pattern of improved post-prandial glycaemia following breakfast consumption compared to breakfast skipping. While calories were matched across the day in the present study, the same research group previously showed that consuming a high-energy breakfast led to significant reductions in daily blood glucose levels compared to a high-energy dinner [5].

In response to breakfast skipping, the significant increase in post-prandial glucose, combined with the decreased insulin secretion and elevation in free-fatty acids, are all indicative of insulin resistance and impaired blood glucose regulation.

T2DM has long had a glucose-focused view of its development, however, this is insufficient to explain the development of the condition and elevated lipids contribute significantly to impaired glucose tolerance and deteriorating beta-cell function [15]. Diabetes management generally remains focused on calorie balance first, with emerging support for carbohydrate reduction/restriction, or in severe cases very-low calorie liquid diets [16]. Meal timing and distribution of energy may provide an additional effective strategy for T2DM management, through a combination of the ' second meal phenomenon' , suppression of FFA, and improved post-prandial glucose responses from a first meal when consumed early in the day in sync with the enhanced circadian variation in blood glucose regulatory processes.

Application to Practice

This is a study in a specific population with a condition characterised by disordered blood glucose regulation, and the applicability of the findings are appropriately confined to this patient population. In this respect, however, this study suggests that consideration of meal patterning may be an important and accessible intervention to improve glycemic control in the context of diabetes management. Consideration could extend to persons presenting with impaired glucose tolerance/prediabetes.

References

1. Lindgren O, Mari A, Deacon C, Carr R, Winzell M, Vikman J et al. Differential Islet and Incretin Hormone Responses in MorningVersusAfternoon after Standardized Meal in Healthy Men. The Journal of Clinical Endocrinology & Metabolism. 2009;94(8):2887-2892.

2. Morris C, Yang J, Garcia J, Myers S, Bozzi I, Wang W et al. Endogenous circadian system and circadian misalignment impact glucose tolerance via separate mechanisms in humans. Proceedings of the National Academy of Sciences. 2015;112(17):E2225-E2234.

3. Morgan L, Aspostolakou F, Wright J, Gama R. Diurnal Variations in Peripheral Insulin Resistance and Plasma Non-Esterified Fatty Acid Concentrations: A Possible Link?. Annals of Clinical Biochemistry: An international journal of biochemistry and laboratory medicine. 1999;36(4):447-450.

4. Hulmán A, Færch K, Vistisen D, Karsai J, Nyári T, Tabák A et al. Effect of time of day and fasting duration on measures of glycaemia: analysis from the Whitehall II Study. Diabetologia. 2012;56(2):294-297.

5. Jakubowicz D, Wainstein J, Ahrén B, Bar-Dayan Y, Landau Z, Rabinovitz H et al. High-energy breakfast with low-energy dinner decreases overall daily hyperglycaemia in type 2 diabetic patients: a randomised clinical trial. Diabetologia. 2015;58(5):912-919.

6. Jakubowicz D, Landau Z, Tsameret S, Wainstein J, Raz I, Ahren B et al. Reduction in Glycated Hemoglobin and Daily Insulin Dose Alongside Circadian Clock Upregulation in Patients With Type 2 Diabetes Consuming a Three-Meal Diet: A Randomized Clinical Trial. Diabetes Care. 2019;42(12):2171-2180.

7. Wehrens S, Christou S, Isherwood C, Middleton B, Gibbs M, Archer S et al. Meal Timing Regulates the Human Circadian System. Current Biology. 2017;27(12):1768-1775.e3.

8. Kobayashi F, Ogata H, Omi N, Nagasaka S, Yamaguchi S, Hibi M et al. Effect of breakfast skipping on diurnal variation of energy metabolism and blood glucose. Obesity Research & Clinical Practice. 2014;8(3):e249-e257.

9. Jovanovic A, Gerrard J, Taylor R. The Second-Meal Phenomenon in Type 2 Diabetes. Diabetes Care. 2009;32(7):1199-1201.

10. Lee S, Tura A, Mari A, Ko S, Kwon H, Song K et al. Potentiation of the early-phase insulin response by a prior meal contributes to the second-meal phenomenon in type 2 diabetes. American Journal of Physiology-Endocrinology and Metabolism. 2011;301(5):E984-E990.

11. Morgan L, Aspostolakou F, Wright J, Gama R. Diurnal Variations in Peripheral Insulin Resistance and Plasma Non-Esterified Fatty Acid Concentrations: A Possible Link?. Annals of Clinical Biochemistry: An international journal of biochemistry and laboratory medicine. 1999;36(4):447-450.

12. Lindgren O, Mari A, Deacon C, Carr R, Winzell M, Vikman J et al. Differential Islet and Incretin Hormone Responses in MorningVersusAfternoon after Standardized Meal in Healthy Men. The Journal of Clinical Endocrinology & Metabolism. 2009;94(8):2887-2892.

13. Monnier L, Lapinski H, Colette C. Contributions of Fasting and Postprandial Plasma Glucose Increments to the Overall Diurnal Hyperglycemia of Type 2 Diabetic Patients: Variations with increasing levels of HbA1c. Diabetes Care. 2003;26(3):881-885.

References

14. 14. Cavalot F, Petrelli A, Traversa M, Bonomo K, Fiora E, Conti M et al. Postprandial Blood Glucose Is a Stronger Predictor of Cardiovascular Events Than Fasting Blood Glucose in Type 2 Diabetes Mellitus, Particularly in Women: Lessons from the San Luigi Gonzaga Diabetes Study. The Journal of Clinical Endocrinology & Metabolism. 2006;91(3):813-819.

15. Taylor R. Causation of Type 2 Diabetes — The Gordian Knot Unravels. New England Journal of Medicine. 2004;350(7):639-641.

16. Guess N. Dietary Interventions for the Prevention of Type 2 Diabetes in High-Risk Groups: Current State of Evidence and Future Research Needs. Nutrients. 2018;10(9):1245.