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Jakubowicz D, Landau Z, Tsameret S, Wainstein J, Raz I, Ahren B, Chapnik N, Barnea M, Ganz T, Menaged M, Mor N, Bar-Dayan Y, Froy O. 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 Dec;42(12):2171-2180.

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

Strategies to reduce overall time spent in a hyperglycemic [i.e., elevated blood glucose] state are of paramount importance to the management of type-2 diabetes [T2D]. The hallmark of progression from impaired glucose tolerance to a diagnosis of T2D is the progressive decline in the capacity of pancreatic beta-cells to produce insulin, to respond to and maintain blood glucose levels within normal ranges [(1)]. The ability of different interventions to reduce the magnitude of hyperglycemia, over a whole day and after each meal, are thus of particular interest to T2D research.

A number of strategies are potentially available to lower the burden of high blood glucose levels, including macronutrient manipulation [low-carbohydrate or very low-fat diets], and meal timing [(2)]. More recent research has looked at additional factors with the overall umbrella of meal timing, in particular the distribution of energy between meals over the day and the effects of breakfast consumption vs. breakfast omission [(3-5)].

The research group of Oren Froy and Daniella Jakubowicz in Israel have contributed a significant body of work to this area. A 2015 study from this group demonstrated that distribution of energy over the day was an important factor in overall 24hr glycemic control in participants with T2D [(5)]. In this study, two dietary regimes were compared: a front-loaded diet with 700kcal at breakfast, 600kcal at lunch, and 200kcal at dinner, compared to the reverse [200kcal breakfast/700kcal dinner, with lunch the same]. The front-loaded energy intervention resulted in a 20% lower whole day glucose area under the curve [AUC]*, and the 700kcal breakfast resulted in a 24% lower glucose AUC compared to the 700kcal dinner.

*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 Study

Male and female adults with the following criteria were enrolled in the study:

- Aged 25yrs and over
- A diagnosis of T2D
- Treated with insulin for a minimum of 1yr prior to the intervention
- Treated with a total daily insulin dose* [TDID] of >25 units for at least 3 months prior to the study
- HbA1c of >6.5% [the threshold for diabetes]

The study was a randomised, parallel-arm [where both intervention and control run at concurrently] intervention conducted over 15-weeks. The first 3-weeks consisted of screening, followed by 12-weeks of the intervention. Participants were randomly assigned to one of two diets:

- 3-meals per day ["3M"], with calories and carbohydrate front-loaded to breakfast
    - 700kcal breakfast [50% daily carbohydrates]
    - 600kcal lunch [40% daily carbohydrates]
    - 200kcal dinner [10% daily carbohydrates]
    - HbA1c of >6.5% [the threshold for diabetes]

- 6-meals per day [“6M”], with calories and carbohydrates equally distributed across meals over the day
    - Breakfast, lunch, and dinner: 20-25% energy [23% daily carbohydrates]
    - 3 snacks: 10% energy [10% daily carbohydrates]

Both diet groups were assigned a 500kcal per day energy deficit, and a macronutrient composition of 25% protein, 35% fat, 40% carbohydrate. Participants in both groups were asked to consume meals within the following time windows:

- Breakfast: Before 09.30hr
- Lunch: 12.00 - 15.00hr
- Dinner: 18.00 - 20.00 hr

The 6M group consumed the 3 additional snacks at 11.00, 17.00, and 22.00hr.

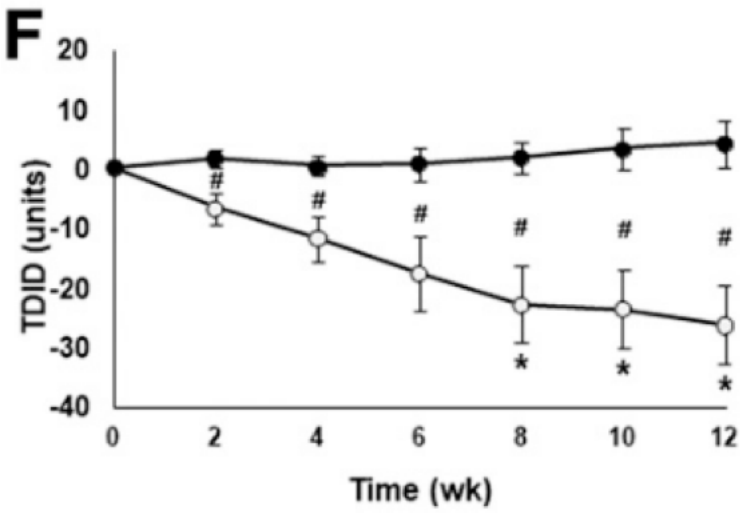
The primary outcome of the study was changes in TDID. Secondary outcomes included body weight, glycemic control, circadian gene expression, appetite and cravings.

*Geek Box: TDID

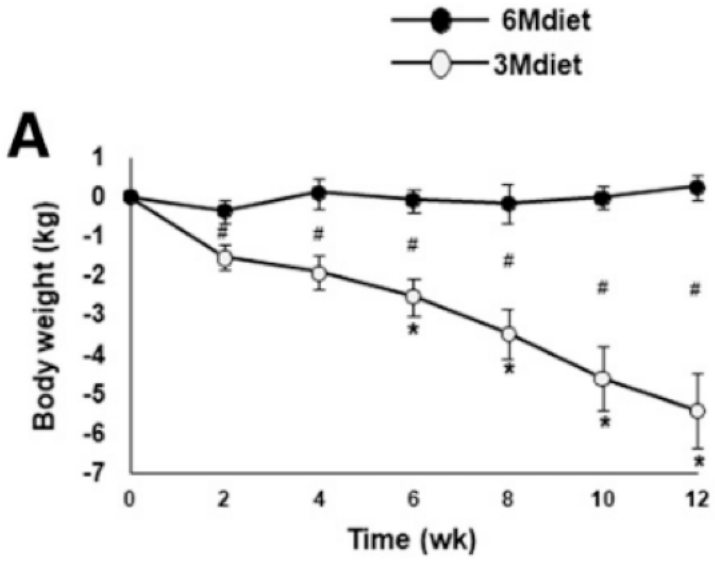
Insulin doses are prescribed for the management of both type-1 diabetes and type-2 diabetes. On average, one unit dose of insulin can dispose of around 12-15g of carbohydrate, but this can range depending on individual insulin sensitivity. Insulin doses need to be titrated according to the individuals level of diabetic control. Insulin is required for both basal insulin requirements for overnight and between meals, to maintain blood glucose homeostasis, and in response to meals to reduce blood glucose levels back into normal ranges. Thus, insulin doses reflect both of these factors: there is a ‘background’ dose for controlling overnight glucose levels and for suppressing hepatic glucose production [which normal insulin would do when the pancreas is functioning], and this represents around 50% of daily insulin requirements. Then there are bolus daily doses required on top of the background dose, which is to cover the postprandial response to meals and snacks, and this represents the balance of daily insulin requirements. For T2D, it is possible - depending on the level of diabetes control - to have individuals require only a background dose, only the bolus doses, or both. One distinction between the two, is that the background doses tend to use long-acting in the form of injections, while the bolus doses for meals tend to be rapid acting insulin drugs. However, the use of insulin pumps [infused under the skin] for the background dose tends to utilise fast-acting insulin.

Results: 28 participants [17 male, 11 female] completed the study [14 in each group]. Average age was 68.8yrs, and participants had T2D for an average of 19yrs, were treated with a TDID of 66 units per day, and on insulin for 7yrs. Baseline HbA1c was 8.1%

TDID: The 3M group had a significant reduction in insulin units by 26 units [from 60 to 34 units per day] at 12-weeks. Conversely, the 6M diet increased dose by 4 units. See ***Figure*** below for differences between groups:



Weight: After 12-weeks, weight loss was 5.4kg in the 3M group vs. 0.3kg weight gain in the 6M group. In the 3M group, 12/14 participants lost >2kg, compared to just 2/14 in the 6M group. See ***Figure*** below for differences between groups:



Glycemic Control:

- HbA1c decreased from 8.1% to 7.2% in the 3M group, while there was no significant decrease in the 6M group.
- Mean 24-hour blood glucose levels decreased by 40mg/dL after 12-weeks in the 3M group, with no significant change during 6M.
- There was a significant reduction in daily hyperglycemia in the 3M group, from 8hr 59min at baseline to 3hr 3min at 12-weeks. There was no change in the 6M group.
- In the 3M group, time spent in a normal blood glucose level ranges increased from 14hr

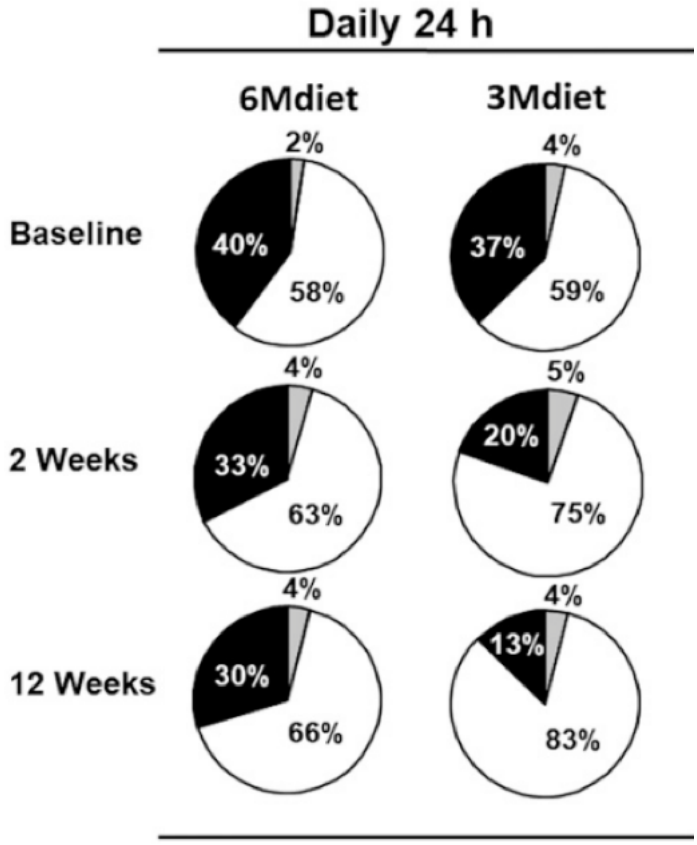


Figure *from paper illustrating the change in glucose ranges over a full 24hr day from baseline to the the end of the intervention. In the pie charts, black represents a range of >10mmol/L [180mg/dL], i.e., hyperglycemia. White represents 3.9-10mmol/L [70-180mg/dL], which covers normal glucose ranges [generally up to 6.5mmol/L (100mg/dL)] up to the threshold for hyperglycemia. The grey indicates hypoglycemia, i.e., low blood glucose ranges. Paying attention to the black slice of the pie, you can see in the 3M group the significant reduction of 24hr hyperglycemia from 37% [of the total 24hr day] to just 13%.*

The Critical Breakdown

Pros: The trial was randomised and the method of randomisation described. Participants were well matched across the inclusion criteria, in particular for diabetes status. Despite the dropouts, both diet groups remained balanced post-randomisation for numbers of participants in each study arm, and for participant characteristics. Participants and researchers were blinded to the randomisation process. Both diet groups were given equal support from the study dietitian, and in addition to biweekly visits participants were contacted by phone twice per week to encourage compliance.

Cons: Other than randomisation, the study was not blinded. While the participants would not be expected to be blind - they have to follow the diet! - it is still possible to blind investigators and statisticians, i.e., single-blind. In effect, this study tested two variables: front-loaded energy early in the day and the meal frequency [more under ***Key Characteristic***, below]. The mean age of the participants was 68yrs, so caution may be required in interpreting the effects with regard to younger populations. Wide eating windows were allowed for the main meals, and it is possible that timing of these meals influenced blood glucose response, e.g., consuming dinner at 5pm would be expected to have a better glucose response vs. a snack at 10pm [(6)]. Diet was free living and other than the basic dietary recommendations, no detail is provided on actual reported intake, thus it is possible that the protocol was deviated from.

Key Characteristic

Which variable had more of an impact; energy distribution, meal frequency, or both? It is ultimately impossible to determine the difference, so the most appropriate interpretation is that the effects related to both variables in the 3M group vs. the 6M group. However, based on the wider literature, manipulating two variables in this way certainly tipped the scales in favour of the 3M group. For example, Bandín et al. compared the effects of timing lunch at 13.30hr vs. 16.00hr, with both breakfast and dinner occurring at 08.00hr and 20.00hr in both conditions [i.e., only timing of lunch change] [(7)]. Diets were matched for energy and macronutrients, and energy distributed equally between meals. The later lunch timing resulted in a 46% higher glucose AUC, compared to the earlier timing.

Another controlled intervention comparing glucose responses to a an oral glucose tolerance test at 08.00hr vs. 20.00hr, found that the post-prandial glucose excursion was significantly greater at 20.00hr [(8)]. The point here is that these studies had matched energy between meals, and equally distributed energy; only the timing of the meals differed. And recall that in the prior study from this group, front-loaded energy with a 700kcal breakfast and 200kcal dinner resulted in a 20% lower whole day glucose AUC [(5)]. The effects in the study are likely a combination of *both* the reduced frequency, i.e., reduced overall postprandial glucose excursions, and the energy distribution, i.e., nutrient timing aligned to more optimal glucose tolerance and metabolism.

Interesting Finding

There was no correlation between body weight and TDID, while on the other hand there was a strong positive correlation between mean daily glucose and TDID. This suggests two things. First, the lack of correlation between body weight and TDID implies that the reduction in TDID occurred independent of weight loss to an extent. Second, the strong positive correlation between the 24hr glucose and TDID implies that the mean glucose levels were reduced independent of the reduction in TDID. Taken together, both of these factors suggest a real effect of the distribution and frequency of energy intake on 24hr glucose profiles, which are both factors that have been shown to improve glucose levels independent of weight loss [(9)]. Nonetheless, no correlation analysis appears to have been conducted between weight loss and glucose levels, and it is certainly possible with a 5.4kg weight loss that this contributed to the overall reduction in daily glucose levels.

Relevance

We are left with the chicken-and-egg question with regard to distribution vs. frequency, so it is important to take this intervention as the sum of both parts. What if the front-loaded energy diet had also had three snacks of 10% daily energy each, between meals? Would we still have seen the same magnitude of effect? Based on the wider literature on distribution of energy in participants with T2D, I think it is arguable that if both diets had 6 eating occasions in this study, but the only difference was distribution, the front-loaded energy diet would still have yielded superior results [(3-8)].

Nonetheless, did the reduced meal frequency add an extra edge? This is also arguable. 2 meals front-loaded to early in the day has been shown to improve glycemic control in participants with T2D compared to 6 meals [(10)]. Another important factor is the difference in the duration of the eating window, with the final snack in the 6M group in this study occurring at 10pm. Although only 10% of daily energy, previous research has shown that consumption of a 200kcal snack at 23.00hr for 2-weeks in healthy, lean [BMI 18.5-25] women reduced 24-hour fat oxidation and resulted in significantly lower fat oxidation in the afternoons following the late night snack [(11)].

Then there is also the distribution of carbohydrate across the day, which was also front-loaded in the 3M group but equally distributed in the 6M group. In an intervention in participants with T2D, Pearce et al. demonstrated that distributing the majority of carbohydrate to lunch or breakfast resulted in significantly lower overall daily glycemic excursions, compared to carbohydrate evenly distributed across the day [(12)].

Finally, there is the weight loss differential: 5.4kg in the 3M group vs. so significant change in the 6M group. The authors suggest that greater diet-induced thermogenesis [DIT] from higher morning energy may explain the difference in weight loss. This is a common assertion in meal timing research, however, it is an overplayed hand: see this previous Deepdive where we really dig into methodological issues with DIT. In brief, while there is a daily variation in DIT which is higher in the morning, the magnitude of the effect is tiny: 0.11-0.17kcal per minute, or 15kcal over 3.5hrs [(13,14)]. The absolute caloric value of DIT, added up to the total 24hr day, is simply insufficient to explain a 5.4kg differential in weight loss having regard to the extent of the energy deficit required.

So, what could explain this difference? Ironically, the research group behind the present study provide some explanation in a 2013 study they published. Using a similar front-loaded energy protocol with high-protein/high-carb breakfasts, they found that this strategy led to significant and persisted reductions in the appetite hormone, ghrelin [15]. In the spirit of "*when you hear hoofbeats, think horses, not zebras*", one is left to conclude that the 5.4kg weight loss likely reflects an energy deficit over the 12-weeks of the intervention, facilitated by the satiating effects of the energy front-loading.

Application to Practice

While there is conflicting evidence regarding an energetic advantage to morning energy intake in the context of energy expenditure and weight loss, the distribution of energy may have profound impacts on post-prandial metabolism, with particular importance for post-prandial glucose levels in the management of T2D. Adding the research on meal frequency in participants with T2D, it does appear that the generic 'little and often' advice in the management of T2D is antiquated at best, and potentially detrimental at worst. Combine both frequency and distribution of energy and carbohydrates, and manipulating these variables may all contribute to a global improvement in diabetes management, from daily hyperglycemia to insulin dosage. However, further research with better control over diet should seek to replicate the findings in the present study. Nonetheless, a growing body of literature supports the role of meal timing considerations for the management of T2D.

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