

Case Report

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Seven Lifestyles Shed Light on Exercise Timing: A Physician-Patient's Perspective

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Abbreviations:

- TIR – time-in-range
- CGM – continuous glucose monitoring
- MG – daily mean glucose
- 1 carb = 15 g carbohydrates
- RE –resistance exercise
- AE – aerobic exercise
- FG – fasting glucose
- PPG – postprandial glucos

Brief Summary

ADA guidelines have not yet specified exercise timing. A physician-patient with type 2 diabetes for over 22 years and equipped with a glucometer and continuous glucose monitoring, I tested different evidence-based exercise options in seven lifestyles toward personalizing my routines. The only intervention during the period was the mode of exercise except in lifestyles 1 and 2, where there was also carb control. All other variables including medications were continued without any change. Not only did these lifestyles agree with the existing data on exercise timing but it accomplished an additional objective: the CGM data also helped mitigate the negative effects of pre-breakfast exercise. After avoiding pre-breakfast exercise for about 16 years CGM made me a convert: a moderate intensity pre-breakfast exercise followed by a morning snack every other day turned out to be my most valuable exercise for metabolic control.

Also, a timely post-meal exercise of appropriate energy expenditure can attenuate post-meal glucose surge of the meal in real time. Post-meal exercise that works consistently for me has been a 20 to 30-minute brisk walk or 12 minutes of moderate resistance exercise (upper body alternating with lower body) plus a short walk at 30-minute post-meal.

Introduction

A physician-patient with type 2 diabetes, I had been searching for the best exercise option for glycemia for over 20 years. My search took me through 7 distinct lifestyles (six of them before I got continuous glucose monitoring (CGM) and the 7th after) before I settled on my current, most successful diabetes lifestyle. I was basi-

cally testing evidence-based exercise options toward optimizing my own lifestyle habits. Most of the lessons I learned from these lifestyles agreed with the literature data, but CGM helped me to go further.

Physical activity of any kind, be it aerobic or anaerobic, light or intense, pre-meal or post-meal, normally has a host of salutary effects on the human body and spirit [1]. A sustained exercise training offers improved physical health, body composition and insulin sensitivity, short-term or long-term, in people with or without diabetes [1, 2]. However, there is risk for hyperglycemia or hypoglycemia with certain exercise activities. The immediate impact of physical exertion on blood sugar levels varies with the hormone system in force and the fuel sources used. Pre-breakfast exercise is controlled by counterregulatory hormones and post-meal exercise usually occurs under the incretin-insulin system.

The fuel sources for pre-meal aerobic exercise (AE) are free fatty acids, muscle glycogen and hepatic glucose from glycogenolysis and gluconeogenesis (for long duration exercise) [3]. Pre-meal AE offers mixed effects on glycemia. The positive effects are no hypoglycemia during the activity, a delayed glucose tolerance improvement that can last for over 24 hours and better fasting glucose (FG) [4-7]. The immediate negative effects are post-exertion glucose elevation leading to glucose dysregulation for 1-3 hours [6, 8-11]. As intensity increases post exertion hyperglycemia can be pronounced and there can be delayed hypoglycemia in some people on insulin [6, 12-17]. Also, oxidative stress does not attenuate after pre-meal exercise [18]. Training during fasting conditions also offers mixed effects: glycogen content, Glut-4 protein levels and AMPK activity (a protein that promotes mitochondrial biogenesis) are increased [19, 20]. On the other hand, A1C and C-reactive protein are worse [2]. Because of the negative metabolic effects of pre-meal exercise its utility is not clear.

Exogenous glucose is the main fuel for a timely post-meal AE and it does not use much liver glycogen or muscle glycogen [2, 8-11, 21-40]. Post-meal AE also has positive and negative effects on glycemia. At the right timing, intensity and duration it attenuates the post-meal glucose surge in real time leading to minimal dia-

betes complications [2, 7-10, 21-40]. On the other hand, glucose tolerance gained from post-meal exercise is short-lived and long duration post-meal exercise does not improve fasting glucose [7, 23, 36]. As energy expenditure increases hyperglycemia or hypoglycemia may occur depending on the status of the liver [41-44]. The right timing and energy expenditure are critical elements for optimal glucose control with post-meal exercise in healthy people and in people with type 2 diabetes [45, 46]. Several studies comparing pre-meal AE to post-meal AE find that the latter is better for attenuating postprandial glycemia [2, 7-10, 26, 33-35, 46, 47]. Endurance training in the fed state offers many health benefits: improvement in fat oxidation, cardiorespiratory fitness, body conditioning, hypoglycemia risk and HDL levels [2]. Post-meal AE improves postprandial lipid levels in healthy people and in people with type 2 diabetes [48, 49]. Post-meal AE also decreases oxidative stress in healthy men [50].

Moderate resistance exercise (RE) pre-meal or post-meal improves glucose tolerance while replenishing the depleted muscle glycogen, but it does not affect liver glycogen or FG significantly [51-69]. Heden et al. find 45 minutes of post-dinner RE better than pre-dinner RE for glucose and lipids [51]. Aoi et al. also report combined (aerobic plus resistance) exercise, pre-meal or post-meal lowering triglycerides in healthy people: post-meal exercise is slightly better [52]. Post-exertion hyperglycemia is seen but it is not a major issue with moderate RE [51]. A short duration (15 minutes) RE with or without a short walk, before or after, at 30-minute post-meal can also blunt the glucose peak well in people with diabetes [46]. Many studies show consistent glycemia benefits with RE and AE, the combination is usually better [51-65]. A mid-postprandial short duration (8 minutes) stair exercise (going up and down) is very potent in lowering postprandial glucose in people with type 2 diabetes [70].

High intensity interval exercise offers multiple health benefits such as better cardiopulmonary fitness, endothelial function, body composition and performance for athletes along with insulin sensitivity improvement and elevated Glut-4 protein levels and glycogen content, in a time-efficient manner [71-84]. Terada et al. report that an hour-long high intensity interval exercise with active recovery pre-meal is better than its post-meal counterpart for overall glycemia benefit [75]. High intensity interval exercise also have negative effects such as post-exertion glucose elevation, glucose dysregulation for a few hours after the activity and lactate eleva-

tion [77, 78, 87, 88]. The negative effects seem to occur more with passive recovery [78, 87]. Lactate levels have been 20 mmol/L for the pre-meal study by Harmer et al. in type 1 diabetes patients and 12 mmol/L for the post-meal study by Larsen et al. in type 2 diabetes patients [78, 87]. Moderate AE, RE or stair exercise generate lactate levels less than 5 mmol/L [23, 66, 70]. In spite of all the benefits offered by interval exercise in a time-efficient manner metabolic benefits are inconsistent: this may be partly explained by the high lactate levels that may be inducing insulin resistance [78, 82-86, 88]. More research is needed to sort out the conditions for minimizing the negative effects of interval exercise on glycemia and lipids. One encouraging report is the 40 min post-meal study by Sohre et al. improving A1C by 26% when the people with prediabetes did post meal interval training with active recovery 3 times a week for 4 months [93]. Hatamoto et al. find a brief periodic, 30-minute interval exercise with passive recovery, but below lactate threshold, better than doing the same activity preprandial or postprandial in healthy men [76].

In spite of decades of data on exercise timing it is not clear how to coordinate meal and exercise to gain metabolic benefits for people with diabetes [89-91]. ADA recommends 150 minutes of moderate exercise or 75 minutes of intense activity or interval exercise per week plus RE 2-3 times a week [92]. The trouble is there is risk for hyperglycemia or hypoglycemia with high intensity pre-meal AE or post-meal AE with high energy expenditure [6, 12-17, 41-44]. Moderate post-meal AE at the right time is a viable option for day-to-day glucose management [21-40].

There are other unanswered questions. Pre-meal AE is the only one that can improve FG consistently [7]. Can the negative effects of pre-meal exercise be minimized and the net metabolic effects optimized? There is a growing awareness of the issue but data are scarce [89-91]. On account of the complexity surrounding these and related questions ADA recommendations about exercise timing for people with diabetes may not be forthcoming any time soon. This paper shows the lessons learned from seven lifestyles of a type 2 diabetes patient using glucometer and CGM.

Seven Lifestyles over 19 years

I found it necessary to test promising exercise options for 6-16 weeks before my biannual blood test keeping meal plan and medications constant.

Table 1: Lifestyles (LS 1 – LS 7) with different exercises; [Medications, metformin 1 gm twice a day + glargine insulin; Meals 5-6 carbs/day during the intervention]

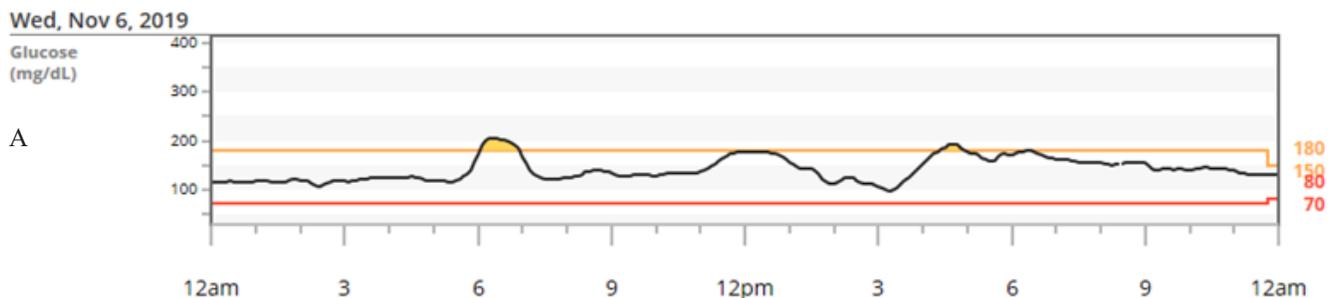
Meal and exercise	Daily carb intake	Glargine Insulin dose (units)	Weight (lbs) BMI	A1C (%)	HDL (mg/dL)
LS-1, 2002 decreased carb intake & daily pre-meal walk X 60 minutes for 4 months	9 → 5-6	None	-20 (14%) BMI (27 - 22)	6.4 → 6.4	39 → 36
LS-2, 2012, decreased carb intake & daily post-meal walk at 30-minute post-breakfast X 60 minutes for 4 months	9 → 5-6	36	-20 (14%) BMI (27 - 22)	7.3 → 6.0	36 → 51
sprint LS-3, 2014, 3-minute + 27-minute walk before breakfast 3x/week for 2 months	5-6	18	Steady BMI 22	6.2 → 7.2	43 → 50
LS-4, 2014, 3-minute sprint + 27-minute walk at 30- minute post-breakfast 3x/week for 2 months	5-6	18	Steady BMI 22	6.6 → 6.2	47 → 43
LS-5, 2015, 12-minute resistance exercise + 18-minute walk at 30-min post-breakfast 3x/week for 2 months	5-6	18	Steady BMI 22	7.2 → 6.4	50 → 44
LS-6, 2015, 3-minute sprint + 7-minute resistance exercise at 30-minute post-breakfast 3x/week for 2 months	5-6	18	Steady BMI 22	6.4 → 6.8	44 → 47
LS-7, 2018, 30-minute pre-meal walk + light breakfast alternating with 30-minute walk at 30-min post-breakfast for 6 weeks	5-6	18	Steady BMI 22	6.0 → 5.8	52 → 50

The first weight reduction program I tried in 2002 had a low-carb meal plan (daily carb servings were reduced from 9 to 5-6) and the exercise was a daily pre-breakfast walk for 60 minutes for four months (Table 1, LS 1). Medication had been metformin, 1000 mg twice a day, for four years prior to the intervention. The outcome of LS 1 was disappointing: in spite of a 14% weight loss, A1C did not improve and HDL was worse. Next weight reduction attempt 10 years later (LS 2 in 2012) involved the same low-carb meal plan as in LS 1 and daily post-breakfast walk at 30-minute post-meal for 60 minutes for four months. Medication also included glargine insulin 36 units/day. This time, I lost 14% of my weight as before, A1C improved from 7.2 to 6.0% and HDL went up from 36 to 51 mg/dL. After 2012 the meal plan was the same and the effect on glucose and HDL shown was mainly from the exercise. I tried a 3-minute sprint both pre-meal (Table 1, LS 3) and post-meal (Ta-

ble 1, LS 4) for 2 months each. A1C went up with the pre-meal training but it improved modestly with the post-meal training. A 12-minute resistance exercise at 30 minutes post-meal followed by an 18-minute walk (Table 1, LS 5) also improved A1C. The post-meal exercise in LS 6, 3-minute sprint plus 7 minute RE, did not help A1C.

CGM Data for some Unresolved Issues

Figure 1 shows the CGM data (Dexcom G6), time-in-range (TIR) and daily mean glucose (MG), when a big breakfast versus small breakfast followed the pre-meal walk. The carb component of the daily meals are 6-carb servings (one carb equals 15 g of carbohydrates) on all three days shown in Figure 1. A big breakfast (1½ carb) is used first and second day (Figure 1 A & B) and a small breakfast (¾-carb) is used on the third day.



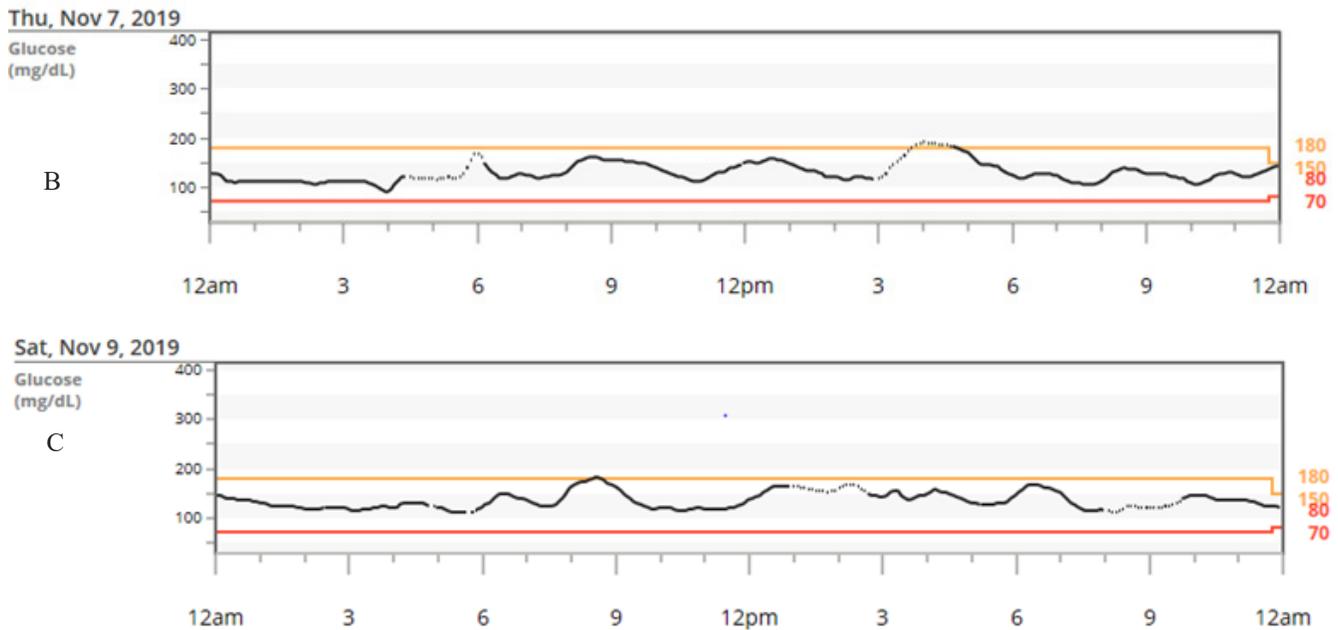


Figure 1

1A shows breakfast PPG, TIR and MG resulting from pre-meal walk for 40 minutes: 205 mg/dL, 94% and 141 mg/dL. The carb components of the daily meals amounted to 6-carb servings including a 1½-carb breakfast.

1B offers the corresponding numbers for post-meal walk for 40 minutes at 30 min post-meal (169 mg/dL, 96% and 130 mg/dL) using identical meal plan with 1½-carb breakfast.

1C shows the corresponding numbers for pre-meal walk when a small balanced (¾-carb) breakfast is eaten with total carb servings similar for the day: 150 mg/dL, 99% and 135 mg/dL.

Figure 1, A and B show postprandial glucose (PPG) of breakfast, TIR and MG resulting from 40 minutes of pre-meal walk (205 mg/dL, 94% and 141 mg/dL) versus 40 minutes of post-meal walk (169 mg/dL, 96% and 130 mg/dL). Figure 1C shows the corresponding numbers for pre-meal walk when followed by a small (¾-carb) breakfast, 150 mg/dL, 99% and 135 mg/dL. Between Figure 1A (pre-meal walk) and Figure 1B (post-meal walk), the latter is clearly the better profile when the meals are similar, with 1½-carb breakfasts. The breakfast peak is bigger with the pre-meal walk, 205 vs 169 mg/dL. When, however, the pre-meal walk is followed by a small breakfast (¾-carb) all numbers improve compared with the big breakfast (Figure 1C). TIR and MG in Figure 1A and 1C confirm that the effect on glycemia can be enhanced if pre-meal walk is followed by a light, breakfast in my case (205 mg/dL, 94% and 141 mg/dL versus 150 mg/dL, 99% and 135 mg/dL).

Discussion

The outcomes of the first six lifestyles agreed with the existing data. Although LS 2 had insulin along with metformin, results from the interventions keeping medication constant, were similar to the findings by Verboven et al [2]. The fasted state training study with endurance exercise, done three times a week for 12 weeks showed worsening of A1C (7.4 to 7.7%) and C-reactive protein (1.2 to 1.5 mg/L) in type 2 diabetes patients [2]. This study also showed multiple health benefits that were comparable to what fed-state training offered: improvements in fat oxidation, cardiorespiratory fitness, body conditioning, hypoglycemia risk and HDL levels. With

identical meal plans, moderate aerobic training during fed state was better than during fasting conditions for A1C and HDL (Table 1 LS1 and LS 2); glucose dysregulation after the pre-meal exercise every day might not have helped glycemia in LS 1. The post exertion glucose elevation and glucose dysregulation after high intensity pre-meal exercise, might explain why a 3-minute sprint during fasting made A1C worse (Table 1, LS 3) but the 3-minute sprint fed state improved A1C (Table 1, LS 4) modestly [7-10, 11-15]. Short-duration high-intensity exercise post-meal, followed by a walk improved A1C and HDL (Table 1, LS 4 and LS 5), which agree with the existing findings (46). However, resistance exercise proved to be more effective than the 3 min sprint post-meal (0.8% vs 0.4%) in my case. Energy expenditure was likely too high for the exercise in LS 6 which made A1C worse [41-44].

Out of the first 6 lifestyles LS 1 and LS 3 have pre-meal exercise and they did not improve A1C. The rest had post-meal exercises, all of them were diabetes-friendly except LS 6 which had the exercise with too much energy expenditure, in agreement with literature findings [41-44]. LS 4 and 5 have short duration high intensity exercises: RE (LS 5) was better than continuous exercise (LS 4) for glycemia. There is growing evidence supporting that short-duration high-intensity exercise with or without a short walk, before or after, post-meal can attenuate post-meal glucose surge [45, 46].

I also tested different short-duration (6-15 minutes) high-intensity exercise plus a short (15-20 minutes) walk post-meal using identical breakfast for 3 days, and exercise was on the second day (95).

The data showed that interval exercise, resistance exercise and stair exercise when followed by a short walk all resulted in improved glycemia. RE and split exercise (Pre-meal walk plus Post meal walk) showed some insulin sensitivity improvement after 24 hours [95].

Lifestyle 7 involved alternating a pre-breakfast walk followed by a morning snack containing half carb with a post-meal walk at 30 min post-breakfast. In about six weeks, A1C was 5.8% and HDL was 50 mg/dL. This was the lowest A1C I ever had.

What is special about moderate pre-meal AE followed by a light snack for people with diabetes? When intensity is moderate and the meal that follows is light, negative effects get minimized bringing out the positive effects. Moderate pre-meal exercise is the only one that I found improving fasting glucose consistently in agreement with the research findings [7, 96]. It is important to start the day with a normal fasting glucose that would help glucose profile throughout the day. A moderate intensity pre-meal walk is also practical and safe for most people with diabetes [96].

In LS 7, pre-meal exercise and post-meal exercise complement each other. On the post-meal exercise days glucose tolerance is better on account of the previous day's pre-meal walk and hyperglycemia can be further moderated by the post-breakfast exercise. Also, liver glycogen is depleted on the pre-meal exercise days helping fasting glucose but muscle glycogen is depleted on the post-meal days when short duration resistance exercise is done: glycogen depletion leads to insulin sensitivity improvement.

Conclusions

Because of the glucose dysregulation for up to three hours pre-breakfast exercise followed by a regular breakfast may not help glycemia for people with diabetes (Lifestyle 1 and Lifestyle 3). A moderate pre-breakfast exercise followed by a morning snack and a moderate breakfast in 90 to 120 minutes would be very valuable for diabetes patients (Lifestyle 7). Time in range and mean glucose from the CGM data confirm that such a meal-exercise combination can mitigate the negative effects of pre-meal exercise (Figure 1) and offer enhanced glycemia benefits including no hypoglycemia during the activity, improved glucose tolerance, controlled fasting glucose and low risk for delayed hypoglycemia. Here the second meal effect from the morning snack is also helping with the glucose surge of breakfast. Overall glucose regulation is better if the pre-breakfast walk is done every other day (Lifestyle 7) compared to every day (Lifestyle 1). Longer pre-breakfast walk offers better glycemia benefits.

Post-meal exercise of high energy expenditure (intensity or duration) may not help people with diabetes (Lifestyle 6): it may generate hyperglycemia or hypoglycemia. A timely post-meal exercise of moderate energy expenditure can blunt post-meal glucose surge of the meal in real time. A 20 to 30-minute brisk walk or a short duration high intensity exercise followed by a short walk (Lifestyles 2, 4 and 5) are found to be effective and safe.

Diabetes patients with CGM can use TIR and MG toward personalizing safe exercise options. It is important that patients testing these evidence-based exercise options monitor glucoses closely, adjust meals and medications as needed with the help of providers.

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Author Contributions

The corresponding author, E.C., is the guarantor of this work and, as such, had full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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