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Original Research

Effects of Red Wine and Daily Exercise on Glycemic Control in Insulin Resistant Individuals

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Abstract

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Alcohol increases insulin secretion in response to ingested carbohydrates and exercise enhances insulin sensitivity; therefore, we tested the hypothesis that the combination of wine and exercise would enhance glycemic control in individuals with type 2 diabetes (T2D) or prediabetes. Eleven participants (8 women, 3 men; T2D n=5 [3 women, 2 men], prediabetes n=6 [5 women, 1 man]) completed four different 1-week treatment periods consisting of no alcohol and no exercise (Con), daily red wine with dinner and no exercise (Wine), no alcohol and daily exercise (60 min at 55% heart rate reserve; Ex), or daily wine with dinner and daily exercise (Ex + Wine). During the last three days of each treatment period, each participant wore a continuous glucose monitor (CGM) to record blood glucose data. Mean 24-hr glucose levels, defined as the average of all CGM values collected at 5-min intervals over 3 consecutive days in each treatment period, were 130 ± 22.7, 130 ± 20.6, 122 ± 17.5, 121 ± 24.9 mg/dl for Con, Wine, Ex, and Ex + Wine treatments, respectively. Exercise lowered mean 24-hr glucose ($p = 0.017$), but wine had no effect. Dinner postprandial glucose (PPG) responses were reduced by wine ($p = 0.003$), but not exercise, and breakfast PPG responses were unaffected by either treatment. There was no wine-exercise interaction detected for any variable. These results suggest that one week of exercise lowers mean 24-hr glucose and that wine was associated with lower evening PPG responses after a mixed meal in this group of insulin resistant individuals.

Keywords: Continuous glucose monitoring, type 2 diabetes, prediabetes, postprandial glucose, alcohol

Introduction

Type 2 diabetes (T2D) and prediabetes are characterized by chronic hyperglycemia caused by the inability of insulin to stimulate glucose uptake and reduced insulin secretion from pancreatic beta cells; therefore, the primary focus in diabetes management is glycemic control. Glycemic control is the maintenance of plasma glucose concentration within a healthy range and is often assessed by measurement of glycosylated hemoglobin (HbA1c) or fasting blood glucose concentrations. While these variables of glycemic control are useful for monitoring disease progression, they do not capture daily fluctuations in glucose levels.[1] For example, elevated postprandial glucose (PPG) may often precede the development of T2D and has been identified as an independent risk factor for cardiovascular disease and mortality, regardless of diabetes status.[2,3] Furthermore, tracking glycemic variability, which is often expressed as the standard deviation (SD) of the mean for glucose concentration, accounts for the magnitude of the rise and fall of glucose levels

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over the course of a day, and provides a more sensitive assessment of glycemic health compared to traditional clinical measurements.[1] Of course, determination of PPG responses and glucose SD requires real-time measurement of plasma glucose in free-living conditions, which is now possible with continuous glucose monitoring (CGM) technology. Indeed, CGM provides data on the direction and magnitude of glucose excursions in response to meals, physical activity, and exercise.

Prevention and management of T2D and prediabetes are often focused on lifestyle interventions such as regular exercise, low carbohydrate diets, and weight loss, as these approaches have been deemed the most effective.[4] Because skeletal muscle represents the largest carbohydrate reservoir in the body and is the primary tissue for postprandial insulin-stimulated glucose uptake, exercise-related improvement in insulin sensitivity may be the primary mechanism of enhanced glycemic control in T2D.[5,6] Indeed, exercise has been shown to enhance insulin sensitivity in obese participants,[7] reduce mean 24-hr glucose concentrations,[8] and improve postprandial glucose (PPG) responses.[9,10]

A dietary intervention that may improve glycemic control is the consumption of alcoholic beverages. Epidemiological studies consistently report that moderate alcohol consumption (0.5-2 drinks per day) is associated with a reduced incidence of T2D, with wine having a greater effect than spirits or beer.[11-13] While the exact mechanism by which ethanol may improve glycemic control is unknown, one possibility is an altered hormonal response to ingested glucose. When alcohol is imbibed prior to a glucose challenge, it increases insulin secretion from the pancreas in both healthy and insulin resistant participants[14-18] and reduces the PPG area under the curve (AUC) in healthy subjects.[14,17] However, in participants with T2D, red wine enhanced insulin secretion during an oral glucose tolerance test (OGTT), but this had no effect on the overall glucose response, likely because higher insulin concentrations induced by alcohol were ineffective at promoting glucose disposal in insulin resistant individuals.[15]

While substantial evidence exists to indicate that exercise increases insulin sensitivity and red wine enhances insulin secretion in response to ingested carbohydrates, we are unaware of any attempt to analyze the potential interaction of these two lifestyle factors. Therefore, the purpose of this study was to examine the individual and combined effects of daily exercise and red wine ingestion on glycemic control in insulin resistant participants. We hypothesized that daily exercise and daily wine consumption would each improve glycemic control and that they would interact to promote further improvements glycemia when engaged in simultaneously. In addition to mean 24-hr glucose, we analyzed PPG responses after breakfast and dinner, glycemic variability, and daily maximum and minimum glucose concentrations. Using CGM technology, we recorded interstitial glucose concentrations in free-living participants with either T2D or prediabetes.

Methods

Participants

Insulin resistant individuals who had been diagnosed with either prediabetes or T2D were recruited through newspaper advertisements, social media, and community message boards. Participant (n=11) characteristics are provided in Table 1. Initially, 18 persons enrolled in the study; however, 4 participants withdrew prior to completing the protocol and 3 were excluded from the final analysis due to non-compliance with food log requirements. Prior to enrolling in

the study, participants were recreationally active, averaging 92 minutes of exercise each week, and average alcohol intake occurred on approximately 2 days per week, with consumption of less than 2 drinks per sitting. Exclusion criteria included cardiovascular or renal diseases, smoking, medication change within three months, and contraindications to exercise training or consuming alcohol. The study was approved by the Transylvania University Institutional Review Board and carried out in accordance with the ethical standards set by the Helsinki Declaration and the *International Journal of Exercise Science.*[19] All participants provided written informed consent.

Table 1. Baseline descriptive characteristics of participants upon enrollment in the study (n=11).

Variable	Value or Mean
T2D	2 male, 3 female
Prediabetes	1 male, 5 female
Diagnosis	5 T2D, 6 Prediabetes
Age (years)	51 ± 14 (range: 30-63)
Body mass (kg)	87.5 ± 23
Height (m)	1.60 ± 0.3
BMI (kg/m^2)	31.1 ± 8.4
Duration since T2D or prediabetes diagnosis (years)	3.3 ± 2.8
Exercise frequency (days/week)	3.8 ± 1.8
Exercise duration (minutes/day)	24.2 ± 15
Alcohol intake (drinks/week)	3.5 ± 3.2
Alcohol intake frequency (days/week)	1.9 ± 1.3

Data are presented as mean ± SD

Protocol

The experiment was designed to test the effects of both red wine and exercise, separately and in combination, on glycemic control in individuals with insulin resistance. Participants were involved in the study for 28 days, comprising four periods of 1-week each. During each 1-week period, subjects engaged either in daily exercise or remained sedentary, and either consumed red wine with the evening meal or abstained from all alcoholic beverages. Thus, all participants completed one week of each of the following lifestyle interventions: 1) no alcohol consumption and no exercise (Con), 2) daily red wine consumption with the evening meal and no exercise (Wine), 3) no alcohol consumption and daily exercise (Exercise), and 4) daily red wine consumption with the evening meal and daily exercise (Wine + Ex). Although some participants periodically consumed alcohol prior to enrolling in the study, alcohol consumption during the study was restricted to only the prescribed amount of red wine with evening meals. The Control condition was always administered first, followed by the other three conditions in random order. During each of these 7-day treatments, continuous glucose monitoring occurred during the last 3 days, as previously reported.[10] For the duration of the study, participants were instructed to continue taking their prescribed medications.

During weeks when exercise was required, participants completed 60 min of supervised moderate-intensity aerobic exercise at 55% of heart rate reserve for seven consecutive days. The target heart rate (THR) was calculated using the Karvonen formula: THR = [(Max HR – RHR) x (Intensity %] + RHR, where RHR refers to resting heart rate. Each exercise session consisted of 20 min treadmill walking, 20 min stationary cycling, and 20 min treadmill walking, as described previously.[10] This protocol is designed to maximize exercise duration while minimizing fatigue. Heart rate was monitored using heart rate monitors (Polar Electro, Kempele, Finland) and exercise intensity was adjusted regularly to maintain target heart rate.

During weeks when wine was consumed with the evening meal, we prescribed a moderate intake which, according to the Dietary Guidelines for Americans,[20] is defined as consuming up to one drink per day for women and up to two drinks per day for men. One "drink" is defined by the Centers for Disease Control and Prevention as 14 grams of pure alcohol. Accordingly, women ingested one glass (131 ml) and men two glasses (262 ml) of red wine (Columbia Crest Grand Estates Cabernet Sauvignon, Paterson, WA) per day. One-half of the volume was consumed 30 minutes prior to eating and the other half concurrently with the evening meal. Participants were instructed to drink no alcohol aside from the prescribed amount for the duration of the study.

On the evening prior to each 3-day glucose monitoring period, a glucose sensor was inserted subcutaneously in the abdominal region and paired with the CGM system (Dexcom G6, San Diego, CA), which recorded interstitial glucose concentration every five minutes. After each glucose monitoring period, CGM data was downloaded using Dexcom Clarity software (Dexcom, San Diego, CA), which yielded average 24-hr interstitial glucose and daily high and low concentrations. Raw glucose data was exported to a spreadsheet (Microsoft Excel, Redmond, WA) to calculate 24-hr glucose SD and PPG data. PPG excursions (delta PPG, post meal minus premeal interstitial glucose) were determined at 5-min intervals and used to calculate PPG area under the curve (AUC). These PPG values were determined for breakfast and dinner during each day of glucose monitoring, from which an average PPG response was generated for each participant. During glucose monitoring periods, participants recorded the exact timing and composition of each meal, with instructions to standardize their food intake over each of the four glucose monitoring periods. This was confirmed by analysis of their diet records for caloric and macronutrient content (My Fitness Pal, Austin, TX).

Statistical Analysis

Statistical analysis was performed using Jamovi 2.6.26 software. The effects of wine and exercise and their potential interaction on mean 24-hr glucose, glucose variability, maximum and minimum glucose values, and PPG responses were determined using a two factor (wine and exercise) repeated measures ANOVA, with effect size expressed as generalized η^2 (η^2_G). Caloric intake and macronutrient data from each participant's food log were compared using repeated measures ANOVA to ensure dietary consistency across all CGM recording sessions. Data are presented as mean ± SD, unless specified otherwise.

An *a priori* power analysis using G*Power software 3.1.9 was completed to determine the minimum number of participants, based on a two-factor ANOVA repeated measures test. A sample size of 17 was needed to achieve statistical power of 0.8 with alpha = 0.05 and a moderate-strong effect size (Cohen's f) of 0.3. We estimated this effect size based on previously reported exercise-induced decreases in 24-hr glucose concentrations using CGM[8] and the hypothesized interaction of exercise with wine consumption. Initially, 18 individuals enrolled in the study; however, because the final analysis included only 11 participants, the study is underpowered to detect treatment interactions.

Results

Average 24-hr glucose values (Figure 1) were 130 ± 22.7, 130 ± 20.6, 122 ± 17.5, and 121 ± 24.9 mg/dl for Con, Wine, Ex, and Ex + Wine, respectively. Two factor repeated measures ANOVA

revealed a significant effect of exercise ($F_{1,10}$ = 8.10, p = 0.017, η^2_G = 0.041), but no effect of wine consumption ($F_{1,10}$ = 0.056, p = 0.818, η^2_G = 0.00) and no wine - exercise interaction ($F_{1,10}$ = 0.005, p = 0.914, η^2_G = 0.00).

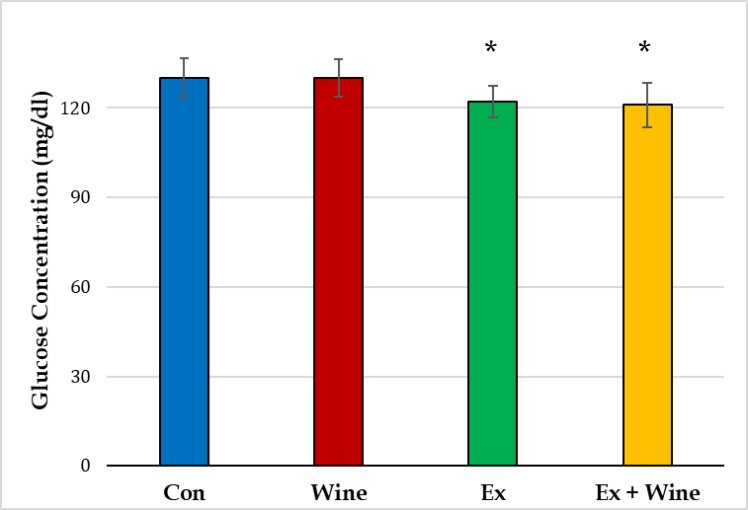
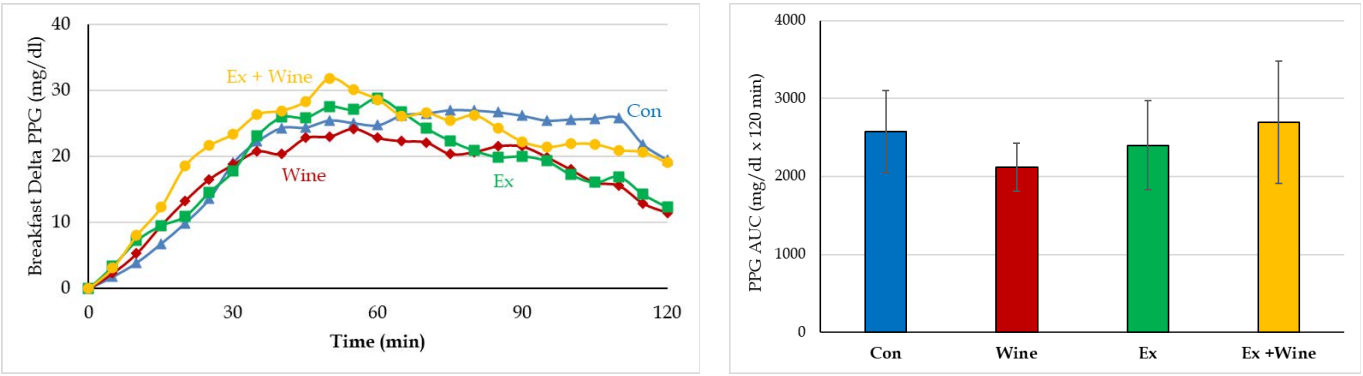


Figure 1. Average 24-hr glucose values for each condition. *Main effect of exercise (p = 0.017). No effect of wine and no wine-exercise interaction. Error bars are ± SE.

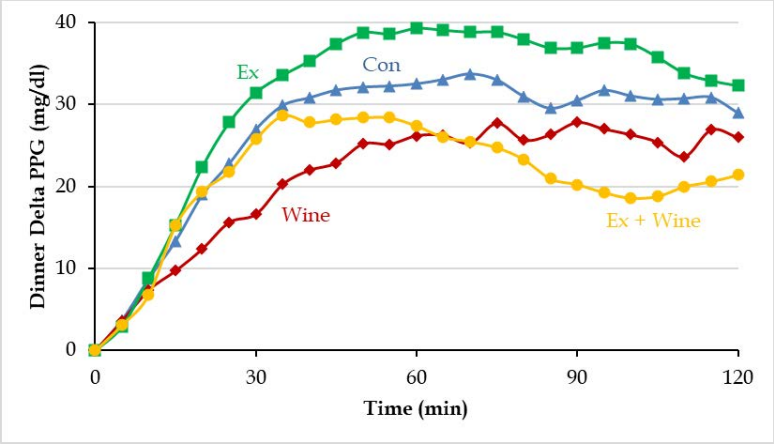
Figure 2 depicts delta PPG and PPG AUC during the first 2-hr after breakfast in each of the four conditions. Because one participant did not eat breakfast, n = 10. Breakfast PPG AUC values were 2577 ± 1674, 2122 ± 973, 2403 ± 1797, and 2701 ± 2483 mg/dl x 120 min for Con, Wine, Ex, and Ex + Wine, respectively. Neither wine ($F_{1,9}$ = 0.081, p = 0.783, η^2_G = 0.001) nor exercise ($F_{1,9}$ = 0.197, p = 0.668, η^2_G = 0.003) affected breakfast PPG AUC and there was no wine - exercise interaction ($F_{1,9}$ = 1.03, p = 0.336, η^2_G = 0.012).



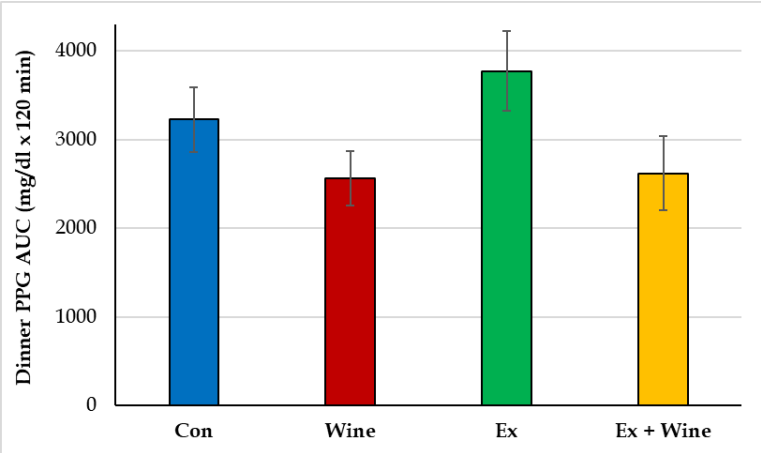
A B

Figure 2. Breakfast delta PPG (A) and PPG AUC (B) for each condition. Error bars in (A) have been omitted for clarity. Error bars in (B) are ± SE.

Dinner PPG AUC values were 3225 ± 1217, 2562 ± 1021, 3772 ± 1479, and 2618 ± 1393 mg/dl x 120 min for Con, Wine, Ex, and Ex + Wine, respectively (Figure 3). Wine consumption resulted in a lower PPG AUC than meals without wine ($F_{1,10}$ = 15.35, p = 0.003, η^2_G = 0.12). Exercise did not affect PPG AUC (F1,10 = 1.083, p = 0.331, η^2_G = 0.015) and there was no wine - exercise interaction (F1,10 = 0.975, p = 0.347, η^2_G = 0.01).



A.



B.

Figure 3. Dinner Delta PPG (A) and Dinner PPG AUC (B) for each condition. Error bars in (A) have been omitted for clarity. Error bars in (B) are ± SE. PPG AUC was lower after meals with wine than without wine (p = 0.003).

Other CGM and dietary intake data are presented in Table 2. Average minimum glucose concentration was lower during the exercise treatment ($F_{1,10}$ = 9.273, p = 0.012, η^2_G = 0.084) than with wine, and there was no interaction between exercise and wine. Otherwise, there were no meaningful differences in glucose variability or average maximum concentrations. Energy intake ($F_{3,12}$ = 0.896, p = 0.472, η^2_G = 0.04) and macronutrient proportions (%CHO: $F_{3,12}$ = 0.229, p = 0.875, η^2_G = 0.005; % Fat: $F_{3,12}$ = 0.028, p = 0.994, η^2_G = 0.001; % Protein: $F_{3,12}$ = 0.676, p = 0.583, η^2_G = 0.033) were also similar across all treatments (Table 2).

Table 2. CGM and dietary intake data.

Variable	Con	Wine	Ex	Ex + Wine
Glucose SD	20.4 ± 5.3	20.9 ± 5.1	21.0 ± 6.4	23.2 ± 6.1
Mean max glucose (mg/dl)	185 ± 35	186 ± 31	177 ± 30	183 ± 41
Mean min glucose (mg/dl)*	92 ± 19	90 ± 14	81 ± 15	80 ± 23
Max – min glucose (mg/dl)	93 ± 18	96 ± 21	96 ± 20	103 ± 30
Energy Intake (kcals/day)	1562 ± 467	1374 ± 274	1420 ± 325	1397 ± 346
CHO (% kcal)	37.5 ± 13.0	38.7 ± 11.6	37.8 ± 12.4	36.3 ± 12.1
Fat (% kcal)	40.3 ± 9.3	39.7 ± 10.3	39.2 ± 12.3	40.5 ± 14.4
Protein (% kcal)	22.3 ± 6.0	21.7 ± 4.0	23.0 ± 6.5	23.1 ± 6.6

Data are presented as mean ± SD. *Mean minimum glucose was lower during exercise (p = 0.012).

Discussion

The purpose of this investigation was to analyze the effect of daily exercise and red wine consumption on glycemic control in insulin resistant individuals. Our primary findings were that exercise reduced mean 24-hr glucose and wine consumed with the evening meal improved the PPG response. Our main variable of interest regarding glycemic control was mean 24-hr glucose. Our finding that exercise reduced daily glucose concentration by approximately 9 mg/dl agrees remarkably with a recent meta-analysis[8] of 23 short-term exercise (≤ two weeks) studies, in which the authors reported that exercise decreased mean 24-hr glucose by 9 mg/dl compared to the control condition. While we cannot ascertain the mechanism of lower average glucose, a 7-day exercise program has been shown to enhance insulin sensitivity, even when aerobic fitness and adiposity remain unchanged.[21,22] It seems likely that, because exercise did not influence PPG responses or the daily maximum glucose concentration, the reduction in the mean minimum daily glucose concentration (Table 2) contributed to the improvement in mean 24-hr glucose. Alternatively, it is possible that the exercise-induced increase in caloric expenditure influenced glycemic control during the weeks in which the participants engaged in exercise. It is well known that the metabolism of carbohydrates and lipids during muscle contractions provides ATP to meet the increase in energetic demand. During these periods of increased physical activity, glucose uptake by active muscle fibers likely contributed to whole body glucose disposal and a decrease in blood glucose concentration. Regardless of the mechanism, the present study adds to the body of evidence supporting the use of exercise in the prevention and treatment of insulin resistance.

Despite the improvement in mean 24-hr glucose, exercise did not affect glucose SD, average maximum glucose concentration, or PPG responses after either breakfast or dinner. This is at odds with other studies that have indicated exercise improved glucose SD,[23] decreased high and low glucose fluctuations,[10] and improved PPG responses.[9,10,23] While we cannot explain why exercise did not improve these variables in our participants, we can speculate on possible reasons. First, we did not control for the timing of the prescribed exercise bouts in relation to meal consumption, a factor that has been demonstrated to affect PPG responses. In a review of PPG responses to exercise either before or after a meal, Engeroff[24] reported that exercise lowered post meal hyperglycemia when undertaken after a meal, but that pre-meal exercise did not blunt the PPG response. The exercise schedules of our participants were quite varied, even within a single CGM recording period, so we did not track this variable. Furthermore, exercise timing, because of its effect on PPG, can also impact maximal glucose excursions, which typically occur in the postprandial period, as well as glucose SD. Second, we did not control for daily physical activity in which our participants engaged. While they were instructed to cease from exercising outside of the 60-min laboratory sessions, they were free to continue their normal lifestyle patterns. It is possible that some participants' baseline activity levels were sufficient to maintain a modicum of glycemic control that was not improved with additional exercise. Finally, it is possible that our participants' insulin resistant status (T2D vs. prediabetes), age range, and sex (8 female, 3 male) may have impacted the influence of exercise on these measures of glycemic control.

Red wine ingestion with the evening meal reduced the PPG AUC response by 25% compared to the non-wine conditions, but breakfast PPG was unaffected, indicating that alcohol's influence on PPG does not carry over into the next day. Although we did not measure plasma insulin at any point in this study, it seems likely that wine ingestion with dinner enhanced insulin secretion in response to the mixed meal, contributing to a greater glucose disposal in peripheral tissues and a lower PPG response. Compared to water, alcohol consumption prior to ingestion of carbohydrates increases insulin secretion[16,18] and has been shown to reduce PPG responses in healthy participants

to both a mixed meal[17] and an OGTT.[14] However, in T2D, Abraham et al[15] reported that, despite an increased insulin AUC, there was no change in glucose AUC during an OGTT. It is not clear why improved PPG was recorded in free-living participants using CGM in the current study but was not demonstrated in a laboratory-based OGTT in insulin-resistant individuals. It is plausible that differences in the nutrient composition of glucose drinks administered in OGTTs (100% carbohydrates) and the mixed meals consumed during the current study's CGM recording periods could affect the rates of gastric emptying and nutrient absorption and may have contributed to the alternate results. Indeed, the current findings agree with other studies[10,25,26] in which PPG changes were detected by CGM in free-living humans but not in a laboratory-based OGTT; this may suggest that PPG responses during an OGTT may not accurately reflect day-to-day glycemic control.

Although red wine improved dinner PPG responses, it did not affect other variables of glycemic control. Mean 24-hr glucose, glucose SD, and high and low glucose excursions were similar with and without wine. This may indicate that alcohol's effect on plasma glucose concentration is only active for a short time after consumption and does not impact glucose levels long-term. This notion is supported by epidemiological evidence in which the lowest risks of T2D were associated with the highest frequency (days per week) of drinking in both men[27] and women.[13] Furthermore, the dose of ethanol may be an important factor. Most epidemiological studies report that approximately two drinks per day yields the greatest reduction in relative risk of developing T2D[11,12]; however, because eight of the 11 participants in this study were women, they were limited to only one drink per day to remain within the limits of moderate alcohol intake as defined by the CDC. Thus, it is possible that a higher dose of alcohol may have generated greater changes in our measures of glycemic control.

Several limitations of this study exist. The small sample size may limit the generalizability of our findings. Nonetheless, we did detect both exercise- and wine-induced differences in two different variables of glycemic control. Additionally, as mentioned previously, meal timing relative to exercise and the amount of daily physical activity were not controlled in our participants. Finally, it is necessary to address that, rather than blood glucose, the CGM measures interstitial glucose concentrations. While there is a delay in the equilibrium of glucose in the capillary blood and the interstitial fluid as measured by CGM,[28] the use of CGM technology to analyze glycemic responses to meal ingestion has been validated.[29] Therefore, we feel confident that our minute-to-minute glucose recordings via CGM that occurred over a 3-day period accurately reflect the magnitude and duration of blood glucose fluctuations.

In summary, this study confirms previous findings that seven days of moderate intensity exercise reduces mean 24-hr glucose and that red wine, when consumed prior to and during a mixed meal, improves the PPG response. However, there was no interaction between daily exercise and wine ingestion in this participant group.

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Authors' contributions: KAA designed the study, obtained funding, analyzed data, and drafted the manuscript. MNB, CBE, ABH, MKW, and HEW collected data and critically reviewed the manuscript.

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