



OPTIMIZING THE TIMING OF EXERCISE AFTER MEAL IN PREDIABETIC INDIVIDUALS

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ABSTRACT

Background: Exercise is essential intervention for managing prediabetes; however, the effective timing of exercise post meal for moderating metabolic parameters in individuals with prediabetes is under debate. The study aims to investigate the effects of exercise timing after meal consumption on glycemic control in prediabetic individuals.

Methods: This crossover study was conducted at Khyber Medical University's Department of Physiology - Sports Research Unit. The study involved 25 prediabetic participants with sedentary lifestyles. Patients who performed standardized exercises (50% PMHR for 30 minutes, 5 minutes warmup and cool down) at different postprandial times (30, 60, 90, and 120 minutes after breakfast) across four sessions. The study assessed changes in glucose, insulin, and C-peptide levels at 4 time points at fasting, pre-exercise, 30 and 60 minutes' post exercise to understand the metabolic response to varied exercise timings.

Results: Significant changes in all parameters (glucose, insulin and C-peptide) were observed when exercise was performed 30 minutes after intake of food

Conclusion: Physical activity carried 30 minutes after meal may contribute to a more stable postprandial glucose profile. These results offered a valued insight in modulating post-exercise glycemic responses, emphasizing on the potential for tailored exercise mediations focusing on timing of exercise in managing postprandial hyperglycemia.

Key words: post-meal, prediabetes, physical activity, insulin sensitivity

INTRODUCTION

Global estimates indicate that approximately 28% of adults, or around 1.4 billion people worldwide, are physically inactive.¹ Because of this postprandial condition and inactivity, macronutrients constantly entering the bloodstream via digestion, where they must be absorbed by various tissues. With the restricted energy expenditure due to reduced physical activity (PA), the body is compelled to store a significant quantity of carbohydrates. Even in healthy people, the resulting glycemic excursions are a risk factor for low-grade inflammatory diseases such as prediabetes, type 2 diabetes,

non-alcoholic fatty liver disease² and cardiovascular illnesses^{3, 4}. Specifically, impaired glucose tolerance (IGT) has been identified as a sole predictor for prediabetes and roughly half of the adult population with this condition is likely to develop type 2 diabetes mellitus (T2DM) during lifetime⁵. Understanding the complex relationship between exercise and glycaemia requires ample examination of exercise timing, glucose sources, and hormonal dynamics⁶. The post meal phase is not uniform but rather comprises three separate segments outlined by the variability of glucose levels: early (0–30 minutes), mid (30–90 minutes), and late (>90 minutes) postprandial periods⁶. This classification of the feeding cycle post meal phase, is marked in individuals with prediabetes, indicating the dynamic shifts in blood glucose levels. The period between 30 and 90 minutes after a meal, characterized by a peak in glucose levels due to the inflow of exogenous glucose, is accepted as an important interval⁶. Consistent aerobic physical activity plays a crucial role in delaying or preventing the onset of T2DM. This is partly due to its temporary beneficial impacts on postprandial metabolism and the enhanced insulin sensitivity of skeletal muscles, which can last for approximately 48 hours after the most recent exercise session⁷. Exercise is widely recognized for its ability to improve physical fitness⁸ and to promote the absorption of glucose into skeletal muscle, thereby helping to maintain stable blood glucose levels and improves insulin sensitivity.⁹ Despite these benefits, the ideal exercise regimen for managing impaired glucose regulation is still to be determined¹⁰. Yet, it remains uncertain if there is an ideal timing for physical activity in relation to meal consumption.

Limited data is available on the timing of exercise and its impact on blood sugar regulation. It is still unknown if the timing of physical activity influences the control of blood sugar levels in prediabetic individuals. This study aims to find out the difference in effects of planned exercise in respect with the post-prandial timing (30 minutes after, 60 minutes after, 90 minutes after and 120 minutes after intake of food) and physical activity commencement and its influence on glycemic regulations in postprandial state in adults with prediabetes.

METHODOLOGY

Study Design

The study was carried out in Khyber Medical University's (KMU) Department of Physiology - Sports Research Unit (SRU) between July 2022 and December 2023. The human ethics committee of the KMU (Institutional Research Ethical Board of IBMS) accepted this study under ethical number (NO: KMU/IBMS/IRBE/meeting/2022/8075) in accordance with Helsinki declaration 1964.

Sample size calculation

Using the G Power 3.1.9.2 software, the sample size was calculated to be 12 individuals in order to impart more power to the study we increased the sample size to be 25. This adjustment was made at a, 'significance level (α) of 0.05 and a high power (β) of 0.80'.¹¹

Techniques for Sampling

In this experiment, non-probability purposive sampling was used. This method involved selecting prediabetes adults selected under the definition provided by the American Diabetes Association (ADA)¹².

Inclusion and exclusion criteria

Participants of either gender were selected as per the ADA criteria. Participants with fasting plasma glucose levels that were higher than normal (above 100 mg/dL) but not high enough to be classified as diabetics (below 126 mg/dL), and HbA1c values that ranged from 5.7% to 6.4%. Participants with inactive lifestyle specified via IPAQ questionnaire, as exercising for less than 30 minutes a day but not more than that¹³. Those ready to exercise as per PARQ physical activity readiness questionnaire were consented and selected.¹⁴ Participants involved in other research program, lactating woman, those on any kind of medications or disability were excluded from the study.

Baseline measurements

On the day of experiment, patients were received in Lab in fasting state, for their baseline measurements of weight, age, BMI, waist to hip W/H ratio. Details about their last night dinner was obtained via an interview. A 24-hour dietary recall through a structured interview was obtained and all the food items consumed by the respondents in past 24 hours were recorded. The participants were called for exercise acclimatization visits before starting the study, this was done to familiarize them with exercise and the speed and controls of treadmill (RT 100, Taiwan).

Borg Rating of Perceived Exertion

The Borg Rating of Perceived Exertion (RPE) scale^{15, 16} is widely used to assess an individual's personal assessment of physical effort and strain during exercise. This scale spans from 6 to 20, with ratings between 6 and 11 indicating "no to light exertion," ratings of 12 to 14 signifying "moderate exertion," ratings between 15 and 19 representing "hard to very hard exertion," and a rating of 20 denoting "maximum exertion." RPE was assessed at the end of each session.

Timing Protocol

The TIMING Protocol was established to determine the best time for people with prediabetes to exercise postprandially, or after eating. This procedure was set up with four distinct lab visits, each scheduled seven days apart. The main objective was to examine the impact of varying exercise timings following a regular breakfast on a range of glycemic markers. Below is a summary of the procedure:
Breakfast: In every visit, participants were provided with a typical breakfast that had a calorie value of 250 Kcal. An iso-caloric meal guaranteed that the breakfast's energy content remained constant during all visits, creating a controlled study environment.

Timing of Exercise: The workouts were arranged for various times following the breakfast:

Visit 1: Exercise began after 30 minutes after breakfast.

Visit 2: Exercise began 60 minutes after breakfast.

Visit 3: Exercise began 90 minutes after breakfast.

Visit 4: Exercise began 120 minutes after breakfast.

During each session, participants worked out for 40 minutes at a moderate effort (50% of their predicted maximum heart rate PMHR), on a treadmill. This included a 5-minute warm-up and a 5-minute cool-down. The predicted maximum heart rate (PMHR) for all participants was calculated from the formula $PMHR = 220 - \text{age in years}$.¹⁷

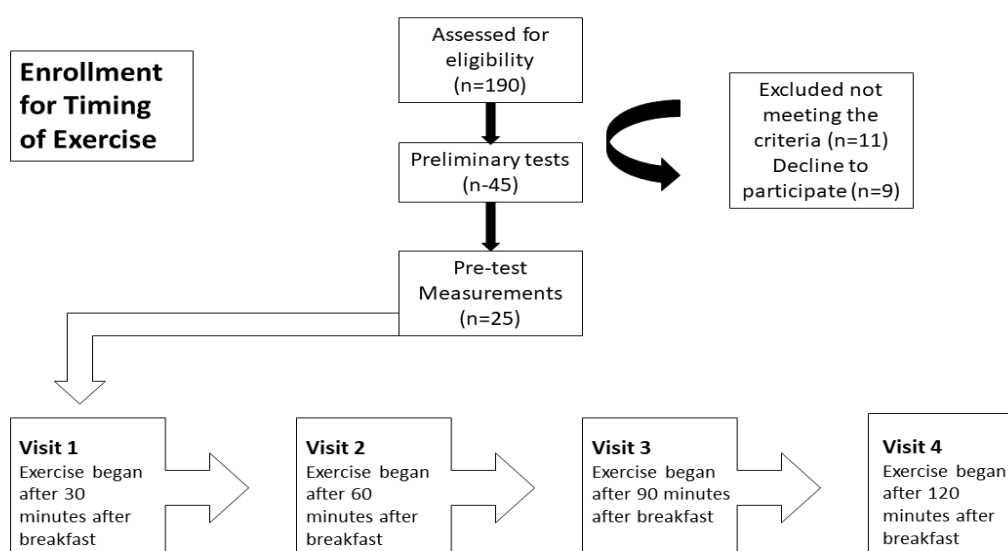


Figure 1 CONSORT flowchart showing the progression of participants through various stages

Figure 1 shows the flowchart of the participant selection and progression in the study. The flowchart begins with the enrollment phase. It follows to 25 participants undergoing initial tests before the pre-test measurements. These participants were then asked to come for four visits, with exercises starting at 30, 60, 90, and 120 minutes after breakfast, respectively.

Analysis: Blood samples, each containing about 5 milliliters, were taken at three different times: right before exercise, and 30 to 60 minutes after exercise. Blood samples were immediately centrifuged upon collection to extract serum for glucose measurement, using the commercially available (Abbott Freestyle glucometer). Serum insulin and C-peptide levels were determined with ELISA kits (Insulin-IN374S, C-peptide: CP179S-USA).

For data analysis, SPSS version 23 and Prism GraphPad version 8 were utilized. The Shapiro-Wilk test was applied to assess the normality of the data. Gender differences in demographics were examined using the Student's t-test. Additionally, the relationship between various time points and diabetes-related metrics was explored through repeated measure ANOVA and applying Bonferroni correction for multiple comparisons.

RESULTS

Demographic details of the participants

The average age of the study participant's was approximately 34.88 years, with females averaging around 32.25 years compared to male participant's 36.11 years. The average height was around 170 cm. On average, the waist and hip circumference of the females was 98.75 and 102.42 cm respectively compared to males having a mean of 103.76 and 106.41 cm respectively. The mean weight across the total population is 87.85 kg, with females weighing an average of (85.21 kg and males 89.1 kgs). There was a statistically significant difference in the mean age, height and mean waist circumference as described in table 1.

Table 1 Demographic and Anthropometric Profile of participants in the study

Demographics	Total	Female (n=8)	Male (n=17)	p-value
Age (years)	34.88±4.11	32.25±4.23	36.11±3.53	0.025
Height (cm)	170±6.70	164.25±2.91	172.70±6.28	0.002
Weight (kg)	87.85±14.56	85.21±13.77	89.1±13.77	0.545
BMI (kg/m ²)	30.34±4.27	31.48±4.30	29.81±4.28	0.372
Waist Circumference (cm)	102.16±12.22	98.75±17.10	103.76±10.73	0.035
Hip Circumference (cm)	105.13±12.43	102.42±17.10	106.41±9.93	0.467
Waist-to-hip ratio (WHR)	0.97±0.04	0.96±0.05	0.97±0.02	0.659

All the values in the table are presented as means ± standard deviation (SD) values for the demographic and anthropometric parameters of the study participant's, categorized overall and by gender, age (years), height (centimeters), waist and hip circumference (centimeters), weight (kilgram), and Body Mass Index (BMI) are presented.

Table 2. Effects of various Timing of exercise on Insulin resistance and Beta cell function

Parameters for Insulin sensitivity	30 minutes		60 minutes		90 minutes		120 minutes		p-values
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
HOMA-IR	10.96	10.01	7.92	4.87	9.06	8.82	8.98	11.00	.574
HOMA-β	47.13	31.84	109.54	105.17	91.45	92.15	93.20	112.18	0.097
FCPGR	0.02	0.00	0.03	0.00	0.03	0.00	0.03	0.01	<0.001

Effects of varying durations of aerobic exercise on markers of insulin resistance and beta-cell function, measured by HOMA-IR (Homeostatic Model Assessment of Insulin Resistance), HOMA-β (Homeostatic Model Assessment of Beta-Cell Function), and FCPGR (Fasting C-Peptide to Glucose

Ratio ng/mL per mg/dL). Data is shown as mean values with standard deviations (SD) for different exercise durations

The findings suggest that while insulin resistance (HOMA-IR) and β -cell function (HOMA- β) do not show significant changes over time, the fasting C-peptide to glucose ratio (FCPGR) does show significant changes, indicating alterations in the balance between insulin secretion and glucose levels.

Changes in Metabolic Markers After varied waiting time postprandially to exercise

Table 3 Effects for varied post prandial timing of exercise on Glucose, insulin and C-peptide levels

Markers	Visits	Fasting	Waiting time (minutes)	pre-exercise	30 min	60 min	P-Values
Glucose (mg/dL)	V1	118.0±3.4	30	195.6±7.8	158.2±9.5	121.2±2.5	<0.001
	V2	119.2±4.1	60	194.6±7.1	167±9.6	124.6±2.8	<0.001
	V3	117.7±3.3	90	156.76±5.1	154.44±8.07	151.28±8.11	<0.001
	V4	116.6±3.2	120	148.04±3.8	141.12±6.3	126.48±33.42	0.272
	P-value	0.079	-----	<0.001	<0.001	<0.001	-----
Insulin (mU/L)	V1	27.2±17.0	30	83.7±50.2	60.3±38.8	20.5±7.6	0.004
	V2	37.3±34.3	60	81.4±44.05	52.1±30.6	34.1±19.3	0.039
	V3	31.0±30.2	90	89.89±36.44	65.72±42.95	47.22±36.91	0.462
	V4	31.6±37.0	120	79.18±65.34	51.24±50.44	44.48±41.39	0.709
	P-value	0.707	-----	0.888	0.546	0.008	-----
C-peptide (ng/mL)	V1	3.4±0.3	30	4.5±0.3	4.3±0.4	3.3±0.3	.018
	V2	3.5±0.3	60	4.7±0.4	4.4±0.4	3.8±0.4	.010
	V3	3.26±0.30	90	4.43±0.38	4.13±0.40	3.97±0.37	<0.001
	V4	3.12±0.29	120	4.28±0.37	4.00±0.40	3.84±0.39	<0.001
	P-value	.000	-----	0.001	0.002	0.001	-----

Glucose Response:

Glucose levels showed a significant elevation postprandially across all visits as shown in Table 3. The levels ranged from 116.64 mg/dL to 195.04 mg/dL, depending on the waiting duration, with the 30-minute wait duration i.e visit 1 produced the highest initial postprandial glucose level of 194.68±7.8 mg/dL. Following the peak, a decline was noted at 30 and 60 minutes postprandial, indicating a recovery towards fasting levels. The magnitude of the postprandial glucose spike decreased as the waiting duration increased, with the 120-minute waiting duration showing the smallest initial postprandial increase and the most notable reduction at 60 minutes postprandial to 126.48±33.42 mg/dL. All changes were statistically significant with p-values <0.001.

Insulin Dynamics:

Postprandial insulin levels exhibited an increase from the fasting state, peaking pre-exercise after food intake. However, unlike glucose, the insulin response did not significantly differ across the various waiting time points, with p-values ranging from (0.004 to 0.709) as shown in Table 3. Insulin levels generally declined at 30 and 60 minutes postprandial, but the changes were not statistically significant, indicating a variable insulin response.

C-Peptide Levels:

C-peptide, a marker of endogenous insulin production, showed a similar trend to insulin. Levels rose postprandially and then gradually decreased. The waiting duration had a statistically significant impact on the C-peptide response, showed significant changes (p-values <0.001) as shown in Table 3. The largest decrease in mean C-peptide levels occurs in the 30-minute visit from pre-exercise to 60 minutes post-exercise, suggesting a substantial insulin response and subsequent decrease after exercise.

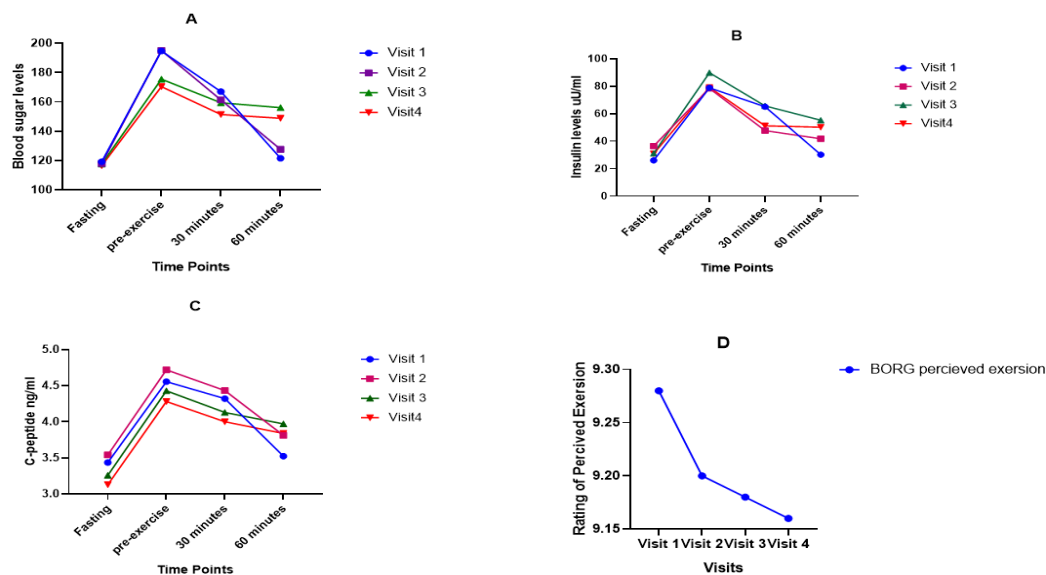
Table 4 Comparative Analysis of Exercise-Induced Changes in Blood Glucose, Insulin, and C-Peptide Levels After varied timing postcranially

Parameters	Blood Time points	Visit 1			Visit 2			Visit 3			Visit 4		
		Mean Difference	S.E	P-value	Mean Difference	S.E	P-value	Mean Difference	S.E	P-value	Mean Difference	S.E	P-value
Blood glucose levels (mg/dL)	Pre-exercise vs 30 min	36.36	1.94	<0.001	27.60	1.72	<0.001	2.310	1.420	.693	6.92	1.34	<0.001
	Pre-exercise vs 60 mins	73.40	1.61	<0.001	70.00	1.62	<0.001	5.48	1.440	0.005	21.56	6.60	0.020
	30 mins vs 60 min	37.04	1.87	<0.001	42.32	2.00	<0.001	3.16	.240	<0.001	14.64	6.62	0.221
Insulin (mU/L)	Pre-exercise vs 30 min	23.41	8.59	0.071	29.25	6.68	0.001	24.16	10.36	0.17	27.94	8.56	0.02
	Pre-exercise mins vs 60 mins	63.12	9.90	<0.001	47.29	7.83	<0.001	42.67	10.27	<0.001	34.70	12.21	0.05
	30 mins vs 60 min	39.70	6.87	<0.001	18.03	4.53	.003	18.50	6.92	0.08	6.75	7.22	1.00
C-Peptide (ng/mL)	Pre-exercise mins vs 30 min	0.23	0.04	<0.001	0.28	0.04	<0.001	0.29	0.05	<0.001	0.28	0.05	<0.001
	Pre-exercise mins vs 60 mins	1.25	0.10	<0.001	0.90	0.05	<0.001	0.46	0.05	<0.001	0.40	0.06	<0.001
	30 mins vs 60 min	1.02	0.11	<0.001	0.62	0.05	<0.001	0.16	0.02	<0.001	0.16	0.02	<0.001

Table 4 presents the post Hoc analysis to examine the changes in blood glucose levels, insulin, and C-peptide levels at different time points across four separate visits. These parameters were measured at fasting (baseline), pre-exercise, 30 minutes', and 60 minutes' post-exercise. The mean differences between these time points, along with standard errors and p-values, were reported to assess the statistical significance of changes.

As shown in Table 4 comparison of mean differences in blood glucose, insulin, and C-peptide levels before and after exercise across four separate visits shows a significant decrease after 30 and 60 minutes of exercise across most visits ($p < 0.001$). The reductions are most pronounced in the initial visit for both time comparisons. Reductions in glucose levels were significant in all visits post-exercise. The largest mean decrease occurs between pre-exercise and 60 minutes in Visit 1. The most significant drop from pre-exercise to 60 minutes is seen in Visit 1, but this visit did not have a significant change from pre-exercise to 30 minutes. Insulin levels also decrease significantly in most visits except for the first 30-minute comparison in Visit 3 and the 60-minute comparison in Visit 4. C-peptide changes were similar to the trend seen in insulin, showing significant decreases, suggesting

effective insulin secretion in response to exercise. Overall, exercise has a statistically significant impact on these metabolic parameters, with the effects most noticeable beginning the exercise shortly post meal.



Metabolic responses and perceived exertion to exercise

Figure 2 provides the responses of blood glucose, insulin, and C-peptide to exercise, along with the BORG perceived exertion rating across four separate visits.

Figure 2-A shows the changes in blood glucose levels (mg/dL), Figure 2-B shows insulin concentrations ($\mu\text{U}/\text{mL}$), and Figure 2-C represents C-peptide levels (ng/mL) measured at Fasting, Pre-exercise and post-exercise at 30 and 60 minutes across 4 visits. Figure 2-D shows the BORG perceived exertion rating, scored after each visit. Data points for each visit are connected via lines to demonstrate the trends over time.

Over all Figure 2 presents the trend of glucose, insulin and C-peptide at all four visits. Visit 1 shows a pattern where the blood glucose levels, insulin levels, and C-peptide levels initially peak but then return closer to baseline levels after exercise. This indicates that the exercise protocol applied in Visit 1 is effective at mitigating postprandial spikes in these metabolic markers. The trend is most clearly observed in fig.2-A for blood glucose, which starts high, peaks pre-exercise and then significantly drops towards baseline levels at "30 min" and "60 min" post-exercise. Graph fig.2-B shows a similar pattern for insulin, and fog.2-C for C-peptide. Fig 2-D represents the Borg perceived exertion scale, which drastically decreases from Visit 1 to Visit 4, suggesting that participants found the exercise less strenuous over time, potentially due to improved fitness levels or adaptation to the exercise protocol.

DISCUSSION

Initiating physical activity shortly after eating, particularly 30 minutes, appears to effectively lessen the rise in blood sugar levels. The current study examines the effects of various timings of exercise on the glycemic control and exercise parameters in prediabetic individuals. Our findings indicate timing of exercise might be a modifiable factor in influencing the post-exercise glycemic control. Specifically, the glucose levels showed a significant reduction from fasting to post-exercise across all time intervals (30, 60, 90, and 120 minutes after a meal) with p-values <0.001 in each case. This pattern was also observed in the insulin readings, which showed a significant decrease from pre-exercise to post-exercise, particularly at the 30-minute mark ($p = 0.004$). However, the significance decreased, with 90 and 120 minutes showing p-values of 0.462 and 0.709, respectively. Similarly, C-peptide levels demonstrated significant reductions post-exercise, with more pronounced effects observed at 60 and 90 minutes post-meal (p-values of .010 and <0.001 , respectively).

These results align with prior research emphasizing the importance of exercise timing for optimal glycemic control. Our study underscores the view that initiating physical activity shortly after meal

consumption particularly within 30 minutes can effectively mitigate the rise in blood sugar levels, thus contributing to a more stable postprandial glucose profile. Participating in physical activity (PA) close to when you eat is the best strategy to deal with high blood sugar rises¹⁸. Exercising 30 minutes to 1 hour after meal intake may have an ideal effect on postprandial glucose excursions, according to Dr. Chacko's findings⁶ suggesting, that exercising within this timeframe may exert an ideal effect on postprandial glucose excursions, potentially offering a practical strategy for individuals with prediabetes to manage their blood sugar levels effectively. Consistent with these findings, Solomon et al.,¹⁹ also reports that the impact of PA following a meal was greater¹⁹. Recently low intensity exercise have gained popularity in patients with impaired fasting glucose²⁰. Studies have reported that when individuals engaged in light activity starting at 30 minutes after the meal, glucose levels began to decline^{21, 22}.

Engaging in an exercise session 30 minutes after breakfast resulted in the reduction of the peak glucose, thus contributing to a more stable postprandial glucose profile. In this study, the impact of exercise timing on postprandial glucose (PPG) levels showed results in line with the Reynolds and Venn study¹⁰. Here, exercising at the peak blood glucose time (30-60 minutes after eating) lowered PPG at 60 minutes in individuals. Their study utilized various exercise intensities and duration used, (10 min of low-intensity cycling vs. 30 min of walking at 50% VO₂max), highlighting the significance of the energy spent during post-meal exercise in managing blood sugar levels. In a recent study by Zhang et al.,²³ reports that a single session of walking for 30 minutes at 50% VO₂max, starting 20 minutes before the peak postprandial glucose period (PPGP), significantly reduced glucose, insulin, and C-peptide levels over 4 hours²³. This suggests that the impact of post meal exercise is more noticeable in individuals with impaired glucose tolerance²³.

Exercise plays a pivotal role in managing and preventing type 2 diabetes by activating alternative pathways that improve glucose uptake in muscles independently of insulin. Regular physical activity enhances muscle mitochondria and increases GLUT4 protein levels, leading to better insulin sensitivity in muscles and overall metabolic health. These changes in skeletal muscle are critical for preventing and managing type 2 diabetes, showcasing the importance of exercise-induced muscle adaptations²⁴.

Overall, these findings regarding exercise timing suggest that the insulin-independent clearance of glucose from the bloodstream might be most efficient immediately after oral glucose consumption²⁵. While insulin-independent GLUT-4 glucose transporter expression on muscle cell membranes could enhance glucose uptake following activities that induce intracellular glycogen replenishment, other mechanisms such as increased enzyme-linked substrate metabolization and skeletal muscle blood flow are more likely to influence glucose spikes as they occur²⁵. The most effective strategy for controlling spikes in blood sugar levels involves engaging in aerobic exercises, starting 30 minutes post-meal²⁶.

The comparative analysis of glucose, insulin, and C-peptide levels at different post-meal intervals provided in our study fills a gap in the existing literature by offering concrete evidence on the efficacy of exercise timing as a modifiable factor in postprandial glycemic control. Our research contributes to a growing body of evidence suggesting that the timing of physical activity relative to meal consumption is a critical component of diabetes management and prevention strategies. By correcting the timing of post meal exercise commencement, inactive adults may improve their postprandial glucose control, subsequently decreasing their risk for developing T2D, cardiovascular disease, and mortality²³. One of the limitations of our study was that single exercise intensity 50% PMHR was considered, limiting understanding of how different types or intensities of physical activity might affect glycemic control differently.

CONCLUSION

The current study reveals that exercise commencement after different time intervals post-meal markedly affects blood glucose levels, with early post-meal activity specially 30 minutes after meal leads to a more noticeable decrease in postprandial glucose spikes. These results propose that the timing of exercise with respect to meal is an acute factor that can improve glycemic control in

prediabetic individuals, possibly providing a good approach in managing prediabetes and averting the onset of T2D. The study highlights the significance of exercise timing as a practicable and effective strategy in improving postprandial glycemic control.

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