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Gender-Related Response to Glycemic Index Following Eccentric Exercise in Type-II Diabetes Mellitus

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ABSTRACT

OBJECTIVE: To determine the gender-based differences in glycemic control following eccentric exercise in type 2 diabetes mellitus.

METHODSOLOGY: This double-blind clinical trial comprised of 12 weeks of eccentric exercise intervention involving n=34 participants diagnosed with Type 2 Diabetes Mellitus, aged 45 to 65 years, non-smokers, with Body Mass Index ranging from overweight to grade II obesity and who were not involved in any exercise training in the last 6 months. Participants were recruited using a non-probability purposive sampling technique, and the study was conducted over 18 months, from September 2021 to February 2023. Ethical principles were followed as suggested by the Declaration of Helsinki. The participants were assessed by glycated hemoglobin (HbA1c) at baseline and after 12 weeks of intervention. The On-Call EZ-II glucometer was used to take blood glucose levels before and after every exercise session. All statistical analysis were done using SPSS version 26.

RESULTS: The mean age of the participants was 50.50±4.57 years. However, the mean age of males and females was 51.44±4.33 and 49.44±4.73 years, respectively. After 12 weeks of eccentric exercises, a significant reduction (p=0.001) of average blood sugar level (HBA1c) was found in males (8.32±0.90) than in females (9.57±1.11). However, average glucose measured by the blood glucometer did not differ significantly (p-value=0.351).

CONCLUSION: It is concluded that eccentric exercise responds more effectively in male than female participants.

KEYWORDS: Diabetes Mellitus, Eccentric exercise, Gender-related response, Glycemic control, Sex differences, Type 2 Diabetes Mellitus.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a progressive chronic metabolic disease that affects 589 million adults aged 20-7 years globally, with an estimated prevalence of 11.11% of the global adult population, and projected to increase to close to 900 million by 2050 [1]. In contrast, Pakistan ranked first in age-specific diabetes prevalence (31.4) globally[2]. Globally, a substantial number of individuals with diabetes live in low- to middle-income countries and are expected to rise in middle-income countries in the coming years, followed by high- and low-income countries[3]. Moreover, a recent study indicates that the disease burden will increase further if no effective intervention is implemented[4].

In T2DM, declining pancreatic insulin production, increased skeletal muscle resistance, and increased glucagon linked to free fatty acids are the main causes[5]. Changes in glucose levels activate counter-regulatory hormones, which ultimately reduce muscle mass, cause metabolic changes, and increase insulin resistance, leading to diabetes complications[6]. Diabetic patients report higher muscular wasting and weakening, particularly in older women[7]. Lifestyle modification in the early stages includes dietary control and exercise intervention, which have proven effective for T2DM[8]. Recent evidence suggests that patient education, exercise, nutrition, and pharmacological interventions are beneficial for better management of T2DM[9].

The selection of exercise also plays a significant role, and recent studies suggest that eccentric exercises predominantly alter muscle contractile properties and produce moderate to strong effects on muscle strength and hypertrophy[10]. Even though the acute effect of eccentric exercise showed significant changes in blood glucose and insulin resistance as compared to concentric exercise[11]. Diabetes awareness, diagnosis, and treatment are influenced by gender, so exercise therapies must consider these complexities since biological and psychological factors interact[12]. Oral glucose insulin sensitivity was higher in females than in males, but this difference disappeared when insulin resistance was assessed in T2DM[13]. A recent study suggests that fuel selection as a source of energy during exercise differs by gender: women rely more on lipid oxidation and less on carbohydrate oxidation than men for the same muscle activation, and men consume carbohydrates as a source of energy during exercise[14]. The variation in response is mainly due to baseline differences in strength, oxygen utilization of muscle, and physiology of muscle fibers[15].

However, while exercise guidelines and gender-based responses to exercise in Type II Diabetes Mellitus management are well defined, limited literature identifies gender-based responses to eccentric exercise in glucose management in T2DM; moreover, eccentric exercise consumes more energy, and genders respond differently to exercise regimens. The role of eccentric exercise in muscle activation has long been controversial because of the risk of injury. The present study aims to determine the gender-related response to eccentric exercise on the glycaemic index in type II Diabetes Mellitus.

METHODOLOGY

Study design

A double-blind clinical trial was conducted over 18 months from September 2021 to February 2023, and the study was approved by the Research Ethics Committee before data collection (**RIPHAH/RCRS/REC/Letter/12650**). The study used non-probability convenience sampling, and participants were randomized using the sealed-envelope method. However, the current study is a secondary, gender-based analysis of clinical trial data. The data were collected ethically, and the principles of Helsinki were followed throughout the study. Participants aged 45-65 years with a history of non-smoking, overweight to grade I Obesity, no history of resistance or aerobic training in the past 6 months, and physician permission to attend the exercise intervention were included in the study. However, those diagnosed with cardiac disease, hypertension, any systemic condition that could affect metabolism, a musculoskeletal condition that limited participation in the study, or advanced complications of T2DM were excluded. The sample size calculated by OpenEpi with a confidence interval of 99.9% and power of 95% was 24. Initially, 257 participants were screened, and 41 were willing to attend the 12-week exercise program. Out of 41 participants, 20 males were allocated to group A and 21 females to group B. However, 34 participants (18 males and 16 females) completed the study. This double-blind experimental study was conducted so that neither participants nor the outcome assessor knew the treatment groups. Numerical coding was used to maintain the confidentiality of participants. (**Figure 1**)

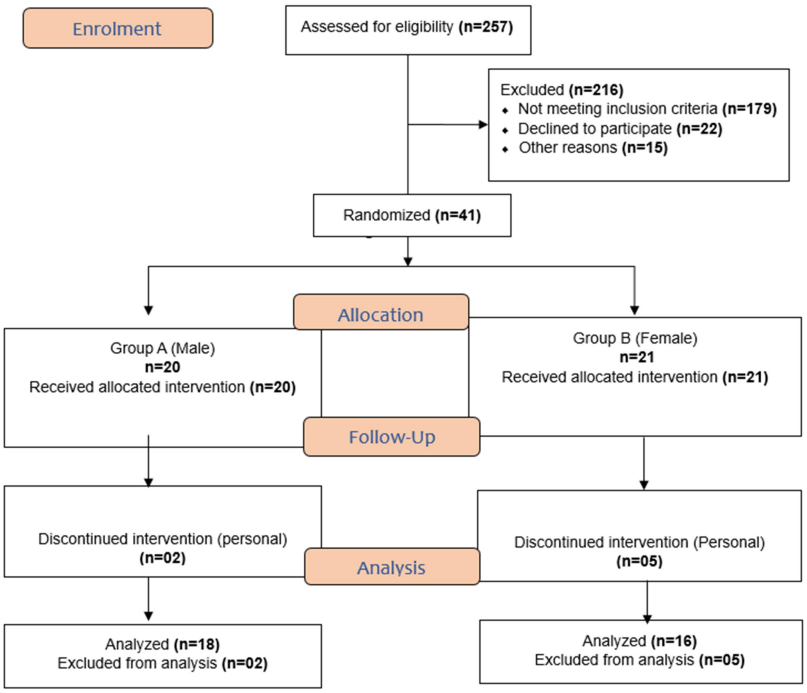


Figure 1: CONSORT diagram

Recruited participants received three sessions per week for 12 weeks of study and were assessed by Glycated Hemoglobin (HbA1c) and an on-call EZ II glucometer. Data were collected using HbA1c at week zero of intervention and after 12 weeks of intervention, as per standard protocol. However, regular blood glucose was monitored using the on-call EZ II glucometer during every

session and assessed before and immediately after each session over 12 weeks. The standard blood extraction method was followed, and a certified technologist collected the sample. The designed intervention given to participants included 5-7 minutes of warm-up (static stretching and low-intensity stationary cycling) followed by 03 reps of eccentric exercise with a duration of 10 minutes per rep and a rest period of 01 minutes between each rep. The treadmill declined to 16%, and the participant was asked to walk at the specified speed (9.7km/hr) on the treadmill[16,17]. Participants received 03 sessions per week for 12 weeks before screening using HbA1c.

For data entry, Statistical Package for the Social Science (IBM-SPSS) version 26 was used. Parametric tests were used for analysis because the data were normally distributed (Shapiro-Wilk test). Independent-samples t-tests were used to compare mean differences between groups. A paired-samples t-test was used to compare within-group effects of the intervention. However, mixed analysis of variance (ANOVA) with Bonferroni adjustment was used to determine interaction effects between gender and time in the assessment of blood glucose levels. Repeated measures ANOVA with pairwise comparison was used to determine the week-wise changes in both genders in T2DM participants. Demographics were analyzed using descriptive statistics, and data were presented as mean±SD for continuous variables and frequency and percentage for categorical variables.

RESULTS

The clinical trial recruited 34 participants who completed the study: 18 (52.9%) males and 16 (47.1%) females. The demographic information of male participants showed that 10(55.6%) were doing private jobs, 04(22.2%) entrepreneurs, 03(16.7%) public jobs and 01(5.6%) were unemployed. In female participants, 05(31.3%) doing private jobs, 05(31.3%) housewives, 03(18.8%) public jobs and 03(18.8%) were entrepreneurs. For diabetes management, 13 (81.3%) females and 13 (72.2%) males took oral medication. However, 03 (18.8%) females and 05 (27.8%) males were using insulin for diabetes management. Demographic characteristics showed of significant differences between male and female participants in age, Body Mass Index (BMI), and duration of diabetes (**Table I**).

Table I: Demographic information of the participants in mean±SD (n=34)

Variables	Overall	Male Mean±SD	Female Mean±SD	P-value
Age (Years)	50.50±4.57	51.44±4.33	49.44±4.73	0.206
Weight (Kg)	76.11±8.59	80.95±6.28	70.62±7.56	0.000***
Height (Inches)	60.56±4.21	62.61±4.06	58.25±3.09	0.001***
Body Mass Index (Kg/m^2)	32.21±3.74	32.09±3.20	32.34±4.37	0.850
Diabetes occurrence (Years)	6.29±3.47	6.89±3.23	5.62±3.70	0.296

P<0.05*, p<0.01**, p<0.01***

The Shapiro-Wilk test of normality was used to identify the normal distribution of data, and data were normally distributed in both groups, so the parametric tests were used to elaborate the results further. The average blood glucose level, measured by glycated hemoglobin (HbA1c), in male and female participants was 11.34±1.15 and 10.52±1.24 at baseline and 8.32±0.90 and 9.57±1.11, respectively, after 12 weeks of eccentric exercise intervention, showing a significant

gender-wise difference (p<0.001, Cohen's d: 2.91 male & 0.81 female). Blood glucose levels were also measured with a glucometer (On-Call EZ-II) three times a week before and immediately after the intervention. The mean and standard deviation of blood glucose level were 242.29±19.09 in males and 236.07±15.80 in females at baseline, and 187.67±10.59 in males and 185.80±3.37 in females after 12 weeks. No significant difference was found in blood glucose levels between male and female participants. However, within-group comparisons showed a significant decline in glucose levels in both genders (P<0.001; Cohen's d: 4.00 in males and 4.00 in females). (**Table II**) The mixed ANOVA with Bonferroni adjustment for post-hoc pairwise comparisons showed no significant interaction effects between gender and time of assessment of blood glucose levels {F=1.09(5.21,166.37), p=0.36, 0.033} in diabetic patients receiving an eccentric exercise intervention thrice a week for 12 weeks. However, HbA1c showed significant improvement in glycemic control in type II diabetes mellitus. {F=75.179(1,32), p>0.001,0.701} (**Figure 2**). Out of 34 participants, blood glucose levels were monitored before and after each exercise protocol, and weekly average blood glucose levels were recorded. Weekly pairwise comparisons showed significant improvement in male and female diabetic participants at the 1st and after the 12th week of intervention. Still, no significant differences were found between weekly comparisons from the 1st to the 12th week, except in the 4th week in male participants. (**Table III**)

Table II: Gender-wise comparison of glycated hemoglobin and regular blood glucose levels

Outcome	Group	Baseline	Post-Intervention	Change (95% CI)	Effect size (Cohen's d)	Within-group P value	Between-group P value	MDC
HbA1c	Male	11.34±1.15	8.32±0.90	2.58-3.45	2.91	<0.001	0.001	Y
	Female	10.52±1.24	9.57±1.11	0.74-1.16	0.81	<0.001		Y
Blood Glucose Level	Male	242.29±19.09	187.67±10.59	45.06-64.17	4.00	<0.001	0.351	Y
	Female	236.07±15.80	185.80±3.37	41.52-59.01	4.40	<0.001		Y

p<0.05, p<0.01**, p<0.01***MDC= Minimal Detectable Change*

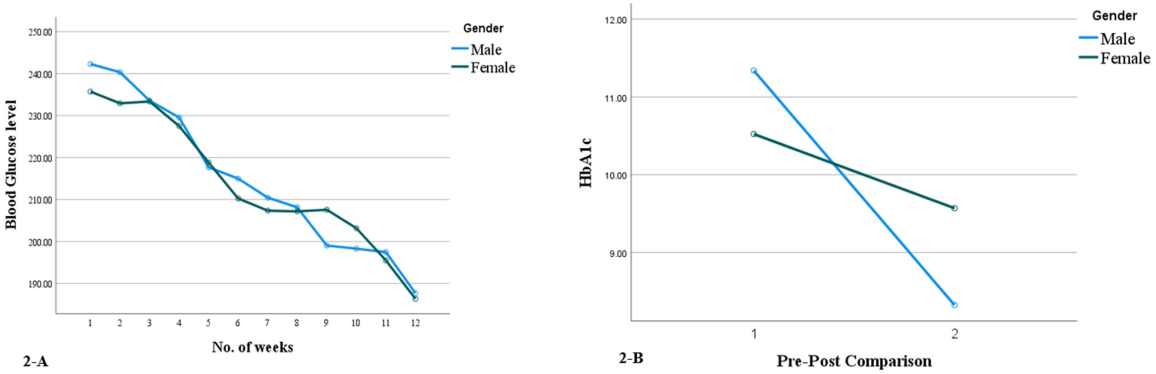


Figure 2-A: Gender-wise interaction in HbA1c (Baseline-12 weeks), and Figure 2-B shows blood glucose level (weekly average up to 12 weeks)

Table III: Weekly comparison of blood glucose levels in male (n=18) and female (n=16) participants

	Male (n=18)				Female (n=16)			
	Mean	**SD**	**MD/F/(df)**	**p-value**	**Mean**	**SD**	**MD/F/(df)**	**p-value**
01 week	242.29	19.10	1.954	1.000[a]	236.07	15.80	3.42	1.000[a]
02 week	240.34	18.91	6.77	1.000[b]	232.65	21.39	2.62	1.000[b]
03 week	233.57	15.47	3.38	1.000[c]	230.03	12.12	3.96	1.000[c]
04 week	229.57	13.57	11.88	0.004*[d]	226.07	10.37	9.60	1.000[d]
05 week	217.69	14.97	2.70	1.000[e]	216.46	15.87	0.396	1.000[e]
06 week	214.99	12.45	4.53	1.000[f]	216.07	18.30	4.13	1.000[f]
07 week	210.46	14.09	2.31	1.000[g]	211.93	15.49	5.81	1.000[g]
08 week	208.14	17.63	9.12	1.000[h]	206.12	7.49	-3.90	1.000[h]
09 week	199.03	12.66	0.731	1.000[i]	210.02	15.10	2.81	1.000[i]
10 weeks	198.31	8.15	0.815	1.000[j]	207.20	14.42	12.75	0.55[j]
11 weeks	197.48	9.38	9.806	0.124[k]	194.45	7.71	8.66	0.215[k]
12 weeks	187.67	10.59	43.84 (4.65-79.02)	0.000***[l]	185.80	3.37	2.46 (0.00-50.61)	0.000***[l]

a: 1st week to 2nd week blood glucose comparison, b: 2nd week to 3rd week blood glucose comparison, c: 3rd week to 4th week blood glucose comparison, d:4th week to 5th week blood glucose comparison, e: 5th week to 6th week blood glucose comparison, f: 6th week to 7th week blood glucose comparison, g: 7th to 8th week blood glucose comparison, h: 8th week to 9th week blood glucose comparison, i: 9th week to 10th week blood glucose comparison, j: 10th week to 11th week blood glucose comparison, k: 11th week to 12 week blood glucose comparison, l: 1st week to 12th week blood glucose comparison. p<0.05, p<0.01**, p<0.01***, MD: week-wise mean difference (with Bonferroni adjustment), F/df: Overall changes from baseline to 12 weeks (for repeated-measures ANOVA)*

DISCUSSION

Out of 41 participants, only 34 participants, including 16 females and 18 males, received 12 weeks of eccentric exercise, and their data were incorporated in this study. Pre- and post-comparison showed a significant reduction in glycemic control (HbA1c) in both genders. It is suggested that combinations of resistance and aerobic training show profound effects in increasing insulin sensitivity and reducing blood glucose levels in T2DM patients[18]. Similarly, a recent meta-analysis concluded that all types of exercise interventions, including resistance, aerobic, and physical activity, are beneficial for improving blood glucose levels in adults with T2DM. However, the process of muscle contraction during workouts drives the mechanism that improves blood glucose levels, ultimately increasing blood glucose levels, improving blood flow, and improving insulin sensitivity[20]. Recent studies comparing eccentric and concentric exercise concluded that eccentric exercise may have more beneficial effects of improving blood glucose levels and insulin sensitivity, along with some markers[21-23]. Skeletal muscle is a primary regulator of glucose metabolism, but impaired glucose metabolism can lead to chronic inflammation, elevated IL-6 and TNF, insulin resistance, and skeletal muscle atrophy[24]. The metabolism of glucose in the muscle is done in two ways: one is directly taken up by insulin or similar factors, and the other is by activating muscle contraction and exercise[25]. The current study used eccentric exercise that activates profound muscle contraction and promotes glucose metabolism. Moderate- to vigorous-intensity aerobic exercise with shorter duration, of recommended by guidelines, has been shown to reduce HbA1c levels by 0.22% [26]. The activation of specific factors, such as insulin receptor (IR), insulin receptor substrate (IRS), Protein Kinase B/AKT (PKB/AKT), and GLUT, especially GLUT-4 translocation, increased and promoted glucose metabolism when performing resistance or endurance training[25].

Moreover, the current study suggested that both genders responded differently to eccentric exercise. HbA1c declined more significantly in male participants than in females. A recent study of 2024 also suggested that male participants showed a greater reduction in glycemic levels after a continuous exercise intervention than females[27]. Biological and psychological differences, as well as differences of diabetes pathophysiology and complications, also exist between males and females; therefore, treatment and adherence require gender-specific attention for glucose management in T2DM[28]. Another study suggested that exercise prescription needs to consider intrinsic and extrinsic factors to achieve a specific goal. Intrinsic factors such as gender, age, and hormonal status influence exercise response and metabolic outcomes[29]. A well-defined gender-based difference exists in the selection of fuel utilization during endurance exercise. This differentiation of fuel selection may impact women's response to nutrition and exercise in the improvement of their health and performance[30]. A recent study reported that male individuals with T2DM are more oriented to maintain health, while females with T2DM are often aimed at monitoring their signs and symptoms of the disease. This study also emphasizes the need for more gender-based studies, as male and female individuals with T2DM reported different exercise behaviors[31]. So, the decline in glycated hemoglobin may be due to adherence to the intervention in male participants.

The current study also used an on-Call glucometer to assess blood glucose levels before and immediately after each intervention. There were no significant interaction effects between gender and time in the assessment of blood glucose levels, although blood glucose levels decreased in both male and female participants after 4 and 12 weeks of intervention. A study by Del Vecchio A et al.[32] concluded that the increase of muscle force after 4 weeks of exercise intervention is primarily due to increased neural output from the spinal cord to the muscle, which may cause a significant gender difference after 4 weeks of exercise intervention. Another study reported that precise reading of the glucometer and identification of factors that can interfere with the measurement need to be taken into account while administering insulin, which may

prevent significant clinical complications of diabetes[33]. Sharif-Nia H 2025[34], in his study, evaluated glucometer accuracy in diabetic patients and concluded that glucometer results can be used to monitor trends in clinically stable diabetic individuals but cannot be used for diagnosis due to their analytical accuracy. Various factors can influence the result of blood glucose in patients of T2DM, including environment, exposure to medicine, operating technique, and other disease status[35]. Exposure to these factors varies regardless of every precautionary measure taken, and it may affect the result.

The prevalence of T2DM is highly associated with socioeconomic status, which could not be observed in the current study. The number of participants who completed the study is moderate, and the results may change if the trial is conducted on a larger scale. The time difference between meal intake and intervention may also affect the blood glucose measurements taken before and after the intervention. Lastly, the half-life of the medication for T2DM management of T2DM may also affect blood glucose measurements. It is suggested to conduct the trial with a large sample size and minimize confounding factors to produce stronger evidence.

CONCLUSION

There is a significant gender-related difference in glycemic control, and males show a more pronounced response to eccentric exercise than females for glucose management in T2DM.

DECLARATION: The study trial was registered in the NIH Clinical Trial Registry (NCT04790526)

Ethical Permission: Riphah International University, Islamabad, Pakistan, REC approval letter No. RIPHAH/RCRS/REC/Letter-12650.
Conflict of interest: There is no conflict of interest between the authors.
Financial Disclosure / Grant Approval: No funding agency was involved in this research.
Data Sharing Statement: The corresponding author can provide the data proving the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publicly.

AUTHOR CONTRIBUTION

Afzal MF: Contribution to conception, analysis and interpretation of data, drafting of work, agreement to be accountable, Final approval
Awan WA: Contribution to conception, analysis and interpretation of data, Final approval
Arif A: Manuscript drafting
Khan MH: Contribution to conception, analysis and interpretation of data, Final approval
Memon AG: Manuscript drafting

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