MODERATE EXERCISE AND ANTIOXIDANT DYNAMICS: UNRAVELLING THE INFLUENCE OF FAMILY HISTORY IN PREDIABETES

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ABSTRACT

Objectives: This study investigates the effects of moderate-intensity physical activity on glycemic control and antioxidant capacity in prediabetics, regardless of whether they have a family history of diabetes.

Methods: It was conducted at the Physiology Department of the Institute of Basic Medical Sciences in Peshawar, Pakistan. The study included a cohort of 50 adult participants who were diagnosed with prediabetes. Out of the total, 25 individuals had a positive family history of diabetes (PFHG), and the other 25 had a negative family history (NFHG). The group consisted of 22 females and 28 males, whose ages ranged from 18 to 35 years. The diagnosis of prediabetes was made based on glycated hemoglobin values falling between 5.7-6.4% and impaired fasting glucose levels ranging from 100-125 mg/dL. Anthropometric measurements and biochemical testing were conducted before and after the exercise session. The Participants engaged in moderate exercise for 30 minutes, with a maximum heart rate of 70% ± 5%, five days a week for eight weeks. Their exercise was tracked using a pedometer. An enzyme-linked immunosorbent test (ELISA) was conducted to measure both individual and total antioxidants.

Results: Anthropometric measurements, fasting blood glucose (P<0.001), and glycated hemoglobin (P<0.001) showed significant changes at post-intervention. A slight rise in uric acid levels (P<0.005) and a substantial increase in total antioxidant concentration (P<0.001) was observed. Peroxidase, vitamin C, and nitric oxide significantly dropped (P<0.001).

Conclusion: Engaging in moderate physical activity for 8 weeks, there was a notable decrease in the levels of individual antioxidants. Additionally, there was a slight increase in overall antioxidant capacity and uric acid. Both groups experienced an apparent fall in their anthropometric measurements and diabetes profile.

Keywords: Antioxidants, Diabetes Mellitus, Family history, Physical activity, Prediabetes.

INTRODUCTION

Prediabetes is an early stage characterized by an elevated vulnerability to acquiring type-2 diabetic mellitus (T2DM) (1,2) The World Health Organization (WHO) has approximated the population of Pakistan to be 12.9 million inhabitants who have been diagnosed with diabetes, and it is projected that an additional 38 million people in the country are at risk of developing prediabetes (3,4).

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The second National Diabetes Survey of Pakistan conducted from February 2016 to August 2017 revealed a diabetes prevalence rate of 26.3% prediabetes prevalence rate of 14.4%. The global prevalence of prediabetes is predicted to be 314 million, with a projected increase to 418 million by 2025 (5).

Major contributing factors for the development of prediabetes and diabetes include a family history of diabetes, a sedentary lifestyle, and a high BMI. Prediabetes can increase the generation of free radicals, which undermines the protective function of the body's natural antioxidant system. Elevated blood glucose levels in individuals with prediabetes can result in a heightened generation of free radicals, compromising the protective function of the body's natural antioxidant system (6, 7, 8)**.** Antioxidants can be categorized into two primary groups: non-enzymatic and enzymatic. Vitamins A, C, and E, glutathione, nitric oxide (NO), uric acid, and antioxidant minerals are nonenzymatic antioxidants. Superoxide

dismutase (SOD), glutathione peroxidase (GPx), catalase, and glutathione reductase are enzymatic antioxidants (9). The total antioxidant capacity (TAC) is a measure of the ability of an organism to defend against oxidative damage by neutralizing free radicals (9,10). It is widely recorded that engaging in physical exercise (either aerobic or anaerobic) increases antioxidant activity in several tissues (10). During muscular action, an abundance of free radicals is generated, which in turn activate genes, elevate antioxidant levels, and influence alternative pathways that provide a defense counter to oxidative stress (11). Regular physical activity produces heightened levels of reactive oxygen species (ROS), which prompt muscles to adapt to regular exercise by offering improved defense against ROS. This adaptation process not only slows down the aging process but also enhances the health, functional abilities, glycemic control, and the postponement of complications associated with prediabetes (11).

The efficacy of planned exercise protocol as a therapeutic modality for diabetes mellitus (DM) and its associated problems is firmly established (12). Furthermore, studies have also documented the impact of exercise in augmenting the antioxidant capacity (13). Nevertheless, there is limited knowledge regarding the impact of extended periods of planned exercise on the specific antioxidant variables and total antioxidant capacity (TAC) in individuals with prediabetes. Due to the absence of any pharmaceutical treatment for prediabetes, exercising regularly could be considered one of the most effective options. It is clear from the literature that the development of diabetes is a complex process induced by multiple factors, and one of the known contributory processes is a disruption in antioxidant capacity. The current study explores the impact of regular physical activity on the antioxidant status of individuals with prediabetes in the context of a family history of diabetes.

We assessed the overall antioxidant capacity, cardiometabolic indicators, and cardiorespiratory fitness in a group of prediabetic individuals from Pakistan. This population was divided into two subgroups based on their family history of diabetes mellitus: one subgroup had a positive family history, and the other had a negative one.

MATERIAL AND METHODS

The study was an experiment that used pre- and post-design and purposive sampling. It lasted for 8 weeks and involved moderate-intensity exercise as an intervention. The study's objective was to determine the effects of this exercise on anthropometric parameters, diabetic profile, and antioxidant status in prediabetic participants from Pakistan who were between 18 and 35 years old. Experimental work was conducted in the Physiology Department of IBMS at KMU in Peshawar, Pakistan, from February 2019 to January 2020. The study received permission from the Ethical Review Board of Khyber Medical University under DIR/KMU-EB/BP/000580 dated 09/04/2019. All operations were conducted in conformity with the Declaration of Helsinki 1964. The study comprised 50 prediabetic volunteers who had no prior history of chronic or active health conditions and were not using any antioxidant supplements. The criteria for including individuals with prediabetes were fasting blood glucose level falling within the range of 100 to 125 mg/dL and their glycated hemoglobin level between 5.7% and 6.4%, as per the criteria set by the American Diabetes Association (14). After explaining the method to each participant, informed consent was acquired. Individuals diagnosed with diabetes mellitus, hypertension, renal disease, or any other acute or chronic illness were not included in the study. The sample size was computed using G Power 3.1.9.2 from two studies. Mean and standard deviation values of TAC, the sample size was calculated as 26: 13 in each group with the power of 0.95 and α=0.05 from Rodriguez *et al.,* 2015 (12). From Mohieldein *et al.*, 2015, TAC values of 1.325 ± 0.16 for prediabetics and 1.711 ± 0.13 for normal glucose tolerance were used, and the sample size was calculated as 10, distributing 5 in each group. Considering possible attrition over 8 weeks of intervention, we recruited 50 participants, 25 in each group (4,12).

Anthropometric measurements

The body fat percentage, fat mass, body weight, lean mass, and body mass index were measured using an impedance meter (Xiaomi scale-2, Model: XMTZC02HM; CMIIT ID: 2016DP6264, Producer: Ltd. 'Anhui Huami Informeyshn Technologies' China). The waist and hip circumference and waist-hip ratio were measured using flexible nylon coated and inelastic tape (Shanghai Harden Tools Co., Ltd.) at pre- and post-exercise intervals.

Initial and post-interventional (8 weeks) blood samples in a fasting state for individual antioxidants and TAC were taken following the protocol of 48-hour abstinence from antioxidant-rich food (list provided to all the

participants during recruitment) in the fasting state. This was followed by centrifugation at 3000 revolutions per minute for 10 minutes to separate serum and storage at -80˚C.

Exercise test

The exercise tests were conducted in the skill laboratory of IBMS, KMU. The Participants were instructed to walk on a power motorized treadmill (model: Revo RT 100) for 30 minutes at an intensity of 70 ± 5 % of their maximum heart rate (15), The number of steps taken during this activity was measured using a software-driven pedometer called Mi band 2, made in China and operated by the Mi Fit program. The initial three visits to the lab confirmed the standardized step count for each participant during the exercise session at the specified intensity. The participants consistently performed an equal number of steps within the designated time frame, five days a week, for eight weeks. They manually documented their daily step count in the given booklet for data entry.

Biochemical assay

Fasting blood glucose (FBG) was computed using Cobas C 311, Roche/Hitachi USA, and HbA1c levels were measured by Roche Cobas e-50, Switzerland. The analysis for antioxidants was carried out through sandwich ELISA (Bioassay Technology Laboratory, Shanghai, China) for SOD (Cat No. E0918Hu), GPX (Cat No. E3696Hu), NO (Cat No. E1510Hu), Vit C (Cat No. E1538Hu) while TAC (Cat No. E-BC-K225) was measured by Colorimetric Assay Kit (FRAP Method) by Elabscience USA. UA levels were determined by TBHBA DIALAB Production, Austria.

Statistical analysis

The data was analyzed employing IBM SPSS Statistics, version 20.0, developed by IBM Corporation in Armonk, NY, USA. The data's normality was assessed by applying the Kolmogorov-Smirnov and Shapiro-Wilk normality tests, as well as histograms. Data was presented as mean and standard deviation. A paired sample t-test was used to evaluate the anthropometrics, body composition, diabetes report, and antioxidants at post-intervention. A 0.05 or lower P-value was found to be statistically meaningful.

RESULTS

Post-intervention, there was a substantial decrease in anthropometrics and body composition ($P < 0.05$). Initially, it was observed that the group with a positive family history (PFHG) had a notably higher BMI, fat mass, and body fat percentage compared to the group with a negative family history (NFHG) ($P \leq 0.001$) as shown in Table 1.

Table 1: Comparison of Anthropometric Measurements and Body Plethysmography in the Study Population in Family History Positive and Negative Groups

Group Statistics	Family History Positive Mean±SD	Family History Negative Mean±SD	P value
Age y	30 ± 5	28 ± 5	0.16
Height cm	161 ± 8	167 ± 6	**0.03**
PreWt kg	76 ± 14	73 ± 12	0.35
Post Wt kg	75 ± 14	71 ±17	0.277
Pre WC cm	96 ± 12	92 ± 10	0.153
Post WC cm	95 ± 12	90 ± 9	0.108
Pre HC cm	105 ± 10	100 ± 7	**0.042**
Post HC cm	104 ± 9	99 ± 6	0.056
Pre WHR	0.91 ± 0.08	0.92 ± 0.06	0.716

Post WHR	0.91 ± 0.08	0.90 ± 0.06	0.720
Pre BMI kg/m^2	29 ± 5	26 ± 3	**0.007**
Post BMI kg/m^2	28.5 ± 4.6	25 ± 3	**0.007**
Pre BF%	36 ± 7	28 ± 6	**< 0.001**
Post BF%	35 ± 7	27 ± 6	**< 0.001**
Pre FM kg	26 ± 8.7	20 ± 5.9	**0.001**
Post FM kg	26.3 ± 8	19.3 ± 6	**0.001**
Pre LM kg	47.5 ± 11.9	52 ± 9.6	0.121
Post LM kg	49.1 ± 9.9	49.6 ± 12.6	0.294

Pre = baseline, Post = Post intervention, WC = waist circumference, Wt = weight, , WHR = waist-hip ratio, HC = hip circumference, , FM = fat mass, BMI = body mass index, BF = body fat, LM = lean mass

At the same time, as shown in Table 2, there were no significant differences in the cardiometabolic markers of FBG, glycated hemoglobin, insulin, and insulin resistance. The remarkable finding was that the decrease in FBS, HbA1c, insulin, and IR was less in PFHG compared to NFHG at post-intervention analysis.

Table 2: Pre- and Post-intervention Cardiometabolic Markers in family history positive and negative groups.

Cardiometabolic markers	**Family Hx Mean ± SD**		**P value**
	Positive	**Negative**	
Pre FBG mg/dL	110 ± 7.1	110 ± 6.4	0.884
PostFBS mg/dL	94 ± 11	92.5 ± 10	0.613
PreHbA1C%	6.02 ± 0.25	6.02 ± 0.23	0.954
PostHbA1C%	5.69 ± 0.37	5.64 ± 0.21	0.511
PreInsulin µIU/ml	20.02 ± 12.37	13.87 ± 9.49	0.057
Postinsulin µIU/ml	13.95 ± 11.16	8.91 ± 4.32	**0.044**
Pre HOMA-IR	5.48 ± 3.47	3.78 ± 2.64	0.059
Post HOMA-IR	3.24 ± 2.63	2 ± 0.86	**0.034**

Positive = Family history of diabetes (PFHG), Negative = No Family History of diabetes (NFHG). Pre = Baseline values before the intervention, Post = post-exercise measurements, HbA1c = glycated hemoglobin, FBG = fasting blood glucose, HOMA = Insulin resistance calculated by HOMA-IR.

At baseline, the levels of antioxidants were greater in NFHG compared to PFHG. However, a statistically meaningful difference was only reflected in NO ($P < 0.022$) and UA ($P < 0.006$) at baseline, as shown in Table 3.

Table 3. Comparison of Pre and Post Intervention Antioxidant levels in family history Positive and Negative groups.

Antioxidants	Family History Mean±SD		P value
	Positive	Negative	
PreSOD U/ml	176 ± 106	229 ± 154	0.17
PostSOD U/ml	135 ± 80	202 ± 163	0.08
PreGPx ng/ml	49.62 ± 44.7	53.6 ± 44.7	0.761
PostGPx ng/ml	32.80 ± 27.5	40.47 ± 34.57	0.402
PreNO mlU/ml	168 ± 136	289 ± 210	**0.022**
PostNO mlU/ml	136.8 ± 143	240.8 ± 198	**0.040**
PreVitC ng/ml	71.40 ± 75.52	96.43 ± 84.53	0.287
PostVitC ng/ml	68.5 ± 76.7	87 ± 76	0.408
Pre UA mg/dL	4.45 ± 1.1	5.23 ± 0.77	**0.006**
Post UA mg/dL	5.37 ± 1.21	5.80 ± 0.87	0.150
PreTAC µg/ml	0.762 ± 0.17	0.790 ± 0.16	0.559
PostTAC µg/ml	0.910 ± 0.17	0.911 ± 0.16	0.990

Positive = Family history of diabetes (PFHG), Negative = No Family History of diabetes (NFHG). Pre = Baseline values before intervention, Post = Post-exercise measurements
GPx = glutathione peroxidase, SOD = superoxide dismutase, NO = nitric oxide, , UA = uric acid, VitC = Vitamin C and TAC = total antioxidant capacity

DISCUSSION

Notably, there were significant differences at the baseline in the mean age, weight, WC, HC (P = 0.042), BMI (P = 0.007), body fat% (P < 0.001), and fat mass (P = 0.001) between volunteers with PFHG and NFHG. WC, HC (P = 0.042), BMI (P = 0.007), BF% (P < 0.001), and FM (P = 0.001) between the two groups. PFHG participants were characterized by being older, having a shorter stature, having a higher body weight, and displaying more characteristics of apple-shaped or android obesity. The study conducted by Jiang *et al.,* 2020 (16) found evidence that individuals with a family history of DM have lesser fat mass, body weight, BMI, body fat percentage, waist-hip circumference, and ratio. Similarly, another study found that people with a family history of diabetes had a higher BF%, lower lean mass compared to controls, and experienced changes in glucose levels. These findings align with our research (17).

It has been reported that the risk of developing prediabetes and diabetes increases two to four times in the PFHG. It may be associated with higher BMI, WHR, and lower physical fitness than those with no family history. These results are consistent with our outcomes. The most likely mechanism involved in the development of prediabetes and diabetes is obesity, leading to insulin resistance. Keeping the body in a positive energy balance for a longer duration leads to the deposition of fats. If not controlled, it may cause the internalization of fats into organs, especially the liver and pancreas, which in turn adds to the occurrence of PD and DM. The role of genetics in the development of diabetes has been studied widely. The mechanism involved is epigenetic variations that are hereditary alterations in gene expression associated with the methylation of DNA and modification of histones. These changes in epigenetics can be transferred to future generations. Thus, genetics and epigenetics contribute to diabetes, and family history is crucial in the early stages of the disease (18)(19).

At baseline, anthropometric measurements were markedly higher in PFHG than in the

NFHG. The remarkable finding was that the decrease in glycemic parameters was less in PFHG compared to NFHG at post-intervention analysis. There can be many reasons, including higher weight in PFHG and genetics (20).

On comparing the PFHG and NFHG, it was seen that FBS and HbA1c decreased in both groups, but the difference was not significantly consistent with the outcomes of Barwell *et al.,* 2008 (21), and Kacerovsky *et al.,* 2009, who reported no difference between the two groups at post-intervention (22).

The investigation by Joseph *et al.,* 2016, has confirmed that individuals who have siblings with diabetes exhibit elevated levels of insulin and are at a greater risk of developing prediabetes and diabetes if they are not aware of their condition. Therefore, it is advisable to undergo early screening and take preventive measures, especially with a family history of diabetes (23, 24).

According to Cederberg *et al.,* 2015, the close relatives (parents and siblings) of patients with DM demonstrate a '30 to 70%' higher risk of developing DM. They also exhibit beta cell dysfunction, IR, abnormal glucose metabolism, and endothelial dysfunction (25).

The levels of GPx and SOD decreased in the prediabetic population in both PFHG and NFHG in our study. The decrease in GPx and SOD might be due to excess free radical (reactive formation during oxidative stress leading to exhaustion of antioxidant stores) (26). In hyperglycemic states, hydrogen peroxide is formed due to oxidation of glucose which causes inactivation of SOD. The build-up of hydrogen peroxide could perhaps account for the reduced functionality of this enzyme (2),

CONCLUSIONS

The positive family history group had greater levels of BMI, fat%, fat mass, insulin, and insulin resistance than the negative family history group. The exercise provided equal benefits for both groups. There was no notable difference in the antioxidant capacity between the two groups. However, exercise reduced antioxidant capacity in both scenarios. Given that our study involved an 8-week exercise regimen, it is plausible that engaging in physical activity for a longer period could yield even greater benefits.

The changes in anthropometrics, adiposity, and diabetic profile provide additional information about the possible quantification of exercise, irrespective of the dietary modifications made to control/reverse the pre-diabetic state into normal.
Moreover, exercise alone improves the antioxidant profile of an average healthy population; however, the prediabetic population may additionally require dietary interventions to improve antioxidant status or exercise for a longer duration.

It is possible that 8 weeks of exercise was not enough for complete adaptation,
and dietary addition of antioxidants is required. This also guarantees that a programmed exercise should be devised for longer than 8 weeks.
Therefore, our results provide an important component for the planning of future studies where moderate exercise training of different durations will be used as a stimulus for exercise-induced adaptations. Furthermore, the findings of our investigation will offer a tool for designing planned exercise programs that enhance metabolic fitness, providing the appropriate structured physical training for the prediabetic population to revert to healthy status. Future Research should prioritize the investigation of optimal preventive strategies, including integrating physical fitness programs, for the prevention and management of diabetes. This is particularly important in resource-constrained settings, such as Pakistan and other diverse environments.

CONFLICT OF INTEREST

The authors report no conflict of interest.

DECLARATIONS

AUTHOR'S CONTRIBUTIONS

Dr. Zubia Shah was responsible for the research project's design, conduct, and analysis. Dr. Inayat Shah helped with the project's concept and design, while Dr. Omar Malik contributed to data analysis and interpretation. Dr. Fatima Fayyaz helped with the exercise sessions and data entry.

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