

# Effect of short duration moderate intensity physical activity on glycemic control and antioxidant status of prediabetic population

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## ABSTRACT

**الأهداف:** تحديد تأثير النشاط البدني معتدل الشدة في التحكم بنسبة السكر في الدم وحالة مضادات الأكسدة في السكان المصابين بمرحلة ما قبل السكري.

**المنهجية:** أجريت هذه الدراسة التجريبية في قسم علم وظائف الأعضاء، معهد العلوم الطبية الأساسية، جامعة خيبر الطبية، بيشاور، باكستان. اشتملت الدراسة على 50 شخصاً بالغاً مصاباً بمرحلة ما قبل داء السكري (22 أنثى، و 28 ذكراً) تتراوح أعمارهم بين 18 و 35 عاماً. شخصنا مرحلة ما قبل السكري عن طريق هيموجلوبين السكري الذي كان في حدود 5.7–6.4%، وخلل في الجلوكوز بالصوم (100–125 مجم/ديسيلتر). أجريت القياسات الأنتروبومترية والمقاييس البيوكيميائية قبل وبعد التمرين العلاجي. كما أجرى المشاركون تمريناً معتدلاً لمدة 30 دقيقة مع معدل ضربات قلب بحد أقصى 7% ± 5% لمدة 5 أيام في الأسبوع لمدة تتراوح 8 أسابيع، ومتابعتها باستخدام عداد الخطى. أجرينا فحص الأنزيم المرتبط المناعي لمضادات الأكسدة الفردية والكاملة.

**النتائج:** أظهرت العلامات الأنتروبومترية انخفاضاً ملحوظاً في تحليل ما بعد التمرين. وقد لوحظت تغيرات مماثلة في صيام الجلوكوز ( $p > 0.001$ ) والهيموغلوبين السكري ( $p > 0.001$ ). كان هنالك زيادة طفيفة في حمض البوليك ( $p > 0.005$ ) وإجمالي تركيز مضادات الأكسدة ( $p > 0.001$ ). ومع ذلك، انخفض ديسموتاز الفائق، وجلوتاثيون بيروكسيداز، وفيتامين C، وأكسيد النيتريك ( $p > 0.001$ ).

**الخلاصة:** أدى النشاط البدني المعتدل لمدة 8 أسابيع إلى انخفاض كبير في مستويات مضادات الأكسدة الفردية وزيادة واضحة في إجمالي قدرة مضادات الأكسدة وحمض البوليك، وكان هناك انخفاض واضح في بيانات القياسات البشرية والسكري لدى السكان المصابين بمرحلة ما قبل السكري.

**Objectives:** To determine the effect of moderate-intensity physical activity on glycemic control and antioxidant status in the prediabetic population.

**Methods:** This experimental study was carried out in the Physiology Department, Institute of Basic Medical Sciences, Khyber Medical University, Peshawar, Pakistan. A total of 50 adult prediabetic subjects having 22 females and 28 males with the age range of 18 to 35 years were included. Diagnosis of prediabetes

was made by glycated hemoglobin falling in the range of 5.7-6.4%, and impaired fasting glucose (100-125 mg/dL). Anthropometric measurements and biochemical assays were carried out at pre and post-exercise intervention. The participants performed moderate exercise of 30 min with heart rate max 7% ± 5% for 5 days a week for 8 weeks, monitored with pedometer. Enzyme-linked immunosorbent assay was carried out for individual and total antioxidants.

**Results:** Anthropometric parameters showed a significant decrease at post-exercise analysis. Similar changes were observed for fasting glucose ( $p < 0.001$ ) and glycated hemoglobin ( $p < 0.001$ ). Slight increase in uric acid ( $p < 0.005$ ) and total antioxidant concentration ( $p < 0.001$ ) were found. However, superoxide dismutase, glutathione peroxidase, vitamin C, and nitric oxide decreased ( $p < 0.001$ ).

**Conclusion:** Moderate physical activity for 8 weeks significantly reduced the individual antioxidant levels, nominal increase in total antioxidant capacity and uric acid, and there was an explicit decline in the anthropometric and diabetic profile of prediabetic population.

**Keywords:** anthropometry, antioxidants, physical activity, prediabetes, total antioxidant capacity

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**P**rediabetes is a preclinical stage with a higher risk of developing diabetes mellitus type-2 (T2DM).<sup>1,2</sup> It has been reported by the World Health Organization (WHO) that 12.9 million people in Pakistan are diabetic with a forecasted 38 million suffering from prediabetes.<sup>3,4</sup> The second National Diabetes Survey of Pakistan (NDSP) conducted from February 2016 to August 2017 showed a prevalence of 26.3% for diabetes and 14.4% for prediabetes. The estimated count of prediabetics in the world is 314 million and is expected to rise by 2025 to 418 million.<sup>5</sup>

High blood sugar levels in prediabetes can lead to an increase in free radical production that weakens the defensive effect of the endogenous antioxidant system.<sup>6</sup> The endogenous antioxidants protect against free radical-mediated injury.<sup>7,8</sup> Antioxidants include 2 main groups: non-enzymatic and enzymatic. Nonenzymatic antioxidants include vitamins (vit) A, C, and E, glutathione, nitric oxide (NO), uric acid, and antioxidant minerals and the enzymatic include superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase, glutathione reductase.<sup>9</sup> The total antioxidant capacity (TAC) reflects the antioxidant defense capacity.<sup>9,10</sup>

It is well documented that physical training (aerobic or anaerobic) enhances antioxidant activity in different tissue.<sup>10</sup> The excess free radicals produced during muscle activity stimulate the genes, raise the antioxidant level, and affect other pathways that protect against oxidative stress.<sup>11</sup> Regular exercise leads to increased reactive oxygen species (ROS) levels that stimulate muscles to adapt to regular exercise by providing better protection from ROS, attenuate the aging process and have beneficial effects on health, functional capacities, glycaemic control and delaying the complications of prediabetes.<sup>11</sup>

The role of exercise as a treatment tool for DM and its complications is very well established.<sup>12</sup> Concomitantly, the effect of exercise in enhancing the antioxidant capacity has also been reported.<sup>13</sup> However, little is known on the effect of planned exercise activity for the prolonged duration on the individual antioxidant factors and TAC in the prediabetic population. Due to the non-availability of any pharmaceutical management for prediabetes, regular physical activity can be

considered as one of the best alternatives. As it is evident from the literature that the development of diabetes is a multi-factorial complex process and derangement in antioxidant capacity is one of the known contributing mechanisms. The current study is therefore designed to investigate the effect of regular exercise on the antioxidant status of prediabetics.

**Methods.** It was an experimental study with pre- and post-design based on convenience sampling of 8 weeks of moderate-intensity exercise, an interventional tool for determining its effects on anthropometric parameters, diabetic profile, and antioxidant status in Pakistani prediabetic participants of 18 to 35 years of age. All experimental work was carried out from February 2019 to January 2020 in the Physiology Department, Institute of Basic Medical Sciences (IBMS) Khyber Medical University (KMU), Peshawar, Pakistan. Ethical approval for the study was granted by the Ethical review board of Khyber Medical University under DIR/KMU-EB/BP/000580 dated 09/04/2019 and all the procedures were carried in accordance with the Declaration of Helsinki 1964. The prediabetic volunteers 18 to 35 years (n=50); were included in the study with no history of chronic or active health problems without taking any antioxidant supplements. The inclusion criteria for prediabetes were fasting blood glucose level of 100-125 mg/dL and glycated hemoglobin between 5.7-6.4% according to the American Diabetes Association.<sup>14</sup> After explaining the procedure to each participant, informed consent was obtained. Those with DM, hypertension, renal disease, or any other acute or chronic disease were excluded from the study.

The sample size was calculated using G Power 3.1.9.2. Mean  $\pm$  (standard deviation [SD]) values of TAC from Rodriguez et al<sup>12</sup> were used for sample size calculation. The TAC values of cases ( $0.23 \pm 0.04$ ) and controls ( $0.27 \pm 0.01$ ) were used. Keeping the power of 0.95 and  $\alpha=0.05$ , the sample size was calculated as 26: distributing 13 in each group. From Mohieldin et al,<sup>4</sup>  $1.325 \pm 0.16$  for prediabetics and  $1.711 \pm 0.13$  for normal glucose tolerant 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.<sup>4,12</sup>

**Anthropometric measurements.** The body weight, body fat percentage, fat mass, lean mass, and body mass index (BMI) were measured using impedance meter (Xiaomi scale-2, Model: XMTZC02HM; CMIIT ID: 2016DP6264, Producer: Ltd. 'Anhui Huami

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Informeyshn Technologies' China). The waist and hip circumference, the waist-hip ratio was measured using tape flexible nylon coated and inelastic (Shanghai Harden Tools Co., Ltd.) at pre and post-exercise interval.

Initial samples and post interventional (8 weeks) blood samples in 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 fasting state. This was followed by centrifugation at 3000 revolutions per minute for 10 minutes to separate serum and storage at  $-80^{\circ}\text{C}$ .

**Exercise test.** The exercise tests were carried out in the skill lab of IBMS, KMU. The volunteers were made to walk on power motorized treadmill (model: Revo RT 100) for 30 min at  $70 \pm 5\%$  of maximal heart rate.<sup>15</sup> Step counts during this activity were counted with a software (Mi Fit, China) driven pedometer (Mi band 2, China). Standardized steps count during the exercise session for each participant at required intensity was confirmed on the initial 3 visits to the lab. The participants completed the same numbers of steps in the provided time for 5 days a week for 8 weeks and recorded their daily step count manually in the booklet provided for data entry

**Biochemical assay.** Fasting blood sugar (FBS) was carried out 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. Uric acid was measured by TBHBA DIALAB Production, Austria.

**Statistical analysis.** Statistical analysis was performed by the IBM SPSS Statistics, version 20.0 (IBM Corp, Armonk, NY, USA). Normality was checked for all variables by Kolmogorov Smirnov and Shapiro Wilk normality tests and histograms. Anthropometric, body composition, diabetic profile and antioxidants were expressed as mean  $\pm$  Standard deviation. Pre- and post-intervention values of study variables were compared by paired sample t-test. A  $p$ -value  $\leq 0.05$  was considered statistically significant.

**Results.** Normality for all data for participants were determined using Kolmogorov Smirnov and Shapiro Wilk normality tests. The data was found to be normally distributed. Of the 50 participants, females were 22 (44%) with a mean age of  $27.64 \pm 6.1$  years

and males were 28 (56%) with a mean age of  $30.18 \pm 3.86$  years. A significant fall in anthropometrics, body composition and fasting blood glucose (FBG) and glycated hemoglobin levels were observed as shown in **Table 1**. At baseline 20% of the participants were obese, 52% were overweight, and 28% had normal BMI whereas at post-exercise stage 12% participants were obese, 42% were overweight while 46% were in the normal range as shown in **Table 1**.

Of the antioxidants SOD, GPX, NO, and vit C showed a decrease in mean concentrations after 8 weeks with  $p < 0.001$  as shown in **Figure 1**. On the other hand, mean level of uric acid and total antioxidant capacity showed increase from the baseline after moderate physical activity for 8 weeks with  $p = 0.005$  and  $p < 0.001$  respectively as shown in **Figure 2**.

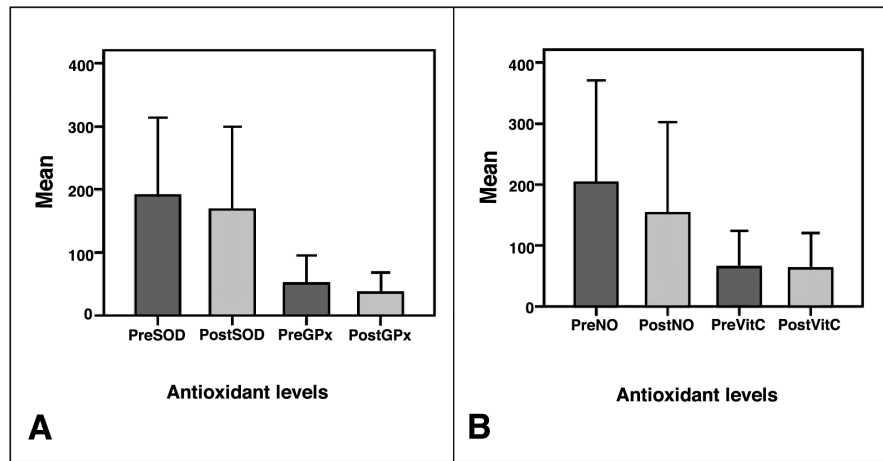
Similarly, when pre- and post-exercise intervention uric acid and TAC levels were analyzed, there was a statistically significant difference as shown in **Figure 2**.

**Discussion.** The prime objective of the study was to determine the total and individual antioxidant capacity in prediabetic individuals before and after moderate exercise at  $70 \pm 5\%$  of the predicted maximum heart rate for 8 weeks. This exercise intervention led to an increase in uric acid and TAC. However, other antioxidants such as SOD, GPX, vit C, and NO showed a decrease. Exercise intervention also decreased weight, waist circumference, fat mass, FBS, and HbA1c with minimal decrease in lean mass.

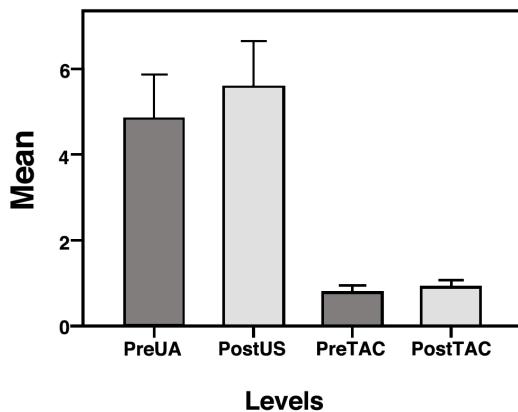
**Table 1** - Comparison of anthropometrics, body composition and diabetic profile before and after exercise intervention.

Statistics	Mean $\pm$ SD		P-value
	Pre-exercise	Post-exercise	
Weight (kg)	74.40 $\pm$ 13.87	73.30 $\pm$ 13.67	<0.001
WC (cm)	94.06 $\pm$ 11.23	92.54 $\pm$ 10.80	<0.001
HC (cm)	102.63 $\pm$ 8.87	101.50 $\pm$ 7.93	<0.001
WHR	0.914 $\pm$ .072	0.908 $\pm$ .0701	0.050
BMI (kg/m <sup>2</sup> )	27.44 $\pm$ 4.43	26.90 $\pm$ 4.29	<0.001
BF percent (%)	31.67 $\pm$ 7.60	30.79 $\pm$ 7.79	<0.002
FM (kg)	23.28 $\pm$ 8.03	22.78 $\pm$ 7.95	0.256
LM (kg)	49.92 $\pm$ 1.55	49.38 $\pm$ 1.58	0.706
FBG (mg/dL)	110.14 $\pm$ 6.69	93.24 $\pm$ 10.47	<0.001
HbA1c (%)	6.02 $\pm$ .24	5.66 $\pm$ .29	<0.001

WC: waist circumference, HC: hip circumference, WHR: waist hip ratio, BMI: body mass index, BF: body fat percentage, FM: fat mass, LM: lean mass, FBG: fasting blood glucose, HbA1c%: glycated hemoglobin percentage



**Figure 1** - Comparison of pre- and post-exercise intervention antioxidant levels. A) Pre-SOD (U/ml)=195.91 ± 126.54 and post-SOD (U/ml)=168.57 ± 131.61 with  $p<0.001$ , pre-GPx (ng/ml) = 51.51 ± 44.32 and post-GPx (ng/ml)=36.47 ± 30.99 with  $p<0.001$ . B) Pre-NO (mIU/ml) = 231.21 ± 186.97 and Post-NO (mIU/ml) = 182.61 ± 173.85 with  $p<0.001$ , pre-vitC (ng/ml) = 73.03 ± 71.19 and post-vit C (ng/ml)=70.31 ± 70.05 with  $p<0.001$ .\*\*\* $p<0.001$ . (dark grey bars: pre-intervention; light grey bars: post intervention). SOD: superoxide dismutase, GPx: glutathione peroxidase, NO: nitric oxide, vit C: vitamin C, Paired t-test comparison of pre- and post-exercise values.



**Figure 2** - Comparison of pre and post exercise intervention uric acid and TAC levels. Pre-UA (mg/dL) = 4.84 ± 1.02 and post-UA (mg/dL) = 5.58 ± 1.06 with  $p=0.005$ , pre-TAC ( $\mu\text{g/ml}$ ) = 0.776 ± 0.16 and post-TAC ( $\mu\text{g/ml}$ )=0.911 ± 0.16 with  $p<0.001$ .\*\*\* $p<0.001$ , \*\* $p<0.01$ . UA: uric acid, TAC: total antioxidant capacity. Dark Grey bars: pre-intervention, light grey bars: post intervention. Paired t-test comparison of pre- and post-exercise values.

The increase in TAC and uric acid was little (although statistically significant). Total antioxidant capacity reflects the strength of antioxidants' defense mechanism and the findings of this study are in accordance with the findings of Farhangi et al.<sup>16</sup> The TAC analysis carried out through ferric reducing ability of plasma (FRAP) assay mainly reflects major contributions of uric acid and vitamin C.<sup>17,18</sup> Uric acid was increased

with intervention in our study and may have a role in increasing TAC.

The levels of SOD and GPX significantly decreased after the exercise. This finding is not in line with studies reported for a healthy population which show an increase in antioxidants with exercise.<sup>18</sup> Superoxide dismutase is the strongest cellular antioxidant and along with GPx constitutes the first line of defense against ROS. It converts the harmful superoxide anion to hydrogen peroxide and molecular oxygen rendering it less harmful.<sup>17</sup> These findings are astonishing and contradictory to the majority of the existing literature. However, thorough searches of the literature yielded that population under consideration in their studies were healthy. Prediabetes is associated with more oxidative stress and people with prediabetes may have a different basal antioxidant level than the normal population.<sup>6</sup>

Nitric oxide plays a significant role in the status of vascular tone and endothelial function in the human body. In our study, NO was decreased with exercise intervention. This is similar to studies in type 2 diabetes people where there was no significant change in nitric oxide levels after exercise, and NO levels were lower than the healthy control group.<sup>19</sup> Wang et al,<sup>20</sup> have reported an increase in nitric oxide concentration with low-intensity aerobic exercise in prediabetic rats but the increase was less as compared to controls. Moreover, they utilized low-intensity exercise as compared to moderate in our study.

Vitamin C levels are mostly determined by diet.<sup>21</sup> Vitamin C in our population exhibited a decrease after 8 weeks. It may either be due to decreased dietary intake or low values of endogenous vit C concentration. Therefore, it can be derived from our study that endogenous vit C is least likely affected by exercise. The dietary element that could have affected the antioxidant level was excluded by 48 hours restriction of a high antioxidant diet.

Besides, the effects on anthropometric and diabetic parameters were also determined. Moderate exercise for 8 weeks significantly improved all the parameters. Weight reduction especially in fat mass and fat percentage has been extensively reported with exercise. Even large weight reduction with exercise based on intensities and durations without dietary modifications has been reported earlier.<sup>22</sup> Our participants were overweight (BMI  $27.44 \pm 4.43$ ) and prediabetic exhibiting a link of imbalance in body composition with metabolic disorders. At baseline, 28% of participants had BMI within a normal range ( $<25\text{kg/m}^2$ ) and after 8 weeks of moderate exercise activity, 34% were in the normal range. Mean BMI at the post-interval stage was still in the overweight range ( $26.90 \pm 4.29$ ). This reflects the importance of incorporation of exercise at the prediabetic stage with precise intensities and duration. Similarly, significant changes in central adiposity and body fat percentages were observed. Due to the link of central adiposity with a metabolic disorder, the proposed protocol can be used for overcoming the increased central adiposity.<sup>22</sup>

Enhanced physical activity has a significant effect on reducing the fasting blood sugar and glycated hemoglobin level that is consistent with our study.<sup>23</sup> It is of significant importance that exercise can be used as an alternative to therapeutics in combating prediabetes evident by the fact that 48% of the participants showed their HbA1c level in the normal range (less than 5.7%) with the rest of the participants also showed a decrease; however, it remained in prediabetic range (for 52% participants). As the exercise in our study was continued for 8 weeks, exercise for a longer duration may prove more beneficial. The changes in anthropometrics, adiposity and diabetic profile provide additional information regarding the possible quantification of exercise, irrespective of the dietary modifications for control/reversal of prediabetic state into normal.

Looking at the presently available evidence, the effect of moderate-intensity exercise on the antioxidant status of prediabetic population has not been explored. This includes endogenous antioxidant profile both enzymatic, non-enzymatic and TAC with the intent to provide novel

information on prediabetes and its prevention through lifestyle changes. Exercise intervention has shown beneficial effects in increasing antioxidants in healthy population.<sup>24</sup> This effect has been noticed in the young population, males,<sup>24</sup> females,<sup>25</sup> elderly population,<sup>16</sup> and also animal studies.<sup>20</sup> However, no robust exercise and antioxidants data is available for type 2 diabetes. Studies conducted on the diabetic population have mostly used nutrient intervention with or without exercise<sup>26</sup> and limited data is available for exercise only studies. The same is true for our study of not finding an increase in antioxidants with exercise intervention only. Prediabetes is inflammatory with increased oxidative stress state.<sup>27</sup> Exercise intervention alone may not be able to increase antioxidants. Moreover, in people with a sedentary lifestyle,<sup>28</sup> oxidative stress increases after initial exercise which can only be abolished after complete adaptations to exercise. It is possible that 8 weeks of the exercise was not enough for complete adaptation and dietary addition of antioxidants is required. This also warrants that programmed exercise should be devised for a duration longer than 8 weeks.

In summary, exercise alone is beneficial in improving the antioxidant profile of a normal healthy population; however, the prediabetic population may require dietary interventions besides improving antioxidant status.

**Study limitations.** The strength of the present study includes recruitment of prediabetic volunteers and comparison of antioxidant status before and after the moderate exercise protocol. Limitations include the duration of exercise, as a longer duration of 16 to 20 weeks or more can give better results in improving individual antioxidant levels. We did not include any control group for comparisons, which may have strengthened results. We did not put the participants on any special diet and only gave dietary advice. Controlling dietary intake and calories would have strengthened our findings.

In conclusion, moderate physical activity for 8 weeks had a significant effect on decreasing weight, BMI and improving FBG, and HbA1c status. However, physical activity unexpectedly decreased individual antioxidant levels in prediabetics as compared to increasing antioxidant levels in the healthy population. In contrast to other antioxidants, TAC and uric acid increased with exercise intervention.

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