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Investigation of Anti-inflammatory, Antioxidative, and Cardioprotective Effects of Combined Metformin and Exercise in Rats

Sıçanlarda Kombine Metformin ve Egzersizin Anti-inflamatuar, Antioksidatif ve Kardiyoprotektif Etkilerinin Araştırılması

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ABSTRACT

Aim: This study aimed to investigate the anti-inflammatory, antioxidative and cardioprotective effects of exercise and metformin treatment applied alone or in combination.
Material and Methods: In this study, 42 male Wistar rats were used. The rats were separated into six groups as control (CONT), exercise (EXE), 100 mg/kg metformin (M100), 200 mg/kg metformin (M200), 100 mg/kg metformin+exercise (M100+EXE), and 200 mg/kg metformin+exercise (M200+EXE). Exercise was applied for 10 weeks including exercise training. Metformin was administered 30 minutes before exercise. At the end of the study, levels of C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-10 (IL-10), cardiac troponin-I (cTn-I), creatine kinase-muscle/brain (CK-MB), catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx) and malondialdehyde (MDA) in serum samples from rats were quantified using the ELISA method.
Results: The combined application of metformin and exercise significantly decreased cTn-I, CK-MB, MDA, TNF-α, CRP and IL-6 levels ($p<0.001$). In contrast, it increased SOD, CAT, GPx, and IL-10 levels significantly ($p<0.001$). Glucose levels of groups treated alone or in combination were found statistically significantly less than CONT group ($p<0.001$).
Conclusion: The findings of this study reveal that both metformin and exercise administration, alone or in combination, exert significant anti-inflammatory, antioxidant, and cardioprotective effects in Wistar rats. These results suggest that combining metformin therapy with regular exercise may offer a synergistic approach to reducing cardiovascular risk factors and enhancing antioxidant defenses.
Keywords: Longevity; cardiovascular diseases; hyperglycemia; oxidative stress; metformin; exercise.

ÖZ

Amaç: Bu çalışmanın amacı egzersiz ve metformin tedavisinin tek başına veya birlikte uygulanmasının anti-enflamatuar, antioksidatif ve kardiyoprotektif etkilerinin araştırılmasıdır.
Gereç ve Yöntemler: Bu çalışmada 42 adet erkek Wistar sıçan kullanılmıştır. Sıçanlar kontrol (CONT), egzersiz (EXE), 100 mg/kg metformin (M100), 200 mg/kg metformin (M200), 100 mg/kg metformin+egzersiz (M100+EXE) ve 200 mg/kg metformin+egzersiz (M200+EXE) olmak üzere altı gruba ayrılmıştır. Egzersiz, egzersiz eğitimi de dahil olmak üzere 10 hafta boyunca uygulanmıştır. Metformin egzersizden 30 dakika önce uygulanmıştır. Çalışma sonunda sıçanlardan alınan serum örneklerinde, C-reaktif protein (CRP), tümör nekroz faktörü-alfa (TNF-α), interlökin-6 (IL-6), interlökin-10 (IL-10), kardiyak troponin-I (cTn-I), kreatin kinaz-kas/beyin (CK-MB), katalaz (CAT), süperoksit dismutaz (SOD), glutatyon peroksidaz (GPx) ve malondialdehit (MDA) ELISA yöntemi kullanılarak ölçülmüştür.
Bulgular: Metformin ve egzersizin birlikte uygulanması cTn-I, CK-MB, MDA, TNF-α, CRP ve IL-6 düzeylerini anlamlı şekilde azaltmıştır ($p<0,001$). Buna karşılık, SOD, CAT, GPx ve IL-10 düzeylerini de önemli şekilde artırmıştır ($p<0,001$). Tek başına veya kombinasyon halinde tedavi edilen grupların glukoz seviyeleri CONT grubundan istatistiksel olarak anlamlı şekilde daha düşük bulunmuştur ($p<0,001$).
Sonuç: Bu çalışmanın bulguları, hem metformin hem de egzersiz uygulamasının, tek başına veya kombinasyon halinde, Wistar sıçanlarında önemli anti-inflamatuar, antioksidan ve kardiyoprotektif etkiler gösterdiğini ortaya koymaktadır. Bu sonuçlar, metformin tedavisinin düzenli egzersizle birleştirilmesinin, kardiyovasküler risk faktörlerini azaltmak ve antioksidan savunmaları güçlendirmek için sinerjik bir yaklaşım sunabileceğini düşündürmektedir.
Anahtar kelimeler: Uzun ömür; kardiyovasküler hastalıklar; hiperglisemi; oksidatif stress; metformin; egzersiz.

INTRODUCTION

Cardiovascular diseases (CVDs) are among the top causes of mortality worldwide. In 2019, an estimated 17.9 million people died from CVDs, accounting for 32% of total worldwide mortality. 85% of these fatalities were caused by heart attacks or strokes (1). Most CVDs can be avoided by addressing lifestyle risks such as tobacco use, poor nutrition, being overweight, lack of exercise, and problematic alcohol consumption (2). Myocardial infarction (MI), sometimes known as a heart attack, is the leading cause of cardiovascular mortality in most nations. MI occurs when one or more of the coronary arteries that feed blood to the heart get clogged, depriving a portion of the heart of oxygen and nutrients and eventually leading to myocardial necrosis (3). Many risk factors for MI are modifiable and can therefore be preventable in many cases. Changes in blood creatine kinase-muscle/brain (CK-MB), lactate dehydrogenase (LDH), and troponin-T/troponin-I levels can be used to determine cardiac injury after MI (4). These alterations are followed by large increases in superoxide anion and hydroxyl radical levels (5). As a result, antioxidants have emerged as an effective technique for preventing oxidative damage in cardiac injury (6).

Metformin, a biguanide often used for diabetic therapy, has been shown to improve ventricular function (6). Metformin therapy has been linked to increased phosphorylation of protein kinase triggered by adenosine monophosphate (AMP), affecting intracellular pathways and mitochondrial function. Experimental findings indicate that administering metformin before and during ischemia-reperfusion may impact these protective mechanisms and sustain left ventricular function regardless of glucose status (7,8). Furthermore, studies conducted in patients with acute myocardial infarction (AMI) have shown that metformin, compared to other antihyperglycemic strategies, is associated with lower peak levels of creatine kinase (CK), myocardial CK-MB band, and troponins in patients with type 2 diabetes (T2DM), as well as improved survival following STEMI (9,10).

Exercise is well-established to enhance oxygen delivery and utilization, thereby improving cardiorespiratory fitness. Furthermore, during high-intensity, short-duration exercise, muscle glycogen serves as the primary energy source (11). Exercise capacity is defined as the maximum level of physical effort that an individual is capable of sustaining. Despite the pronounced cytokine response to exercise, there is limited indirect or direct evidence linking oxidative stress with proinflammatory cytokine production. One study reported that acute exercise-induced oxidative stress did not influence cytokine release 30 minutes post-exercise (12). However, following a repeated cycling exercise for three days (90 minutes/day), it was found that plasma interleukin-6 (IL-6) concentration significantly increased at the 30th minute of exercise on the first day, while reactive oxygen species (ROS) production occurred 60 minutes later (13).

In light of the above information, it is suggested that the increased oxidative stress induced by exercise can be modulated by the antioxidant activity of metformin. This study aimed to investigate the anti-inflammatory, antioxidative, and cardioprotective effects of exercise and metformin treatment when applied alone or in combination.

MATERIAL AND METHODS

Animals

The rats used in this study were obtained from the Experimental Animals Application and Research Center of Düzce University. Experiments were conducted in a laboratory environment with a room temperature of 23°C, 60±5% humidity, and a 12:12 hour light-dark cycle. A total of, forty-two male Wistar rats, weighing 230±30 g and aged 2-3 months, with ad libitum access to food and water, were used in this study. Ethical approval for this study was obtained from the Düzce University's Local Ethics Committee for Animal Research with the code 2021/11/01. The Animal Research: Reporting of in Vivo Experiments (ARRIVE) standards require the reporting of all study methodologies.

Groups, Substances, and Doses

The rats were divided into six groups, each consisting of seven rats: control (CONT), exercise (EXE), 100 mg/kg metformin (M100), 200 mg/kg metformin (M200), 100 mg/kg metformin+exercise (M100+EXE), and 200 mg/kg metformin+exercise (M200+EXE). Metformin (Biovision Inc., Milpitas, CA, USA) dissolved in saline was given intraperitoneally (i.p.) at dosages of 100 and 200 mg/kg. Metformin and saline were given 30 minutes before the exercise (Figure 1). Anesthesia was administered intramuscularly (i.m.) with 90 mg/kg ketamine hydrochloride and 10 mg/kg xylazine hydrochloride. All drugs were prepared fresh daily.

Treadmill Exercise Protocols

Exercise training was given to the rats to train them to run regularly ensuring they would not have difficulty in subsequent running-based exercises. Exercise training protocols for the treadmill were adapted from the literature (14-16). Rats in the exercise groups (EXE, M100+EXE, and M200+EXE) were given a 2-week acclimatization period to adjust to their new surroundings, followed by 8 weeks of exercise training. The rats were trained for 15 minutes each day to run on a horizontal treadmill (May Time 0804, Animal Treadmill). For the training of the animals, the treadmill speed was set to 2 m/min for the first 2 days (Days 1 and 2). Then, the speed was increased to 5 m/min between Days 3 and 5, and for the final 5 days (Days 6 to 10), it was raised to 8 m/min. The exercise protocol described in the literature was followed for

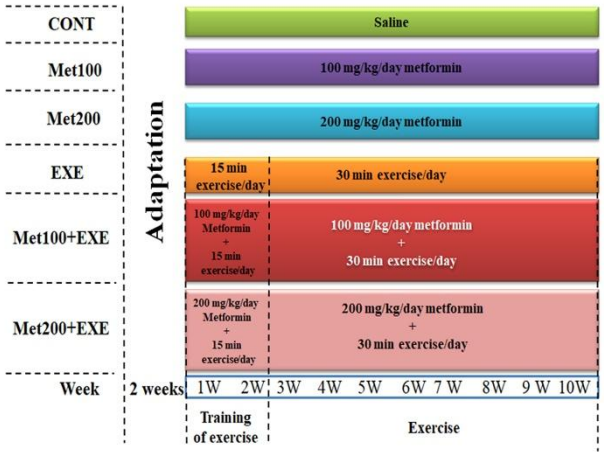

Figure 1. Representative illustration of the experimental procedure

the main study. The rats were exercised for 30 minutes a day, 6 days a week, between 08.00 am and 10.00 am for 10 weeks. Every day, the rats were put through three phases of exercise: 2 m/min for 5 minutes, 5 m/min for 5 minutes, and 8 m/min for 20 minutes. Rats in the CONT, M100, and M200 groups spent an equal amount of time on a static treadmill with no activity.

Termination of the Study

Blood was drawn from the rats' hearts via cardiac puncture under ketamine/xylazine anesthesia 24 hours following the last injection. The animals were subsequently sacrificed via cervical dislocation under anesthesia. Blood samples were centrifuged at 4000 rpm for 15 minutes, and serum was kept at -80°C until analysis.

Determination of Biochemical Biomarkers

Cardiac troponin-I (cTn-I), CK-MB, tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), IL-6, interleukin-10 (IL-10), malondialdehyde (MDA), glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) in serum samples from rats were quantified using the sandwich enzyme-linked immunosorbent assay (ELISA) method. ELISA kits from SunRed (SunRed, China) and ELK (ELK Biotechnology CO., Ltd., Wuhan, China) were used in the study. Following the manufacturer's protocols, IL-10 (Cat: 201-11-0109), IL-6 (Cat: 201-11-0136), TNF-α (Cat: 201-11-0765), CRP (Cat: 201-11-0054), CK-MB (Cat: 201-11-0312), cTn-I (Cat: 201-11-0640), GPx (ELK2222), CAT (ELK5986), SOD (ELK5616), and MDA (ELK8616) levels were determined by ELISA reader was measured in serum.

Statistical Analysis

Compliance with normal distribution was evaluated by the Shapiro-Wilk test. All data were analyzed using means and standard deviations. The groups were compared using a one-way analysis of variance (ANOVA), and the different groups were identified using Tukey's multiple comparisons test. A p-value of ≤ 0.05 was accepted as statistically significant. All statistical analyses were performed using the IBM SPSS software v.22.0.

RESULTS

Cardioprotective Effect of Combined Administration of Metformin and Exercise

When the serum CK-MB levels of the groups were compared, a statistically significant difference was observed between groups ($p<0.001$, Table 1, Figure 2A). The EXE group had significantly greater CK-MB levels compared to the CONT, M100, M200, M100+EXE, and M200+EXE groups ($p=0.001$, $p=0.010$, $p=0.003$, $p<0.001$, and $p=0.001$, respectively).

When cTn-I levels were examined between groups, there was a substantial difference ($p<0.001$, Table 1, Figure 2B). In-depth analysis revealed that the EXE group had significantly greater cTn-I levels than the CONT, M100, M200, M100+EXE, and M200+EXE groups ($p=0.008$, $p=0.010$, $p<0.001$, $p<0.001$, and $p<0.001$, respectively).

Pro- and Anti-inflammatory Effects of Combined Application of Metformin and Exercise

When serum TNF-α levels of the groups were compared, a statistically significant difference was identified between the groups ($p<0.001$, Table 1, Figure 3A). The EXE group had significantly greater TNF-α levels compared to the CONT, M100, M200, M100+EXE, and M200+EXE groups ($p<0.001$, $p<0.001$, $p=0.020$, $p<0.001$, and $p=0.002$, respectively).

When the groups were compared in terms of CRP levels, a statistically significant difference was found between the groups ($p<0.001$, Table 1, Figure 3B). The EXE group showed significantly greater CRP levels compared to the CONT, M100, M200, M100+EXE, and M200+EXE groups ($p<0.001$ for all comparisons). Similarly, the M200+EXE group had significantly greater CRP levels than the M100 group ($p=0.050$).

When IL-6 levels were examined between groups, there was a substantial difference ($p<0.001$, Table 1, Figure 3C). The EXE group had significantly greater IL-6 levels compared to the CONT, M100, and M200 groups ($p<0.001$ for all comparisons). Similarly, the M100+EXE ($p=0.010$) and M200+EXE ($p=0.020$) groups had significantly greater IL-6 levels compared to the CONT group.

When IL-10 levels were examined between groups, there was a substantial difference ($p<0.001$, Table 1, Figure 3D). The CONT group had significantly reduced IL-10 levels compared to the EXE, M100, M200, M100+EXE, and M200+EXE groups ($p<0.001$ for all comparisons).

Oxidative and Antioxidative Effect of Combined Application of Metformin and Exercise

When the groups were compared in terms of serum MDA levels, a statistically significant difference was determined between the groups ($p<0.001$, Table 1, Figure 4A). The EXE group showed significantly greater MDA levels compared to the CONT, M100, M200, M100+EXE, and M200+EXE groups ($p<0.001$ for all comparisons). In contrast, the CONT group had significantly lower MDA levels than M100+EXE and M200+EXE groups ($p=0.007$, and $p=0.001$, respectively). Similarly, the M100 group had significantly lower MDA levels than M100+EXE ($p=0.007$) and M200+EXE ($p=0.001$) groups.

Serum GPx levels were examined between groups, there was a substantial difference ($p<0.001$, Table 1 Figure 4B). The CONT group had significantly lower GPx levels than the EXE, M100, M200, M100+EXE, and M200+EXE groups ($p<0.001$ for all comparisons). Additionally, the EXE group showed substantially reduced GPx levels compared to the M100, M200, M100+EXE, and M200+EXE groups ($p<0.001$ for all comparisons).

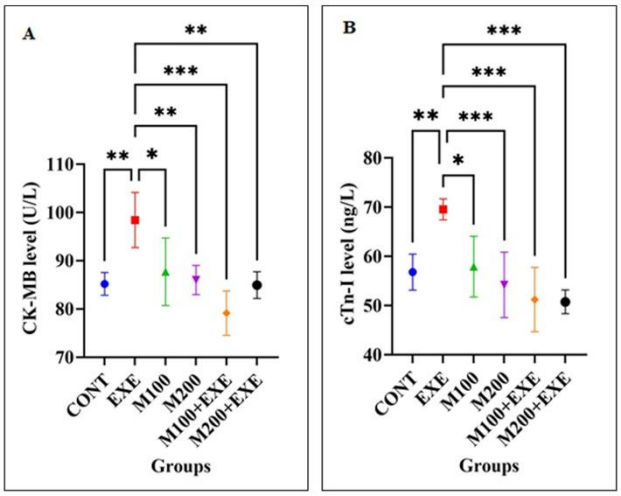

Figure 2. The effect of combined metformin and exercise on cardiac biomarkers (*p<0.05, **p<0.01 and ***p<0.001)

A statistically significant difference was found in CAT levels, between groups (p<0.001, Table 1, Figure 4C). The CONT group had significantly lower CAT levels compared to the M100+EXE and M200+EXE groups (p=0.001, and p=0.005, respectively). Similarly, the EXE group had significantly lower CAT levels than the M100+EXE and M200+EXE groups (p=0.008, and p=0.030, respectively). Serum SOD levels were examined between groups, there was a substantial difference (p<0.001, Table 1, Figure 4D). The CONT group showed significantly reduced SOD levels compared to the EXE, M100, M200, M100+EXE, and M200+EXE groups (p<0.001 for all comparisons).

Table 1. Effect of combined exercise and metformin on biochemical biomarkers

	CONT	EXE	M100	M200	M100+EXE	M200+EXE	p
CK-MB (U/L)	85.19±2.35$^{\Delta}$	98.43±5.72	87.73±6.99$^{\Delta}$	86.00±3.01$^{\Delta}$	79.14±4.60$^{\Delta}$	84.94±2.76$^{\Delta}$	**<0.001**
cTn-I (ng/L)	56.80±3.64$^{\Delta}$	69.56±2.14	57.92±6.17$^{\Delta}$	54.20±6.64$^{\Delta}$	51.22±6.53$^{\Delta}$	50.76±2.41$^{\Delta}$	**<0.001**
TNF-α (ng/L)	64.01±3.88$^{\Delta}$	74.79±2.67	62.46±4.43$^{\Delta}$	67.08±3.96$^{\Delta}$	64.43±4.37$^{\Delta}$	65.40±3.22$^{\Delta}$	**<0.001**
CRP (ng/mL)	34.02±3.14$^{\Delta}$	46.40±3.23	31.90±2.94$^{\Delta\#}$	33.10±2.07$^{\Delta}$	35.20±1.90$^{\Delta}$	36.40±1.61$^{\Delta}$	**<0.001**
IL-6 (pg/mL)	34.45±2.73$^{\Delta}$	47.80±5.25	37.63±5.04$^{\Delta}$	36.20±2.14$^{\Delta}$	42.52±2.96$^{\Delta}$	42.25±3.76$^{\Delta}$	**<0.001**
IL-10 (ng/mL)	19.18±1.37	30.13±4.06*	32.27±3.05*	33.35±7.30*	29.89±2.13*	31.26±3.27*	**<0.001**
MDA (pg/mL)	641.5±64.67$^{\Delta}$	1415±157.90	663.5±65.33$^{\Delta}$	742.30±82.99$^{\Delta}$	826.8±44.52$^{*\Delta\#}$	863.20±54.02$^{*\Delta}$	**<0.001**
GPx (pg/mL)	85.68±3.27	101.30±2.65*	125.60±9.52$^{*\Delta}$	124.10±10.53$^{*\Delta}$	133.80±2.94$^{*\Delta}$	127.00±8.34$^{*\Delta}$	**<0.001**
CAT (ng/mL)	11.15±0.27	12.39±0.39	15.26±5.51	14.54±3.77	18.71±0.69$^{*\Delta}$	17.74±2.00$^{*\Delta}$	**<0.001**
SOD (U/mL)	0.755±0.12	1.611±0.37*	1.679±0.04*	1.809±0.19*	1.991±0.24*	1.761±0.28*	**<0.001**
Glucose (mg/dL)	206.30±10.42	180.90±5.90*	175.00±21.59*	179.00±14.87*	167.10±7.19*	175.30±4.64*	**<0.001**

CONT: control, EXE: exercise, M100: 100 mg/kg metformin, M200: 200 mg/kg metformin, M100+EXE: 100 mg/kg metformin+exercise, M200+EXE: 200 mg/kg metformin+exercise, CK-MB: creatine kinase-muscle/brain, cTn-I: cardiac troponin-I, TNF-α: tumor necrosis factor-alpha, CRP: C-reactive protein, IL-6: interleukin-6, IL-10: interleukin-10, MDA: malondialdehyde, GPx: glutathione peroxidase, CAT: catalase, SOD: superoxide dismutase, *: significant difference compared to CONT group; Δ: significant difference compared to EXE group; #: significant difference compared to M100 group

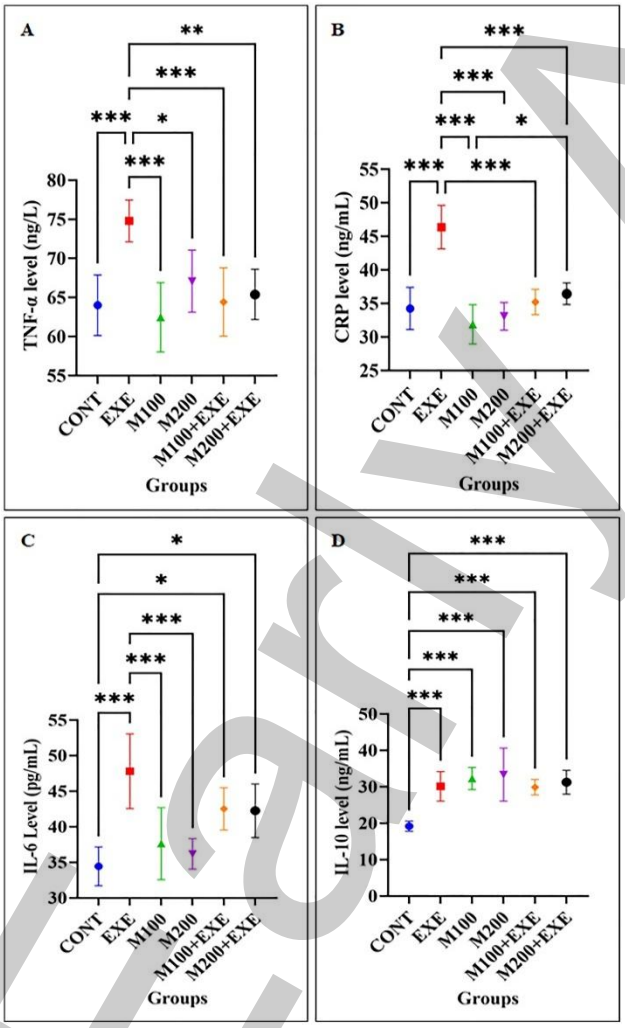

Figure 3. The effect of combined administration of metformin and exercise on oxidative and antioxidative parameters (*p<0.05, **p<0.01, and ***p<0.001)

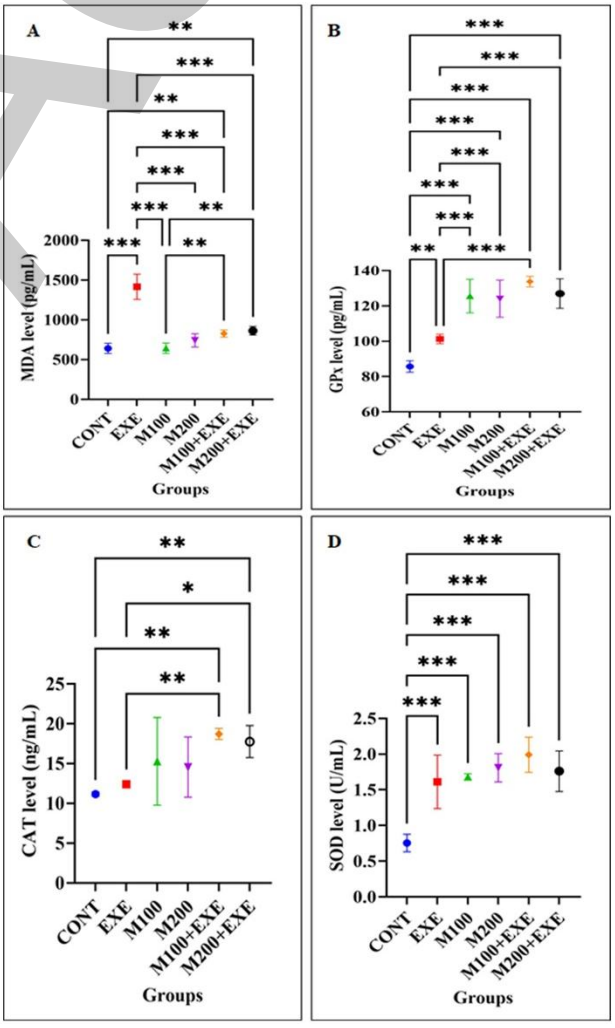

Figure 4. The effect of combined administration of metformin and exercise on pro- and anti-inflammatory parameters (*p<0.05, **p<0.01, and ***p<0.001)

The Effect of the Combination of Metformin and Exercise on Blood Glucose Levels

In terms of blood glucose levels, a statistically significant difference was determined between the groups ($p<0.001$, Table 1, Figure 5). The CONT group had significantly higher blood glucose levels than the EXE, M100, M200, M100+EXE, and M200+EXE groups ($p=0.005$, $p<0.001$, $p=0.002$, $p<0.001$, and $p<0.001$, respectively).

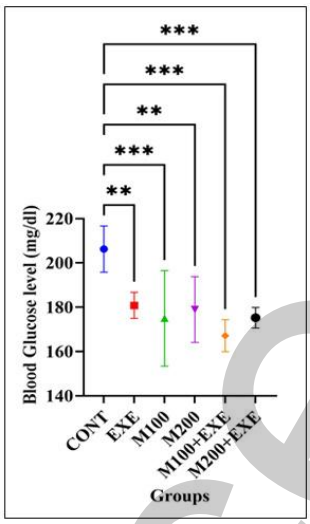

Figure 5. The effect of combined administration of metformin and exercise on blood glucose level (**p<0.01, and ***p<0.001)

DISCUSSION

In this study, the effects of alone or combined exercise and metformin administration on serum cardiac biomarkers, glucose, oxidant, and antioxidant parameters were evaluated. The CK-MB and cTn-I levels were found to be higher in the group subjected to exercise alone, whereas the CK-MB and cTn-I levels were lower in the groups where metformin was administered alone or in combination with exercise. Similarly, the TNF-α and CRP levels were lower in the groups where metformin was administered alone or with exercise compared to the EXE group. The IL-6 levels were lower in the groups where only metformin was administered compared to the EXE group, while the IL-6 levels were higher in the groups where exercise and metformin were administered together compared to the CONT group. The IL-10 levels were found to be higher in all groups where either exercise, metformin, or their combination was applied compared to the CONT group. However, the blood glucose levels were found to be lower than those in the CONT group. The MDA level, an oxidative marker, was higher only in the exercise group, while it was lower in the groups where metformin was administered alone or in combination with exercise. Conversely, the levels of antioxidant parameters SOD, CAT, and GPx were particularly higher in the groups where metformin and exercise were administered together.

Studies aimed at increasing the healthspan—the period of life free from chronic diseases—are on the rise (17,18). Recently, it has been shown that chronic diseases grow increasingly resistant to treatment as people age, and while medication may lower the chance of death from one disease, it may raise the risk of death from others (18). The present medical strategy is limited to therapy after illness onset, sustaining competing risks. Preventing disease onset is an alternate technique for shortening the duration of illness. According to a widely recognized definition of healthspan, a therapy targeted at prolonging healthspan begins before the onset of chronic disease and stops when chronic disease begins (17). While there are acknowledged flaws with this definition, it is useful in distinguishing a time of general health from one defined by the buildup of chronic disorders. Therefore, strategies to preserve healthspan are inherently preventive.

The therapeutic benefits of exercise in preventing and treating various chronic diseases are indisputable (19). Regular exercise not only prevents the onset of disease but also slows the progression of disease in the absence of physical activity. Aerobic capacity refers to a physiological system's robust ability to provide and utilize oxygen during high-intensity activity. Low aerobic capacity increases the risk of several illnesses, including CVD, cancer, and diabetes (20). Individuals with high or moderate aerobic capacity, on the other hand, are at a much-decreased risk of chronic illnesses and early mortality (18). Intense endurance exercise alters immune system homeostasis, resulting in leukocytosis and immunological suppression from neutrophils in the systemic circulation (21,22). Numerous studies have found increases in IL-6, IL-10, IL-1ra, and IL-8 during prolonged endurance exercise (22-24). However, during and after short-term intense exercise and eccentric contraction exercise, changes in the levels of these cytokines appear to be negligible (23,25). These data imply that cytokine responses are more closely connected to exercise intensity and duration (physiological load/stress) than to exercise-induced muscle injury (23,26).

Metformin is a biguanide widely used in the treatment of T2DM (27). Its antihyperglycemic effect is not due to stimulation of insulin secretion, rather its influence on peripheral tissues renders them more susceptible to insulin action. Metformin's influence on glucose levels has been demonstrated in vitro and in vivo by its capacity to diminish hepatic glucose production while increasing peripheral glucose absorption (28). Metformin primarily targets the liver, but it also influences metabolic processes in skeletal muscle, adipose tissue, the gut, the brain, and cardiovascular tissues (29-32). Metformin reduces hepatic glucose synthesis by decreasing gluconeogenesis and boosting glucose absorption in skeletal muscle (29,32). In addition to its glucose-lowering efficacy, studies in preclinical models over the past two decades have recognized other beneficial effects of metformin (33). Different durations and doses of metformin administration have been shown to reduce cTn-I and CK-MB levels (34-36). The antioxidant activity of metformin in cardiomyocytes occurs through AMP-activated protein kinase (AMPK) activation. This reduces ROS production in animal models of heart failure. Metformin can protect cardiomyocytes from oxidative stress induced by H_2O_2 or TNF-α (33). A multicenter prospective study reported that a 2-year metformin treatment in prediabetic patients with stable angina and nonobstructive coronary stenosis reduced inflammation and oxidative stress markers. The same study also reported improvements in epicardial endothelial dysfunction (37). A decrease in CRP, IL-6, and TNF-α levels after a 3-month metformin treatment was reported in patients with carotid artery atherosclerosis (38). In patients with metabolic syndrome, a 7-day metformin pretreatment significantly reduced CRP, CK-MB, and cTn-I levels (39).

The combination of exercise and metformin administration appears logical for two reasons. Firstly, although their targets (liver and skeletal muscle) are different, they are complementary. Secondly, both metformin and exercise partly exhibit their beneficial effects through AMPK. Metformin and exercise capacity are intricately linked. Muscle contraction activates AMPK. There is mounting evidence that metformin boosts AMPK activation in the liver, muscle, and other tissues (40). Due to energy depletion, glycolysis, and phosphocreatine energy systems are activated to maintain normal cellular metabolism (41). Metformin has anti-inflammatory properties, albeit the mechanisms are not fully understood (42). However, metformin has been shown to exert anti-inflammatory effects in various disease models and humans. Studies have reported that metformin reduces TNF-α, IL-1β, and IL-6, and increases IL-10 (43,44). Another study reported that metformin reduces CRP levels (45).

Metformin and exercise were given to prediabetic male Wistar rats that had been fed a high-fat diet and sugary beverages for four weeks (46). Rats that received both exercise and metformin showed lower levels of inflammatory factors, improved lipid metabolism, and reduced mitochondrial oxidative stress levels. Another study reported that the combination of exercise and metformin alleviated diabetes-induced cardiac complications (47). In a study investigating the effects of the combination of metformin and exercise on inflammation and apoptosis mechanisms in rats, it was found that the combined application of metformin and exercise reduced TNF-α and IL-6 levels (48). In a study examining the effects of exercise and metformin in adult patients with T2DM, 699 patients were subjected to either exercise or metformin treatment for twenty-four weeks. By the end of the therapy, both groups had normalized their fasting blood glucose, HbA1c, BMI, and lipid profile values (49).

Hyperglycemia triggers the excessive production of ROS, which can lead to harmful effects through various pathways, including lipid peroxidation and the production of highly reactive aldehydes like MDA. It also leads to the degradation of antioxidant defense systems such as GPx, SOD, and CAT (50). In streptozotocin (STZ)-induced diabetic rats, the combined application of metformin and exercise significantly reduced the MDA levels and improved antioxidant status (CAT and SOD), thereby significantly reducing oxidative stress compared to the diabetic group (51).

CONCLUSION

This study highlights the beneficial effects of combining exercise with metformin in reducing oxidative stress and improving antioxidant defenses. The significant reduction in MDA levels and enhancement in antioxidant enzyme activities, such as SOD, CAT, and GPx, suggests that this combination can effectively reduce oxidative damage and improve overall cellular health. This, in turn, may contribute to lower levels of cardiac biomarkers like CK-MB and cTn-I, indicating a potential positive impact on cardiovascular health. While these findings support the therapeutic potential of combining exercise with metformin, further research is essential to fully elucidate the cardioprotective mechanisms underlying this combination. Ultimately, this may pave the way for broader adoption and implementation of these interventions in promoting cardiovascular health, both in individuals with existing conditions and in those seeking preventive measures.

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