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# The Effect of Selen plus Supplementation during Aerobic Training on Nitric Oxide and Myeloperoxidase in Women with Metabolic Syndrome

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**ABSTRACT**

**Introduction**: Obesity and metabolic syndrome are associated with inflammation, vascular endothelial dysfunction and cardiovascular complications. In this study, the aim was to investigate the effect of aerobic training combined with Selen Plus supplementation on the serum levels of nitric oxide and myeloperoxidase in obese women with metabolic syndrome.

**Methods**: In this quasi-experimental study, 48 obese women (30 ≤ BMI ≤ 36) with metabolic syndrome aged 30-45 years were randomly divided into 4 groups: control (no intervention); Selen Plus (1000 grams/daily); aerobic training (every other day) and combined group (aerobic training + selen plus). Fasting levels of nitric oxide and myeloperoxidase and anthropometric indices were measured before and 48 hours after the final training session in each group. ANCOVA statistical test was used to compare the data and paired t-test was used to determine intra-group changes ($p < 0.05$).

**Results**: Compared to the control group, serum nitric oxide significantly increased and myeloperoxidase significantly decreased in the aerobic, selen plus and combined groups (p=0.001). Nitric oxide in the combined group increased significantly compared to selen plus group (p=0.042).

**Conclusion**: Selen plus supplementation during aerobic training is associated with improvement of vascular endothelial function indices in women with metabolic syndrome compared to its use alone.

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## Introduction

Metabolic syndrome, sometimes called dysmetabolic syndrome, includes a set of cardiovascular risk factors such as increased body mass and obesity and blood pressure with low levels of low-density lipoprotein (HDL) (1,2). Although this disease obviously has no symptoms, abdominal obesity and high blood pressure are its external symptoms, and if you see these external symptoms, you should look for other non-external symptoms (3). This illness has wide-reaching effects, impacting cardiovascular diseases, type 2 diabetes, fatty liver, ovarian cysts, strokes and asthma. (4,5).

People with metabolic syndrome suffer from some kind of cardiovascular disorders and oxidative stress or specifically vascular endothelial disorder (6). Obesity and metabolic syndrome lead to endothelial dysfunction because of vascular dilatation damage of the endothelium, which is the first step in the spread or progression of cardiovascular diseases (7). Hence, recognition and evaluation of oxidative, antioxidant or vascular endothelial stress agents in metabolic syndrome patients is of special importance in clinical sciences. The endothelium plays an important role in regulating vascular function, and nitric oxide

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(NO) is a key marker of vascular endothelial function. As such, a reduction in vasodilation properties has been found to result from a decrease in NO (8).

Nitric oxide with a molecular weight of 30 kilodalton is one of the 10 small molecules in nature, whose synthesis and secretion from the vascular endothelium is mainly stimulated by the nitric oxide synthetase enzyme. It has a potential (9,10) and has been introduced on indicator of cardiovascular and vascular endothelial function. Its role as a vasodilator in controlling vascular tone has been reported (11).

Myeloperoxidase (MPO) is a cationic homodimer glycoprotein with a molecular weight of 15 kilodaltons, as a member of the heme peroxidase enzyme family, which in physiological conditions plays a role in the innate immune system and in fighting against microbial pathogens. However, its inflammatory role or oxidative stress in pathological conditions or obesity-related oxidative stress is associated with impaired vascular function, and its high levels in arterial plaques lead to cardiovascular damage. Its increase leads to dysfunction of the vascular endothelium by inhibiting and reducing the induction of nitric oxide (NO) production (12,13). Based on the mentioned evidence, MPO is introduced as an independent risk factor for predicting vascular endothelium dysfunction.

Although Selen Plus is known among antioxidant supplements, based on the evidence, it is a combination of several non-enzymatic antioxidants that contains 50 micrograms of selenium, 8 milligrams of zinc, 400 micrograms of vitamin A, 125 milligrams of vitamin C, and 40 milligrams of vitamin E. 14). Vitamin E by effectively reducing the oxidation of the lipid membrane of cells (15), vitamin C by making LDL-C resistant to reducing the level of oxidative stress caused by active free radicals (16), vitamin A by cell differentiation, reducing cell-to-cell adhesion and regulating Antioxidant defense system (17), zinc as a receptor of free oxygen radicals and regulating the expression of the nuclear receptor of vitamin A and selenium play a potential role in strengthening the antioxidant system by detoxifying the body from free oxygen radicals. If we want to mention the physiological effects of selenium plus, selenium leads to vasodilation and blood pressure reduction because of its antioxidant effect on nitric oxide. (15). Despite the potential antioxidant effect of Selen Plus, there is no study that follows its separate or combined effect with exercise on the components of oxidative stress or vascular endothelial function (18). In the study of Kardashi et al (2016), 3 months of aerobic training led to an increase in nitric oxide in obese diabetic patients (19). On the other hand, Shameshki et al (2012) reported no change in MPO after a period of stationary exercise in inactive women (20). Nevertheless, the study of Ojaghi et al (1400) has pointed to the decrease of MPO along with the increase in the activity of antioxidant enzymes and the decrease of myeloperoxidase in the heart tissue of rats suffering from cardiac ischemia following increasing endurance exercises (21).

Despite the mentioned evidence, there is still no consensus regarding the effect of exercise training in combination with antioxidant supplements on oxidative stress agents and vascular endothelial function, and there is a contradiction in this field depending on the type, duration, intensity and repetition of training sessions and the studied population. Therefore, due to the divergence of the findings

in this field and the paucity of studies regarding the effect of exercise training with Selen Plus on antioxidant performance, the current study seeks to find out the effect of 8 weeks of aerobic training + Selen Plus on some indicators of oxidative stress and vascular endothelial function in women with metabolic syndrome.

## Material and Methods

### *Subjects*

This investigation used a quasi-experimental research method and an experimental research design that included pre- and post-testing. The statistical population consists of adult obese women (30 ≤ BMI ≤ 36, 163 ± 5.35 of height) with metabolic syndrome aged 30 to 45 who volunteered to participate in the study following a purposive sampling. The Ethics Committee of Islamic Azad University approved our study (Ethical Code: IR.IAU.CTB.REC.1401.139) (Autumn 2022). The study sample is 48 adult obese women with metabolic syndrome (30 ≤ BMI ≤ 36) who were randomly divided into 4 groups: 1) Aerobic exercise group "8 weeks of aerobic training every other day", 2) Selen plus group "8 weeks of taking Selen Plus supplement, 1000 mg daily", 3) combined group "8 weeks of aerobic exercises with Selen Plus supplement and 4) control group "no intervention".

#### *Inclusion or Exclusion Criteria*

The study subjects are non-athletes, non-smokers and non-pregnant. So that they have not participated in a regular training program during the last 6 months. Also, in the last 6 months, they did not have a defined diet and their weight fluctuation was less than one kilogram. The lack of a history of kidney disease and cancer, as well as seizures is among the inclusion of the study. Not taking part regularly in training sessions and not taking supplements or suffering from any disease that affects the dependent variables are exclusion criteria.

### *Anthropometric Measurements*

The levels of anthropometric indexes were measured before and after the aerobic intervention. Height was measured using a inflexible tape measure, without shoes, with an accuracy of 0.1 cm. Hip and abdominal circumference after a normal exhalation in the thickest area was measured by an inflexible tape measure with an error accuracy of less than 0.1 cm. A Seca balance was used to measure the weight with an accuracy of 0.5 kg. Body mass index was measured by dividing weight (kilograms) by height (square meters). Body fat percentage was measured by a body composition analyzer (OMRON-BF 508, Finland).

#### *Interventions*

Selen Plus group experienced the use of Selen Plus in the form of a 1000 mg tablet daily for eight weeks and were prohibited from participating in any sports activities. The aerobic group experienced eight weeks of aerobic exercise every other day, and they were also advised not to participate in any exercise program apart from pre-designed aerobic exercises during this period. Combined group (Aerobic + Selen Plus) experienced eight weeks of aerobic exercise along with Selen Plus consumption (1000 mg daily). The control group maintained their usual lifestyle for eight weeks and did not engage in any physical activity program.

In aerobic intervention, exercise intensity ranged 55-75% of maximal heart rate (HRmax). Each session started by 10 min warm up, 15-40 min of aerobic exercise and 5–10 min of cool down. Aerobic exercises in each session included running with no slop. In the first and second week, subjects exercised at low intensity and the intensity of exercise was gradually increased to 75% of HRmax in last weeks (22, Modified). In each session, the exercise intensity was controlled using the Polar heart rate tester (made in the US).

### *Laboratory and Clinical Measurements*

A venous blood sample was collected from all the subjects who followed a 12-h overnight fast between the hours of 8 to 9 am (pre-training). Subjects were asked to avoid doing any heavy physical activity for 48 hours before blood sampling. After the last training bout, subjects rested for 48 h, and then fasting blood samples were taken similar to pretest (post training). After each blood sampling, serums were immediately separated and stored at -80° until the assays were performed. Nitric oxide and myeloperoxidase were measured calorimetrically using a specialized kit from Navand Salamat (Iran).

### *Statistical Methods*

Statistical comparisons were made in IBM SPSS Software v. 22 at a significance level of less than 5 percent. Kolmogorov-Smirnov test was used to ensure the normal distribution of the data. To compare the data between the groups, ANCOVA test was used along with Bonferroni's post hoc test. Paired t-test was also used to determine the level of intra-group changes.

**Table 1.** Distribution of exercise intensity while running during the training program (19 modified)

| weeks | Exercise intensity (%HRmax) | Time of running |
|---|---|---|
| First and second | %55 ≤ intensity ≤ %60 | 3 × 5 minute |
| Third and fourth | %60 ≤ intensity ≤ %65 | 2 × 10 minute |
| Fifth and Sixth | %65 ≤ intensity ≤ %70 | 2 × 15 minute |
| Seventh and eighth | %70 ≤ intensity ≤ %75 | 2 × 20 minute |

**Table2.** Intra-group variations of anthropometric indices in the pre-test and post-test conditions in the studied groups

| Group | Time | Control | Exercise | Selen plus | Combine |
|---|---|---|---|---|---|
| **Weight** (kg) | Pre-test | 85 ± 3.95 | 83.9 ± 4.68 | 84.1 ± 2.71 | 83.7 ± 6.49 |
| | Post-test | 85 ± 3.88 | 79.2 ± 4.67 | 83.3 ± 2.29 | 79.5 ± 6.77 |
| | Sig | 0.586 | 0.001 | 0.017 | 0.001 |
| **AC** (cm) | Pre-test | 115 ± 4.88 | 115 ± 5 | 114 ± 4 | 116 ± 6 |
| | Post-test | 115 ± 4.85 | 109 ± 5 | 113 ± 4 | 112 ± 6 |
| | Sig | 0.220 | 0.001 | 0.063 | 0.001 |
| **HC** (cm0 | Pre-test | 114 ± 3.46 | 116 ± 2 | 116 ± 2 | 117 ± 2 |
| | Post-test | 114 ± 3.55 | 111 ± 2 | 115 ± 3 | 113 ± 2 |
| | Sig | 0.112 | 0.001 | 0.191 | 0.001 |
| **BMI** (kg/m2) | Pre-test | 32.07 ± 1.48 | 32.35 ± 1.39 | 32.36 ± 1.33 | 32.18 ± 1.99 |
| | Post-test | 33.13 ± 1.3 | 30.55 ± 1.42 | 32.07 ± 1.48 | 30.56 ± 2.05 |
| | Sig | 0.612 | 0.001 | 0.021 | 0.001 |

**- AC**; abdominal circumference, **HC**; hip circumference, **BMI**; body mass index
- Data compared by paired t-test ($p < 0.05$)

## Results

Table 2 presents the anthropometric characteristics at pre and post-test of studied subjects used. One-way ANOVA test was used to compare the basic levels (pre-test) of anthropometric indices between groups. Based on statistical calculations, no significant difference was observed in any of the anthropometric indices between the groups ($p > 0.05$). Also, the intra-group changes by the paired t-test revealed that aerobic training alone and with Selen plus supplement led to a significant reduction in weight, abdominal circumference, hip circumference and body mass index ($p < 0.05$). On the other hand, although the weight and body mass index decreased in the Selen Plus group, there was no significant change in the circumference of the abdomen and hips ($p > 0.05$).

Based on the results of the ANCOVA test, a significant difference was observed in the changes in nitric oxide levels between the studied groups ($p = 0.001$). On the other hand, the results of the Benferoni test revealed that compared to the control group, nitric oxide levels increased significantly in response to all 3 interventions. Also, no

significant difference was observed between the exercise group and Selenium plus and combined groups. Nevertheless, a significant difference in nitric oxide levels was observed between the combination group and the selenium plus group. In other words, the levels of nitric oxide in the combined group increased significantly compared to the selen plus group (Table 3). Also, the intra-group changes of nitric oxide by paired t-test revealed that in all three groups, the intervention leads to a significant increase in nitric oxide compared to the pre-test, but the change in the control group was not significant (Table 4, Fig 1).

**Table 3.** Benferroni post hoc test results for nitric oxide between the studied groups

| Group | Group | Average difference | Standard error | sig |
|---|---|---|---|---|
| **Control** | **Aerobic** | *- 10.293* | *1.170* | *0.001* |
| | **Selen plus** | *- 9.682* | *1.186* | *0.001* |
| | **Combined** | *- 13.031* | *1.169* | *0.001* |
| **Aerobic** | **Selen plus** | *0.611* | *1.197* | *0.999* |
| | **Combined** | *- 2.738* | *1.171* | *0.145* |
| **Selen plus** | **Combined** | *- 3.349* | *- 3.349* | *0.042* |

**Table 4.** Data of intra group changes of nitric oxide in the studied groups

| Group | Control | Aerobic | Selen plus | Combine |
|---|---|---|---|---|
| **Pre test** | *34.11 ± 3.18* | *33.78 ± 1.77* | *35.31 ± 2.71* | *34.25 ± 2.26* |
| **Post test** | *32.14 ± 2.42* | *42.35 ± 3.83* | *42.13 ± 2.61* | *45.21 ± 2.51* |
| **Sig** (paired t test) | *0.155* | *0.001* | *0.001* | *0.001* |

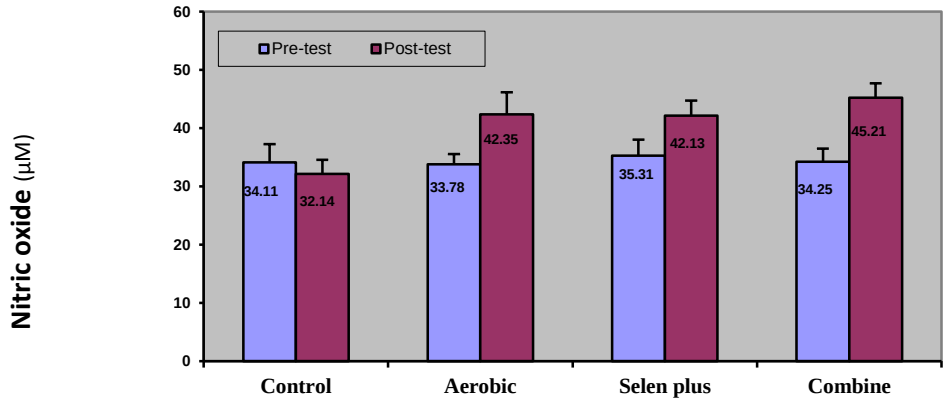


**Figure 1.** The changes pattern of nitric oxide in studied groups.

Based on the results of the ANCOVA test, no significant difference was observed in the changes in myeloperoxidase levels between the studied groups, and it can be said that there is no significant difference in myeloperoxidase changes between the studied groups (p = 0.072). The intra-group changes of myeloperoxidase by t-test revealed that in all three groups, the intervention leads to a significant increase in myeloperoxidase compared to the pre-test, but the change in the control group was not significant (Table 5, Fig 2).

**Table 5.** Data of intra group changes of myeloperoxidase in the studied groups

| Group | Control | Aerobic | Selen plus | Combine |
|---|---|---|---|---|
| **Pre test** | *24.37 ± 1.19* | *25.73 ± 4.44* | *26.03 ± 5.13* | *26.34 ± 5.48* |
| **Post test** | *24.13 ± 2.06* | *21.86 ± 4.46* | *22.19 ± 4.38* | *20.88 ± 3.64* |
| **Sig** (paired t test) | *0.547* | *0.001* | *0.006* | *0.001* |

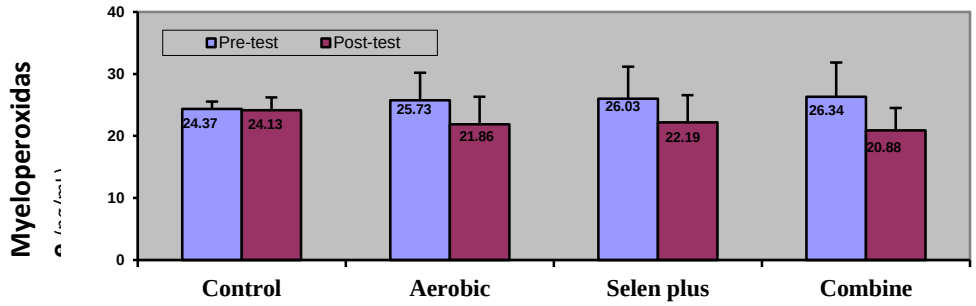


**Figure 2.** The changes pattern of myeloperoxidase in studied groups

## Discussion

The findings of the study showed a significant increase in nitric oxide along with a decrease in myeloperoxidase in obese women with metabolic syndrome compared to the control group. Conversely, the consumption of Selen Plus alone led to a substantial increase in nitric oxide along with a substantial decrease in myeloperoxidase in obese women with metabolic syndrome in comparison to the control group that did not participate in any intervention. On the other hand, aerobic training combined with Selen plus, although associated with improvement of nitric oxide compared to their application alone, did not change myeloperoxidase levels compared to them. These findings somehow support the vascular endothelial effectiveness of selen plus supplement during aerobic training in women with metabolic syndrome.

If we want to refer to previous studies regarding the response or adaptations of the dependent variables in the current study, similar to other hormonal or metabolic components, contradictory responses of nitric oxide and myeloperoxidase to different exercises can also be seen. In line with our findings, Farahti et al (2012) have pointed out the increase in nitric oxide as indicator of vascular endothelial function following 8 weeks of aerobic training in postmenopausal women (23). On the other hand, in the study of Qardashi et al (2015), the improvement of vascular endothelial function was reported with an emphasis on the increase of nitric oxide along with the decrease of fasting glucose in response to 3 months of aerobic training in obese type 2 diabetic patients (19). However, contrary to the aforementioned findings, in the study of Zaros et al, despite the improvement in blood pressure following 6 months of regular aerobic training in women, nitric oxide levels did not change significantly (24).

On the other hand, Shameshki et al (2011) reported no change in myeloperoxidase in response to 8 weeks of stationary exercises in inactive women (20). In the study of Moghadam et al (2022), a significant decrease in myeloperoxidase along with an increase in the total antioxidant capacity of inactive middle-aged people was reported after an intense exercise in the form of Bruce's incremental test (25). In another study, a 33% decrease in myeloperoxidase was reported in trained rats compared to the

control group (26). Nevertheless, in the study of Rahimi et al (2018), a significant change in myeloperoxidase was not observed after an intense resistance exercise session between people who consumed placebo and caffeine (27). Nevertheless, in the study of Stefanello et al (2016), a significant decrease in myeloperoxidase was observed after 4 weeks of swimming training in mice that consumed caffeine compared to those that consumed placebo (28). It should be noted that myeloperoxidase has been introduced as an indicator of degranulation of neutrophils in response to exercise, and its increase is proportional to the intensity of exercise. So that the increase or its plasma concentrations in response to intense exercise is much higher than moderate exercise (29).

Apart from aerobic training, although the antioxidant or endothelial effects of Selen Plus are not well defined, several studies have pointed to the distinct characteristics of its components. Laboratory studies have revealed that some dietary antioxidants, especially vitamins C and E and beta-carotene, act in a cooperative function as an intracellular antioxidant defense system, and their simultaneous consumption will be more effective than each of them alone (30). ). Deficiency of antioxidants such as vitamin C and E and selenium lead to oxidative stress and disorder in immune system response (31). It should be noted that obese people have lower levels of vitamins C and E compared to normal weight people (32). On the other hand, vitamin E has been introduced as one of the antioxidants that inhibit the lipid peroxidation process, which, due to its position in the cell membrane, protects the membrane from peroxyl free radicals caused by lipid oxidation (33). Consumption of vitamin C or ascorbic acid also leads to the reduction of oxidative stress damage by neutralizing and reviving O2, OH and H2O2 free radicals, hydroxyl radicals, and nitrogen oxide (34). Selenium also acts as an antioxidant as a cofactor of glutathione peroxidase. As a micronutrient, it participates in the decomposition of H2O2 with glutathione peroxidase. The rejuvenating and decomposing effect of H2O2 by selenium is shown by increasing the glutathione peroxidase enzyme content, which leads to the reduction of cell damage caused by H2O2 (35). On the other hand, the combination of selenium and vitamin E complement each other to protect the biological membrane against lipid oxidation and detoxification from hydroperoxides. Vitamin A or retinol is a non-enzymatic antioxidant of carotenoid products that is obtained from the breakdown of beta-carotene in the intestine (36). Although zinc does not directly affect free radicals, it participates in preventing their formation and acts as a cofactor for the production of metallomethionine, which is an inhibitor of hydroxyl radicals. On the other hand, in a competitive process with copper, by binding to the cell wall, it leads to inhibiting the production of hydroxyl radicals. It also acts as an inhibitor of NADPH oxidases that enables the production of singlet oxygen radical (O2) from oxygen (37).

Despite the existence of evidence that confirms the direct response of the desired variables to selenium plus, but considering the potential effects of its constituent compounds, the improvement of myeloperoxidase and other effective indices in vascular endothelial function in response to its supplementation is not far from expected and this expectation It was somehow observed in the findings of the present study. So, in the present study, in addition to aerobic exercises, 8 weeks of selenium plus consumption alone or during aerobic exercises was associated with a

significant decrease in myeloperoxidase in women with metabolic syndrome. In this regard, clinical and experimental studies have introduced increased levels of myeloperoxidase as one of the predictors of tissue damage such as muscle, liver and heart (38,39). The main function of myeloperoxidase is the production of oxidants and reactive oxygen species to deal with inflammatory factors and pathogens, and as the only enzyme capable of producing high levels of hypochlorous acid, which has been introduced as one of the most effective oxidants in many cellular processes (40,41). However, the increase in its production in response to the increase in myeloperoxidase leads to oxidative damage to proteins and DNA of host cells, which leads to tissue damage and chronic diseases such as atherosclerosis, kidney, lung, Alzheimer's, Parkinson's and cancer (42). On the other hand, myeloperoxidase increases lipid peroxidation by interacting with unsaturated fatty acids in the cell membrane (43). Also, the role of oxidative or inflammatory stress related to obesity in pathological conditions is associated with impaired vascular function, increasing its systemic levels has been confirmed with damage to cardiovascular function. Clinical studies have revealed that the inhibition or reduction of nitric oxide levels, which leads to the damage of vascular endothelial function, has been reported in response to increased myeloperoxidase (13,44). On the other hand, reduction of total antioxidant capacity and increase of myeloperoxidase have been reported as consequences of nitric oxide reduction, which leads to endothelial dysfunction. (13).

## Conclusion

The synergy between taking Selenium Plus and engaging in aerobic exercise yields greater results than either method used alone. While these findings have been noted, due to the lack of research regarding the combined effect of aerobic exercises and selenium plus on cardiovascular or endothelial vascular function, particularly in people with metabolic syndrome, it is not possible to confidently draw conclusions from the present data.Nevertheless, by ignoring the lack of myeloperoxidase difference between the groups, but by relying on the improvement of vascular nitric oxide, it is emphasized that aerobic exercise combined with Selen Plus is more effective on vascular endothelial function than any of them.

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## Conflict of Interest

No conflict of interest has been declared by the authors.

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