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Evaluation of the Effect of Nano-Selenium Particles on the Immune System Functions Suppressed by Dexamethasone

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ABSTRACT

Introduction: Controlling nutrition and exercise can affect the density and metabolism of bone tissue. Therefore, the aim of the present study was to investigate the effect of eight weeks of moderate intensity continuous training (MICT) and high intensity interval training (HIIT) along with Citrus aurantium (CA) on bone metabolic markers of elderly female rats.

Methods: In this experimental study, 64 elderly female rats (14 ± 2 months old and weight of 290 ± 25 grams) were divided into 7 groups including 1) control, 2) MICT, 3) HIIT, 4) MICT+CA, 5) HIIT+CA, 6) CA and 7) sham (normal saline) groups. HIIT with an intensity of 85- 110% VO_{2max} and MICT with an intensity of 65% VO_{2max} were performed and CA was injected at the doses of 300 mg/kg/day intraperitoneally. The variables were measured using the ELISA method with the Pars Azmoun kit. The data of the present research were analyzed using one-way analysis of variance and Tukey post hoc test (P≤0.05).

Results: In MICT group the PTH and Na levels were significantly lower and Ca levels were higher than the C group (P≤0.05). PTH and Na levels in the MICT group were lower than the HIIT group (P≤0.05). Ca levels in the CA group were higher than the C group (P≤0.05). In MICT+CA and HIIT+CA groups, PTH levels were lower and Ca levels were higher than the C group (P≤0.05). Also, PTH and Na levels in HIIT+CA group were lower than the MICT+CA group (P≤0.05).

Conclusion: it seems that MICT has a better effect on bone metabolic markers than HIIT; meanwhile, HIIT with an antioxidant such as CA has more favorable effect on bone metabolic markers.

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Introduction

Corticosteroids are routinely used to reduce edema in patients with intracranial lesions as the first drugs to counter immune-related side effects caused by blocking critical points of the immune system. In this case, the most important glucocorticoid prescribed to people is dexamethasone to suppress the immune system in many patients with various diseases, including organ transplant patients, inflammatory diseases, and autoimmune diseases (1). Exposure to dexamethasone causes defects in cell division for CD4 and CD8 cells (2). When T lymphocytes are exposed to dexamethasone, progenitor frequency, defined as the intrinsic probability of cell division and indicate whether or not a cell will perform at least one division, decreases (5). Similarly, the proliferation index is also reduced in T cells exposed to dexamethasone. This index is an extracellular statistic used to express the fold increase in the number of final cells compared to the number of initial cells (including non-dividing cells). Finally, the proliferation index, which indicates how many divisions a cell has undergone post-mitotically, is moderately reduced by dexamethasone. Thus, cell proliferation statistics show that dexamethasone impairs CD4 and CD8 cells' ability to divide and limits these populations' expansion potential (2). B lymphocytes are also affected by dexamethasone (4) and release compounds called immunoglobulins to deal with antigens. Among the types of immunoglobulins, type G (IgG) has the most practical effect, and immunoglobulin A (IgA) is found in all body fluids due to the secretory component (6). As the dominant immune antibody, immunoglobulin A (IgA) plays

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a fundamental role in mucosal homeostasis in the gastrointestinal tract, respiratory tract, blood, and genitourinary tract. IgA has an active anti-inflammatory role in the body, which leads to allergic diseases and autoimmune conditions in case of deficiency. A decrease in secretory IgA weakens the mucosal barrier, allowing more allergens to enter the bloodstream, and IgA deficiency can produce anti-IgA and IgG antibodies (6). Immunoglobulin G is an antibody that represents approximately 75% of serum antibodies in humans as the most common type of antibody found in circulation, which plays a vital role in humoral immunity. The antioxidants in different foods may change the concentration and function of antioxidant enzymes, thereby creating a better function in the immune system. In this regard, selenium (Se), as a rare mineral element in specific physiological doses, acts as a powerful antioxidant, especially in the composition of intracellular selenoproteins (7). Many recent researches have shown that selenium improves immune cell function (8, 9, 10). In this context, Se has been demonstrated to increase the production of IL-2 and immunoglobulins M and G (11). In addition, studies have stated that Se is essential in protecting T and B lymphocytes and neutralizing some toxic substances in the body. (12). The primary mechanism responsible for the protective properties of selenium is its antioxidant protection of cells (7, 19, 20, 21). Selenium is part of necessary antioxidant enzymes such as superoxide dismutase and glutathione peroxidase, among the most critical (20). Selenium also has anti-inflammatory effects and reduces the expression of some inflammatory genes, such as NF-kB (20 and 21). Therefore, the findings show that Se can be considered a drug for treating and preventing immune system damage caused by the effects of dexamethasone. However, the potential mechanisms of the positive impact of Se on immune function have not been clearly defined (7). Therefore, this study hypothesized that the change in the subclasses of B lymphocytes and the antibodies produced by them is one of the effective mechanisms of Se to strengthen the immune system. Therefore, the present study aimed to evaluate the effect of selenium nanoparticles on some markers of humoral immunity in rats with weakened immune systems caused by dexamethasone.

Materials and Methods

Subjects: The subjects of this study included 24 Wistar male rats (with an average weight of 180g). The samples were stored in standard conditions and special animal cages at 22 ± 4.1℃. The light-to-dark cycle was 12:12 hours, and the humidity was controlled at 55.6±4%. After transferring the samples to the laboratory environment, the rats were familiarized with the environment for one week and then randomly divided into three healthy control groups, an immunocompromised control group, and an immunocompromised + nano-selenium group.

Suppression of the immune system: This study used Dexamethasone to simulate a weakened immune system. For this purpose, the immune system of the samples was weakened by intraperitoneal injection of 0.4mg/kg/d dexamethasone for three days (12). A week before the start of the training protocol, 0.4mg/kg/d of dexamethasone was injected into the samples for three days, and their immune system was weakened (12). The healthy control group received the same amount of normal saline solution.

Obtaining nano-selenium supplement: The nano-selenium used in this study was given to rats by gavage in a size of 250nm using the instructions provided for this purpose. The amount of supplement used was 100mg every other day. In the control group, the oral solution was used as gavage at the same time instead of a nano-selenium supplement.

Measurement of variables: 48 hours after the last training session and the application of the independent variable, all samples were anesthetized in precisely the same conditions and baseline conditions with an intraperitoneal injection of a combination of ketamine (60mg/kg) and xylazine (5mg/kg) 48 hours after the previous training session and 12-14 hours of fasting. Blood was taken from the heart tissue to obtain serum and plasma samples and was kept at -20 to evaluate blood variables after plasma separation and homogenization. Sampling started at 8:00 and ended at 11:30 to avoid the effect of circadian rhythm. The study variables were the serum concentrations of two immunoglobulins, A and G, measured using a special laboratory kit for measuring serum IgA and IgG levels (biosystem S-A company, made in Spain) by the immunoturbidimetric method.

Data analysis: The Shapiro-Wilks test was used to test the data normality, and the one-way ANOVA method was utilized to compare the average of the variables in the research groups. Tukey's post hoc test was used to compare the groups after comparing the groups using SPSS software version 24.

Table 1. Serum concentration of immunoglobulins A and G in different research group

Variable group	IgA (ng/dl)	IgG (ng/dl)
Control	173.11±20.970	1070.46±102.335
Immunosuppression	76.86±12.258	490.71±47.993
immunosuppression + nanoselenium	160.39±17.676	946.45±82.977

Table 2. Results of the one-way analysis of variance test comparing serum immunoglobulins A and G in the research groups.

	Sum of Squares	df	Mean Square	F	Sig.
IgA	78174.227	4	19543.557	62.022	.000*
IgG	1896861.066	4	474215.267	66.493	.000*

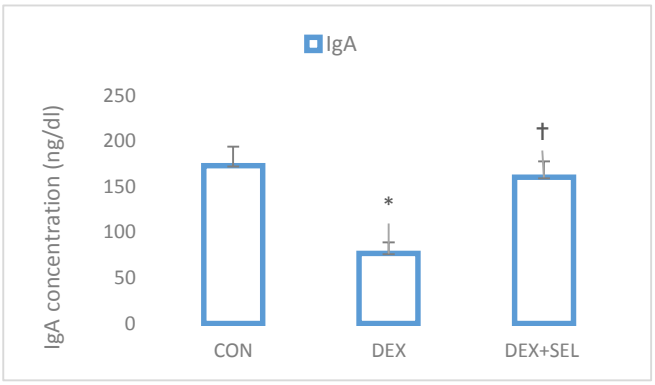

Figure 1. Comparison of serum IgA concentration in different research groups
*: significant difference with the healthy control group at α≥0.05 level
†: significant difference with dexamethasone group at the level of α≥0.05

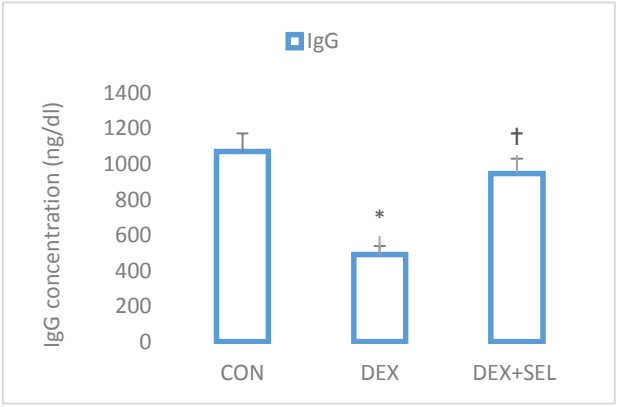

Figure 2. Comparison of serum IgG concentration in different research groups
*: significant difference with the healthy control group at α≥0.05 level
†: significant difference with dexamethasone group at the level of α≥0.05

Results

Table 1 and Figure 1 show the results of the serum concentration of immunoglobulins A and G in different groups. Table 2 presents the results of data analysis using one-way ANOVA. These results reveal a significant difference between different groups in the serum concentration values of immunoglobulin A at a significance level of P=0.0001 and immunoglobulin G at a significance level of P=0.007.

The comparison of serum IgA and IgG concentration in different research groups indicated that its concentration in the DEX group

differed from healthy control groups (p=0.0001) and DEX+SEL (p=0.0001).

Discussion

The results showed that the consumption of selenium significantly prevents the decrease in the serum immunoglobulins concentration in the weakened immune system samples with the drug dexamethasone. These results indicated that the concentration of immunoglobulins A and G was significantly reduced due to the weakening of the immune system with the drug dexamethasone. This issue has been well demonstrated in other studies, and it has been found that the application of glucocorticoids leads to a decrease in the serum levels of serum immunoglobulins (14). However, the reduction in IgA was more than IgG serum levels. B lymphocytes release compounds called immunoglobulins, including A, D, I, M, and G, to deal with antigens. Immunoglobulin G (IgG) has the most significant number, and immunoglobulin A (IgA) is one of them, which can be found in all body fluids. Reducing the secretion of IgA due to the injection of glucocorticoids in mucous fluids was reported, and a part of the decrease in the serum concentration of IgA depends on its secretory component (SC) made by the liver. The lack of activation of B lymphocytes by other immune cells, such as T lymphocytes and macrophages, causes a reduction in the serum concentration of immunoglobulins. Another published study found that dexamethasone injection decreases helper T lymphocytes' cell lines and inflammatory and anti-inflammatory cytokines such as IFN-γ and IL-4 (8). Therefore, dexamethasone may be related to reducing the activation of B lymphocytes in the production and secretion of immunoglobulins. The present study also showed that the consumption of selenium prevents the decrease in the concentration of serum immunoglobulins in the weakened samples of the immune system with the drug dexamethasone to a large extent, indicating the strengthening role of selenium in the function and activation of B lymphocytes. Selenium, a component of many selenoproteins and, in addition to acting as an essential antioxidant, also plays a role in regulating the immune system and response. Selenium increases the phagocytic activity of macrophages (by increasing their cytotoxicity) and stimulates B lymphocytes' production of antibodies (IgG and IgM classes). In this context, antioxidant compounds seem to be related to B lymphocytes' performance and level of immunoglobulin secretion. The study in the same field found that a deficiency of selenium and vitamin E leads to a significant decrease in some serum immunoglobulins, such as IgG and IgM. In contrast, excessive consumption of selenium in mice leads to the deficiency of these proteins to a large extent in the blood (15). Selenium may exert its effect through a mechanism involving free thiols, reducing oxidative stress conditions and increasing the proliferation of lymphocytes (16). Based on the results, dexamethasone drug injection leads to a decrease in serum immunoglobulins A and G in male Wistar rats. This issue can lead to an increase in the probability of viral and bacterial infections. However, receiving selenium supplements and their nanoparticles is likely to increase the antioxidant capacity and concentration of selenoproteins related to increasing the capabilities of the immune system, including the production of T lymphocytes and Cytokines that activate B lymphocytes and improve their ability to produce immunoglobulins. Patients who use dexamethasone as a therapeutic agent for various reasons may need to be aware of this issue.

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