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Original Research

Decrease of plasma TNF-α and CRP levels in response to post-exhaust resistance training and vitamin D supplementation in overweight healthy women

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Abstract

Introduction: Diabetes are the most common diseases in the world and is related to nutritional status and lifestyle. The purpose of this study was to investigate the simultaneous effect of resistance training and vitamin D supplementation on plasma CRP and tumor necrosis factor alpha (TNF-α) levels in overweight healthy women. **Method:** The participants were randomly divided into four groups including: (1) placebo, (2) resistance training (RT), (3) vitamin D, and (4) RT + vitamin D. Interventions were performed for 8 weeks (3 days per week), consisting of resistance training protocol (60% 1-RM) and taking vitamin D (1000 IU/day). Fasting blood samples were collected 48 hours before and after the interventions. **Result:** A significant decrease in CRP was reported among the studied groups (p=0.001, F=11.4). These changes showed a difference between RT+ vitamin D compared to other groups. The CRP values of the RTand vitamin D groups were also significantly lower than the placebo group (p=0.03). TNF-α was significantly decreased among the studied groups (p=0.003, F = 5.4). These changes showed a difference between the RT + vitamin D group compared to other groups. TNF-α was significantly lower in the RTand vitamin D groups than in the placebo group (p=0.03). **Conclusion:** The findings of this study confirm that adaptation to resistance training, if combined with vitamin D intake, has significant effects on decreasing inflammatory biomarkers at rest. In addition, TNF-α alteration appears to be less effective than resistance training, which may be due to eccentric contractions caused by resistance training.

Keywords: Exercise rehabilitation, Inflammation, Post-exhaust, Resistance Training, Supplementation.

Introduction

Obesity, poor nutrition and sedentary life style, and systemic inflammation are important communication for diseases and the most important reason is the secretion of cytokines and inflammatory agents caused by adipose tissue [1, 2]. Researchers are looking for the best and least risky ways to control overweight and reduce adipose tissue. Nutritional controls, medications, and regular exercise or combinations of these techniques are highly recommended [2]. Obesity is associated with chronic inflammation, which is characterized by the infiltration of immune cells into adipocytes that contribute to the release of cytokines which induce inflammation, which, in turn, leads to inflammatory signaling pathways [1]. Cytokines are a group of low-molecular-weight regulatory proteins secreted by adipose tissue, white blood cells, and other types of body cells. Cytokines generally act as intracellular messenger molecules that initiate specific biological activities after binding to a receptor on the target cells [3–5].

Cytokines may require other physiological functions to play a role in inflammatory responses especially if they are secreted from adipose tissue [3, 4, 6, 7]. Cytokine is a generic title and is specifically called adipokine if expressed by adipose tissue. Most evidence suggests that the presence of mild inflammation in obesity is

associated with changes in the levels of several circulating biomarkers, such as increases in plasma C-reactive protein (CRP) and tumor necrosis factor alpha (TNF-α) [3–7].

Regular exercise is one of the methods recommended to reduce inflammation biomarkers including TNF-α and CRP [8–9]. These findings were established in overweight and metabolic syndrome [10]. Among all kinds of exercises, resistance training has been shown to improve CRP levels, although no integrated information is available on TNF-α change [11]. Obese people have been reported to be more prone to vitamin D deficiency and inflammation [12–14]. Inflammation and metabolic syndrome develop in people who have symptoms of obesity, diabetes, inflammation, hypertension and dyslipidemia, which are reduced by vitamin D supplementation [12–14]. Vitamin D is one of the types of fat-soluble vitamins called calciferol. The ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) are its metabolites [12–14].

In summary, some studies have investigated the concomitant effects of physical activity and vitamin D supplementation on various domains of exercise physiology [15], but few studies have investigated the concurrent medication effects of resistance exercise training and vitamin D on inflammatory markers in overweight healthy women. Differences in the methodology of these limited studies also, make it difficult to come up with an integrated viewpoint. There is not a clear finding about the effective dose of vitamin D [12]. In addition, there is no specific and effective method for reducing inflammatory cytokines based on the specificity principle of exercise training [11]. It has to be noted that the tendency to perform resistance training in indoor spaces has increased and this has led to the deprivation of sunlight. It is also important to examine this issue in women's health because of their important role in family and community. Therefore, the aim of this study was to evaluate the effect of vitamin D supplementation with resistance training on inflammatory markers in overweight healthy women.

Materials and Methods

A total of 103 university student women were assessed for eligibility. Forty sedentary overweight healthy women were equally divided into four groups including: (1) placebo, (2) vitamin D, (3) resistance training (RT), and (4) resistance exercise + vitamin D (Table 1). There were no serious side effects associated with regular exercise, and no one withdrew due to side effects. The participants were overweight (Table 1) and their vitamin D levels were normal in the lower extremities (Table 1) (reference range minimum for health bone: 20–32 ng/ml), so they needed to be prescribed daily vitamin D, according to doctor's prescription. Body mass index was calculated in kg/m^2 using BMI equation through measuring height (Seca 213, Germany recorded

Table 1: Anthropometric characteristics of the subjects and measured variables among the studied groups. Data are presented by mean and standard deviation.

Groups	RT + vitamin D		resistance training (RT)		vitamin D		placebo	
Time	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Age	27.9±3.8	—	29.2±3.3	—	29.2±3.2	—	27.4±1.4	—
Height	162.2±4.8	—	161.4±4.08	—	162.2±3.4	—	163.8±6.1	—
Weight (kg)	71.4±3.7	70.4±4.05	70.9±4.2	70.2±5.3	69.1±4.8	68.9±3.1	72.6±6.1	72.4±6.2
BMI (kg/m^2)	27.9±1.3	27.5±1.4	27.2±1.8	27±2.4	26.2±0.7	26.2±0.7	27.4±1.5	26.9±1.5
TNFα (ng/ml)	0.96±0.1	0.83±0.05	0.91±0.1	0.8±0.03	0.95±0.1	0.91±0.08	0.89±0.2	0.87±0.1
CRP (ng/ml)	3.01±0.82	1.96±0.71	2.93±0.5	2.61±0.63	2.99±0.62	2.67±0.62	2.98±0.52	2.91±0.46
25-OH-Vit D (ng/ml)	23.7±1.3	28.2±1.6	22.9±1.2	24.7±1.8	23.6±1.7	27.2±1.5	22.8±1.4	23.4±1.3

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to the nearest 0.1 cm.) and weight (SECA Digital Scale Model 727: with precision of 2 g).

The participants were provided with information and knowledge on how to conduct the research stages. A questionnaire was used to collect information about the physical activity and health of the participants. Consent form was given to the participants. The introductory program was held two weeks prior to the start of intervention to attend the gym. Anthropometric measurements were taken at a separate session. The participants were familiarized with exercise protocol, vitamin D supplementation, and blood sampling timing.

Resistance training protocol (eight weeks and three sessions per week) was performed by 50–60% 1-RM (three courses, 10 repeats, and a 2-minute rest between each movement). Exercises training included engaging chest, triceps and shoulder (first session), abdomen and dorsalis (second session), and leg muscles (third session). Major muscles using multiple joint movements at first and single muscle movements were applied at the end of each session (post exhausting method). Vitamin D supplementation groups (produced by the United Kingdom-Health Aid Company) received 1000 IU/day, which was administered for eight weeks. Blood samples were collected 48 hours before and after the intervention. Fasting blood samples were collected at the laboratory at 8 a.m. Resistance exercises were held at 5 p.m. Vitamin D was prescribed daily along with lunch.

Fasting blood samples were discharged into tubes containing EDTA. The samples were centrifuged at 4°C for 15 minutes at a speed of 10,000 rpm. Isolated plasma was stored at –70°C and used to measure the research variables. The plasma CRP and TNF-α levels were measured using a particle enhanced turbidimetris assay (Roche, Germany) and an enzyme-linked immune sorbent assay (ELISA. eBioscience, Austria) respectively, according to the manufacturer instruction. The LIAISON 25-OH Vitamin D TOTAL Assay (DiaSorin) was used to measure plasma concentration of 25-hydroxyvitamin D (25(OH)D).

The Kolmogorov-Smirnov test was used to determine the normal distribution of data. The ANCOVA was used to test the research hypotheses after determining the pre-test and post-test differences. The sphericity of the data was confirmed by performing variance analysis (Mauchly's Test of Sphericity). Tukey's*post hoc* test was used for between-group comparisons. Statistical analyses were performed using SPSS 21 computer software at the significant level $p \leq 0.05$.

Results

The research data and measured characteristics of the participants, including age, height, weight, and BMI, are presented in Table 1.

The significant differences for vitamin D levels were reported among the studied groups after interventions (p=0.03, F=8.62). These changes showed a difference between the vitamin D and RT + vitamin D groups compared to the RT (p=0.03) and control (p=0.02) groups. The significant differences forplasma CRP levelswere reported amongthe studied groups (p=0.001, F=11.4). These changes showed a difference between the RT+ vitamin D compared to theRT group (P=0.03), RT + vitamin D compared tothe vitamin D group (p=0.001), RT + vitamin D compared to the placebo group (p=0.001) and RTcompared to the placebo group (p=0.03). In addition, plasma TNF-αlevels were significantly different among the studied groups (p=0.003, F=5.4). These changes showed a significant difference between the RT + vitamin D group compared to the vitamin D group (p = 0.03), RT + vitamin D group compared to the placebo group (p = 0.003) and RTcompared tothe placebo group (p = 0.03). Despite some reductions for weight and BMI variables, there was no significant difference amongthe studied groups.

Discussion

The aim of this study was to evaluate the effect of vitamin D supplementation with resistance training on plasma TNF-α and CRP levels in overweight healthy women. In summary, in the present study, combination of regular resistance training with vitamin D supplementation significantly reduced the CRP and TNF-α rest levels.

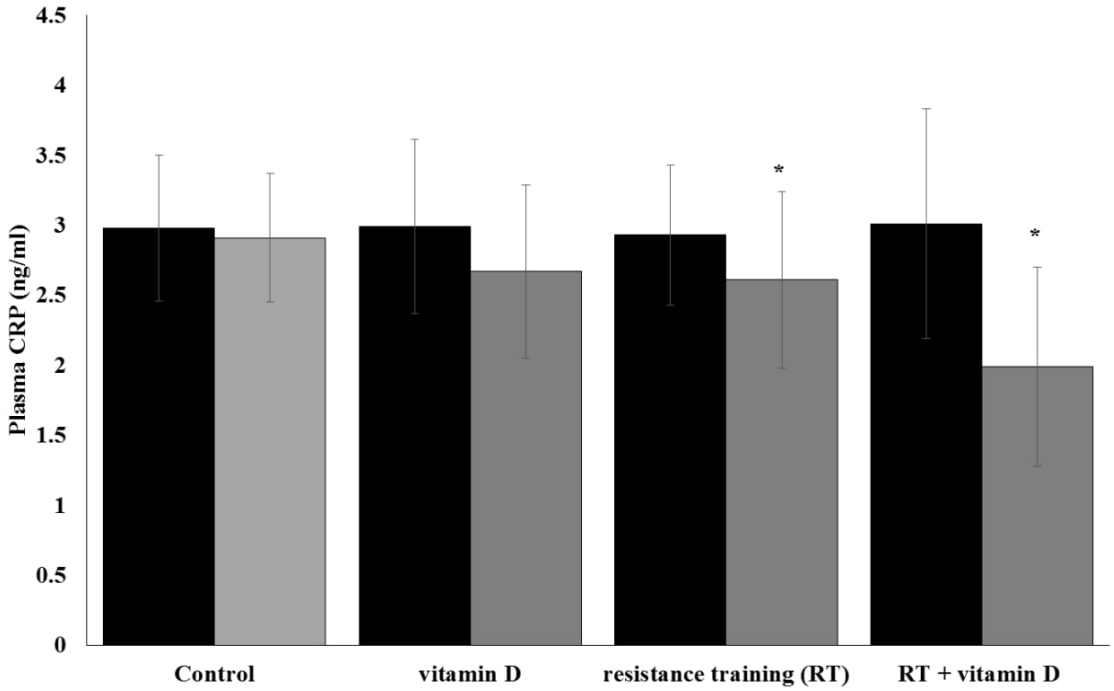

Figure 1: Plasma CRP level changes among the studied groups. Data are presented by mean and standard deviation. *Significant difference with other groups.

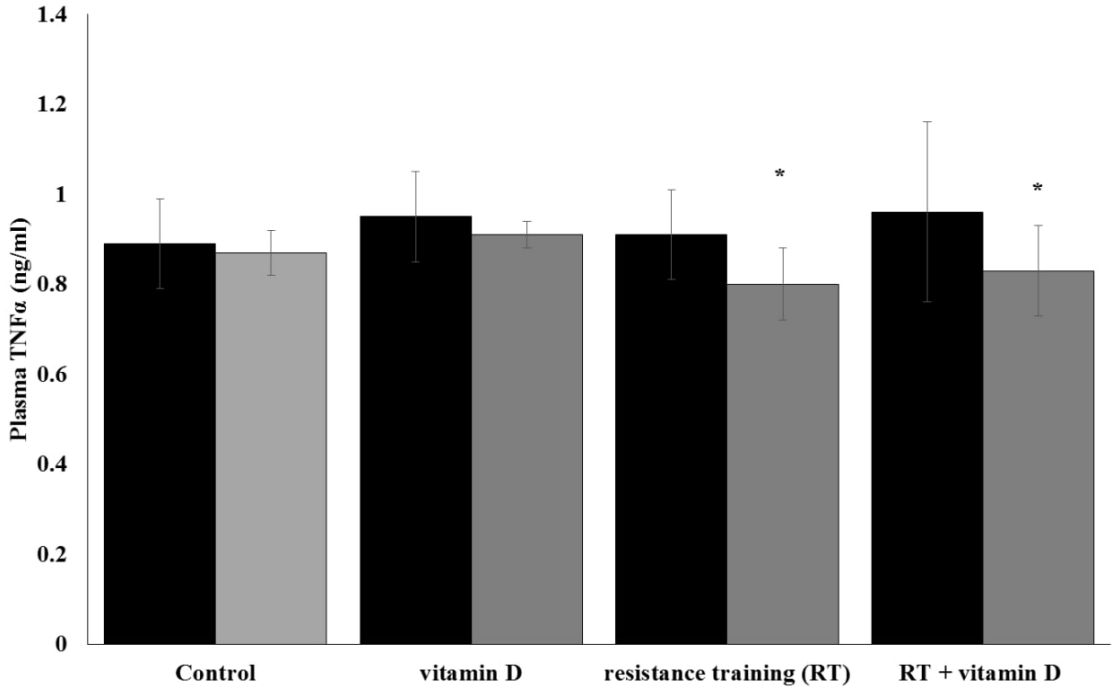

Figure 2: Plasma TNFα level changes among the studied groups. Data are presented by mean and standard deviation. *Significant difference with other groups.

The effect on the exercise training groups was also greater than the vitamin D group. However, the combination of resistance training and vitamin D showed a high decrease in plasma CRP and TNF-α rest levels.

Several mechanisms have been proposed to elucidate the inverse relationship between obesity and vitamin D that center around inflammation and include the role of adipokines, epigenetics, calcium, and adipose tissue type [16]. Simultaneous effects of vitamin D and calcium on hsCRP and TNF-α reduction in metabolic syndromehave been confirmed [17]. The association between calcium and vitamin D has been an

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important factor in improving glucose levels in obese and overweight women who have ovarian problems and vitamin D deficiency [18]. It has to be noted that exercise increases calcium pump function in the sarcoplasmic reticulum and is one of the possible pathways to regulating glucose entry into the muscle cell during exercise [19], whereas increased TNF-α is one of the major factors of fatigue caused by resistance training [5]. However, this is likely reduced by adaptation to resistance training.

Measuring the variables 48 hours after training is also very effective. In many studies, acute responses to exercise increased inflammatory responses, whereas the present study aimed to evaluate the adaptation with interventions. Since one of the major sources of inflammatory cytokines is adipose tissue, vitamin D and resistance training may reduce the concentration of inflammatory markers by reducing the body fat. Although weight and BMI in the present study did not show a significant decrease, it could also be due to increased or maintained muscle mass resulting from resistance training. However, some studies have reported changes in inflammatory markers independent of adipose tissue changes [20]. Low intensity exercise with 50% strength training at four sessions per week in postmenopausal and obese women decreased weight and waist circumference but did not significantly change CRP and TNF-α levels [21].

It is likely that daily food intake interventions can also be effective on inflammation. Due to the variety of research methods, the effect of daily foods on the production of inflammatory markers remains unknown [22]. There is limited information on the relationship between vitamin D receptors in metabolic syndrome and inflammation. However, it has been suggested that Fokl-type receptors are associated with moderate inflammation and insulin resistance [23]. It has also been reported that vitamin D levels affect exercise performance through association with iron levels [24]. Therefore, the presence of female participants in the study who are likely to have lower sports performance and lower iron levels compared to menwas effective in the results of this study.

The effect of vitamin D on reducing inflammation has also been identified, but the mechanisms of this effect are not fully understood. Vitamin D has been reported to have a modest effect on reducing inflammation in cardiovascular patients [25]. Meta-analysis studies have not conclusively confirmed the therapeutic effect of vitamin D alone on improving metabolic syndrome and inflammatory biomarkers [14]. Other articles that have even used a one-year course of vitamin D treatment have shown some inadequate efficacy of vitamin D treatment alone, despite improving inflammatory markers such as TNF-α, CRP, and IL-6 [26]. Inflammatory markers of TNF-α, CRP, and IL-6, unlike metabolic syndrome indices, did not change significantly in response to low doses of vitamin D [27]. Patients who also used dyslipidemia medication had improved vitamin D levels and subsequently metabolic syndrome indices, but no significant change in TNF-α levels was observed [28]. Probably one of the missing factors in this area is the combination of vitamin D intake with regular physical activity. An increase in vitamin D has been observed in response to a long period of regular exercise and lifestyle modification [29].

This topic has been well demonstrated with resistance training in obese and overweight adults [30, 31]. Adaptation to combined physical activity reduces CRP and TNF-α in healthy and active individuals [32]. Physical activity, especially if exposed to the sunlight, can be effective in boosting vitamin D that leads to improve athletic performance [33]. Therefore, reducing inflammation may require higher doses of vitamin D and complementary therapies such as regular physical activity. For example, changes in CRP have been observed at high doses and longer periods [34]. As mentioned, another reason for the improvement of inflammatory markers in the present study was the use of resistance training as a supplement to vitamin D. Regarding the health status of participants, it is very important in methodological studies as it was mentioned.

The exercise training and vitamin D supplementation have better effects on healthy groups. It has been shown that lean people have better improvement in low-dose (400–800 IU/d), moderate dose (1600–2400IU/d) and high dose of vitamin D (3200–4800 IU) compared to

obese. This may be due to differences in baseline vitamin D levels [35]. Meta-analysis studies have reported that vitamin D intake in overweight or obese groups may not have a significant effect on CRP and TNF-α [13]. Therefore, presence of overweight healthy women may be one of the reasons for the improvement of inflammatory markers in the present study. Inflammatory biomarkers may have a better response to exercise interventions in healthy individuals than patients, especially for CRP [36]. Probably one of the possible reasons for the better response of CRP to TNF-α in the present study, which has been reported in other studies, is the effect of eccentric contractions induced by resistance training on the increase of TNF-α [5]. Therefore, attention to this issue is especially important in weight loss in order to maintain muscle mass. However, this condition is improved by adaptation to exercise.

A comparison between aerobic and resistance training and their effects on inflammation in metabolic syndrome has been investigated. Some studies have suggested that the effect of aerobic activity on inflammatory biomarkers reduction including CRP and TNF-α is better than resistance training because of its direct effect on adipose tissue lipolysis [37]. However, TNF-α decreased significantly in response to aerobic training and CRP in response to both aerobic training and combination of resistance training and flexibility training [37]. In support of these findings, it has been reported that changes in TNF-α levels and adipose tissue in response to aerobic exercise and CRP level in response to resistance training were further reduced [38]. As noted, TNF-α changes in response to resistance training may be due to the eccentric contractions and differences in the source of secretion. Therefore, it seems necessary to incorporate resistance training or more intense training than the pattern of aerobic exercise to complete adaptations from exercise training. It is also important to use resistance training to stimulate intramuscular signaling pathways by stimulating intramuscular calcium pumps and simultaneously reducing adipose tissue and increasing or maintaining muscle mass [19]. However, it has been shown that the incorporation of resistance training specifically has maximized the effect of regular aerobic exercise on reducing inflammation [36].

Conclusion

There is a significant relationship between weight control, vitamin D intake and inflammation reduction. However, combining regular physical activity with these interventions increases the effectiveness on health. In fact, weight loss is associated with changes in the levels of inflammatory biomarkers, including TNF-α and CRP. It should be borne in mind that various studies have examined these multiple approaches on different variables that each biomarker has its own signaling pathways. Each biomarker according to the secretion source can have a unique signaling pathway. It is likely that each signaling pathway will have an optimal response to some type of specific exercise. Therefore, considering different aspects of a particular variable and the specificity principle of training are the most important aspects of studies in the field of exercise physiology for future research.

Submission statement

The manuscript has not been published and is not under consideration for publication elsewhere.

Each authors' contributions

Narges Kallantar did Investigation, Methodology, Project administration, Resources, Software.

Hoseyn Fatolahi did Investigation, Methodology, Project administration, Resources, Software, Formal analysis, Conceptualization, Supervision, Data curation, Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

The authors of this paper would like to express their thanks to all participants in this study. The experimental protocol in this study was approved by the ethics committee of Islamic Azad University, Central Tehran Branch (No. 10121436962029). The researchers' Ethics Committee initially approved the experimental procedures and study protocols, which were fully explained to all participants, and a written consent form was signed after having read and understood the details of the experiments. The research was also conducted in accordance with the principles stated in the Declaration of Helsinki.

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