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# Serum Interleukin-17 Alterations in Patients With Chronic Kidney Disease Undergoing Eight Weeks of Aerobic Training

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**Abstract**

**Introduction:** Regular physical activities may have effect on the course of chronic kidney disease (CKD). Here, we aimed to ascertain the changes of serum interleukin-17 (IL-17) following eight weeks of aerobic training in CKD patients.

**Methods:** The CKD patients referred to Zahedan Edalat Clinic and Ali-Ibn Abi Talib hospital in Zahedan city (Iran) were enrolled. Sixty patients aged between 30 and 50 years old were chosen by a random method and assigned into the control and intervention groups (each group constituted 30 people). In this study, aerobic exercises were performed at 50%–80% of the maximal heart rate. Peripheral blood was obtained one day before the beginning of exercise and one day after the end of the intervention. Serum IL-17 level was quantified using a commercial specific ELISA *kit*.

**Results:** The mean values of IL-17 in CKD patients before and after 8 weeks of aerobic exercise were 1.67 ± 0.403 pg/mL and 1.58 ± 0.170 pg/mL in the intervention group (*P* value= 0.039) whereas the mean values of IL-17 in the control group before and after the intervention were 1.31 ± 0.529 pg/mL and 1.35 ± 0.505 pg/mL (*P* value= 0.794).

**Conclusion:** Eight weeks of aerobic training can significantly reduce serum IL-17, an inflammatory marker, in CKD patients.

**Keywords**: Interleukin 17, CKD patients, Aerobic exercises

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## Introduction

Patients with chronic kidney disease (CKD) present with varying degrees of renal insufficiency and decreased glomerular filtration rate (GFR).[1,2] Those progressing to end-stage renal disease (ESRD) are characterized with a uremic syndrome *associated* with a very poor prognosis. It is believed that *CKD* is a major determinant predisposing or aggravating cardiovascular diseases (CVDs),[3,4] anemia,[5,6] electrolyte disorders,[7,8] bone diseases,[9,10] cognitive and psychiatric disorders, and many other diseases.[11] In Iran, the annual incidence rate of the disease is 53 per a million people while its frequency is higher, standing on 250 cases per a million population.[12]

The role of systemic inflammation in atherosclerosis[13,14] and as a predictor of CVDs in patients with CKD has been suggested. In the patients undergoing hemodialysis, inflammation is always an issue of major concern.[15-17] In fact, signs and markers of inflammation have been detected in the sera of around a third to half of CKD or dialysis patients,[18,19] such as C-reactive protein (CRP).[20-22] The reason for this proinflammatory state in these patients; however, is still not fully understood.[14] Among other inflammatory markers, a variety of immune functions have been dedicated to cytokines, which can promote immunosuppressive, as well as pro-inflammatory and anti-inflammatory functions.[23] Intense exercise has been shown to be a trigger for the release of

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a number of pro-inflammatory markers, e.g., tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), IL-1, etc. Intermittent and low-moderate exercise activities may also contribute to an inflammatory balance, immune system regulation, and reducing the level of chronic inflammation.[24-26]

A variety of immune cells including lymphocytes can produce a proinflammatory cytokine known as IL-17.[27-30] This cytokine has been shown to bind to its various receptors (different types of isoforms) in different body tissues. Patients with arthritis, cancer, and asthma have been reported to have elevated IL-17 levels.[31] Among various immune cells, IL-TH17 lymphocytes are major producers of IL-17. In addition, IL-17 has been noted to contribute to the autoimmune process in diseases such as diabetes, rheumatoid arthritis, and multiple sclerosis.[32] As a chemokine, IL-17 may impart a role in recruiting neutrophils to inflamed tissues (e.g., the intestine, central nervous system, joints, lungs).[32] On the other hand, it has been shown that up to half of the patients undergoing peritoneal dialysis may have a proinflammatory state, as evidenced by elevated CRP levels.[33,34] Therefore, in view of the contribution of inflammation to atherosclerosis development, it is necessary to assess inflammatory factors and mitigate the condition in patients undergoing dialysis.[16]

The immune regulatory role of exercise (as shown by elevated levels of proinflammatory cytokines) has been investigated in multiple.[35] According to Chang and Dong, IL-17 function is interrelated with other cytokines, including IL-6, as shown in a study on cardiovascular patients.[36] Also, IL-17 level has been shown to be influenced by exercises, as reported by Duzova et al who described that IL-17 level raised after eight weeks of an exercise training protocol.[37] However, the results of studies are contradictory in this regard, as Golzari et al did not discover a significant change in IL-17 level following exercise, which may be due to the short duration of the exercise protocol (i.e., two sessions) in the recent report.[38] In another study, performing intense exercises for 12 weeks significantly increased IL-17 level compared to the participants who either performed moderate-intensity exercise or no exercise (i.e., the control group).[38] Balducci et al also showed no significant decrease in IL-6 levels after 12 months of physical activities in type 2 diabetic patients.[39] Other studies have reported changes in cytokine levels after 6 to 12 weeks of exercises.[40,41] Given the lack of research on the impact of exercise activities on the level of IL-17 in CKD patients, we here assessed the impact of eight weeks of aerobic training on serum IL-17 level in these patients.

## Materials and Methods

This is a case-control study conducted design conducted on patients with CKDs referred to Zahedan Edalat Clinic and Ali-Ibn Abi Talib hospital, Zahedan (Iran) in 2017 and 2018.

### *Inclusion and Exclusion Criteria*

Male patients with CKDs diagnosed by nephrologist based on having a GFR of 30 to 89 (CKD stages *3* to 4) were enrolled. Exclusion criteria were the diagnosis of other chronic diseases, Mental illness, performing regular exercises during the last three months, histories of myocardial infarction, uncontrolled arrhythmia, atrioventricular block III, severe hypertension (over 100/200 mm Hg), and diabetes complications such as diabetic foot ulcer or proliferative diabetic retinopathy. The subjects were also excluded if they were exposed to infectious diseases during the study.[38]

### *Sample Size*

Population study consisted of all CKD patients referred to Edalat clinic and Ali-ibn Abi Talib hospital in Zahedan city, Zahedan-Iran. From these, 60 patients were selected and randomly assigned into two control and intervention groups (n=30 per group).

### *Blood Sampling and IL-17 Measurement*

At the start of the study, 5 ml of peripheral venous blood was taken. After clotting, the isolated serum was stored at -80 °C until analysis. After applying the eight-week exercise program, blood samples were taken again. Serum IL-17 level was assessed before and 24 hours after the exercise program using an ELISA kit (eBioscience, BenderMed, UK). The sensitivity of the kit was 0.18 pg/mL within a standard range of 1.56 to 100 pg/mL.

### *Exercise Procedure*

Aerobic exercise was done over a period of 8 weeks as three sessions per week with one hour for each session. The protocol included initial warms-ups followed by the main exercise protocol and then cooling down at the end of each session. The exercise program included a treadmill running ranging from 50%-80% of the maximum heart rate.[2]

### *Data Analysis*

The results were evaluated by SPSS 18 software using descriptive statistics (mean ± standard deviation) to express IL-17 levels. The Kolmogorov-Smirnov test was utilized to assess data distribution. Within-group and between-group comparisons were made by paired and independent samples student *t* test.

## Results

Our results showed the means and standard deviations of age in case and control groups were obtained as 42.57±4.49 and 43.00±4.20 years old, respectively. No statistically significant difference was found between the

patients' mean ages in the case and control groups (*P* value= 0.48) (Table 1).

Our results also indicated a significant decrease in IL-17 levels in CKD patients after the intervention, but serum level of IL-17 in CKD patients did not change significantly in the control group (Table 2).

## Discussion

This work was conducted to quantify the impact of one course of physical activity (8 weeks) on the serum level of IL-17 in patients with CKD. The mean serum levels of IL-17 among CKD patients in the intervention and control groups were 1.67±0.40 and 1.31±0.53 ng/mL before eight weeks of aerobic training, respectively. In addition, the mean serum IL-17 levels of CKD patients significantly decreased (1.58±0.17 ng/mL) after eight weeks of aerobic training ($P=0.039$). In the control group, no significant change was detected after the study period (1.35±0.50, $P=0.79$).

During recent years, CKD and ESRD incidence and prevalence have markedly increased, doubling in the US in the past decade.[42] These patients are unable to survive without renal replacement therapy that was provided to 1 900 000 patients around the world until 2015.[43] The global population of ESRD patients has exceeded two million in 2006 with a growth rate over 6%. Likewise, about 13 000 Iranian patients undergo dialysis, receiving 150 000 dialysis sessions per month.[44,45]

According to studies, increased level of CRP has is seen in 30 to 50% of dialysis patients before undergoing dialysis.[34,46] Therefore, in the view of the importance of inflammation in the development of atherosclerosis, it is necessary to assess inflammatory factors in the patients undergoing dialysis.[16] Lymphocytes and microglia cells, along with other cells, are important sources of IL-17 as a marker of inflammation.[27-29] This cytokine promotes a variety of functions including the stimulation of the production of other cytokines such as IL-4, IL-6, IL-8, and IL-10, contributing to the persistence and enhancement of inflammation. The functions of IL-17 require its binding to its receptor on different cell types. The serum level of this cytokine has been proposed as a potential indicator for acute inflammation.[37] Among other activities of IL-17 are inducing fibroblasts and macrophages and promoting the production of acute phase proteins (e.g., CRP), CPK, nitric oxide, and prostaglandin E2.[47] Our results indicated that regular exercises reduced the level of IL-17 in the body, which could improve CKD clinical course. In this regard, Duzova et al found that IL-17 concentration elevated in the participants performing prolonged or intensive training while did not change following moderate short-term exercise.[37] Our results were inconsistent with those of Golzari et al demonstrating that an 8-week combined exercise programs, including aerobic exercises, did not increase IL-17 level, and in some cases, there was even a reduction in those performing low intensity exercises.[38] Our findings also contradicted the results of Tofighee et al who indicated that IL-17 level did not change significantly after an intensive anaerobic exercise session.[48] but it was in line with Khazaei et al. who found that IL-3 and IL-6 levels significantly changed after aerobic exercise.[49]

## Conclusion

Overall, we can conclude that exercise (55%-80% of maximum heart rate) can reduce IL-17 level in serum, which can probably mitigate the inflammatory status in patients with CKD. This can be important for the elimination of waste materials in the body and improving renal function in these patients, as well as in preventing kidney disease in early stage and delaying or halting its progression. However, further studies are needed to corroborate the present results.

**Table 1.** Description and Comparison of the Age and BMI in Population Study

| | Group | Mean | SD | Minimum | Maximum | *P* Value |
|---|---|---|---|---|---|---|
| Age (y) | Control | 43 | 4.20 | 36 | 49 | 0.48 |
| | Case | 42.14 | 4.81 | 33 | 48 | |
| | Total | 42.57 | 4.49 | 33 | 49 | |
| Body mass index (kg/m$^2$) | Control | 25.43 | 2.949 | 21 | 31 | 0.133 |
| | Case | 24.29 | 2.651 | 21 | 29 | |
| | Total | 24.68 | 2.838 | 21 | 31 | |

**Table 2.** Paired *T*-test for Comparison of Mean Serum IL-17 (ng/mL) Level in Patients With CKD in Both Control and Intervention Groups Before and After Intervention

| Groups | Before 8 Weeks of Aerobic Training | | After 8 Weeks of Aerobic Training | | Comparison of Both Groups | | |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Paired *T*-test | df | *P* Value |
| Intervention | 1.67 | 0.403 | 1.58 | 0.170 | 2.296 | 13 | 0.039 |
| Control | 1.31 | 0.529 | 1.35 | 0.505 | -0.267 | 13 | 0.794 |

## Authors' Contribution

HK conducted the research plan with cooperation of AJ who conducted the aerobic training program. AAR, *SC*, and RS conducted data collection and analysis. AA supervised the research plan. All authors approved the last version of the manuscript.

## Ethical Approval

This study was approved by the ethics committee of Zahedan University of Medical Sciences (IR.ZAUMS.REC.1397.353).

## Competing Interest

All investigators of this work declare no conflicts of interest.

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