Biochemical and Biophysical Research Communications xxx (2018) 1–5

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Association of circular Klotho and insulin-like growth factor 1 with cardiac hypertrophy indexes in athlete and non-athlete women following acute and chronic exercise

Sepideh Rahimi [a], Kamal Khademvatani [b], Mohammad Reza Zolfaghari [a, *]

[a] Department of Physical Education, Faculty of Sport Sciences, Urmia University, Urmia, Iran
[b] Cardiology Department, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran

ARTICLE INFO

Article history:
Received 14 September 2018
Accepted 21 September 2018
Available online xxx

Keywords:
Cardiac hypertrophy
Exercise
IGF-I
Klotho

ABSTRACT

Owing to the role of insulin-like growth factor 1 (IGF-I) in cardiac hypertrophy and the ability of Klotho in inhibiting the IGF-I action, we investigated effects of exercise on plasma Klotho and IGF-I and their association with cardiac hypertrophy. In this study, 10 non-athlete and 10 athlete women underwent a Bruce test (acute exercise) and 12-weeks water aerobics training (chronic exercise). Electrocardiographic parameters, plasma IGF-I and Klotho levels were measured in different time courses. The exercise training could significantly increase left ventricular end-diastolic diameter index (LVEDDI) in the non-athletes. Plasma levels of IGF-I significantly increased following acute and chronic exercises. The Klotho levels at the baseline were higher in athletes than non-athletes and its levels significantly increased immediately after acute exercise in both groups. The Klotho levels significantly decreased in non-athletes 24 h after chronic exercise, but its level was still higher than the baseline in the athletes. We found positive and negative correlations between cardiac hypertrophy indexes (LVEDDI and left ventricular mass index) with respectively IGF-I and Klotho. In conclusion, we found a stimulatory effect of acute and chronic exercises on plasma IGF-I and Klotho and association of IGF-I with exercise-induced cardiac hypertrophy. Moreover, Klotho could act as a negative regulator for exercise-induced cardiac hypertrophy.

1. Introduction

The heart adjusts its mass or weight to sustain hemodynamic load due to physiological activity (such as exercise) or pathological changes [1]. The hemodynamic load causes cardiac myocardial stretching and induces production of cardiac growth factors [2]. Isotonic and isometric exercises can induce heart changes, especially in the left ventricle to increase cardiac performances that called physiological or athletic cardiac hypertrophy [3]. Cardiac growth factors involved in physiological hypertrophy have been not fully identified, but it is likely that there are similarities between the factors involved in the pathological and physiological hypertrophy [4]. In this regard, increased levels of insulin-like growth factor 1 (IGF-I) have been observed in both pathological hypertrophy and isotonic exercise-induced hypertrophy [5,6]. It has also been reported that IGF-I acts through the PI3K-Akt pathway in both types of hypertrophy [7]. In an animal study, it has been demonstrated that administration of IGF-1 could increase heart weight in rats [8].

Klotho is an anti-aging protein that acts as a co-receptor of fibroblast growth factor-23 (FGF23) [9]. The soluble form of Klotho (sKlotho) is also present in the serum, which is likely due to the breakdown of the membrane form or different gene splicing [10]. sKlotho can bind to the unknown cell surface receptors and inhibit the IGF-I-induced PI3K-Akt pathway [11]. Moreover, Kenneth Lim et al. [12] have reported that Klotho deficiency could cause pathological hypertrophy of heart due to induction of FGF23 resistance and its excessive production. On the other hand, studies have shown that Klotho inhibits cardiovascular disease [13]. Few studies have investigated the association of Klotho and physical activity. In a study on mice with Klotho deficiency, lower running endurance compared to normal mice has been documented [14]. Matsubara and colleagues have reported an increase in Klotho

* Corresponding author. Department of Physical Education, Faculty of Sport Sciences, Urmia University, Urmia, Iran.
E-mail address: zolfaghari60@gmail.com (M.R. Zolfaghari).

https://doi.org/10.1016/j.bbrc.2018.09.138
0006-291X/

levels and a decrease in arterial stiffness following a 12-week aerobic training [15].

Athletic hypertrophy is a useful adaptation of the cardiac system to tolerate extreme physical activities, but severe hypertrophy, as seen in pathologic conditions, can lead to heart failure. Owing to the role of IGF-I in both athletic and pathological cardiac hypertrophy and the ability of soluble Klotho in inhibiting the IGF-I action and consequently modulating cardiac hypertrophy [11], it seems that Klotho acts as a regulator of cardiac hypertrophy and prevents from abnormal hypertrophy following physical exercise. In this study, we investigated the effects of acute and chronic exercises on levels of Klotho and IGF-I and their association with cardiac remodeling in athletes and non-athletes.

2. Materials and methods

2.1. Subjects

For this study, 10 healthy non-athlete women without specific exercise activities and 10 athlete women who exercise regularly (at least 5 times a week and each time for 2 h) were recruited. The inclusion criteria were, having no history of medication at least for last three weeks before the study, being nonsmoker, free of renal, thyroid, diabetes, liver, cardiovascular diseases as indicated by their medical history, being in premenopausal age, and aged 30 ± 10 years. The participants were not taking dietary supplements and instructed to not change current dietary behaviors. All the procedure was approved by the Ethical Committee of Urmia University and an informed consent was obtained from all participants.

2.2. Experimental design and exercise intervention

First of all, electrocardiographic analysis was done for all participants to evaluate heartbeat, Septal thickness, Posterior wall thickness (PWT), left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter index (LVEDDI), left ventricular mass index (LVMI), end-systolic stress (ESS), and relative wall thickness (RWT). LVEF was measured based on the previously described method [16]. LVMI was calculated using the Devereux formula [17] and indexed for body surface area. RWT was calculated according to the previously published formula [18]: RWT=$(2 \times \text{PWT})/\text{LVIDD}$, where LVIDD is left ventricular internal diastolic dimension. The ESS was also evaluated using systolic blood pressure according to Reichek et al. [19] reported method. Then two experiments were designed to evaluate the effect of acute and chronic exercises. In experiment 1 (acute exercise), the participants underwent Bruce test on a treadmill. The blood samples were collected before and after this exhaustive exercise in tubes with anticoagulant and kept in $-80\,^{\circ}C$ for hormonal assay. In experiment 2 (Chronic exercise), all subjects underwent three sessions a week of Water Aerobic training for totally 12 weeks. Initially, the exercises were performed for 30 min each session with a low intensity (60% of maximum heart rate), and as the condition of the subjects (especially non-athlete women) was improved, the training time of each session increased up to 40–60min with the intensity of 70–80% maximum heart rate. To avoid interference of the acute effect of the exercise training, the blood samples were taken 24 h after the last exercise session. Moreover, to evaluate the long-term effects of the exercise, the last time of blood collection was performed three days after the previous sampling while the participants did not have any physical activities after the last exercise session. Again, an electrocardiographic analysis was done for all the subjects after the experiments. The collected samples were used to measure hormones level.

2.3. Hormonal assay

Human IGF-1 ELISA kit (ab100545, Abcam, Massachusetts, USA) was used for measurement of IGF-1 levels in plasma. IGF-1 ranged 0.1–30 ng/ml with a sensitivity of <0.2 ng/ml. The kit precision was <10% and <12% for intra- and inter-assay, respectively.

The soluble α-Klotho levels in the plasma samples were analyzed in duplicate using a commercial ELISA kit (Human soluble α-Klotho assay kit-IBL, D-22335, Hamburg, Germany). The kit measurement ranged between 93.75 and 6000 pg/ml, with a sensitivity of 6.15 pg/ml and precision of 3.1–3.5 (C.V.%) for intra-assay and 2.9–11.4 (C.V.%) for inter-assay.

2.4. Statistical analysis

Considering the sample size of the present study, non-parametric tests were used for data analysis. For this purpose, the Friedman test was performed to compare the data obtained for different time courses in one group. Evaluation of the data between the athlete and non-athlete groups was done using the Mann-Whitney test. The Spearman test was employed to evaluate possible associations between the evaluated factors. p-values <0.05 were considered significant. SPSS V.16 software was used for the statistical analysis.

3. Results

There was no significant difference in age (32 ± 7 vs. 31 ± 9 year), body mass index (23 ± 1.4 vs. 22.6 ± 2.5 kg/m^2), and Body surface area (1.68 ± 0.20 vs. 1.71 ± 0.12 m^2) between control and athlete groups ($p > 0.05$). Echocardiogram data analysis showed that heartbeat was significantly higher and LVEDDI and LVMI were statistically lower in control subjects than athletes before exercise (baseline level). However, we did not find such differences between the groups after 12-weeks of water aerobics training. Comparison of the echocardiogram parameters before and after the training in each group demonstrated that the exercise training could significantly decrease and increase respectively heartbeat and LVEDDI in just the control group and the athletes were not affected (Table 1).

Plasma levels of IGF-I and sKlotho at baseline, immediately after acute exercise, 24 h and 72 h after chronic exercise in the study population were presented in Table 2. Plasma levels of IGF-I significantly increased following acute exercise in both groups, but the amount of enhancement was higher in the athletes compared to control subjects. Chronic exercise also had the similar effect on plasma IGF-I when the level was evaluated 24 h after the exercise. However, it should be mentioned that in athletes IGF-I reached to the baseline level 72 h after the chronic exercise, but in non-athlete individuals, the level was still higher compared to the baseline ($p < 0.05$). The sKlotho levels at the baseline were also higher in athletes than non-athletes subjects and similar to IGF-I, its levels significantly increased immediately after acute exercise in both groups. Even after the acute exercise, the sKlotho level was higher in athletes compared to the control group ($p < 0.05$). Twenty four hours after chronic exercise (12 weeks water aerobic exercise training), we found a significant reduction in sKlotho levels in comparison to the amount immediately after acute exercise and this decline was even stronger in the control group as the sKlotho reached to the baseline levels; however in the athletes sKlotho level 24 h after chronic exercise was higher than the baseline level ($p < 0.05$). Seventy-two hours after the chronic exercise, the reduction was also more, although the sKlotho level in the athletes was still higher than the control subjects ($p < 0.05$).

The Spearman correlation analysis was used to address the possible association between echocardiogram parameters with

Please cite this article in press as: S. Rahimi, et al., Association of circular Klotho and insulin-like growth factor 1 with cardiac hypertrophy indexes in athlete and non-athlete women following acute and chronic exercise, Biochemical and Biophysical Research Communications (2018), https://doi.org/10.1016/j.bbrc.2018.09.138