International Journal of PharmTech Research
CODEN (USA): IJPRIF, ISSN: 0974-4304, ISSN(Online): 2455-9563
Vol.9, No.8, pp 22-30, 2016

Response of Interleukin-6to two different aerobic training programs after renal transplantation: A pilot randomized controlled trial

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Abstract : Background: Interleukin-6 (IL-6) is an inflammatory cytokine that plays a role in transplant rejection. Appropriate dose of physical training represent a useful, safe and non-pharmacologic contribution to renal transplants treatment.**Purpose:** to compare between the effect of walking and stationary bicycle as physical therapy approaches in decreasing of interleukin 6 in patients after renal transplantation. **Method:** Forty' patients of both sexes who undergone renal transplantation with age ranged from 30 to 45 years old participated in this study. They were recruited from Educational Cairo university hospitals. They were assigned into two groups equal in number: Group A included 20 patients who received aerobic exercise in the form of walking for 30 minutes 3 times per week for 12 week.Group B included 20 patients who received aerobic exercise on stationary bicycle for 30 minutes 3 times per week for 12 week. Interleukin 6 was measured before and after training program. **Results:** Statistical analysis revealed a significant improvement in interleukin 6 in both groups A and B and non-significant difference between group A and group B after aerobic exercise training. **Conclusion:** Regular aerobic exercise in the form of walking and bicycles are an effective low cost treatment that reduces levels of interleukin-6 (IL-6) in renal transplant's patients. Accordingly, patients who undergone renal transplantation are advised to perform regular aerobic activities.

Key words: Walking, Stationary bicycle, Interleukin 6, renal transplantation.

Introduction

Renal transplantation is the surgical placement and vascular integration of a human kidney from a living or cadaveric donor into a patient who has end stage renal disease (ESRD). It is considered the only treatment that restores reasonably normal kidney function and health although renal transplantation brings many benefits to patients; it is potentially associated with a number of drawbacks, which include constant risk of rejection and the need to comply with a complex medication regimen capable of producing pronounced side effects[1].

Interleukin -6 is a protein that in humans is encoded by the IL6 gene- that acts as both, proinflammatory and anti-inflammatory cytokine. It's secreted by T-cells and macrophages to stimulate immune response. IL-6 is also a "myokinge" a cytokine produced from muscle, and is decreased in response to as contraction. It's significantly decreased with exercises and precedes the appearance of other cytokines in the circulation. During exercise, it's thought to act in hormone like manner to mobilize extra cellular subtracts (glycoproteins) and/or augment substrate delivery[2].

Uremic patients' survival is conditioned by an increased cardiovascular risk; the main cause of this raised risk is the accelerated atherosclerosis, which is now considered to be the expression of an inflammatory process. Pro-inflammatory cytokines are secreted by immune cells within the atherosclerotic plaque. These include interleukin (IL)-1 IL-2, IL-6, IL-8, IL-12, IL-10, tumor-necrosis factor, interferon-γ and platelet-derived growth factor. The accelerated atherosclerosis is the most important late complication for all organ recipients also [3].

Moreover, it has been widely demonstrated that IL-6 plays a significant role in the progression of meningeal proliferative glomerulonephritisand that it is an important risk factor with respect to the relapse of IgA nephropathy in transplanted kidney [4]**.**

The low level of physical endurance in patients with (chronic renal failure) CRF is an important factor affecting health related quality of life and even the level of mortality and morbidity [5]**.**

Regular physical activity and training decrease the levels of inflammatory markers and decrease the risk of coronary heart disease .The results of the studies conducted in this field have shown that regular exercise significantly decreases the levels of TNF-α, IL-6, IL-1and (c-reactive protein) CRP and that there is a relationship between higher levels of physical activity, physical fitness and lower levels of these inflammatory markers [6]**.**

Persons who are more physically active have lower concentrations of IL-6 and CRP and other markers of inflammation (fibrinogen and white blood cells). Moreover, chronic exercise training may attenuate the inflammatory process, thereby reducing circulating concentrations of proinflammatory cytokines [7].

Cycling at a moderate intensity for 45 minutes decreased systemic markers of inflammation {white blood cells}(WBC), serum IL-6, IL-10, and CRP concentrations) and stress hormones. Therefore, repeated moderate cycling has an anti- inflammatory effect and may protect individuals from chronic disease [8].

Aerobic exercise produces a short-term inflammatory response, whereas both cross-sectional comparisons and longitudinal exercise training studies demonstrate a long-term anti-inflammatory effect However, it is still unclear whether long-term exercise associated anti-inflammatory effects might be entirely explained by decreased body weight, improved insulin sensitivity, glucose metabolism, and/or fitness level in individuals with impaired glucose metabolism [9].

Aerobic exercise has increased work capacity, improved cardio respiratory fitness, improved ventilator muscle endurance, enhanced the immune function and brings favorable changes in body mass and body composition, even without dietary restriction. The aerobic conditioning phase of the exercise sessions utilizedseveral modalities; treadmills, lower-extremity ergometers, arm ergometers, combined upper and lower ergometers, were used. Aerobic exercise therapy consisting of a track or treadmill walking, upright or recumbent cycling, rowing, stair-stepping, elliptical trainer exercise, and arm-ergometer training. The advantages of the treadmill are to be independent as the speed and grade can be varied and the work load can be1measured accurately [10].

Everyone has experienced normal fatigue, which improves with rest, however there is a difference between the fatigue patients feel after a long day and the fatigue patients may experience while undergoing treatment . Chronic fatigue associated with a disease or treatment of a disease does not improve with rest and can seriously affect a person's ability to function and his/her quality of life. Fatigue can impact quality of life in many different ways physically, emotionally, socially, and spiritually. In the acute Fatigue**;** symptoms begin quickly, symptoms are intense, of short duration, less than 7 days, relieved by a rest or a good night's sleep and usually related to excessive physical activity, lack of exercise, poor diet, dehydration, increase in activity, or other environmental factor. While in the chronic Fatigue; symptoms are unusual, excessive and constant, of long duration, two weeks or more, can interfere with normal life activities and symptoms do not get better with rest [11].

Although there is an association between activity levels and inflammatory factors, it is unclear as to whether this is due to a protective role of regular physical activity. This observed association may be attributed to the role of inflammatory cytokines in muscle catabolism, and subsequent reduction in physical capacity and physical activity levels. However, since numerous training studies have been shown to yield favorable

adaptations to aerobic and functional capacity, a two-way negative relationship between physical activity and inflammation is likely [12].

Even after a successful renal transplantation, the renal transplant recipients (RTRs) keeps on suffering the consequences of the uremic sickness such as increased cardiovascular risk, elevated level of inflammatory cytokines (IL-6), decrease work capacity and quality of life. Since biological and psychological problems are not completely solved by pharmacological treatment, physical training is able both, to improve graft function, work capacity and quality of life, and to reduce cardiovascular risk [3].

Patients and methods

A Parallel group, randomized clinical trial was conducted between January and April 2016, at Educational Cairo university Hospitals. Fortypatientsof both sexes(22 male and 18 female) who undergone renal transplantationwere selected and recruited randomly fromEducational Cairo universityHospitals. Patient's ages ranged from 30-45 years. The patients participated in the study after signing an informed consent form prior to data collection .The study begins after healing of the wound and after taking the permission from the renal transplantation team.

Exclusive criteria: patients were excluded if they had Instability of medical condition,Patients who had diabetes, Patients who had history of medical chronic relevant diseases, Patients who had acute or chronic hepatitis, Patients who had pacemaker and Patients who had genitourinary infections.

In the first contact with the patient they were allowed to complete the evaluation form. Laboratory investigations for interleukin-6 was conducted for all patients before the study and at the end of the study. Patients were selected from Educational Cairo university Hospitals after initial evaluation, patients were randomly divided into two equal groups in number (n=20), two study groups. The patients were randomly assigned to two groups by an independent person who took a selected opaque envelope from a box following a numerical sequence; the envelope contained a letter indicating whether the patient would be allocated to group A or group B.

Treatment procedure

The patients in group A (aerobic walking group) participated in a supervised exercise program in the form of walking, strengthening and stretching exercisefor the lower limb muscles performed three times per week for 12 weeks. Each session of exercise contains the following categories, Warming up exercise (strengthening and stretching exercise for the lower limb muscles for 5 minutes), Active phase (walking for 20 minutes) and Cool down exercise (strengthening and stretching exercise for the lower limb muscles for 5 minutes). At each training session, walking speed would be slowly increased until the maximum heart rate (60-70%), at the beginning walking speed was 60% from max HR and then gradually increase to 70%from max HR at the end of study [11]. Patients in group B (stationary bicycle group) were participated in a supervised exercise program on a stationary bicycle performed 3 times per week for12 weeks. At each training session, cycling speed would be slowly increased until the maximum heart rate (60-70%), at the beginning cycling speed was 60% from max HR and then gradually increase to 70%from max HR at the end of study.

Outcome measures:

The primary outcome measure for determining treatment assessment was laboratory investigations of interleukin-6 after the completion of the study. Each subject was examined medically in order to exclude any abnormal medical problems which previously mentioned. Each subject's history was taken in previously prepared questionnaire to collect information about, name, age and determination about any functional, social, psychological problems. The purpose of evaluation procedures were explained in steps for each patient in each group.

Sample size: by using G power program a preliminary power analysis [power (1α error p) = 0.85, α= 0.01, effect size = 0.5] determined a sample size of 40 for this study. This effect size was chosen because it yielded a realistic sample size [24].

Statistical analysis

The statistical package for social science (5pss, vision 17) utilized for data analysis.

It was hypothesized that treadmill and stationary bicycle as a physical therapy intervention are not an effective treatment approach on interleukin 6 in patients after renal transplantation.

Each hypothesis was tested separately by using the appropriate statistical tools. The data analysis and level of significance was set 0.05 level, Paired T-test was used to compare the dependent variable (interleukin 6), within each group (pretreatment and post treatment to patients in both study groups) to detect level of significance, Un paired T- testwas used to compare the dependent variable and independent variables between both groups to detect level of significant.

Results

In group Atwenty patients with renal transplantation were included in this group thatreceived walking training. Their mean ± SD age, weight, height, and BMI were 36.85 ± 3.52years, 65.5 ± 4.53 kg, 168.6 ± 3.92cm, and 22.97 ± 1 kg/m² respectively.In group B twenty patients with renal transplantation were included in this group that received stationary bicycle training. Their mean ± SD age, weight, height, and BMI were 36.55 ± 3.7 years, 65.8 ± 3.69 kg, 167.7 ± 3.13 cm, and 23.35 ± 0.9 kg/m² respectively comparing the general characteristics of the subjects of both groups revealed that there was no significance difference between both groups in the mean age, weight, height or BMI ($p > 0.05$).

Table 1. Descriptive statistics and t-test for comparing the mean age, weight, height, and BMI, of both groups (A and B).

	Group A	Group B	MD	t- value	p- value	Sig
	$\overline{X}$ ±SD	$\overline{X}$ ±SD				
Age (years)	36385 ± 3.52	36.55 ± 3.7	0.3	0.26	0.79	**NS**
Weight (kg)	65.5 ± 4.53	65.8 ± 3.69	-0.3	-0.22	0.82	**NS**
Height (cm)	168.6 ± 3.92	167.7 ± 3.13	0.9	0.8	0.42	**NS**
BMI (kg/m²)	22.97 ± 1	23.35 ± 0.9	-0.38	-1.24	0.22	**NS**

$\overline{X}$: Mean **SD: Standard deviation** **MD: Mean difference**
t value: Unpaired t value **p value: Probability value** **NS: Non significant**

Pretreatment mean values of interleukin 6 of both groups (A and B):

The mean ± SD interleukin 6 pretreatment of group A was 4.12 ± 0.1pg/mL a3nd that of group B was 4.13 ± 0.09 pg/mL. The mean difference between both groups was -0.01 pg/mL. There was no significant difference in interleukin 6 between group A and B pretreatment ($p = 0.76$).

Table 2. T test for comparison between pre treatments mean values of interleukin 6 of group A and B.

	Interleukin 6 (pg/mL)	MD	t- value	p-value	Sig
	$\overline{X}$ ± SD				
Group A	4.12 ± 0.1	-0.01	-0.3	0.76	**NS**
Group B	4.13 ± 0.09				

$\overline{X}$: Mean **MD : Mean difference** **p value : Probability value**
SD : Standard deviation **t value : Unpaired t value** **NS : Non significant**

Post treatment mean values of interleukin 6 of both groups (A and B):

The mean ± SD interleukin 6 post treatment of group A was 3.79 ± 0.1 pg/mL and that of group B was 3.83 ± 0.08 pg/mL. The mean difference between both groups was -0.04 pg/mL. There was no significant difference in interleukin 6 between group A and B post treatment (p = 0.19).

Pre and post treatment mean values of interleukin 6 of group A:

The mean ± SD interleukin 6 pretreatment of group A was 4.12 ± 0.1 pg/mL and that post treatment was 3.79 ± 0.1 pg/mL. The mean difference between pre and post treatment was 0.33 pg/mL and the percent of improvement was 8%. There was a significant decrease in interleukin 6 of group A post treatment compared with pretreatment (p = 0.0001).

Pre and post treatment mean values of interleukin 6 of group B:

The mean ± SD interleukin 6 pretreatment of group B was 4.13 ± 0.09 pg/mL and that post treatment was 3.83 ± 0.08 pg/mL. The mean difference between pre and post treatment was 0.3 pg/mL and the percent of improvement was 7.26%. There was a significant decrease in interleukin 6 of group B post treatment compared with pretreatment (p = 0.0001).

Table 3. Paired t test for comparison between pre and post treatment mean values of interleukin 6 of group B:

	Interleukin 6 (pg/mL) $\bar{X} \pm SD$	MD	% of improvement	t- value	p-value	Sig
Pre	4.13 ± 0.09	0.3	7.26	11.46	0.0001	S
Post	3.83 ± 0.08					

$\bar{X}$: Mean MD : Mean difference p value : Probability value

SD : Standard deviation t value : Paired t value S : Significant

Table 4. T test for comparison between pre treatment mean values of interleukin 6 of group A and B.

	Interleukin 6 (pg/mL) $\bar{X} \pm SD$	MD	t- value	p-value	Sig
Group A	4.12 ± 0.1	-0.01	-0.3	0.76	NS
Group B	4.13 ± 0.09				

$\bar{X}$: Mean MD : Mean difference p value : Probability value

SD : Standard deviation t value : Unpaired t value NS : Non significant

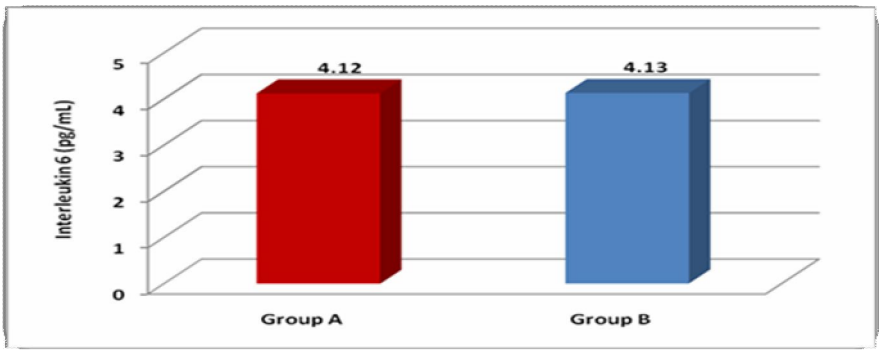

Fig. (4): Pre treatment mean values of interleukin 6 of group A and B.

Table 5. T test for comparison between post treatment mean values of interleukin 6 of group A and B.

	Interleukin 6 (pg/mL) $\overline{X} \pm SD$	MD	t- value	p-value	Sig
Group A	3.79 ± 0.1	-0.04	-1.3	0.19	**NS**
Group B	3.83 ± 0.08				

$\overline{X}$ **: Mean** **MD : Mean difference** **p value : Probability value**

SD : Standard deviation **t value : Unpaired t value** **NS : Non significant**

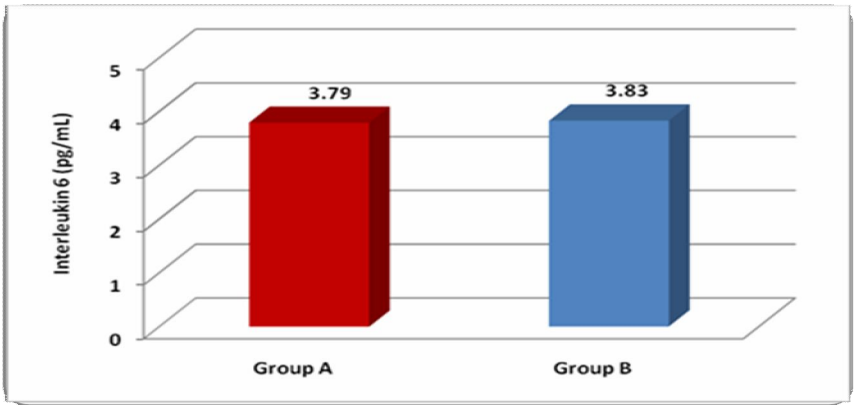

Fig. (5): Post treatment mean values of interleukin 6 of group A and B.

Discussion

Kidney transplantation is a surgical procedure in which an individual whose kidneys have stopped functioning (chronic end stage renal failure disease) receives a new kidney (graft or donor kidney) to take over the task of cleansing the blood of waste materials. Graft kidneys may come from donors who are living or dead and who are related or unrelated to the recipient [13]. Important requirements for successful transplantation include a careful match between the recipient's and the donor's blood and tissue types. When the graft kidney comes from a living donor, it is most often from a close family member (parent, child, and sibling). New laparoscopic techniques are making living donation more appealing to potential donors. Although all kidney transplants have a high success rate, donation from a well-matched family member is most successful of all [14].

Months 1-6 after transplantation are associated with the highest levels of immunosuppression and thus the greatest risk of viral and opportunistic infections. CMV is responsible for more than two thirds of febrile episodes during this period. Patients often present with fever, malaise, lymphadenopathy, arthralgia's, and myalgia. Leukopenia with atypical lymphocytes and mild hypertransaminasemia may be noted. Diagnosis is based on isolation of virus or antibody titers. Untreated (cytomegalicvirus) CMVinfection is associated with mortality as high as 15 % [15].

Interleukin-6 (IL-6) is a multifunctional cytokine that exerts its modulatory effects on cells that express membrane bound IL-6 receptors; however, IL-6 in a complex with soluble IL-6R can bind to any cell that express glycoprotein 130 (gp130). Thus, all cell types may respond to the pro- as well as anti-inflammatory properties of IL-6 [16].

Strenuous exercise on treadmill acutely increases systemic IL-6 levels, as well as concentrations of other cytokines and acute phase reactants. However, chronic muscle contractions performed on a regular basis decrease systemic IL-6 concentrations. The physical activity intervention in the life study utilized a combination of aerobic (mainly walking) and light lower extremity resistance exercise. This intervention does not allow us to distinguish whether one type of training have greater anti-inflammatory effects over another, nor does it provide

information regarding possible dose-response effects of increasing the exercise intensity or the overall caloric expenditure of physical activity [17].

Cycling at a moderate intensity for 45 minutes increased systemic markers of inflammation (WBC, serum IL-6, IL-10, and CRP concentrations) and stress hormones. Therefore, repeated moderate cycling has an anti- inflammatory effect and may protect individuals from chronic disease [18].

Regarding to [19] who stated that the inflammatory markers CRP and IL-6, adjusted for traditional risk factors, are predictive for future cardiovascular events and all-cause mortality in renal graft recipients. Although CRP and IL-6 are correlated, the observation that both markers were predictive for outcome parameters strengthens the notion that inflammation is an important risk factor for cardiovascular events and all-cause mortality in renal transplant patients.

These results were supported by [20] who stated thatelevated levels of IL-6 represent a trigger factor of inflammation; they may significantly contribute to the cardiovascular risk of RTRs. Increased basal levels of this cytokine have been measured in RTRs.

The results of this study agreed with results obtained by [21] who found that interactions among organs can influence muscle protein metabolism. Specifically, AngII stimulates an interaction between the liver and skeletal muscle because the liver becomes the major source of IL-6 and SAA. The result is stimulation of protein breakdown in muscle. This interaction is of special interest because circulating IL-6 rises in a number of catabolic conditions, including (chronic kidney disease) CKD.

In agreement with the results of the current study [22] showed that regular physical training inhibits the release of the inflammatory mediators IL-1β, IL-6 and TNF-α from fat tissues by decreasing the stimulation of the sympathetic system and increasing the production of anti-inflammatory cytokines; as a result, the concentration of cell adhesive molecules decreases.

These results were Supported by [23] who stated that exercise training consisting of thirty 40-minute sessions, three times a week, performed with the interval training technique decrease IL-6 from 2.8 ± 0.6 to 1.7 ± 0.5 pg/mL ($p < 0.01$) in renal transplant recipients**.**

The results of this study agreed with results obtained by [24] that showed thata one-year physical activity intervention results in reduced systemic concentrations of IL-6 in elderly individuals at risk for disability. Despite these caveats, this study points to the benefit of regular physical activity even in the absence of weight loss as an effective therapy for reducing systemic concentrations of IL-6 in the elderly and similar responses were observed between men and women.

In contrast results achieved by [25] showed that an aerobic exercise period caused no sensible changes in elderly women IL6 factor level but changed their TNFa factor level, also had no effects on CRP factor level. Indeed, sport increased TNFa factor level after 8-weeks exercise and this was statistically significant. Totally, Results showed that performing long-term aerobic exercise with middle severity might create a potential for immunity responses increase by means of increasing t-cells production in elderly people.

In contrast results achieved by[26] showed that after the 10-wk exercise training period, the IL-6 concentration of both the exercise groups and the control group remained unchanged; however, a significant reduction in CRP concentration was experienced by the resistance training group.

Aerobic exercise is a brisk physical activity that requires the heart and lungs to work harder to meet the body's increased oxygen demand. Aerobic exercise promotes the circulation of oxygen through the blood for example walking, running, jumping rope, ski machines, treadmills, rower, health rider, aerobics to music and aerobic videos. Treadmills are safe, easy to use and extremely convenient. Exercising on a treadmill is a very efficient cardio workout to burn calories [27].

In comparison with sedentary subjects and after adjustment for gender, age, smoking habits, body mass index (BMI), total cholesterol, glucose, and blood pressure, subjects devoted to high physical activity reported 29% and 32% lower concentrations of CRP and IL-6, respectively. Hence, reduced aerobic exercise capacity

and sedentariness seem to be associated with increased presence of chronic systemic inflammation and may provide a rationale for the use of exercise as a therapeutic modality [28].

Limitation of the study:

A lot of effort was exerted with each patient to reduce influence of possible errors inherent in the study. This study was limited by the following factors: physical and psychological condition of the patient during period of treatment, possible human error in application of measurement or therapeutic procedures, cooperation of the patient, life style and practicing exercising, and variability between patients and their reaction effects on the rate of recovery.

Conclusion

Finally it can be concluded that aerobic exercise in the form of walking and stationary bicycle for 12 week in renal transplants patients significantly decrease level of interleukin 6 and prevents the morbidity cardiovascular risks associated with this patients. So it was recommended that renal transplants patients use our aerobic exercise to IL-6 more efficiently. The mechanism by which chronic exercise alter IL-6 concentrations in the circulation must be through either an inhibitory effect on IL-6 production or through a stimulatory effect on IL-6 clearance.

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