ANNALS OF TRANSPLANTATION

ORIGINAL PAPER

e-ISSN 2329-0358
© Ann Transplant, 2019; 24: 569-575
DOI: 10.12659/AOT.917047

Received: 2019.04.18
Accepted: 2019.08.09
Published: 2019.10.08

Effects of a Structured Physical Activity Program on Serum Adipokines and Markers of Inflammation and Volume Overload in Kidney Transplant Recipients

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Data Interpretation D
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Source of support: Departmental sources

Background: Kidney transplantation (KTx) reverses most abnormalities related to chronic kidney disease (CKD), but sedentary lifestyle persists in most kidney graft recipients. Physical inactivity has been associated with altered adipokine profile and inflammation in CKD. We postulated that increased physical activity achieved through an individually-tailored program can reverse these changes.

Material/Methods: We included 25 clinically stable KTx recipients at least 12 months after transplantation and with eGFR >30 mL/min and 15 age-matched non-dialysis patients with CKD stage 3. Body composition, pattern of daily physical activity, and serum concentrations of leptin, adiponectin, NT-proBNP, and hsCRP were assessed at baseline. All patients in both groups participated in a 12-week supervised exercise program with short cell phone text reminders. All measurements were repeated after 3 months.

Results: Active energy expenditure increased significantly during the 3 months in both the KTx and CKD patients, compared with baseline by 47% (p<0.001) and 20% (p=0.01), respectively. Time spent daily on physical activity was also increased (129±83 *vs.* 194±142 and 81±56 *vs.* 124±57 min, respectively, p<0.001). Adipose tissue mass decreased significantly in the KTx group (from 40.8±11 to 38.5±10.3 kg, p=0.01). Serum leptin decreased significantly in both KTx and CKD patients (from 11.5±7.0 to 10.0±5.6, p=0.03 and from 14.1±8.3 to 12.2±6.1 ng/mL, p=0.01, respectively). Serum adiponectin increased only in the KTx group (from 1900±953 to 2015±1133 ng/L, p=0.004). Serum CRP decreased in both groups (from 15.1±5.2 to 14.0±5.6 mg/L, p=0.01 in the KTx group and from 16.5±3.9 to 15.4±4.3 mg/L in the CKD group p=0.05). NTpro-BNP was unchanged during the study.

Conclusions: Increased physical activity induces beneficial effects on adipokine profile and inflammation but does not seem to affect volume overload in kidney transplant recipients and CKD patients.

MeSH Keywords: Adipokines • Inflammation • Kidney Transplantation • Physical Exertion • Renal Insufficiency, Chronic

Full-text PDF: https://www.annalsoftransplantation.com/abstract/index/idArt/917047

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Background

As in the general population, low physical activity level has been associated with increased risk of all-cause and cardiovascular mortality in patients with chronic kidney disease (CKD) [1] and in patients after kidney transplantation (KTx) [2].

Recent studies have shown that KTx recipients have on average 4 times higher risk of cardiovascular complications compared to the healthy population [3,4], but their risk is still much lower than in patients with chronic kidney disease on the waiting list for kidney transplantation [4].

A significant deterioration of general condition of patients with CKD, especially those with end-stage renal disease, causes a gradual decline in physical activity observed in this group of patients, and their sedentary lifestyle frequently persists after KTx [5]. Decreased physical activity not reduces quality of life and mental state, but is also associated with a number of detrimental consequences such as worsening of already existing inflammation and altered metabolic and heart conditions. These changes lead to a progressive injury to the cardiovascular system and other organs and systems, resulting in a number of complications [6].

Early introduction of modifications in daily lifestyle can significantly reduce the metabolic disturbances and extend the survival of patients and grafts [7]. Fat tissue has been found to be hormonally active, with the expression of several adipokines that regulate energy metabolism. Adiponectin and leptin are mostly expressed in adipocytes [8,9]. Adiponectin increases insulin sensitivity without influencing insulin levels [9] and has strong anti-atherosclerotic and anti-inflammatory effects. Leptin, in turn, reduces the synthesis of insulin, decreases lipogenesis, increases lipolysis in adipose tissue, and increases the activity of the sympathetic nervous system [10].

Wolf et al. found that increased leptin concentrations in obese patients can play a role in the pathogenesis of diabetic changes in the kidneys, mainly through the binding of leptin to its receptors expressed in the proximal kidney tubules [11]. This shows that the kidney is not only the location of leptin metabolism but is also its target organ [11].

C-reactive protein is a marker of inflammation and has also been used as a marker of cardiovascular risk [12]. There is a tight inverse relationship between serum CRP and physical activity [13], but this relation is ambiguous because physical activity can lead to higher CRP concentrations [14].

Brain natriuretic peptide (BNP) is a natriuretic hormone secreted by cardiomyocytes, and its concentration reflects the volume of load on the cardiovascular system. Its serum concentration has been recognized as an independent cardiovascular risk factor in patients with impaired kidney function [15].

Most of the recent studies related to physical activity in CKD and KTx patients have focused on the dialysis population, and only a few included patients after kidney transplantation and compared them to the patients with CKD without a history of kidney transplantation. One recent study, conducted in a group of 32 subjects, revealed that physical activity increased by 30% in the first year after transplantation. Despite the increase, the level of physical activity in these patients was still comparable to the population of elderly people without renal insufficiency [16].

Another study revealed that an increase in habitual activity levels in CKD patients led to reduced systemic inflammation. The patients with highest baseline concentration of serum inflammation markers had the greatest benefits from physical training [13].

The aim of the present study was to compare the effects of a structured physical activity program on the biomarkers of inflammation and volume overload in patients after renal transplantation and in subjects with stage 3 and 4 chronic kidney disease.

Material and Methods

In this single-center prospective interventional study, we assessed and compared the effects of a physical exercise program on markers of inflammation and adipokines in 2 groups of patients. The first group included 24 kidney transplant recipients with stable graft function (13 women, 11 men, mean age 46±13 years). The second group included 15 patients with chronic kidney disease stages 3 and 4 without a history of kidney transplantation (8 women, 7 men, mean age 47±9 years).

The study protocol was approved by the Local Ethics Committee and written informed consent was obtained from all patients.

The inclusion criteria were: kidney transplantation from a deceased donor performed more than 12 months prior to the study, stable function of the transplanted kidney (serum creatinine ±5% in the last 3 months), and use of corticosteroids in a stable dose of ≤5 mg/24 h for the last 3 months prior to the study. CKD patients were qualified if they had a stable kidney function ±10% for at least 6 months and 24-h protein excretion <1.0 g/day. The patients with CKD had no history of dialysis. All KTx subjects had been dialyzed before they received a kidney graft.

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Table 1. Baseline clinical characteristics of study patients.

	All patients	KTx patients	CKD patients	P value (KTx *vs.* CKD patients)
Sex (male/female)	19/20	11/13	8/7	NS
Age (y)	46.9±11.8	47±13	47±9	NS
Body mass (kg)	77.1±16.1	75.3±16.8	79.8±14.9	NS
BMI (kg/m^2)	26.8±4.2	26±4	27±4	NS
SBP [mmHg]	131.8±12.6	132±12	132±13	NS
DBP [mmHg]	77.3±9.2	76±9	79±9	NS
Active smokers	7 (17.9%)	2 (8.3%)	5 (33.3%)	<0.05
Creatinine (mg/dl)	2.2±0.8	1.8±0.5	2.7±0.8	0.04
Estimated GFR (ml/min/1.73/m^2)	47.1±21.3	53±23	36±11	0.02
Hemoglonin (g/dl)	13.2±2.0	13.7±1.8	12.4±2.0	NS
Fasting glucose (mg/dl)	94.1±10.9	90.5±9.1	92.1±8.9	NS
HDL-cholesterol (mg/dl)	49.4±11.7	50.6±10.1	47.5±14.1	NS
Total cholesterol (mg/dl)	242.3±56.8	230.5±45.1	261.3±69.3	NS
LDL-cholesterol (mg/dl)	143.2±30.8	142.9±32.5	143.8±28.9	NS
TG (mg/dl)	231.1±141.5	100.4±127.9	290.1±152.5	NS
HDL-cholesterol (mg/dl)	49.4±11.7	50.6±10.1	47.5±14.1	NS
hs-CRP (mg/l)	15.3±4.9	15.1±5.2	16.5±3.9	NS
Adiponectin	131.8±12.6	132±12	132±13	NS
Leptin	77.3±9.2	76±9	79±9	NS
Cause of CKD				
Glomerular disease	16 (41%)	11 (46%)	5 (33%)	NS
Polycystic kidney disease	7 (18%)	4 (17%)	3 (20%)	NS
Hypertensive nephropathy	4 (10%)	2 (8%)	2 (13.5%)	NS
Tubulointestinal nephritis	5 (13%)	3 (12%)	2 (13.5%)	NS

BMI – body mass index; * calculated by Cockcroft and Gault formula; CKD – chronic kidney disease; DBP – diastolic blood pressure; eGFR – estimated glomerular filtration rate; HDL – high-density lipoprotein; hs-CRP – high sensitive C-reactive protein; KTx – kidney transplant; LDL – low-density lipoprotein; NT-proBNP - SBP – systolic blood pressure.

The exclusion criteria were: anemia with Hb <9 g/dl, pre-transplant diagnosis of diabetes mellitus, use of corticosteroids for indications other than kidney transplantation, acute inflammation, uncontrolled arterial hypertension, heart failure (NYHA stage 3 or 4), history of cancer, persistent hyperparathyroidism, neurological disorders, mental disorders, and severe restriction in daily physical activity.

A detailed physical examination, electrocardiography, and basic laboratory tests were carried out at baseline. Complete clinical characteristics of study patients is shown in Table 1.

Each patient was asked to participate in a 12-week program based on endurance activities, including one or more of the following: walking, jogging, cycling, swimming, and gymnastics.

Physical exercises were performed 5 times a week. In the first week, each of the exercise sessions lasted 20 min, and in the following weeks the time was gradually increased up to 2 h.

An individual exercise plan was prepared by the hospital physiotherapist based on the baseline measurements of daily physical exercise performed, taking into account the results of

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accelerometry. Each of the patients received short text messages reminders 3 times a week to motivate exercise.

The level of physical activity, expressed in units of energy expenditure MET min./week, was assessed with the International Physical Activity Questionnaire (IPAQ). Its expanded version in the local language, containing 27 questions, was used. The questionnaire allowed the evaluation of overall physical activity, as it covers all kinds of activities, ranging from those related to activities at work and at home, through communication activity (even on the way to work), to exercise in leisure time spent on recreation, entertainment, tourism, and sports. In addition, 4 questions were asked to gather demographic data (gender, age, education, and occupation). During data collection session, we recorded data on frequency (the days of the week), duration (minutes), and intensity (low, moderate, vigorous).

Weekly physical activity (expressed as MET minutes/week) was calculated by summing the MET values obtained during vigorous and moderate activity, as well as walking, performed throughout the week: minutes of activity/day x the number of days of the week x MET value (MET – metabolic equivalent of work=1 kcal/kg/h). The MET value=3.3 – corresponded to low activity, MET=4 – moderate, MET=8 – vigorous physical activity [*https://health.gov/paguidelines/2008/appendix1.aspx*].

Body mass was assessed in the morning after an overnight fast at the same time every day. Electronic calibrated scales were used to take the measurements. The measurements were carried out in patients wearing light cotton clothing.

We assessed the general state of hydration, anthropometric measurements, and body composition at baseline.

The assessment of nutritional status and anthropometric measurements consisted of the measurement of body mass and height, waist circumference, and, using a skinfold caliper, arm skin fold thickness over the triceps brachial muscle, below the shoulder blade at an angle, and on the abdomen, as well as of hand grip strength using a hydraulic hand dynamometer.

Body composition was assessed with bio-electrical impedance, using a BCM device featuring 50 different frequencies (Fresenius Medical Care, Bad Hamburg, Germany). The electrodes were placed on the upper and lower extremity on the same side.

Before commencing the measurements, the patient remained at rest for at least 5 min. Measurements were performed by a single technician trained for this purpose.

Blood pressure was measured using calibrated devices (Omron M6, Omron Health-care Europe, Milton Keynes, UK). Each measurement was performed in a sitting position.

Two times during the course of the study (at baseline and at 3 months) blood samples were collected to assess the following parameters: total protein, albumin concentration, creatinine, uric acid, lipids, sodium, potassium, NT-pro-BNP, leptin, hsCRP, and adiponectin. The blood samples were collected after an overnight fast. The samples were immediately centrifuged at 3000 rpm at 4°C for 10 min, and supernatants were frozen at -80°C until analysis. Most tests were performed in the local laboratory using standard automated methods. NT-pro-BNP, leptin, hsCRP and adiponectin tests were performed using ELISA (Phoenix Pharmaceuticals, Burlingame, CA, USA).

Daily physical activity was evaluated using the SenseWear Pro Armband accelerometer (SWA; Body Media, Pittsburgh, PA). The measurements were carried out at baseline and at 3 months after the beginning of the individual physical activity program. The device was programmed individually for each patient; the measurements lasted 3 days and included 1 weekend day.

The parameters obtained with the Sense Wear Pro Armband included total energy expenditure, metabolic equivalent, number of steps, duration of physical activity, time of rest, and the sleep time.

During the individual computer registration of each patient, basic demographic data were collected on age, sex, weight, height, right or left-handedness, and cigarette smoking.

Statistical analysis

The results are presented as mean±SD. P value <0.05 was considered statistically significant. Data distribution was checked with the Kolmogorov-Smirnov test. Within-group comparisons were made using ANOVA for repeated measurements. The unpaired *t* test or Mann-Whitney test were used to test the differences between the 2 study groups. For dependency analysis between 2 variables, Pearson's r correlation coefficient was calculated. The statistical analysis was performed using Statistica (v. 10PL, StatSoft, Tulsa, OK, USA).

Results

Active energy expenditure increased significantly compared with baseline after completion of the 3-month physical training program in both KTx and CKD patients, (by 47%, p<0.001 and 20%, p=0.01, respectively). The time spent daily on physical activity followed the same pattern of changes (129±83 *vs.* 194±142 and 81±56.7 *vs.* 124±57.3 min, respectively, p<0.001). Adipose tissue mass decreased significantly only in KTx recipients (from 40.8±1.6 to 38.5±10.3 kg, p=0.01).

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Table 2. Energy expenditure, daily physical activity, adipose tissue mass, Adiponectin/ATM, Leptin/ATM and NT-proBNP.

	KTx				CKD			
	Baseline	After 12 wk	p-Value	Absolute change from baseline	Baseline	After 12 wk	p-Value	Absolute changefrom baseline
Active energy expenditure (cal/min)	0.19± 0.13	0.3± 0.18	<0.001	0.1 [0.03; 0.17]	0.3± 0.17	0.36± 0.25	p=0.01	727 [81.6; 137.8]
Daily physical activity duration (min)	129± 83	194± 142	<0.001	64.3 [17.1; 111.4]	80.8± 56.7	124.7± 57.3	<0.001	43.9 [27.5; 60.3]
Adiponectin (ng/L)	1900± 953	2015± 1133	0.004	348 [168; 528]*	1881± 909	1905± 925	ns	85.9 [–151.5; 168.7]
Leptin (ng/L)	11.57± 7.0	10.0± 5.6	0.003	–1.5 [–2.6; –0.4]	14.1± 8.3	12.2± 6	0.01	–1.9 [–2.8; –0.9]
Adipose tissue mass (kg)	40.81± 11.5	38.5± 10.3	p=0.01	–2.4 [–6.9; 22]	33.2± 6.3	33.3± 6.3	ns	–4.6 [–8.0; 1.2]
Adiponectin/ATM (ng/lxkg)	484.6± 185.3	548.5± 234.3	p=0.002	106 [53.9; 158.5]	484.4± 191.8	564.2± 215.7	ns	50.4 [–4; 10.8]
Leptin/ATM (ng/lxkg)	0.36± 0.3	0.34± 0.3	p=0.022	0	0.38± 0.2	0.38± 0.2	ns	0
NT-proBNP (pg/m)	544± 294	537± 317	ns	–6.1 [–27.9; 14.4]	514± 170	512± 161	ns	0.5 [–3.3; 4.3]

ATM – adipose tissue mass; CKD – chronic kidney disease; KTx – kidney transplantion; NT-pro BNP – N-terminal pro-brain natriuretic hormone, * p=0.02.

Serum leptin decreased significantly in both KTx and CKD patients (from 11.5±7.0 to 10.0±5.6, p=0.03 and from 14.1±8.3 to 12.2±6.1 ng/mL, p=0.01, respectively). Serum adiponectin increased in KTx patients (from 1900±953 to 2015±1133 ng/L, p=0.004) but not in CKD patients (1881±909 and 1905±925 ng/L, respectively).

Adiponectin expressed per body fat mass (ATM) increased significantly after 3 months of physical activity only in the KTx group (from 484.6±185.3 to 548.6±234.3 ng/lxkg, respectively, p=0.002). A significant decrease of leptin/ATM after 3 months of training was observed only in the KTx group (0.36±0.3 to 0.34±0.3 ng/lxkg, p=0.022). The changes in adiponectin/ATM and leptin/ATM in the CKD group were not significant (p=0.10). These results are shown in Table 2.

The percentage changes of active energy expenditure, physical activity, serum adiponectin, serum leptin, and adipose tissue mass are presented in Figure 1.

Serum CRP decreased in both groups – from 15.1±5.2 to 14.0±5.6 mg/L (p=0.01) in KTx patients and from 16.5±3.9 to 15.4±4.3 mg/L (p=0.05) in CKD patients). A significant positive linear correlation between serum leptin and CRP in KTx group was found at baseline (r=0.59, p=0.007) and after 3 months of exercise training (r=0.72, p=0.0004, respectively). No significant correlations between serum leptin and CRP were found in the CKD group.

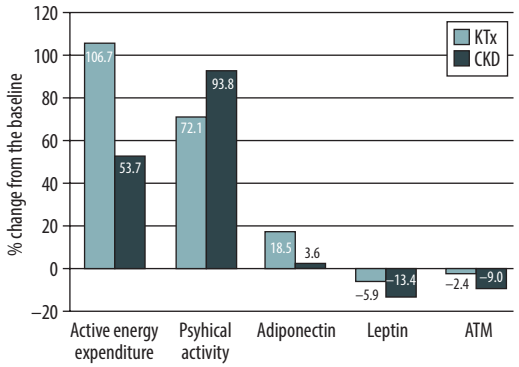

Figure 1. Percentage changes of active energy expenditure, physical activity, adiponectin, leptin, ATM from the baseline. ATM – adipose tissue mass; KTx – kidney transplantation; CKD – chronic kidney disease.

In the KTx group, we also found a significant negative correlation between CRP and adiponectin at baseline and at 3 months (r=–0.69, p=0.001; r=–0.77, p=0.001).

NT-proBNP at 3 months did not significantly change in either group (544±294 *vs.* 537±317 and 514±170 pg/mL *vs.* 512±161 pg/mL, respectively).

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Discussion

The main finding of the study was the observation that the significant increase in physical activity in both KTx and CKD patients led to a simultaneous decrease of adipose tissue mass and increase of serum adiponectin concentration.

Although adiponectin is secreted by adipose cells, its concentration is inversely related to BMI [17], and this was also seen in our study. Our study showed that the changes in adiposity and serum adiponectin were inversely correlated in KTx patients. However, Boudou et al. found that serum adiponectin concentration remained unchanged despite a reduced adipose tissue mass and increased insulin sensitivity after 8 weeks of physical exercises in 16 middle-aged men with type 2 diabetes and without significant impairment of kidney function [18].

It has been recently shown that serum adiponectin levels are higher in patients with CKD and in patients receiving renal replacement therapy including hemodialysis and peritoneal dialysis [19], most probably due to reduced clearance of adiponectin by the kidneys [19,20]. We observed higher concentrations of adiponectin after the training program, both in TX and CKD patients.

Taherimahmoudi et al. found that the level of adiponectin was higher in kidney transplant candidates than in healthy subjects, and remained increased even after kidney transplantation [21]. In this context, it would be worth analyzing to what extent our findings were the result of increased physical activity, and to what extent they were caused by the kidney function impairment itself.

It is noteworthy that the higher beneficial effect in the group of kidney transplant patients may be related with the difference in psychological status between the 2 groups.

In CKD patients, there was decreased leptin concentration at the end of the study, despite the fact that adipose tissue mass did not change in these patients. Recent studies reported that leptin level is correlated with high CRP level [22,23]. At the end of our study, CRP levels in both groups were significantly lower than at baseline, which might be influenced by the significant reduction of adipose tissue mass in both groups.

Scotece et al. [24] showed that despite the important role played by leptin in the initiation of inflammation processes, the use of agents that inhibit inflammatory cytokines did not affect its serum concentration.

We showed a significant reduction of serum C-reactive protein in both groups, which may be indirect evidence of a potentially beneficial effect of physical activity on chronic inflammation in patients with CKD and in KTx patients. It is important to mention that CRP can increase immediately as a response to exercise, but in our study the long-term effect was assessed [25]. However, CKD patients are a sedentary population with physical activity levels that are significantly lower than recommended by national guidelines [26,27]. Physical capacity is markedly lower in CKD stages 3–5 compared to healthy subjects, and higher CRP directly after exercise might not occur or might be lower than would be expected due to the much less strenuous exercise performed [28–30]. Moreover, in our study, we did not measure serum CRP immediately after exercise [26].

NTpro-BNP has been recognized as a serum marker of overhydration. Booth et al. showed that NT-pro BNP expression is modulated not only by volume overload, but is also affected by malnutrition [31]. It was demonstrated that high fluid status and high fat tissue index were associated with impaired upper and lower extremity muscle endurance in CKD patients [32].

In our study, NTpro-BNP concentration was unchanged despite the changes in ATM and adipokines in CKD and KTx patients. Our results contrast with some previous studies. Neeland et al. [33] showed that higher concentrations of BNP were independently associated with reduced visceral and hepatic adipose tissue mass and increased adipose tissue mass of the lower body parts, suggesting a direct relationship between adipose tissue mass and its hormonal activity and the production of the natriuretic peptides.

Our patients were encouraged to undertake physical activity through short text message reminders. Sarabi et al. confirmed the role of mobile technologies in patient compliance [34], but it has not been confirmed by other studies [35].

Our study has several limitations. We did not measure interleukin-6, which is directly secreted from visceral fat to the portal circulation and reaches the liver in high concentrations [36]. Another important issue is the lack of a thoroughly conducted assessment of the effect of medicines taken by the patients during the study, especially renin-angiotensin-aldosterone system blocking drugs, but it is noteworthy that the dose of all the concomitant drugs was unchanged for at least 3 months before and, more importantly, during the study. Another limitation of our study is that much of the biologically active adiponectin molecule is thought to arise from high molecular weight forms, and total levels may be only be a surrogate indicator of this [37].

Conclusions

In summary, the beneficial impact of physical activity on adipokines in both groups was demonstrated, with more pronounced effect in patients after kidney transplantation. This physical activity program benefit KTx recipients.

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