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Randomized Controlled Trial

Metabolic and functional effects of exercise training in diabetic kidney transplant recipients

Michou V *et al.* Exercise on diabetic KT recipients

Abstract

BACKGROUND

Physical activity levels are significantly lower on kidney transplant (KT) recipients compared to the general population. The effects of exercise training in KT recipients with diabetes mellitus remain unclear and so little is known about the role of increased exercise on cardiovascular risk and metabolic profile of KT patients.

AIM

To investigate the effects of a 6-mo home-based exercise training program on functional capacity, glucose levels, and lipid profile of diabetic KT patients.

METHODS

21 type II diabetic KT recipients were randomly assigned into two groups: The exercise ($n = 11$, aged 52.9 ± 10.1 years) and control ($n = 10$, aged 53.01 ± 9.5 years). All participants at baseline and the end of the study underwent biochemical tests for fasting plasma glucose (FPG) levels, glycated hemoglobin (HbA1c) and lipid profile, and cardiopulmonary exercise testing for maximum oxygen uptake $[(VO_2)_{peak}]$ estimation. The exercise group followed a 6-mo supervised home-based aerobic and progressive resistance exercise program, of moderate intensity, 3 times per week, while the control group continued to receive usual care.

RESULTS

At the end of the 6-mo study, the exercise group had significantly lower values in FPG by 13.4% (from 120.6 ± 28.9 to 104.8 ± 21.9 mg/dL, $P = 0.01$), HbA1c by 1.5% (from 6.7 ± 0.4 to 6.6 ± 0.4 %, $P = 0.01$) and triglycerides (TG) by 8.5% (from 164.7 ± 14.8 to 150.8 ± 11.6 mg/dL, $P < 0.05$) and higher values in high-density lipoprotein by 10.2% (from 51.4 ± 8.8 to 57.2 ± 8.7 mg/dL, $P < 0.05$) and $(VO_2)_{peak}$ by 4.7% (from 22.7 ± 3.3 to 23.8 ± 4.2 , $P = 0.02$) than the control group. There were statistically significant differences between the two groups at the end of the study for FPG (decreased by 9.6%, $P < 0.05$), TG

(decreased by 4.5%, $P = 0.04$), and $(VO_2)_{\text{peak}}$ (increased by 4.4%, $P = 0.01$). Finally, after training, there was a moderate, positive linear relationship between $(VO_2)_{\text{peak}}$ and HbA1c in the exercise group ($r = 0.408$, $P = 0.03$).

CONCLUSION

The results demonstrated that a 6-mo home-based mixed type exercise training program can improve the functional capacity, levels of glucose, and lipid profile of diabetic KT recipients.

Key Words: Renal transplant recipients; Diabetes mellitus; exercise; Lipid profile; Glucose control; Functional capacity

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Core Tip: Physical activity levels are significantly lower on kidney transplant (KT) recipients compared to the general population. The effects of exercise training in KT recipients with diabetes mellitus remain unclear and so little is known about the role of increased exercise on cardiovascular risk and metabolic profile of KT patients. This randomized controlled trial aimed to investigate the effects of a 6-mo home-based exercise training program on functional capacity, glucose levels, and lipid profile of diabetic KT patients. The results of the present study demonstrated that a long-term exercise training program is feasible and effective in diabetic KT recipients.

INTRODUCTION

Renal transplantation is an effective treatment option for end-stage kidney disease patients, which aims to improve quality of life and reduce mortality. Kidney transplant (KT) patients are dealing with many non- or modifiable risk factors after the

transplantation surgery, especially due to the use of maintenance immunosuppression^[1,2]. Dyslipidemia, abnormal glucose tolerance, hypertension, anemia, and nephrotoxicity are common immunosuppressive therapy side effects in KT patients^[2,3]. Unfavorable alterations in lipid and glucose profiles, contribute to high cardiovascular risk^[4], while low functional capacity due to comorbidities, corticosteroids, and inactivity is common among these patients^[5].

Diabetes mellitus (DM) incidence among the KT patients population is also high. Regular physical exercise can be an adjunct therapeutic modality for patients with DM, as it reduces the risk of cardiovascular disease (CVD), increases insulin sensitivity^[5], leads to better glucose control, and reduces lipid disorders^[1]. High CVD risk in KT patients^[6], is strongly associated with low physical activity levels^[7,8]. And despite physical exercise benefits KT patients' general health, only a few of them include physical activity in their daily routine^[9]. This may be due to the non-normalized physical fitness after transplantation and comorbidities^[10,11].

Although most of the studies on KT recipients have previously evaluated functional capacity and metabolic profile compared to healthy individuals, only a few studies have investigated the effects of structured exercise programs on glucose levels and lipid profile. Results from the few studies on functional capacity in KT recipients have shown that physical inactivity is a risk factor contributing to a patient's low physical fitness, which increases the risk of morbidity and mortality^[5,9].

By increasing, physical activity levels during their daily life KT recipients show favorable results, such as improvements in their cardiovascular fitness^[6], even though the exact type, frequency, or intensity recommended is not yet clear. Home-based exercise programs have previously largely applied in hemodialysis and patients undergoing cardiovascular rehabilitation^[4,12], while only two studies have so far provided home-based exercise rehabilitation programs for KT recipients^[13,14]. This study aimed to examine the effects of a 6-mo home-based exercise training program on glycemic control, lipid profile, and functional capacity of diabetic KT recipients.

MATERIALS AND METHODS

Patients

Twenty-eight adult KT recipients with type II DM were recruited from the Transplant Surgery Clinic of the Hippokration General Hospital of Thessaloniki, Greece. Exclusion criteria included age older than 70 years, body mass index over 40 kg/m², presence of autoimmune disorders (such as systemic lupus erythematosus, multiple sclerosis, ulcerative colitis, Chron disease, or rheumatoid arthritis), history of recent coronary heart disease (CHD) (myocardial infarction, unstable angina) within the previous 6 mo, serious musculoskeletal problems, that may limit the patient's participation in this study, non-compliance with diabetes' medication and previous patients' participation in an exercise training program.

Study design

Initially, all patients who met the inclusion criteria underwent clinical examination [electrocardiography, hemodynamic [blood pressure and heart rate (HR)] and anthropometric (weight and height) measurements], blood sampling, and cardiorespiratory testing for their physical fitness estimation. After baseline measurements, patients were randomly assigned by simple randomization (drawing lots) to either an exercise group or a control group. Participants in the control group were asked to maintain their regular lifestyle and their current physical activity level during the study period. At the end of the 6-mo study, all patients underwent the same assessment. All tests were conducted by the same researcher, who was blinded to group allocation. Patients' medications were asked to remain unchanged during the study period. This randomised controlled trial (RCT) protocol was approved by the Ethics Committee of the Aristotle University of Thessaloniki (Protocol number:117461/2019). All participants received all the necessary study information before the enrollment and provided written informed consent. The clinical trial started in September 2019 and ended in February 2020.

Functional capacity assessment

To assess patients' functional capacity, patients underwent a symptom-limited cardiopulmonary exercise testing (CPET) on a treadmill using a Bruce protocol^[15] during morning hours (9:00-11:00 am). Breath-by-breath gas exchange was measured by the Med Graphics Breeze Suite CPX Ultima (Medical Graphics Corp, MN, United States). The electrocardiogram was continuously monitored throughout each test, and the blood pressure was measured at every stage. The endpoint was set as the respiratory exchange ratio ≥ 1.10 . From each test, the peak oxygen uptake $[(VO_2)_{peak}]$, pulmonary ventilation (VE), ventilatory equivalents for oxygen (VE/VO₂), and carbon dioxide (VE/VCO₂), and the ratio between VO₂ and maximum HR (VO₂/HR_{max}) were measured.

Lipid and glucose profile assessment

At baseline and the end of the study, blood samples were taken from the brachial artery, between 7:00-9:00 am, after a 12-h fast by the same blinded microbiologist at the Hippokration General Hospital of Thessaloniki. Blood samples were drawn from each group, to determine by photometric method Hematocrit, by computational method hemoglobin (Hb), by ion-selective electrode method serum concentrations of sodium (Na), Potassium (K), calcium (Ca), magnesium (Mg) and electrolytes (K, Na, Ca, P, Mg), by enzymatic colorimetric method fasting plasma glucose (FPG) (mg/dL), serum triglycerides (TG), glycated and HbA1c and by enzymatic method serum total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL). Results were analyzed through biochemical auto-analyzer devices.

Exercise program design

Participants in the exercise group received a home-based exercise program for 6 mo. The exercise program included aerobic exercise and muscle strengthening exercises, 3 times per week for 60-90 min, with moderate intensity, *i.e.*, 60%-80% of the maximum HR reached during CPET. Training intensity was increased gradually throughout the

study according to each patient's capacity and adaptations. Each exercise session started with a 10-min warm-up and finished with a 10-min recovery (upper and lower limb stretching).

The aerobic part of each exercise session consisted of walking through going up and downstairs, or cycling on a stationary bike, initially for 15 min, with a consequent gradual increase of time by 5 min, every 2 wk, reaching 40 min in the last 2 wk before the end of the program. After a 5 min break, patients continued with the strengthening part of the exercise program. Patients were asked to perform 6 dynamic muscle strengthening exercises using just their body weight at the beginning. During the first week, each patient had 3 familiarization sessions with a physical education teacher experienced in exercise rehabilitation for patients with chronic disease, who also gave him/her an information booklet with exercise instruction images and a detailed description of the strengthening part of the program. Strengthening exercises were performed in 2 sets of 8-10 repetitions (with a 1-min passive break between the sets), in a progressive sequence from sitting to standing position. The exercise prescription included 3 strengthening exercises for the upper limbs (such as shoulder press, bicep curl, triceps extension) and 3 for the lower limbs (such as leg flexion extension). Progressively they were asked to perform the same exercises using rubber bands, balls, and dumbbells (1 kg). Patients were advised to firstly perform 2 sets (8-10 repetitions) of upper limb strengthening exercise with balls and 2 sets with the 1 kg dumbbells (8-10 repetitions) in a sitting position. Secondly, patients were asked to place the rubber bands on their feet, tie them to the bottom of their bed or chair, and do strengthening exercises in a sitting position (2 sets, 8-10 repetitions). Lastly, patients were asked to place the dumbbells on their feet in a standing position and move their legs back and forth, right, and left of their torso, with hands placed in the middle of their body.

To ensure each patient's autonomy, the interventional 6-mo home-based exercise program was individualized, while the progress and adherence to the program were monitored by telephone every week and a home visit every month, to control improvement and possible modification of the program by the researcher. To enhance

compliance, participants were asked to fill in individual diaries, describing the type, frequency, and duration of each exercise session and significant notes, which were collected every week through telephone communications. Moreover, researchers contacted patients for possible modifications or recommendations for exercise prescription.

Furthermore, it was essential for patients to measure before each exercise session (at least 30 min before) their blood glucose, blood pressure, and HR levels and note down the results in their diary. If glucose concentration was below 70 or above 130 mg/dL, patients were advised to avoid starting exercise. Moreover, intake of a small number of carbohydrates (10-15 gr) before exercise or having a carbohydrate snack available, in case of signs of hypoglycemia was an important preventive measure. Patients were also informed about the area of insulin injection that should be done in the abdominal cavity and not in the exercised limbs.

Statistical analysis

IBM Statistical Package for Social Sciences (SPSS 27.0 for Windows, Chicago, IL, United States) was used for the statistical analysis. The Kolmogorov-Smirnov test was used to evaluate variables' normality of distribution. Mean differences within time and between the two groups were analyzed using two-way ANOVA with repeated measures. Linear regression was used to study the association between variables that revealed statistically significant changes over time. Data were expressed as mean \pm SD for normally distributed variables. The two-tailed *P*-values < 0.05 were considered statistically significant.

RESULTS

Patient demographic data and characteristics

At baseline, 40 KT patients were screened for eligibility, 28 were included in our study and randomized to either exercise or control group. During the 6 mo, 3 patients from the exercise group and 4 patients from the control group withdraw from the study, due

to health reasons (such as infection or musculoskeletal problems) or personal reasons (such as lack of time). Therefore 21 patients completed the study (exercise group: $n = 11$; control group: $n = 10$).² The flowchart of participants was based on recommendations³ from the Consolidated Standards of Reporting Trials (Figure 1). There was no statistically significant difference between the two groups' demographic and clinical data (Table 1). There were no exercise-induced musculoskeletal, cardiovascular, renal, or other complications during the study.

Lipid and glucose profile results

After the 6-mo home-based exercise, a statistically significant reduction of FPG by 13.4% ($P = 0.01$), TG by 8.5% ($P < 0.05$), and HbA1c by 1.5% ($P = 0.01$), as well as a significant increase in HDL by 10.2% ($P < 0.05$) compared to the baseline values in the exercise group was noted. In contrast, there was no statistically significant difference in any biochemical parameter studied in the control group at the end of the study (Table 2). Concerning changes between groups at the end of the study, the mean concentrations of FPG and TG were decreased by 9.6% ($P < 0.05$) and 4.5% ($P = 0.04$), respectively.

Functional capacity results

Exercise group results from the CPET revealed a statistically significant increase in $(\text{VO}_2)_{\text{peak}}$ by 4.7%, ($P = 0.02$) at the end of the study (Table 3). At baseline, there was no statistically significant difference between groups, but at the end of the study, there was only a significant inter-group difference in $(\text{VO}_2)_{\text{peak}}$, which was increased by 4.4% ($P = 0.01$) in the exercise group compared to controls.

Correlations

Lastly, linear regression analysis showed that there was a moderate, positive correlation only between $(\text{VO}_2)_{\text{peak}}$ and HbA1c, after training in the exercise group ($r = 0.408$, $P = 0.03$) (Figure 2).

DISCUSSION

The results of the present study demonstrated that a home-based aerobic and strengthening exercise training program improved serum lipids by lowering the TG and increasing the HDL levels and glucose metabolism, as reflected by fasting glucose and HbA1c levels in diabetic KT patients. Moreover, the improved cardiorespiratory fitness observed in the exercise patients was found to be linearly related to the improved HbA1c. Randomized controlled trials on exercise training programs in KT patients are few and so little is known about their positive or negative effects, or even the type, frequency, or intensity of exercise in this population. Painter *et al*^[13] was the first that studied the clinical effects of exercise training on CHD risk profile through the first year of renal transplantation. Results showed that even though exercise led to a statistically significant increase in HDL and decreased high TC-HDL ratio, which categorized patients at high CHD risk, exercise as the only modifiable parameter did not significantly reduce CHD risk in KT patients. Pooranfar *et al*^[16] showed that a 10-wk, non-pharmaceutical, aerobic (at 45%-65% of maximum HR) and resistance exercise program, statistically decreased TG, TC, and LDL, while HDL remained unchanged. While a few years ago Juskowa *et al*^[17] by assessing the effects of early rehabilitation on the musculoskeletal system and blood atheromatic indices, found that after day by day 30 min of exercise, FPG and HDL levels were statistically improved in the exercise group, while TC-HDL ratio did not. There was also noted a positive correlation between improved graft function and muscle strength in the intervention group. The results of our study showed that a 6-mo mixed type exercise program led to a significant decrease in TG, FPG, and HbA1c and an increase in HDL, without affecting the TC and LDL levels.

Interestingly, a 6-mo combined exercise program in our diabetic KT recipients led to a significantly improved lipid and glucose profile, while their functional capacity was enhanced, too. These results are very important, as cardiovascular mortality in KT patients is almost 10 times higher than in the general population^[18], and the type 2 diabetes (T2D) prevalence according to global estimates, will increase by 3.0%-6.0% at

the end of 2025, with approximately 3 million T2D patients^[19]. According to our results, combined exercise training in diabetic patients seems to be the most dominant choice. De Feyter *et al*^[20] showed that after a 5-mo progressive resistance training with high-intensity interval training, T2D patients under regular diabetes medication, had lower FPG and HbA1c levels, while HDL, LDL, and TG did not statistically improve. Furthermore, Yavari *et al*^[21] in a 52-wk aerobic, resistance, or combined training program in 80 T2D patients found that aerobic or combined exercise statistically reduced TG, but the long-term combined exercise was associated with higher reductions both in HbA1c and TG levels, compared to aerobic or resistance training groups. Similarly, Cauza *et al*^[22] compared the effects of short-term (4 mo) and long-term (8 mo) strength and endurance training on glucose and lipid control in 20 T2D patients. Results showed that HbA1c, TC, LDL, and TG were statistically decreased in the group of the 8-mo combined training program, while the group in the 4-mo exercise program developed, after the end of the exercise training, an atherogenic lipid profile and did not improve glycemic control, compared to those who continued exercising. Our study revealed statistical differences between groups after a 6-mo combined exercise program in FPG and TG levels under a stable diabetic medication for both groups, similarly to the above-mentioned studies. Maintenance of diabetic medication therapy is important to understand glycemic control and lipid profile relationship and to exact results towards effects of exercise on dyslipidemia without the impact of drugs^[23].

According to a recent systematic review^[24], structured exercise programs for KT patients have shown short-term improvements in aerobic capacity and muscular strength, while De Smet and Van Craenenbroeck^[1] mentioned that exercise towards long-term effects is slightly investigated. Improving functional capacity is very important for KT patients, with or without diabetes. According to Calella *et al*^[24] exercise training improves the cardiovascular fitness of KT patients. However, $(VO_2)_{peak}$ improvements were observed only after aerobic exercise training. In a recent RCT, O'Connor *et al*^[14] showed that $(VO_2)_{peak}$ values have notably increased after a 12-wk

non-supervised moderate-intensity aerobic exercise program and that after a 9-mo follow up there were statistically significant differences in the $(VO_2)_{peak}$ values between exercise and control group. On the contrary, Riess *et al*^[25] showed that a supervised endurance and strength exercise program, although it improved the aerobic capacity and muscle strength of the KT recipients, who were taking statins and immunosuppression medication, it did not improve the CVD score. Moreover, in a previous study of ours a 15.8 % increase in $(VO_2)_{peak}$ after a 6-mo aerobic exercise training on KT patients was also noted^[26]. At the end of the study, we found a statistically significant increase of 4.7% in $(VO_2)_{peak}$ of the exercise group and a significant intergroup difference in $(VO_2)_{peak}$.

This study has some limitations that need to be taken into consideration. Firstly, the sample size was small, which may decrease the power of our findings. However, this study included a 6-mo intervention, which is a considerably long period for patients. Secondly, the biochemical tests were performed only at baseline and after 6 mo. Unfortunately, there was neither an assessment in the middle of the study nor a follow-up. Thus, larger RCTs should be implemented in the specific population to confirm the favorable effects of exercise on their metabolic profile.

CONCLUSION

In conclusion, long-term aerobic and strengthening exercise training in diabetic KT patients was found to have many beneficial effects on patients' metabolic profile and functional capacity. The results of the present study demonstrated that a long-term exercise training program is feasible and effective in diabetic KT recipients. It is a major challenge to change their daily routine into active living to sustain their physical fitness and the benefits achieved by systemic exercise training.

ARTICLE HIGHLIGHTS

Research background

According to the existing literature, kidney transplant (KT) recipients with diabetes mellitus (DM) seem to have low physical activity levels, while dyslipidemia and abnormal glucose profile are common cardiovascular risk factors.

Research motivation

As little is known about the effects of systematic exercise on metabolic profile and cardiovascular risk of KT patients, we believe that this study will positively contribute to the literature gap.

Research objectives

This study aimed to investigate the effects of a mixed type 6-mo exercise program on functional capacity, glucose, and lipid profile of KT patients with DM.

Research methods

KT patients were randomly divided into 2 groups. Both exercise and control group underwent at baseline and at the end of the study through biochemical blood analysis, in order to determine lipid and glucose levels, while cardiopulmonary exercise testing was also done to assess functional capacity.

Research results

At the end of the 6-mo study, fasting plasma glucose, hemoglobin (Hb)A1c, triglycerides, high-density lipoprotein and the peak oxygen uptake $[(VO_2)_{peak}]$ were statistically improved in the exercise group, while a positive linear relationship between $(VO_2)_{peak}$ and HbA1c was also found ($r = 0.408$, $P = 0.03$).

Research conclusions

According to the results, a 6-mo home-based mixed type exercise training program can significantly improve metabolic profile and functional capacity of diabetic KT recipients.

Research perspectives

It is crucial for future larger randomised controlled trials to explore the side effects of exercise on the metabolic profile and respiratory responses of diabetic KT recipients.

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Vasiliki Michou, Maria Nikodimopoulou, Evangelia Kouidi, Asterios Deligiannis. "MO1014: The Effects of a 6-Month Exercise Training Programme on Glycemic Control, Lipid Profile and Functional Capacity of Diabetic Kidney Transplant Recipients", Nephrology Dialysis Transplantation, 2022

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