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CICLO XXXI

POSTURAL BALANCE, MUSCLE STRENGTH AND HISTORY OF FALLS IN KIDNEY TRANSPLANT RECIPIENTS

EQUILIBRIO POSTURALE, FORZA MUSCOLARE E STORIA DI CADUTE NEI PAZIENTI NEFROTRAPIANTATI

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INDEX

ABSTRACT

Background. Although post-transplantation improvement in quality of life can lead to increased levels of physical activity, the amount achieved still remain lower than those measured in general health population. Moreover, the prevalence of sarcopenia and frailty is also higher among kidney transplant recipients (KTRs) and seems to occur at a younger age compared to the general population. In particular, postural instability has been identified as one of the main factors that can lead to adverse outcomes such as falls in the elderly; so, it is plausible to speculate that people living with a renal transplant may thus also be at increased risk for falling. Additionally, muscle atrophy, commonly reported in KTRs, has consistently been associated with impaired postural control and increased risk for falling. Finally, the side effects of immunosuppressive therapy, that include central neurologic disorders (tremors) and peripheral neuropathy may also hinder the postural control of KTRs. Starting from these assumptions, the overall aim of this project is to characterized KTRs from the functional point of view. Specifically, the project was set up in three steps: compare the static balance control in KTRs with healthy adults, explore the falls' risk profile of KTRs population, and finally involve patients in an adapted and personalized training program. At the best of our knowledge, this is the first protocol investigating static balance control in KTRs and the effects of an exercise program on this skill.

Material and Methods. For the three aims were recruited three different samples. The first was composed by 19 KTRs and 19 healthy adults (HA), with same mean height, weight and age, which are the three determinants of static balance. In this protocol were assessed static balance in three different conditions: open eyes (EO), closed eyes (EC) and dual-task (DT). The second sample for the second project aim was composed by 59 KTRs divided in two groups, the first with 20 KTRs with history of falls in the previous year, and the second with 39 non-fallers. For this study were assessed fall efficacy scale (FES), static balance in the same three conditions of the first protocol, upper and lower limb strength respectively with handgrip strength test and isometric and isokinetic tests for knee and ankle muscles. For the third aim project were recruited 31 KTRs. They were involved in an adapted and personalized training program (10 sessions, 1 hour per session, 2 per week) to improve quality of life, strength and balance. Before and after training period patients' physical function was evaluated using field tests included in the Senior Fitness Test.

Results. The first experiment confirmed that KTRs are generally sedentary, and the differences between KTRs and HA in postural sway in all conditions (EO, EC and DT) reveal that KTRs had higher postural sway scores than HA. Regarding the second study, 20 out of the 59 investigation participants (33.9%) reported at least one fall in the previous year. Our findings, on falling behavior, suggest that the prevalence of falls in KTRs patients is 1.6 to 4.3 times greater than in age-matched healthy people, which is indicative of an increased risk of falling. Moreover, the muscle strength analysis highlighted an overall trend of poorer upper and lower limb strength in fallers compared to non-fallers. Regarding the last part of the project, despite the little number of training sessions and the training period, improvements in all field tests were statistically significant.

Conclusions. Results corroborated the hypothesis that adapted physical activity should be prescribed as preventive therapy in KTRs, because despite the improvements in quality of life derived from the transplantation the risk of falls still remain high and strength level still remain low, increasing the risk of fracture, and accidental falls which may worsen quality of life and the health burden of these patients.

1. INTRODUCTION

1.1 End Stage Renal Disease

Chronic kidney disease (CKD) is a general term for heterogeneous disorders affecting kidney structure and function. CKD is a category of kidney disease in which there is a gradual loss of kidney function, meaning that kidneys are damaged and cannot filter blood properly. CKD arises from many heterogeneous disease pathways that may alter the normal and physiological function and structure of the kidney irreversibly, over months or years. Most patients with CKD have other diseases that cause CKD or contribute to the risk of cardiovascular events or death. Managing these comorbidities is an open challenge nowadays. Hypertension, cardiovascular disease, diabetes and anaemia are more common in CKD patients than in individuals who do not present CKD condition, and the prevalence of these comorbidities increases as CKD progresses [1]. In particular:

- Hypertension is the most common comorbidity; indeed, the prevalence of hypertension is about 84% in patients with CKD, compared with 23% of adults without CKD [1]. Furthermore, hypertension is generally associated with accelerated progression of kidney disease as well as development and worsening of cardiovascular disease. The goals of antihypertensive therapy in patients with CKD are to lower blood pressure to < 130/80 mm Hg, reduced risk of cardiovascular disease, and slow progression of kidney disease [2].
- Cardiovascular disease is present in 63% of patients with advanced CKD, compared with 5.8% of adults without CKD [3]. Patients with CKD are more likely to die from cardiovascular events than progress to dialysis, and cardiovascular events account for 45% of deaths in dialysis patients [4]. Additionally, cardiovascular disease reveals in 1 of 3 primary forms in patients with CKD: atherosclerosis, arteriosclerosis, and cardiomyopathy [4]. Atherosclerosis is the most common because a more atherogenic lipid profile is usual in CKD, which promotes occlusive vascular disease. Finally, arteriosclerosis may be also common in CKD due to chronic volume overload and mineral metabolism abnormalities in addition to hypertension.
- Type 2 diabetes mellitus (T2DM) is one of the leading causes of chronic kidney disease (CKD), with previous estimates suggesting close to 40% of patients with T2DM having evidence of CKD in the US [5]. Concordant with the high prevalence of CKD in this population, diabetes was attributed as the cause of end-stage renal disease (ESRD) in 44.2% of incident dialysis patients in 2011 [6].

The diagnosis of CKD rests on establishing a chronic reduction in kidney function and structural kidney damage. The best available indicator of overall kidney function is the glomerular filtration rate (GFR), which equals the total amount of fluid filtered through all of the functioning nephrons per unit of time. The definition and classification of CKD have evolved over time, but current international guidelines define CKD as a decreased kidney function shown by GFR of less than 90 mL/min per 1.73 m^2, or markers of kidney damage, or both, of at least 3 months duration, regardless of underlying cause [7].

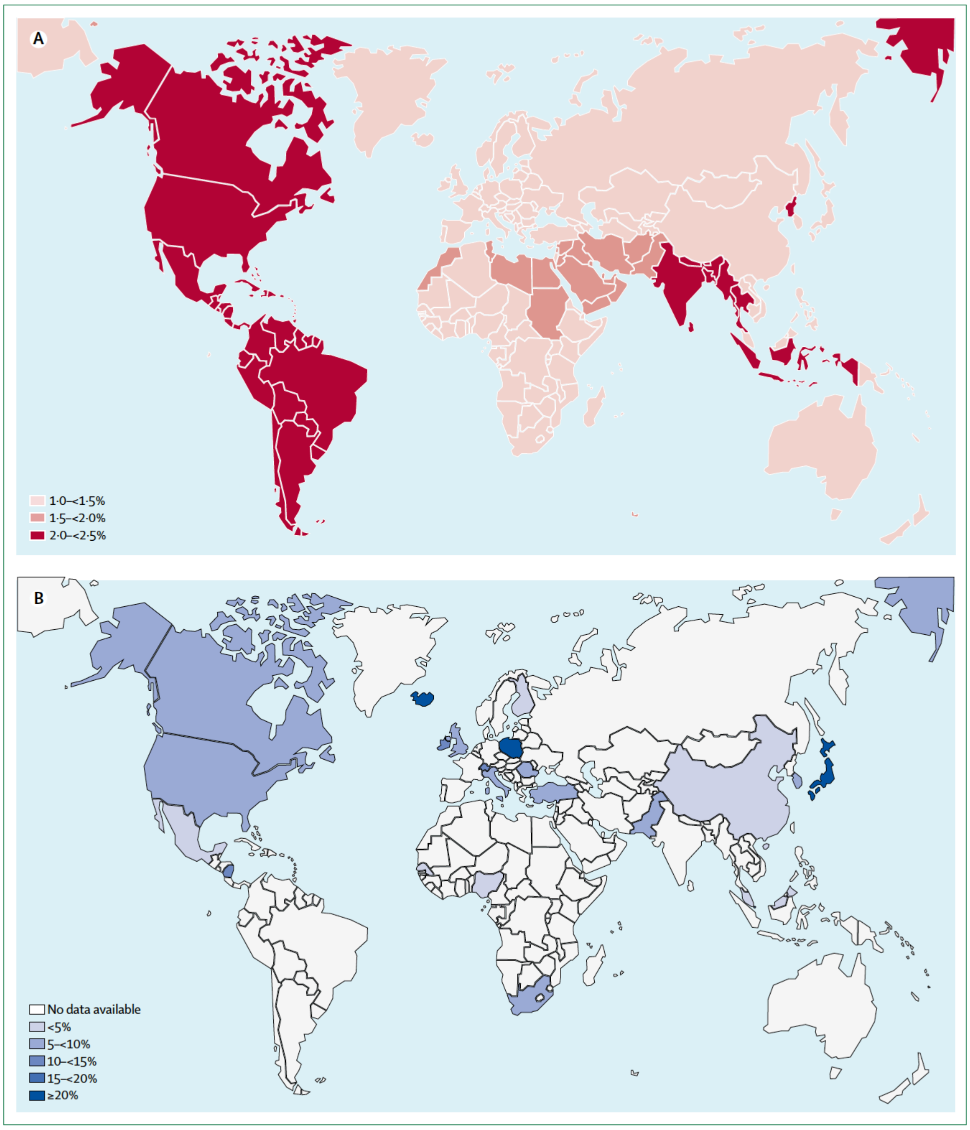
There are 5 stages of kidney damage, from very mild damage, defined stage 1, to complete kidney failure, which is the stage 5. Stages of kidney disease are based on how the kidneys filter waste and extra fluid out of the bloodstream. In the early stages of kidney disease, kidneys are still able to filter out waste, contrary to the later stages, where kidneys' filtering become harder, and may stop working altogether. More specifically the current classification articulates in:

- Stage 1: GFR ≥90 mL/min/1.73 m^2. Kidneys function is normal, but the first signs of kidney disease appear. Often, there is no symptoms, but there is an hyperfiltration.
- Stage 2: GFR 30-59 mL/min/1.73 m^2. Mild kidneys disfunction. No symptoms, but protein leaking in urine (<200 mcg).
- Stage 3: GFR 30-59 mL/min/1.73 m^2. Moderate kidneys disfunction. Some symptoms like: edema (swelling), fatigue, back pain, darker urine, microalbumin (<200 mcg).
- Stage 4: GFR 15-29 mL/min/1.73 m^2. Severe kidneys disfunction. Symptoms get worse: nausea, vomiting, difficulty in concentration, loss of appetite, sleeps problems, kidney dialysis, tingling in toes/fingers.
- Stage 5: GFR <15 mL/min/1.73 m^2. This stage concretely means as kidney failure.

When GFR is inferior than 15 mL/min per 1.73m^2, the patient reaches the end-stage kidney disease (ESKD), at that point kidney function is no longer able to sustain life over long term. Options for patients with ESKD are kidney replacement therapy (in the form of dialysis or kidney transplantation), or conservative care (also called palliation or non-dialytic care).

The burden of CKD is substantial. According to World Health Organization (WHO) global health estimates, 864 226 deaths were attributable to this condition in 2012 worldwide [7]. Ranked fourteenth in the list of leading causes of death, CKD accounted for 12 deaths per 100 000 people. Since 1990, only deaths from complications of HIV infection have increased at a faster rate than deaths from CKD. Projections from the Global Health Observatory suggest that although the death rate from HIV will decrease in the next 15 years, the death rate from CKD will continue to increase to reach 14 per 100 000 people by 2030. Moreover, the incidence and prevalence of end-stage kidney disease vary globally. More than 80% of patients receiving treatment for ESKD reside in countries with large elderly population with access of affordable health care. Worldwide variations in the incidence and prevalence of CKD are less clear because data are mainly from cohort studies, which screen heterogeneous populations, estimate GFR using varying formulas, and measure proteinuria using variable methods. Despite these limitations, the prevalence of CKD is consistently reported to be around 11% in high-income countries, including USA and Australia, pointing out how the burden is severe (Figure 1.).

Figure 1. Burden of kidney disease globally (A) Proportion of total mortality attributed to kidney disease. (B) Prevalence of chronic kidney disease. Chronic kidney disease was defined variably in different cohort studies; see appendix for specific details.



Regarding the causes of CKD, those are: diabetes, high blood pressure, glomerulonephritis and polycystic kidney disease. Risk factors include a family history for the condition, and factors associated with progression including cause of CKD, level of GFR, concentration of albuminuria, acute kidney injury, age, sex, race or ethnicity, raised blood pressure, hyperglycaemia, dyslipidaemia, smoking, obesity, history of cardiovascular disease, and ongoing exposure to nephrotoxic agents [7]. Initial treatments may include medications to manage blood pressure, glycaemia, and lower cholesterol. Other recommended measures include the increase of physical activity and certain dietary changes. Severe disease may require haemodialysis, peritoneal dialysis, or a kidney transplant. Treatments for anaemia and bone disease may also be required.

The severity of physical dysfunction in people receiving dialysis has been well documented. Severely deconditioned patients on dialysis are more likely to interrupt working activity, more frequently become hospitalised, reach disability levels, suffer from depression and other mental health problems and utilise a greater proportion of the renal care team's time and resources [8]. Physical inactivity has been identified as prognostically important risk factor for cardio vascular disease (CVD) and also for all-cause mortality in patients with CKD [9,10]. Quantity of physical activity, physical function limitations, muscle mass and muscle-function-related measures, have been identified as strong predictors of disease progression and survival rates in patients for all stages of CKD [11-13]. Furthermore, low levels of physical activity, smoking and morbid obesity (BMI>35 kg/m2) were strong predictors of developing CKD in a cohort population of 9,250 individuals [13]. Therefore, it appears that physical activity plays a pivotal role in CKD patients to inhibit or minimise the risks of developing functional limitation, disability, worsening CV function and residual renal function. However, there is an unexplored question which needs to be replied "Physical activity assumes the same prognostical added-value in kidney transplant recipients?".

1.2 Kidney Transplantation

One opportunity for patients with ESKD is the kidney transplantation. Transplant Information System (SIT) in 2016 counts 2072 kidney transplants, 276 from living people and 1796 from died persons. Just in Padova (Italy) it has been performed 161 kidney transplantations in 2016.

Inclusion criteria for transplantation are:

- GFR <15 mL/min/1.73 m^2
- Hypertension
- Polycystic kidney
- Diabetes

- Recurrent infections

On one hand, kidney transplantation has many advantages. Operation concretely eliminates the need for dialysis and helps patients to take on they own life with less hindrances. Successful kidney transplantation treats also provides a better quality of life and is therefore a preferable treatment for many patients. Usually patients after surgery have less restrictions on fluid intake, and also return to work and lead a full life after transplant. However, many patients who have received a kidney transplant will attest to the positive impact on their lives since they had a transplant. On the other hand, there are also some disadvantages, such as the need of immunosuppressant (anti-rejection) drugs or the risk of rejection of the new organ. In fact, calcineurin inhibitors (anti-rejection drugs) have many side effects. These drugs can cause mild symptoms such as tremor, neuralgia, and peripheral neuropathy, and in 5% of patients' severe symptoms include psychoses, hallucinations, blindness, seizures, cerebellar ataxia, motoric weakness, or leukoencephalopathy [14,15]. Moreover, kidney transplantation surgery entails different effect on patients' postural behaviours. Indeed, during surgery, doctor makes an incision in patients' abdomen and places the donor kidney inside. This procedure surely compromises abdominal muscles function, strength and could alter postural balance. Although there is no evidence about acute effects of kidney transplantation on strength and balance, even if in chronic kidney transplant recipients report being afraid to activate abdominal muscles not to damage new kidney. Despite these, renal transplantation ideally represents the preferred treatment modality for patients with ESRD [16], as kidney transplant recipients (KTRs) have been shown to have prolonged survival and improved CKD-related quality of life compared to dialysis patients [17].

1.3 Frailty and balance in Kidney Transplant Recipients (KTRs)

Although post-transplantation improvement in quality of life can lead to increased levels of physical activity [18], levels achieved still remain lower than those measured in the general health population. Moreover, KTRs also present with compromised functional capacity that reflects the combined effects of deconditioning, muscle atrophy and immunosuppressive therapy [8]. The prevalence of sarcopenia and frailty is also high amongst KTRs and seems to occur at a younger age compared to the general population [19]. In particular, postural instability has been identified as one of the main factors that can lead to adverse outcomes such as falls in the elderly. Given the prevalence of poor physical functioning and pharmacologic therapy among KTRs, both of which are implicated in the aetiology of falls in the elderly, it is plausible to speculate that people living with a renal transplant may thus also be at increased risk for falling. Additionally, muscle atrophy, commonly reported in KTRs, has consistently been associated with impaired postural control [20] and increased risk for falling. Furthermore, the side effects of immunosuppressive therapy, that include central neurologic disorders, such as tremors, and peripheral neuropathy [21] may also hinder the postural control of KTRs. In particular, peripheral nerve dysfunction is associated with calcineurin inhibitors use in KTRs [14] and is one of the mechanisms that may lead to postural instability [22]. Laboratory based studies have shown that, in static balance conditions, CKD patients undergoing haemodialysis (HD) therapy exhibited increased postural sway when compared to age and body mass matched healthy individuals [23,24] with further impairment of postural control evident during the execution of a concurrent cognitive task [23]. ESRD patients are usually characterized by a higher grade of cognitive impairment than people at the early stages of CKD [25]. In KTRs, alterations of the mental status may represent a symptom of a central nervous system infection, a common complication of renal transplantation, which is associated with the amount of immunosuppression [26]. Particularly, McAdams-DeMarco et al., (2017) [27] reported that the prevalence of frailty in a cohort of KT recipients was 19.5%, approximately three-fold higher than in community-dwelling older adults [28]. In addition, kidney transplant (KT) recipients have been shown to have a higher risk of fracture compared to the healthy general population and to non-dialysis CKD patients [29].

Impairments of postural balance and muscle strength are commonly recognized as risk factors that can lead to adverse outcomes such as falls in the geriatric population [30]. Recent evidence suggests that postural balance, assessed by means of posturography, is poorer in patients living with a KT compared to healthy people [31]. In addition, lower extremity impairment is highly prevalent among these patients, and that is independently associated with a higher risk of mortality [32].

These perspectives seem to suggest that, due to the relatively high prevalence of frailty and functional disability as well as the potential balance impairment, patients living with a KT may be at increased risk of falls compared to the general healthy population, and some preliminary data seem to support this hypothesis [33]. Nevertheless, the question about whether this group of patients is ostensibly at high risk of falls or not remains unexplored yet.

1.4 Project Aims

The overall aim of this project is to characterized kidney transplant recipients from the functional (physical function / physical efficiency) point of view. The project was set up in three steps (three secondary sub-aims) listed below. First and last sub-aims and experiments were designed from literature exploration; whereas second sub-aim and investigation was planned starting from first sub-aim results to deepen falls' risk profile in KTRs.

1) compare the static balance control in KTRs with healthy adults (HA). We hypothesized that KTRs will be more unsteady than HA and also that the performance of a concurrent cognitive task will highlight an increased deterioration of static balance in KTRs compared to HA.
2) explore the falls' risk profile of KTRs population by determining the prevalence of falls in a group of ESRD patients living with a KT, and testing the association of objective postural balance/strength performance measures with the history of falls of these patients. We hypothesized that the prevalence of falls would be higher than in the age-matched, non-uremic population, and that a lower performance in postural balance and muscle strength will be associated with history of falls in patients living with a KT.
3) involve patients in an adapted, personalized training program to improve quality of life, strength and balance.

At the best of our knowledge, this is the first protocol investigating static balance control in KTRs and the effects of an exercise program on this skill.

2. MATERIALS AND METHODS

2.1 Participants

For the first project step, nineteen KTRs and nineteen HA were recruited respectively from patients of the Sport and Exercise Medicine Division, Department of Medicine (University of Padova, Italy), or from a public announcement visible on the notice board in the same Division. Both patients and healthy volunteers expressing a preliminary interest in the participation were subsequently provided an information sheet and written informed consent was sought and obtained. Upon consent, a medical history questionnaire to assess the eligibility of potential healthy participants was administered by a physician. The only one inclusion criterion for KTRs group was that patients have been transplanted for at least three months. Exclusion criteria for both groups were: uncorrected visual impairment, manifest neurologic pathology (e.g., Parkinson's disease, stroke, epilepsy), diabetes, orthopaedic surgery to the lower limbs, and inability to walk independently. Moreover, KTRs with clear diagnosis of neuropathy were excluded, so as to minimize the possible confounding adverse effects of overt neuropathy on balance performance [22].

For the second project aim, fifty-nine ESRD patients living with a kidney transplantation (KT) were recruited, aged ≥ 18 years, able to provide written informed consent, male or female, and fluent in Italian were considered eligible for this protocol. Inclusion criteria was the same for the first project aim, while exclusion criteria were: severe cognitive impairment, lower limb amputees without prosthesis, uncorrected visual impairment, manifest neurologic pathology (e.g. Parkinson's disease, epilepsy), and inability to walk independently. Patients were then divided in fallers and non-fallers group.

For the third project step, thirty-one KTRs were recruited. Those patients expressed the interest to became active or to learn what kind of exercise they can perform. The only one exclusion criterion was the qualifying examination achieved by a licensed physician. Also, for this protocol as for the other two, all participants provided a written and informed consent before starting trials and training activities.

2.2 Procedure

2.2.1 Experiment One

Sociodemographic characteristics: All participant demographics (age and gender), and clinical characteristics (dialysis and transplant vintage, transplant type, comorbidities, medications and blood biochemistry data) were obtained from the patients' medical records. Height, weight, and body mass index (BMI) were measured by means of a stadiometer (Ayrton Corporation, Model S100, Prior Lake, MN) and an electronic scale (Home Health Care Digital Scale, Model MC-660, C-7300 v1.1) on the day of assessment. The mini mental state examination (MMSE) was also administered to all participants on the day of assessment, as a screening tool for cognitive impairment [34].

Physical activity: The physical activity status of the project participants was also measured, as sedentary behaviour may represent a confounding factor in the data analysis, given that low levels of physical activity constitute one of the core components of frailty [28], a known risk factor for falls in ESRD patients [37,27].

The participants' physical activity levels were measured by means of the Global Physical Activity Questionnaire (GPAQ) [38]. Time spent in moderate to vigorous physical activity (min/week), as well as time spent in sedentary behaviour (min/day) were taken for the analysis.

Postural balance: Postural balance was measured by means of posturography with an ARGO stabilometric platform (RGMD, Genova, IT), as one of the potential risk factors for falls.

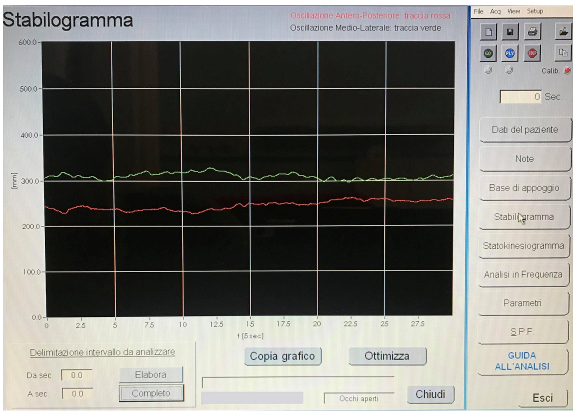
The following variables were calculated and taken for the analysis: center of pressure (CoP) velocity (CoPv), sway area (SA), and CoP range of displacement in the anterior-posterior (AP) and medio-lateral (ML) directions [39]. These variables were collected at a sampling rate of 100Hz, and raw data was filtered by the ARGO software (RGDM, Genova, IT), which uses a post-processing low-pass filtering with a 10 Hz frequency cutoff.

CoPv defines the displacement of the CoP divided by the elapsed time between measurements (mm/s), while SA represents the area covered by the CoP displacement within the base of support (mm^2/s). Lastly, AP and ML represent the range of CoP displacement in the sagittal and frontal planes (mm), respectively.

Centre of pressure velocity (COPv), SA, AP, and ML were recorded in static bipedal conditions, by means of the Romberg test with eyes open (EO), and eyes closed (EC): the reliability of these COP measures, assessed in such conditions, is deemed generally good and has been synthesized elsewhere [40]. Participants were instructed to stand upright, and as still as possible, on the stabilometric platform with feet together. All COP measures were also recorded during a dual task (DT) condition, consisting of counting backwards aloud. This cognitive task requires articulation and attention [41], and has been shown to elicit a higher postural sway compared to concurrent mental tasks during static balance testing [42]. Participants were provided a starting number, randomly selected from 90 to 100, and were asked to count backwards aloud as fast and as accurately as possible for 30 s, while standing still on the platform [43]. In order to gain acceptable test-retest reliability of the postural balance variables, each testing condition (EO, EC, DT) was executed twice, data was recorded for 30 seconds during each test, and results of the two trials were averaged for data analysis [44]. The order of the testing conditions was randomized, and the measurements were interspersed with short recovery times to reduce potential fatigue effects.

Figure 2. Balance assessment example. Romberg position on stabilometric platform.

Figure 3. Balance assessment output. Stabilogram: anterior and posterior oscillations (red and green lines respectively)



2.2.2 Experiment two

In addition to evaluations already described, in the second protocol were assessed:

History of falls: A positive history of falls was defined as the occurrence of at least one self-reported fall in the previous 12 months. Patients reporting at least 1 fall were classified as fallers, while patients who were falls-free were classified as non-fallers. This information was collected by means of a single-item survey, in which the following operational definition of a "fall" was provided: "an unexpected event in which the participant comes to rest on the ground, floor, or lower level" [35]. Was administered this survey to all participants on the day of assessment, and further information relating to the perceived cause of the falls experienced was also collected.

In addition, the Italian version of the short falls efficacy scale: 7 item (FES) was also administered as a measure of fear of falling [36].

Muscle strength: Dominant and non-dominant handgrip strength was measured with a calibrated dynamometer (Baseline, Elmsford, NY, USA). Grip handle was adjusted to accommodate the size and comfort of the participant's hand, and the elbow was flexed to 90° to guarantee the strongest grip strength measurement [45]. Three trial per hand were administered and the mean was collected.

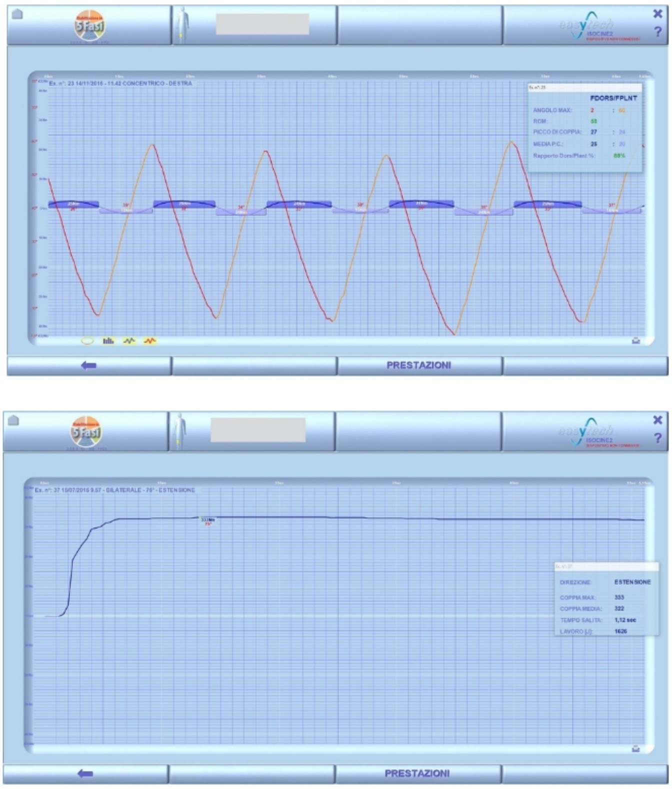
Knee isometric and isokinetic strength and ankle isokinetic strength were recorded using the multi-joint evaluation system (Prima Plus, Easytech, Italy). Data were acquired at 100 Hz. All testing procedures were performed three times and for each one the maximum torque produced (in newton-meters) was recorded. For the analysis, the average of three trials was taken into consideration. With the same procedure, also the mean of average power was calculated [46]. For isometric and isokinetic tests subjects were seated on the multi-joint evaluation system with the backrest angled at 90° to the seat. Belts were placed across the thighs, the pelvis, and the shoulders to minimize body movements and to optimally isolate the movement of knee joints and ankles. Subjects folded their arms across their chest and were not permitted to hold on to the equipment during the tests. The assessed parameters were: maximal isometric bilateral knee extension at 75° of extension (Figure 4 and 5), maximal isokinetic bilateral knee extension and flexion with a range of movement between 0° (anatomic 0°) to 85° of knee flexion**,** dominant isokinetic ankle plantar and dorsal flexor with a range of movement between 0° (anatomic 0°) to 65° of ankle plantar flexion.

During knee trials the lever fulcrum was aligned with the rotation axis of knee, with the lateral femoral epicondyle used as landmark, and the shin pad was placed 2 cm above the medial malleoli. Instead, during the ankle trials, the lever fulcrum was aligned with the medial malleoli. Before all isokinetic tests, the weight of the legs and the ankles were noted and a gravity adjustment was made using the computer software.

Four measures were quantified: maximal isometric bilateral knee extension, maximal isokinetic bilateral knee extension and flexion, maximal isokinetic ankle plantar and dorsal flexion (dominant ankle). During the maximal isometric bilateral knee extension, the leaver arm was set at 75° extension, calculated on the maximum knee extension of each participant. Subjects had to push as stronger as possible, with both legs, the shin pad for 5 seconds. Differently, during maximal isokinetic bilateral knee extension and flexion participants pushed and pulled the shin pad as fast as possible for five times uninterruptedly. The velocity of isokinetic movement was set at 90°/sec. Finally, during maximal isokinetic ankle plantar flexion and extension participants had to push down and pull up the ankle support as fast as possible for five times continuously (Figure 4 and 5). The velocity of this isokinetic movement was set at 90°/sec.

Figure 4. Strength assessment example (isokinetic ankle assessment and isometric knee assessment respectively).

Figure 5. Strength assessment output (isokinetic ankle assessment and isometric knee assessment respectively)



2.2.3 Experiment three

KTRs patients who took part in the training program (third part of the project) were evaluated before and after training period using field tests included in the Senior Fitness Test [47]. These tests were chosen because in literature there are no motor tests validated for KTRs, and these assessments are validated for elderly population which has some similarities with KTRs, for example strength loss and sarcopenia. Moreover, these field tests are easily repeatable and investigate many motor skills, such as balance, flexibility, upper and lower limb strength. Specifically, in addition to sociodemographic data, tests administered were:

- 30 Seconds Chair Stand Test, which assess leg strength and endurance. The aim of this test is to do as many stands up as possible in 30 seconds. The subject sits in the middle of the seat, with their feet shoulder width apart, flat on the floor. The arms are to be crossed at the wrists and held to the chest. From the sitting position, the subject stands up, then back down, and this is repeated for 30 seconds. Count the total number of complete chair stands.
- Arm Curl Test, which measures upper body strength and endurance. The aim of this test is to do as many arm curls as possible in 30 seconds. This test is conducted on the dominant arm

side. The subject sits on the chair, had to hold the weight and to curl the arm up completely (full range of motion) s many times as possible within 30 seconds.

- Chair Sit and Reach Test, which measures lower body flexibility. The subject sits on the edge a chair. One foot had to remain flat on the floor. The other leg is extended forward with the knee straight, heel on the floor, and ankle bent at 90°. The subject had to place one hand on top of the other with tips of the middle fingers even, and then reach forward toward the toes by bending at the hip, keeping the back straight and head up. The distance is measured between the tip of the fingertips and the toes. If the fingertips touch the toes then the score is zero. If they do not touch, measure the distance between the fingers and the toes (a negative score), if they overlap, measure by how much (a positive score).
- Back Scratch Test, which assesses upper body flexibility test. This test is done in the standing position. Subject had to place one hand behind the head and back over the shoulder, and reach as far as possible down the middle of his/her back. Indeed, had to place the other arm behind his/her back, and reach up as far as possible attempting to touch or overlap the middle fingers of both hands. If the fingertips touch then the score is zero. If they do not touch, measure the distance between the finger tips (a negative score), if they overlap, measure by how much (a positive score).
- 8-Foot Up and Go Test, which measures speed, agility and balance while moving (dynamic balance). In this test the subject had to rise up from a chair walk as quick as possible around a cone (place 8 feet from the chair), return to the chair and sit down.

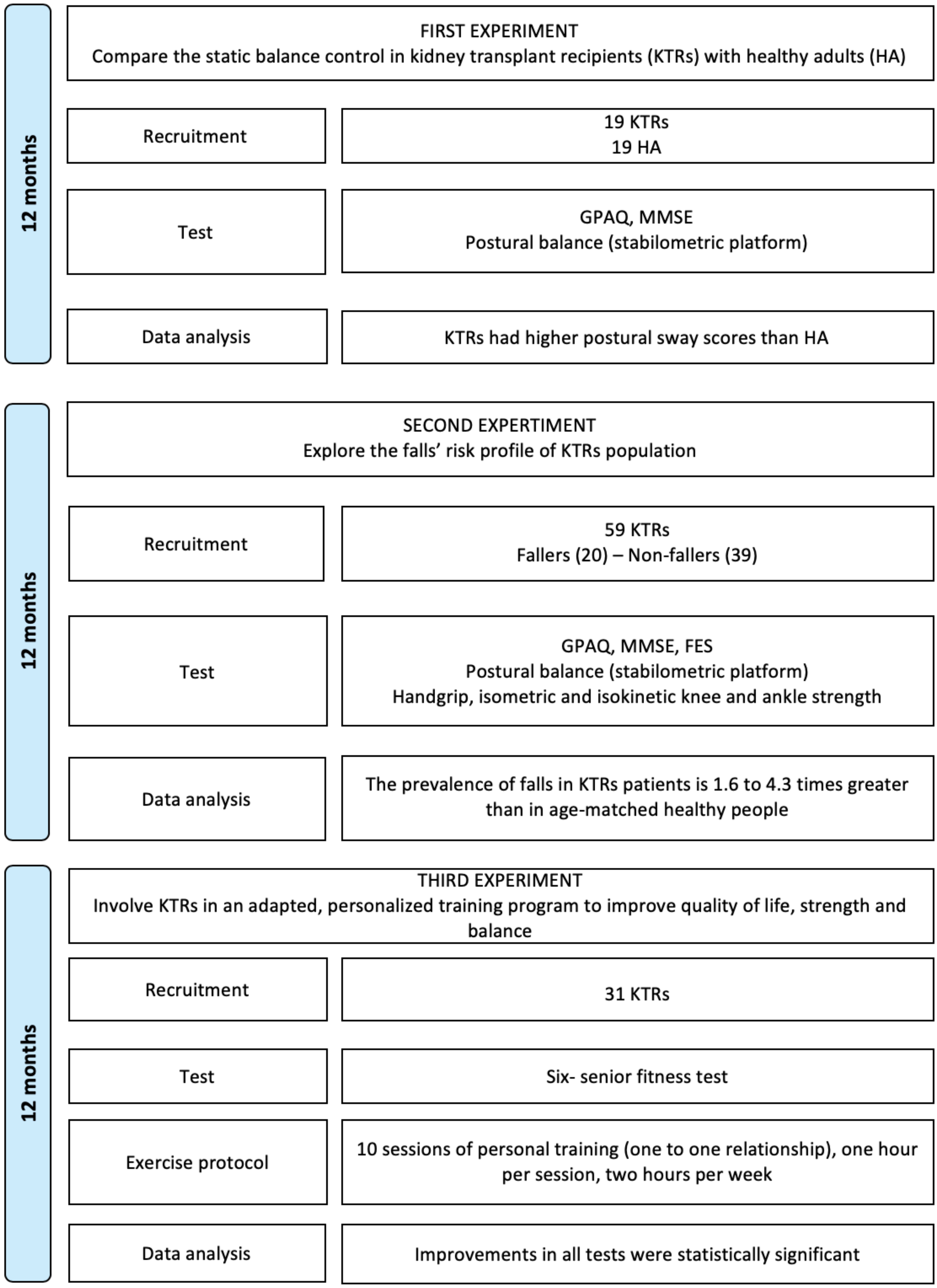
Before training, all patients were also evaluated by physician in Sport and Exercise Medicine Division. Training programme consists in ten sessions of personal training (one to one relationship), one hour per session, two hours per week (Figure 6). Activities were planned considering physician's exercise prescription, comorbidities, field tests result and patient's targets and physical needs. All sessions were divided in warm up, main training activity and cool down. During the warm up, patients were instructed to consciously activate biggest muscle district associated to breathe exercises as well as joint mobility drills. All warm up activities were performed at 60-65% of maximum heart rate calculated by physician during cardiopulmonary exercise test, performed in Sport and Exercise Medicine Division ambulatory. Main training activity included a variety of strength, flexibility, coordination and balance exercises with a progressive load depending of the patients' level and skills, and based on the patient's targets and physician's exercise prescription. The end of the session consisted on some exercises prescribed to alleviate the generated tensions during the training including some active stretching. During the three training phases activity intensities were supervised using rate of perceived exertion scale (Borg Scale 6-20 points). During warm up rate of perceived exertion had to be at 11 points (fairy light), during main training at 12 or 13 points (somewhat hard) and during cool down activities at 10 or 11 points if there was not comorbidities, contraindications or special recommendations presented in exercise prescription.

Figure 6. Examples of training session and progression.

TYPE	EXERCISE	INTENSITY (HR/RPE)	REPETITIONS SERIES / MIN	PROGRESSION
Warm-up	Mobility exercise	11 RPE	5 minutes	8 minutes
	Bike	85-90 HR	10 minutes	12 minutes
Strength circuit	Half squat with fit-ball	12 RPE	12	With 1 kg per hand
	Crunch	12 RPE	15	
	Traction with tera-band	12 RPE	12	
	Lateral Step	13 RPE	6++6	
	Chest Press with tera-band	12 RPE	12	
	French Press with tera-band	12 RPE	12	
Aerobic	Bike	85-90 HR	10 minutes	12 minutes
Balance circuit	Walk over different surface	12 RPE	5 minutes	
	Stepladder	12 RPE	5 minutes	
Cool Down	Stretching	10 RPE	5 minutes	

Abbreviation: RPE, rate of perceived exertion; HR, heart rate.

Figure 7. Flowchart diagram.



2.3 Statistical analyses

Three statistical analyses were conducted, all using SPSS (Version 21.0 for Windows, SPSS Inc., Chicago, IL).

For the first project aim, the Shapiro-Wilk Test (S–W) was applied to check normal distribution of all data. Differences in demographic characteristics were analysed by means of a Chi-Squared test for gender and physical activity status, and by either Mann-Whitney U or independent t-tests, as appropriate, for continuous variables: results are expressed as means ± standard deviation (SD). A one-way Analysis of Covariance (ANCOVA) was conducted to determine a statistically significant difference between groups on each COP measure, controlling for physical activity levels (weekly min of moderate to vigorous physical activity). In addition, we performed a further ANCOVA to establish the differences between KTRs and HA on the DTC for each COP measure, in order to test the secondary hypothesis of decreased balance performance in KTRs while executing a concurrent cognitive task. Homogeneity of variances assumption was checked through the Levene's test. Partial Eta-Squared (pη2) values are reported as an effect size measure, and significance limits were set at alpha level of $p = 0.05$.

For the second project aim, the Kolmogorov-Smirnoff test (K-S) was used for the normal distribution checks of all data. Differences between "fallers" and "non-fallers" in demographic and clinical characteristics were analyzed by means of a Chi-Squared test for categorical variables, and by either Mann-Whitney U or independent t-tests, as appropriate, for continuous variables: results are expressed as mean ± standard deviation (SD) for continuous variables, and as frequencies (percentage) for categorical variables. Differences between fallers and non-fallers, in terms of the potential risk factors for falls (postural balance/muscle strength) and confounding factors (e.g. physical activity status) were preliminary explored by means of either parametric (independent t-tests) or non-parametric (Mann-Whitney U) independent comparisons, based on normal distribution assumptions.

For the third aim, the Kolmogorov–Smirnov test was carried out to check if data were normally distributed, and Levene's test was performed to analyse the homogeneity of variance. Student's t test for dependent samples was used to evaluate each variable within groups before versus after exercise intervention. Significance limits were set at $p < 0.05$ and results are expressed as mean ± standard deviation (SD).

3. RESULTS

3.1 First Step Results

Demographic results are reported in Table 1. The GPAQ highlighted lower physical activity scores for KTRs compared to HA. The weekly duration, expressed in minutes, of moderate to vigorous physical activities, was lower in KTRs ($p = 0.009$) as calculated by the Mann-Whitney U test. In addition, a Chi-Squared test confirmed the higher proportion of physical inactivity among KTRs ($p = 0.001$), with a Phi value of $\varphi = 0.563$, indicating a larger effect size. Figure 8 displays the differences between KTRs and HA in the four COP measures in EO, EC and DT conditions. Overall, KTRs had higher postural sway scores than HA. The one-way ANCOVA confirmed a lower static balance performance of KTRs for ML ($F = 6.064$; $p = 0.019$; $p\eta^2 = 0.148$) in the EO condition, and for COPv ($F = 4.776$; $p = 0.036$; $p\eta^2 = 0.120$), SA ($F = 8.469$; $p = 0.006$; $p\eta^2 = 0.195$) and ML ($F = 5.912$; $p = 0.020$; $p\eta^2 = 0.145$) in the EC condition, whereas no differences between groups were detected in the DT condition. The one-way ANCOVA also highlighted a lower DTC for ML in KTRs compared with HA (−13.26% vs 1.02%; $F = 5.783$; $p = 0.022$; $p\eta^2 = 0.145$). Results of the between-groups analysis are presented in Table 2. No differences were found for number of errors while counting backwards aloud (Table 1).

Table 1. Characteristics of participants for the first aim (mean ± standard deviation).

	Kidney transplant recipients (KTRs)	**Healthy adults (HA)**
Number	19 (12 male; 7 female)	19 (12 male; 7 female)
Age (years)	50.53±6.54	51.32±4.57
Weight (Kg)	69.52±11.1	73.21±9.95
Height (m)	1.69 ±0.08	1.73±0.1
BMI (Kg * m^{-2})	24.57±3.24	24.22±2.87
TV (months)	4.79±3.6	n.a.
DV (months)	24.21±18.62	n.a.
MMSE	28.63±1.07	28.58±1.39
Errors during DT (number)	0.26±0.55	0.23±0.54
PA status (active vs sedentary)	7vs12	17vs2**
Weekly moderate to vigorous duration of PA (m	317.11±407.93	549.74±375.89**
Medications (number)	9.21±2.88	0.26±0.57

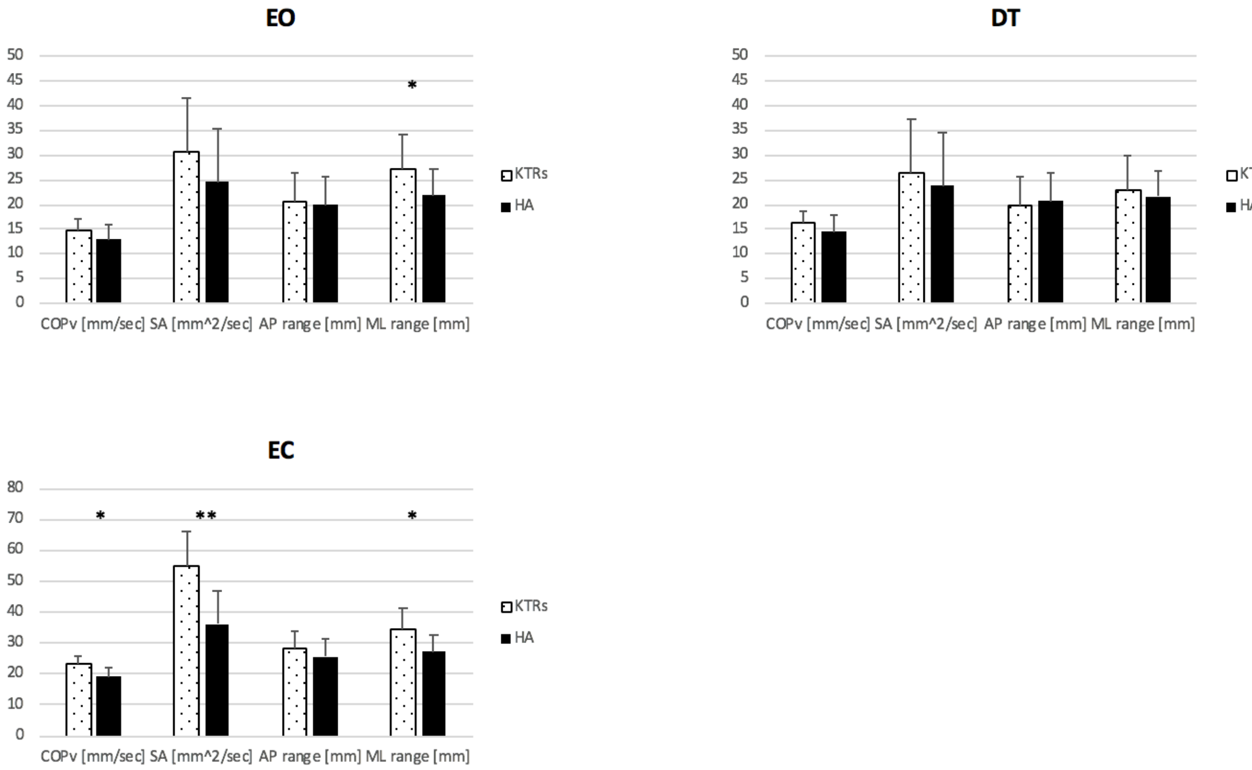
Abbreviation: BMI, body mass index; MMSE, mini mental state examination; DT, dual task; PA physical activity; DV, Dialysis vintage is defined as the time in months elapsed from the first day of dialysis to transplantation; TV, Transplant vintage represents the time in months from the day of transplantation to the assessment day; ** indicates a statistically significant difference between groups ($p < 0.01$).

Table 2. Static balance and dual task performance: differences between groups (mean ± standard deviation).

Condition	Group	COPv (mm/sec)	SA (mm/sec^2)	AP range (mm)	ML range (mm)
EO	KTRs	14.92±2.3	30.56±10.81	20.76±5.78	27.28±6.82
	HA	12.94±3.15	24.49±10.78	20.0±5.58	21.82±5.3*
EC	KTRs	23.52± 5.25	55.23±19.39	28.0±5.54	34.34±8.43
	HA	19.04±5.85*	36.12±15.68**	25.56±7.03	27.18±7.58*
DT	KTRs	16.15±4.62	26.46±9.77	19.82±4.62	23.38±7.22
	HA	14.58±3.01	23.56±6.91	20.83±5.5	21.62±5.27
DTC (%)	KTRs	-10.26±11.99	9.65± 24.69	0.19±22.60	13.26±17.52
	HA	-15.67±20.80	-9.14±40.31	-7.67±30.13	-1.03±20.26*

Abbreviations: COPv, centre of pressure velocity; SA, sway area; AP, anterior posterior; ML, medio lateral; KTRs, kidney transplant recipients; HA, healthy adults; EO, eyes open; EC, eyes closed; DT, dual task; DTC, dual task cost; * indicates a statistically significant difference between groups ($p < 0.05$); ** indicates a statistically significant difference between groups ($p < 0.01$).

Figure 8. Difference between KTRs and HA in the four COP measures under different conditions.



Abbreviations: COP, center of pressure; COPv, center of pressure velocity; SA, sway area; AP, anterior posterior; ML, medio lateral; KTRs, kidney transplant recipients; HA, healthy adults; EO, eyes open; EC, eyes closed; DT, dual task; * indicates a statistically significant difference between groups ($p < 0.05$); ** indicates a statistically significant difference between groups ($p < 0.01$).

3.2 Second Step Results

The sample characteristics are summarized in Table 3. As expected, fear of falling was higher in "fallers", as indicated by the higher FES score, and it was the only factor to be significantly different between the two groups. Twenty out of the 59 investigation participants (33.9%) reported they experienced at least one fall in the previous year, and those were therefore classified as fallers. The most common cause of falling reported by faller patients was simple slip (50%), followed by dizziness or hypotension (25%), collapse (10%), stairs (10%), and lower limb muscles' weakness (5%).

Concerning postural balance, muscle strength and quantity of physical activity, the independent comparisons between fallers and non-fallers are synthetized in Table 4. All the postural balance variables except two (ML in EO and COPv in DT) were significantly higher, describing a higher postural sway and therefore a worsening in the balance control, in fallers compared to non-fallers.

The right handgrip strength test resulted significantly higher in non-fallers group compared to the fallers one, however no significant differences in the left handgrip and knee extension/flexion between groups were detected, while ankle dorsiflexion strength, as assessed by means of IK-ankle-flex, was significantly lower in fallers. No differences in the quantity of physical activity were found between the two groups. Finally, figure 9 displays the differences between "fallers" and "non-fallers" in the four COP measures in EO, EC and DT conditions. Overall, fallers had higher postural sway scores than non-fallers in all condition. Figure 10 displays the differences between "fallers" and "non-fallers" in GPAQ, handgrip, knee, right ankle strength.

Table 3. Characteristics of participants for the second aim (mean ± standard deviation).

Variables	**All patients**	**Fallers**	**Non-fallers**	**P-value**
Number	59	20	39	
Sex (% M)	62.7	50	69.2	0.148
Age (years)	53.2±11	56.6±12.2	51.4 ±10.1	0.08
Weight (Kg)	69.8±12.3	67.8±13.8	70.9±11.6	0.36
Height (cm)	170±8.7	168.7±7.5	170.2±9.4	0.532
BMI (Kg * m^{-2})	24.2±3.5	23.7±4.2	24.4±3.2	0.501
Clinical and falls history				
Dialysis vintage (months)	39.4±32.4	34.5±20.2	41.4±36.1	0.918
Transplant vintage (months)	27.8±37.9	27.1±36.5	28.2±39.1	0.49
Diabetes (%)	12.7	20	8.6	0.221
CCI (score)	3.6±1.4	4±1.4	3.4±1.4	0.058
Transplant type (% cadaveric)	69.2	76.5	65.7	0.430
MMSE (score)	28.9±1.2	28.7±1.2	28.9±1.3	0.338
History of falls (%)	33.9	100	0	n.a.
FES (score)	7.8±1.6	9.1±1.3	7.1±1.3	<0.001
Prescribed medications				
Medications (n°)	10.6±2.5	10.7±2.8	10.6±2.4	0.867
Tacrolimus use (%)	93.1	89.5	94.9	0.446
Ciclosporine use (%)	8.6	10.5	7.7	0.718
Everolimus use (%)	32.6	36.8	30.8	0.644
Mycophenolate use (%)	65.5	57.9	69.2	0.394
Glucocorticoids use (%)	96.6	89.5	100	0.195

Beta-blockers use (%)	62.1	78.9	53.8	0.064
ACE-inhibitors use (%)	3.5	5.3	2.6	0.611
Ca channel-blockers use (%)	36.2	21	43.6	0.094
Alpha-blockers use (%)	31	36.8	28.2	0.505
≥ 1 antihypertensive drug use (%)	44.8	52.6	41	0.404
Antidepressants use (%)	6.9	15.8	2.6	0.189
Laboratory values				
Hb (g/dL)	125.6±18.8	121.8±14.2	127.9±21	0.343
eGFR (mL/min/1.73m^2)	55.8±16.7	47.9±18.2	59.7±14.8	0.055
Creatinine (μmol/L)	127.7±32.1	131.4±36.4	125.7±30.1	0.599

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; MMSE, mini-mental state examination; FES, falls efficacy scale; ACE, angiotensin-converting enzyme; Ca, calcium; Hb, hemoglobin; eGFR, estimated glomerular filtration rate; n.a., not applicable.

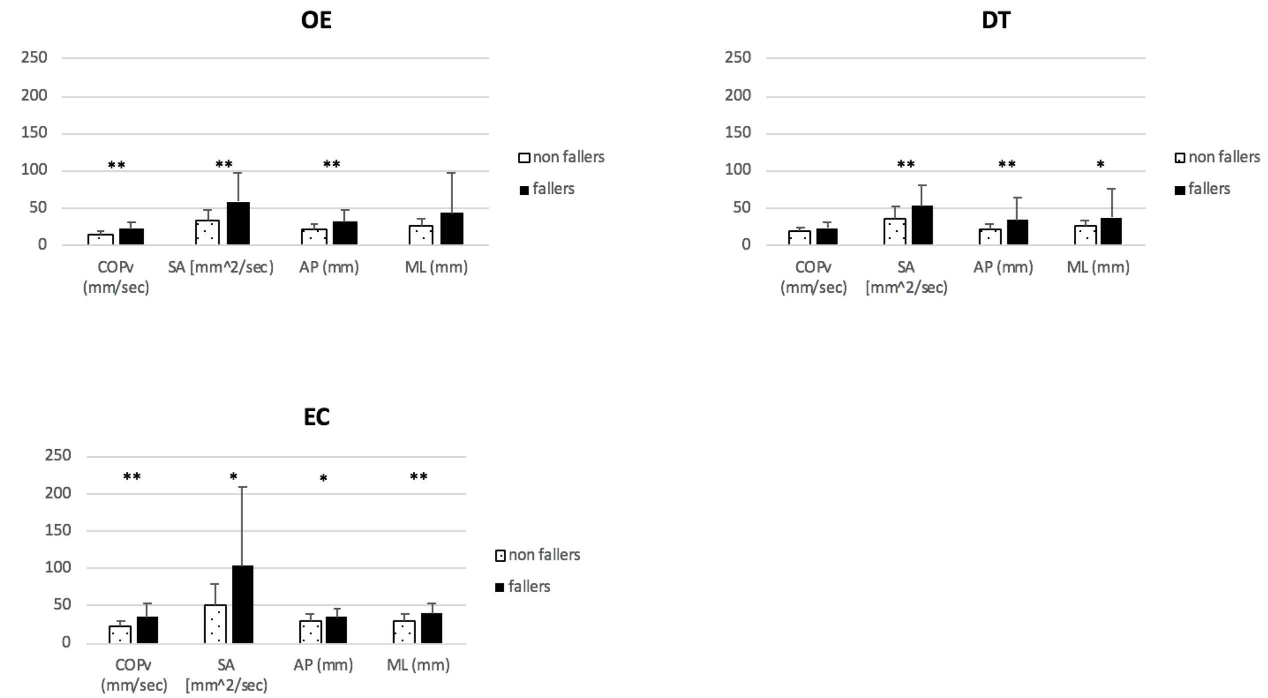
Table 4. Postural balance, muscle strength, and physical activity. Independent comparisons of fallers and non-fallers (mean ± standard deviation).

Variables	**Fallers (20)**	**Non-fallers (39)**	**P-value**
Postural balance in EO			
COPv (mm/s)	22.5±8.6	15.7±3.7	<0.001
SA (mm/s^2)	58.8±38.3	33.6±15	0.006
AP (mm)	31.9±16	22.5±6.5	0.002
ML (mm)	43.7±53.7	27.1±8.2	0.061
Postural balance in EC			
COPv (mm/s)	34.8±19.9	22.9±7.2	0.001
SA (mm/s^2)	103.8±105.6	51.6±26.8	0.009
AP (mm)	35.6±12	28.8±10.4	0.012
ML (mm)	39.8±13.8	30.5±8.3	0.002
Postural balance in DT			
COPv (mm/s)	23.86±8.44	18.74±4.89	0.206
SA (mm/s^2)	52.76±28.24	36.45±16.88	<0.001
AP (mm)	34.35±30.52	22.34±6.62	<0.001
ML (mm)	37.62±37.59	25.37±7.03	0.034

Muscle strength			
Handgrip right	28.47±7.32	34.52±10.80	0.022
Handgrip left	24.32±7.15	29.38±10.21	0.102
IM-knee-max	185.8±62.6	234.7±89.9	0.078
IM-knee-avg	155±54.6	186.9±69.8	0.117
IK-knee-ext	110.6±42.9	133.3±57.1	0.124
IK-knee-flex	63±28.5	77.9±35.1	0.106
IK-ankle-ext d	14.2±11.1	17.7±10.4	0.244
IK-ankle-flex d	16.3±3.9	20.4±7.4	0.024
Physical activity			
Moderate to vigorous PA (min/week)	410.4±358.9	416.9±500.1	0.737
Sedentary behavior (min/day)	361.5±139.9	332.1±155.5	0.325

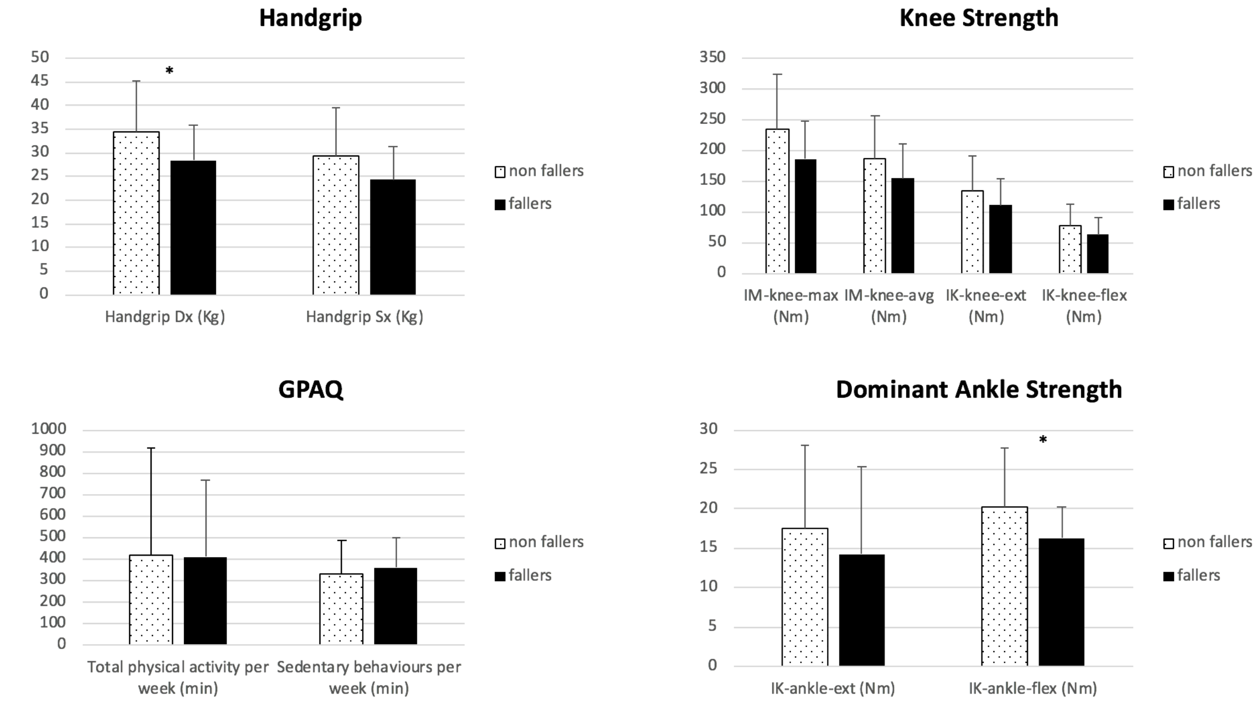
Abbreviations: EO, eyes open; EC, eyes closed; DT, dual-task; COPv, center of pressure velocity; SA, sway area; AP, range of COP displacement in the anterior-posterior axis; ML, range of COP displacement in the medial-lateral axis; IM-knee-max, maximal isometric knee strength; IM-knee-avg, average isometric knee strength; IK-knee-ext, maximal isokinetic knee extension strength; IK-knee-flex, maximal isokinetic knee flexion strength; IK-ankle-ext d, maximal isokinetic dominant ankle extension strength; IK-ankle-flex d, maximal isokinetic dominant ankle flexion strength; PA, physical activity.

Figure 9. Difference between Fallers and Non-Fallers in the four COP measures under different conditions.



Abbreviations: COP, centre of pressure; CoPv, centre of pressure velocity; SA, sway area; AP, anterior posterior; ML, medio lateral; EC, eyes closed; DT, dual task; * indicates a statistically significant difference between groups ($p < 0.05$); ** indicates a statistically significant difference between groups ($p < 0.01$).

Figure 10. Difference between Fallers and Non-Fallers in GPAQ, handgrip, knee, ankle strength.



Abbreviations: IM-knee-max, maximal isometric knee strength; IM-knee-avg, average isometric knee strength; IK-knee-ext, maximal isokinetic knee extension strength; IK-knee-flex, maximal isokinetic knee flexion strength; IK-ankle-ext, maximal isokinetic ankle extension strength; IK-ankle-flex, maximal isokinetic ankle flexion strength; GPAQ, Global Physical Activity Questionnaire; * indicates a statistically significant difference between groups ($p < 0.05$).

3.3 Third Step Results

The demographic and clinical characteristics of the study participants are summarized in Table 5. All functional skills assessed by field tests (lower and upper limb strength and flexibility, dynamic balance and agility) improved statically significant. Specifically, analysis revealed that in 30 seconds chair stand test $p<0,001$, in 8 foot up and go test $p<0,001$, in arm curl right $p<0,05$ and left $p<0,05$, in sit and reach test right $p<0,001$and left $p<0,001$, in back scratch test right $p<0,05$ and left $p<0,05$. Table 6 and figure 11 summarized and described all improvements.

Table 5. Characteristics of participants for the third aim (mean ± standard deviation).

	Kidney transplant recipients (KTRs)
Number	31 (12 male; 8 female)
Age (years)	50.41±10,02
Weight (Kg)	71.02±20.45
Height (m)	1.69±0.08
BMI (Kg * m^{-2})	25.98±5.10
TV (months)	6.91±4.5
DV (months)	32.11±20.21
MMSE	28.63±1.07
PA status (active vs sedentary)	1 vs 30
Weekly moderate to vigorous duration of PA (min)	36.03±46.70
Medications (number)	10.09±3.76
FES	8.3±1.1

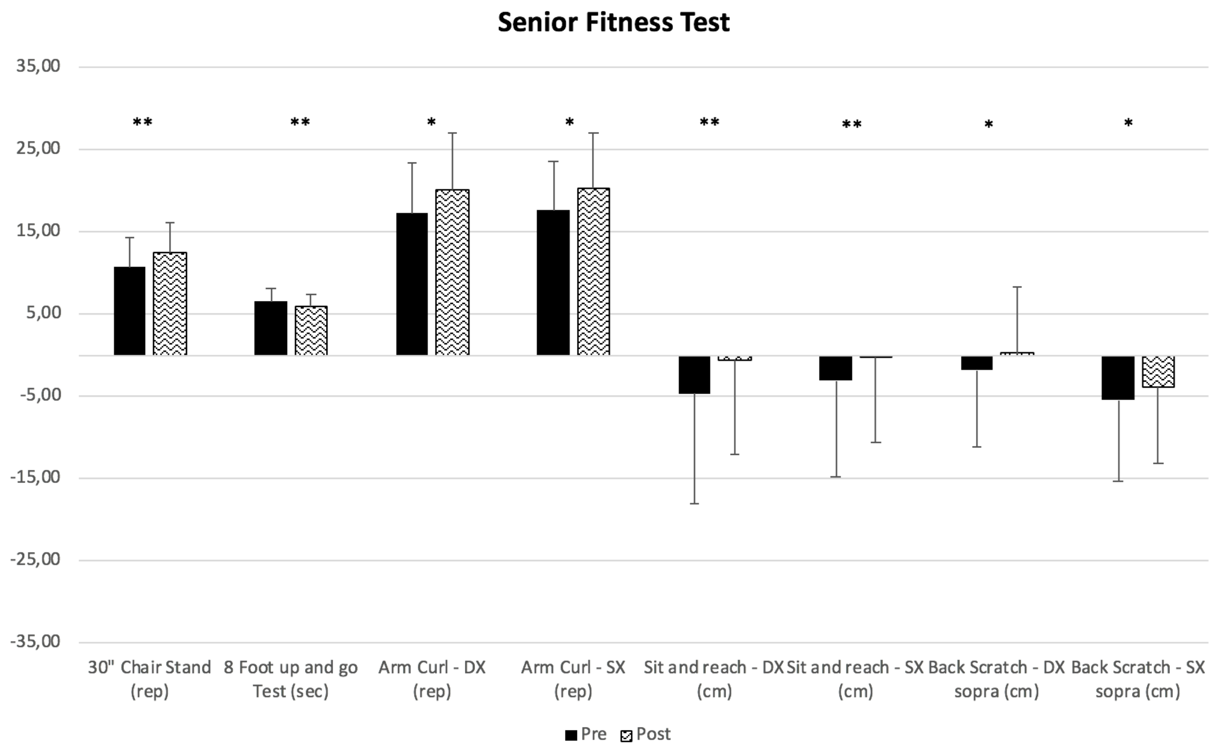
Abbreviation: BMI, body mass index; MMSE, mini mental state examination; DT, dual task; PA physical activity; DV, Dialysis vintage is defined as the time in months elapsed from the first day of dialysis to transplantation; TV, Transplant vintage represents the time in months from the day of transplantation to the assessment day; FES, falls efficacy scale.

Table 6. Field tests, *pre* and *post* training (mean ± standard deviation).

Variables	*Pre*-training	*Post*-training	P-value
30’’ chair stand (reps)	10.71±3.56	12.58±3.60	<0.001
8 foot up and go test (seconds)	6.52±1.69	5.94±1.40	<0.001
Arm curl right (reps)	17.32±6.18	20.06±6.99	0.021
Arm curl left (reps)	17.67±5.97	10.27±6.70	0.018
Sit and reach right (cm)	-4.65±13.48	-0.52±11.59	<0.001
Sit and reach left (cm)	-3.15±11.60	-0.20±10.37	<0.001
Back scratch right (cm)	-1.85±9.24	0.16±8.22	0.042
Back scratch left (cm)	-5.45±9.82	-3.82±9.39	0.013

Abbreviations: reps, repetitions; cm, centimetre.

Figure 11. Difference in field tests before and after training.



Abbreviations: rep, repetitions; sec, seconds; cm, centimetre; * indicates a statistically significant difference ($p < 0.05$); ** indicates a statistically significant difference ($p < 0.01$).

4. DISCUSSION

4.1 Primary Findings

The starring aim of the project was to characterize the physical efficiency of kidney transplant recipients, therefore we decided to start studying bodily balance since this aspect is one of the more important problems, in term of physical motor function in ESRD and CKD patients. For this reason, we firstly compared postural control in a group of KTRs compared to a group of HA. The primary finding of the first project part is that overall postural control was impaired in KTRs with respect of HA. The GPAQ results revealed that physical inactivity was higher in KTRs compared to HA ($p=.001$; $\varphi=.563$), therefore we sought to control the two groups for physical activity levels, with the ANCOVA design. Doing that, we decreased the chances of finding lower balance as a result of a general physical deconditioning due to the overall detrimental effects of physical inactivity on balance performance [48].

The one-way ANCOVA revealed a significant effect of grouping on ML, and on COPv, SA and ML, in the EO and EC conditions respectively (Table 4). Since three out of the four variables demonstrated a significant deterioration during the EC condition, as opposed to one variable only during the EO condition, our data suggest that static balance performance is particularly challenged in KTRs when the visual feedback is missing. The increased postural sway observed in KTRs during the EC condition may imply an impaired capacity to rely on proprioceptive and vestibular information [49] compared to HA. For instance, an increased postural sway, observed by means of static posturography, during upright stance with eyes closed, has been reported to be indicative of a proprioceptive, rather than vestibular, disturbance of balance [50]. Given that proprioception is regulated by an integration process, in the central nervous system, of information arising from a complex network of muscle, joint, and cutaneous mechanoreceptors, then for KTRs, the amount of information coming from proprioceptors located in the peripheral limbs, and consequently the global efficiency of proprioception, might be undermined by the high prevalence of muscle atrophy and sarcopenia [19].

Even though we did not measure muscle strength in our investigation, the higher proportion of physical inactivity in KTRs, as highlighted by the GPAQ results (Table 1), might have caused alterations in muscle quality, thereby affecting the overall integrity of proprioception. In addition, a wide spectrum of medications taken by KTRs could hinder postural control by further affecting proprioception. It is noteworthy that 100% of KTRs were taking calcineurin inhibitors, as part of their immunosuppressive therapy. This class of drugs can induce neurotoxic side effects, via alteration of the sensory motor functions, in 10-28% of cases [51], potentially affecting postural control by impairing the proprioceptive regulatory mechanism of balance [51,24]. Moreover, 89.5% of KTRs, and none of HA met the criteria for polypharmacy, defined as the concurrent use of 5 or more medications [52], which is also associated with impaired balance control in older adults [53]. Thus, it appears the baseline differences in terms of medications taken by the two groups may account in part, at least, for some of our findings.

The addition of a cognitive assignment to the postural task did not affect significantly any of the COP measures in the between-groups comparison (p values≥ .145). Similarly, the one-way ANCOVA did not show a higher DTC for KTRs, therefore we retained the null hypothesis for the secondary research question. These findings are in contrast with those of Shin et al., [24], who reported an overall higher DTC in HD patients compared with a group of healthy subjects. The discrepancy is not surprising at the light of two main considerations. First off, kidney transplantation has been consistently reported to improve cognitive function in HD patients [54]. Therefore, albeit remaining at higher risk of cognitive impairment in comparison with healthy individuals, KTRs might have a better DT performance, compared with HD patients, due to their relatively higher cognitive function. Secondly, the concurrent cognitive task administered in the DT condition in Shin's et al. study [24], namely a semantic/phonetic word generation task, is undoubtedly more challenging than counting backwards aloud. Although both tasks imply articulation and attention [41], the word generation task very likely requires more attentional resources than simply counting backwards, and might have therefore exerted a higher disturbance on the primary task, i.e. postural control, according to the capacity theory on DT performance [55].

In addition, counting backwards aloud is a cognitive task that produces systematic errors which are attributable to short term memory disturbances [56]. It has been suggested that long term memory deficits in KTRs might reflect hippocampus impairments as a result of the necessarily prolonged period of corticosteroid therapy [57]. Even though the two groups did not differ for the number of errors committed while counting backwards, during the DT condition, it is possible that a more complex memory task, such as remembering words, or listing items, might have produced a higher number of errors, and consequently a worse DT performance in KTRs. Similarly, the MMSE results do not seem to suggest there were any cognitive differences between the two groups (Table 1). Nevertheless, it should be acknowledged that the MMSE might not be sensitive enough to detect mild cognitive impairments [58], and it is still possible that KTRs might have had some undetected cognitive deficits.

Some limitations should be acknowledged when reading the findings from this protocol. First and foremost, we did not report muscle strength data, another possible confounding factor, which would have provided more mechanistic insight on the differences in static balance that emerged between the two groups. In addition, it should be acknowledged that, despite our efforts to exclude patients with a clear diagnosis of neuropathy, some of the patients might have presented a latent form of neuropathy as a result of the side effects of their anti-reject therapy with calcineurin inhibitors [14]. Therefore, it is ultimately difficult to establish to what extent the use of this class of medications affected our results, and what proportion of the effect size is due to the side effects of the medication.

Even though the exploratory nature of this investigation limits the clinical implications that can be drawn from our findings, two main conclusions can be inferred.

The results highlighted significant differences between groups in many COP measures, indicating the static balance performance was generally lower in KTRs compared to HA, which corroborates our research hypothesis. A lower static balance performance might be of clinical relevance when discriminating the risk of falling status in populations with augmented risk of falling [51]. Such increased risk has already been shown in HD patients [59] and since KTRs present with a similar health profile, despite the improved quality of life associated with renal transplantation, one could speculate that these patients may remain at higher risk of falling compared to the general population. Future research should seek to determine whether the risk of falling in KTRs is higher than in the general population, and whether a poor balance is predictive of falls in KTRs.

In conclusion, our findings suggest that a proprioception deficit is the main component involved in the lower static balance performance of KTRs, as highlighted by the higher postural sway during the EC condition.

4.2 Characterization of Kidney Transplant Recipients

The aim of the second part on the main investigation was to characterised explore the falls' risk profile of KTRs population and evaluate the association of objective measures of postural balance and strength performance outcome with the history of falls of those patients. For this reason, we decided to add strength performances to the balance assessments, comparing fallers and non-fallers KTRs.

We then hypothesized, starting from the first protocol results, that the prevalence of falls in KTRs would be higher than in the non-uremic population. In addition, we hypothesized that a lower performance in postural balance and muscle strength will be associated with history of falls. As shown at table 2, data seemed to confirm the first hypothesis since a prevalence of falls equal to 33.9%, an estimate considerably higher than in age-matched non-uremic populations [60-62]. Our findings, on

falling behavior, suggest that the prevalence of falls in KTRs patients is 1.6 to 4.3 times greater than in age-matched healthy people [60,62] compared to the results from population-based studies conducted on non-uremic individuals, which is indicative of an increased risk of falling.
In the context of ESRD, the falls' risk profile of the participants seemed to be analogous with the risk profile of patients on dialysis, since a 26.7% to 55% of these patients have been reported to have experienced at least one fall per-year [63,64], and have also been acknowledged as a group at high-risk of falling [65]. This finding raises the question that if, despite the overall improvement in quality of life associated with transplantation [17], those patients who had a significant history of dialysis treatment may remain at high risk of falls even after receiving the KT.
Interestingly, although our sample was considerably of younger age, we found a higher prevalence of falls than Kasbia et al. study [33], which reported that only the 21% of KTRs (mean age = 69.4 years) recalled falling at least once in the previous 12 months. Despite older age is an well-established risk factor for falls, in the context of ESRD, the relationship between the occurrence of adverse geriatric outcomes, such as falls, and age is often confounded by the presence of chronic inflammation, oxidative stress, and consequent muscle wasting, all of which contribute to a model of premature aging [66].
The clinical implications of the high prevalence of falls emerging from this protocol are concerning in light of the increased risk of facture observed in KTRs patients [29]. Previous research has already shown that a history of falls with hospitalization is associated with a two-fold higher risk of fractures in this population [67]. In addition to traditional risk factors for impaired postural control, such as muscle wasting [20], KTRs patients may have an additional critical point, the side effects of the immunosuppressive therapy [68]. Indeed, patients living with a KT are prescribed with various immunosuppressive agents, as part of the anti-reject therapy, and common complications associated with this unavoidable treatment comprise neurological disorders, such as tremors and peripheral neuropathy [69], which could lead to impaired postural balance [20]. Another interesting observation is that even though fallers and non-fallers did not differ in terms of immunosuppressive therapy in our protocol, it is still possible that the use of calcineurin-inhibitors in particular may be responsible for at least a degree of peripheral nerve dysfunction in our patients [68], as 93.1% and 8.6% of the participants were prescribed with tacrolimus and ciclosporin respectively.
The protocol findings on muscle strength also highlighted an overall trend of poorer lower limb strength in fallers compared to non-fallers. However, only Right Handgrip and IK-ankle-strength were significantly different between the two groups (respectively $p=0.022$ and $p= 0.024$). This observation is interesting in light of the perceived etiology of falling reported by the investigation participants: 50% of fallers described either tripping or slipping as the main cause of falls, which

reflects indirectly how poor ankle dorsiflexion mobility and strength may be implicated in the etiology of this kind of fall accidents. In addition, only 5% of fallers reported thigh muscles' weakness as perceived cause of the falls experienced, which also suggests that ankle dorsiflexion strength may be a better predictor of falling behavior compared to quadriceps strength in this population. Nevertheless, it should be acknowledged that, due to some limitations of this investigation, a cautious interpretation of the protocol findings is required. Indeed the risk of experiencing falls is determined by a myriad of biological, environmental, behavioural, and socio-economic factors [70]. Therefore, due to the relatively small sample size, it would be impossible to adjust the analysis by controlling for all of these confounding factors.

The statistical analysis did not detect any differences between "fallers" and "non-fallers" in many of the possible confounding factors, such as age, physical activity levels, diabetic status, cognitive status (MMSE scores), and prescribed medications. In addition, the classification of fallers and non-fallers was based on self-reported information relative to the previous one year, which is subject to a recall bias [71,72] that may have determined misclassification in the group allocation to some extent.

Concluding, the high risk of falls emerging from this protocol is of clinical concern because patients living with a KT have an increased risk of fracture, and accidental falls may worsen quality of life and the health burden of these patients, who tend to have low functional status and high frailty rates already.

Postural balance and muscle strength are exercise-modifiable skills as shown by previous research. Therefore, exercise-based or multifactorial interventions aimed to decrease the occurrence of falls, and fall-related injuries, in this population should include balance and strength training.

4.3 Exercise in Kidney Transplant Recipients

As introduced postural balance and muscle strength are exercise-modifiable skills, even more if the physical activity levels are low as seems to be in KTRs patients compared to healthy population (Table 1). Indeed, GPAQ is a self-report questionnaire so could report false levels of activity, considering story and status of KTRs. For example, many KTRs decided to join the experimentation because nobody said they could train or what they had to avoid after surgery and this is the reason why many of them became sedentary. For these motivations the last project aim is to involve patients in an adapted, personalized training program to improve quality of life, strength and balance. Despite the little number of training sessions (ten) and the training period (five weeks), due to the fact that patients come from all Italy Regions and stayed in Padua only for follow-up visits, improvements in all field tests were statistically significant. In particular, in 30 seconds chair stand test and 8 foot up and go test, which respectively assesses lower limb strength and dynamic balance (agility), improvements are noteworthy. Indeed, even if the sample was young (mean age 50.41) the mean score of 30 seconds chair stand test results below average of elderly population aged 85-89 years, while after only ten training sessions become like elderly aged 75-79, ten years less [47]. Instead, 8 foot up and go test mean score results in average with elderly population aged 75-79 years, and after training with elderly aged 70-74 [47].

These results corroborated the hypothesis that adapted physical activity should be prescribed as preventive therapy in kidney transplants recipients, because despite the improvements in quality of life derived from the transplantation the risk of falls still remain high and strength level still remain low, increasing the risk of fracture, and accidental falls which may worsen quality of life and the health burden of these patients. The intensity and amount of exercise might vary daily due to fluctuating health conditions, and should be individually modulated. Moreover, no injuries were report during all activities, so one to one training modality seems to be indicated in this kind of patients. About that, a one to one approach could guarantee a safe and personalized exercise training, to improve clinical best-practice. Finally, the maintenance of the effects of exercise should be controlled with a follow-up assessment. This evaluation is already scheduled (6 months after the training programme) but data were not complete. Preliminary data seems to be promising because seven of thirty-one kidney transplant recipients evaluated remain active after the training programme.

5. CONCLUSION

The overall aim of this project was to characterized KTRs from the functional point of view. The first part of this project proves that KTRs static balance in single and dual-task conditions is worse than healthy adults matched per age, weight and height, which are the fundamental factors that influenced balance; and above all our findings suggest that a proprioception impairment is the main component involved in the lower static balance performance of KTRs. Checked these, the second project step verified the hypothesis that KTRs have a high prevalence of falls, which is higher than in age-matched non-uremic populations. Moreover, the low level of strength in KTRs, emerging from this protocol, corroborated the idea that transplantation improves quality of life, but not so much to decrease the risk of falls and the consequences. Finally, an exercise prescription is concretely necessary for those patients, to avoid falls and to improve quality of life and personal autonomy. In fact, our protocol increases the physical fitness of all patients, but future researches have to clarify what kind of exercise provides the best results and which is the safest. Future research perspectives based on the findings of this PhD project have to check other training modalities such as training group, only balance or strength training to attest if one induces a better improvement in quality of life and fall risk. Additionally, to corroborate training importance and power a follow-up test session after three and six months after training period should be assessed.

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