Assessment of Cardiovascular Risk in Special Patient Populations

Ph.D. dissertation

Dora Praksch, M.D.

Clinical Medicine

Experimental Cardiology

Program leader:

Prof. Kalman Toth, M.D., Sc.D.

Project leaders:

Eszter Szabados, M.D., Ph.D.

Peter Szakaly, M.D., Ph.D.

1st Department of Medicine, Medical School, University of Pécs

Hungary

2019

Table of contents

List of abbreviations

ACE	angiotensin-converting enzyme	GFR	glomerular filtration rate
ADP	adenosine diphosphate	Hct	hematocrit
AGE	advanced glycation end products	HDL	high density lipoprotein
AHA	American Heart Association	IGF-1	Insulin-like growth factor 1
ASA	acetylsalicylic acid	LDL	low density lipoprotein
AZA	Azathioprine	MET	metabolic equivalent
BB	beta blocker	MMF	Mycophenolate-mofetil
BMI	body mass index	PA	physical activity
BP	blood pressure	PAK	Pancreas after Kidney
CAN	chronic allograft nephropathy	PPP	platelet poor plasma
CHD	coronary heart disease	PRED	Prednisolone
CIT	cold ischemic time	PRP	platelet rich plasma
CKD	chronic kidney disease	PV	plasma viscosity
CN	carbamide nitrogen	RBC	red blood cell
COX	cyclooxygenase	SCORE	Systemic Coronary Risk Evaluation
CV	cardiovascular	SD	standard deviation
CVD	cardiovascular disease	SF-36	36-Item Short Form Survey
CSA	Cyclosporin A	SPK	Simultaneous Pancreas Kidney
DGF	delayed graft function	SRAR	Steroid resistant acute rejection
DM	diabetes mellitus	$SS_{1/2}$	shear stress required for half of EI_{max}
e.g	exempli gratia	TAC	Tacrolimus
ECG	electrocardiography	TC	total cholesterol
EF	ejection fraction	USRDS	United States Renal Data System
EI_{max}	maximal elongation index	VO_{2max}	peak maximal oxygen consumption
ESC	European Society of Cardiology	WBV	whole blood viscosity
ESRD	end stage renal disease	WHO	World Health Organization

Introduction

Definition of cardiovascular prevention

Cardiovascular disease (CVD) prevention is defined as an organized process at population and individual levels aimed at eradicating or minimizing health damage resulting from CVDs and their related complications (1).

Geoffrey Rose determined two main prevention strategies. The population-level strategy was aimed at reducing the incidence of cardiovascular (CV) risk factors via long-term environmental and lifestyle changes targeting the population. This set of actions included the restriction of smoking, the reduction of salt-, and the regulation of trans-fatty acid intake, the reduction of CV medication prices, and the improvement of social and economic status of the population. This approach has a large potential for the population as a whole. On the other hand, the disadvantages are also meaningful, such as the "prevention paradox" which means that there is a small benefit for the individual but more considerable benefit for the population. Regarding the population strategy, an important issue is the insufficient level of motivation of both the subject and the physician (2). The high-risk strategy targeting high-risk patients aims to manage existing CV risk factors with medication therapy, psychosocial care and dietary consultation on the individual level. This is the conventional medical approach to CVD prevention. Advantages include interventions tailored to the individual, resulting in an improved level of motivation of both the subject and the physician. However, it does have disadvantages: it is not radical, it is not cost effective, and the potential for the population is limited. Nonetheless, the efficiency of the high-risk strategy has remained undebatable at the individual level (2).

Three levels of CV prevention can be distinguished (Figure 1). Primordial prevention encompasses the prevention of the development of CV risk factors via health preservation with promoting a physically active lifestyle, adequate healthy nutrition, maintaining the ideal bodyweight and facilitating and promoting the avoidance of smoking. Primary prevention is aimed at preventing the occurrence of the first cardiovascular event by treating CV risk factors with hypertension therapy, hyperlipidemia therapy, diabetes control, quitting smoking and lifestyle modification. Secondary prevention means preventing

recurrent cardiovascular events with evidence-based medicine and the above mentioned risk factor management strategies, life-long lifestyle change and the combination of medication and non-medication therapy.

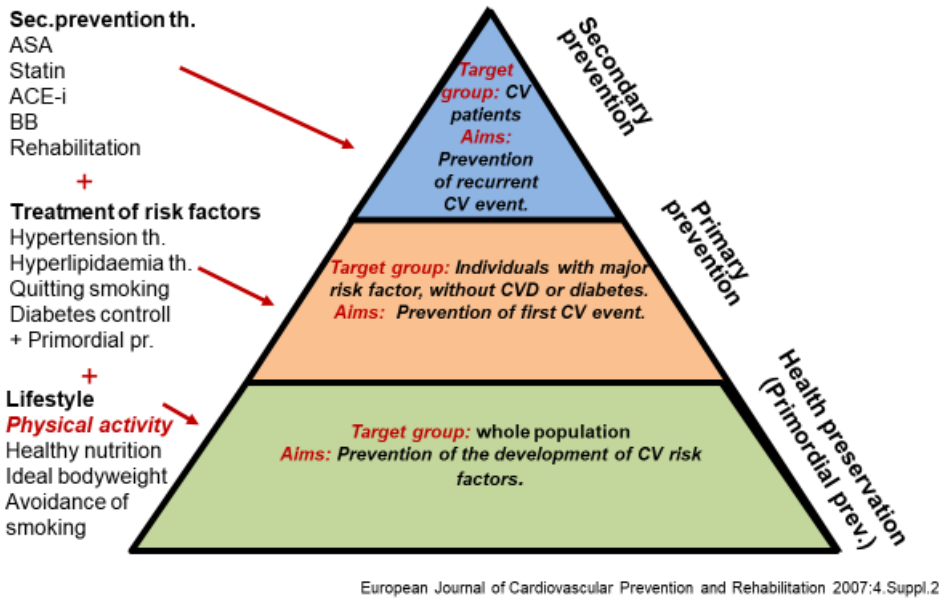


Figure 1. Levels of CV prevention

Population characteristics of the present work

Regarding cardiovascular diseases, the selected populations are interesting and special. Thus, CV prevention and health promotion, especially for elderly women, simultaneous pancreas kidney- and kidney alone transplanted recipients is an important and challenging task.

Elderly women with CV risk

It has been well established that aging predisposes senior populations to developing CVD and other multimorbid conditions which could fundamentally modify the management of CVD (3). Due to improved public health and achievements in areas of general medical care and prevention, the aging population has become a worldwide phenomenon and a global issue to tackle. Sex (biological) and gender (sociocultural) differences are dominant contributors to the clinical diversity of the older age spectrum, particularly regarding CVD and its outcomes (4). While CVD is more likely to develop with increasing age in both sexes, in several countries more women die due to CV illnesses than men (1,4).

In European countries, 42% of women and 38% of men die due to a disease of CV origin under 75 years of age (1). The occurrence of coronary heart disease (CHD) increases above 60 years of age in women, furthermore, one in three women has proof of developing CHD after 65 years of age (5). These epidemiological data contradict the old hypothesis that men primarily at risk of CVD. Thus, CVD prevention is essential with regard to maintaining the health of every woman, even moderate management could have a considerable impact (6).

In European countries the SCORE (Systemic Coronary Risk Evaluation) chart is routinely used, which predicts the 10-year risk of the first fatal atherosclerotic event (myocardial infarction, stroke or peripheral arterial disease) using age, gender, smoking habits, systolic blood pressure, and total cholesterol level (1,7). Stratification in the SCORE chart shows geographical variabilities within the European countries, thus different SCORE systems have been established for low-risk (e.g. Austria, Belgium, Denmark, Finland, France, Germany) and high-risk (e.g. Hungary, Poland, Slovakia) countries. Very-high-risk countries (e.g. Bulgaria, Russian Federation, Ukraine) show levels of risk that are more than double that of low-risk countries (1).

On the other hand, there are additional factors needed to assess total CVD risk. According to the ESC prevention guideline, four risk groups can be established. Patients at very high risk have documented CVD including previous cardiovascular and/or cerebrovascular event, and/or aortic aneurysm and/or peripheral arterial disease; diabetes mellitus with target organ damage or with a major risk factor; severe chronic kidney disease (CKD) (GFR <30ml/perc/1.73m^2) or a calculated SCORE ≥10%. High-risk patients are those with one markedly elevated risk factor such as cholesterol >8 mmol/L or BP ≥180/110 mmHg or diabetes-mellitus (with the exception of young people with type 1 DM) or moderate CKD (GFR 30–59 mL/min/1.73 m2) or a calculated SCORE ≥5% and <10%. Patients have moderate risk with SCORE ≥1 and <5%, while low risk subjects have a SCORE <1% (1).

After risk stratification there are general goals to be achieved such as cessation of smoking, lifestyle changes (adequate nutrition and physical activity), ideal body mass index (20-25kg/m^2), waist circumference (men <94cm, women <80cm), and blood pressure <140/90 mmHg. According to ESC guidelines for CV prevention there are no strong evidence based recommendations for HDL-C and triglyceride levels, but > 1 mmol/l HDL-C for men and > 1.2 mmol/l for women seems to be beneficial

and triglyceride level <1.7 mmol/l should be achieved in both gender. Very-high-risk patients are recommended to have LDL-C levels < 1.8mmol/l, or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L. High-risk subjects should not exceed LDL-C levels higher than 2.6 mmol/l, or a reduction of at least 50% if the baseline is between 2.6 and 5.2 mmol/L. Low- to moderate-risk persons should be advised to maintain their low- to moderate-risk status and LDL-C level < 3.0mmol/l is recommended (1).

It has been well proved that physical activity has a pivotal role in health preservation as well as in primary and secondary prevention of cardiovascular diseases (1,8). When we organize physical training for elderly female patients it is important to consider that the program should be enjoyable, achievable, should be designed in a way that there is no risk of potential injury or exacerbation of comorbidities. These specific programs can help to manage the physical requirements of daily living and recreational activities (5). Although physical inactivity is more likely to occur among women, it is well-known that domestic activities (child care, housekeeping) are not taken into account when measuring physical activity (PA), which may explain the detected differences (3,5). Previous studies have shown, that exercise capacity is an independent predictor of all-cause mortality and cardiac mortality in asymptomatic women (9). According to the "Women Take Heart Project" there was a threefold increased risk of mortality among women who were unable to implement 5 metabolic equivalents (MET) on the treadmill test (9). Physical training should be distributed in daily bouts and should be tailored to the individual's cardiac risk profile. International studies have reported that moderately active (1-3, 49hours/week) and active (≥3,5hours/week) women had 43% and 58% lower risk of coronary artery disease (CHD) compared to women leading a sedentary lifestyle (<1hour/week) (10).

Simultaneous Pancreas Kidney (SPK) transplanted patients

Type 1 diabetes mellitus is one of the most common chronic diseases among children, in which very little or no insulin is produced by the pancreas. The number of children younger than 15 years who will be diagnosed with DM is rising rapidly. According to international surveys, the incidence of type 1 DM will have risen by 71% in children younger than 15 years and will have doubled in children younger than 5 years of age by 2020 (11). This childhood disease fundamentally determines life expectancy and

without appropriate management, it can result in severe long-term macrovascular complications including the cardiovascular system. Furthermore, type 1 DM can also lead to microvascular disorders including nephropathy, neuropathy and retinopathy (12). Mostly hyperglycemia and advanced glycation end products (AGE) are responsible for these complications. Although it has been well proved that intensified insulin therapy can slow the progression of microvascular complications, exogenous insulin intake has not been able to sustain normoglycemia as efficiently as a well-functioning pancreas (12). Diabetic nephropathy, which is classically characterized by the presence of proteinuria, can lead to end-stage renal disease (ESRD), a life threatening complication of type 1 DM (13). At present, ESRD patients with diabetes have three therapeutic alternatives. Initially, additional insulin therapy and peritoneal or hemodialysis are required. Unfortunately, the 21% 5-year survival rate seems quite low. As a second option, patients can undergo kidney alone transplant with supplemental insulin administration. This one is a favorable option, 5-year survival rates are 70-85%. Simultaneous pancreas-kidney (SPK) or pancreas after kidney (PAK) transplantation could be the best therapeutic option for ESRD patients with type 1 DM with 85% survival in 5 years (Figure 2) (14,15). Vascularized pancreas transplantation reestablishes normoglycemia while the freedom from insulin therapy becomes achievable (12,14,16). Although SPK transplantation involves increased operative and immunological risks, and it is a more expensive intervention than kidney transplant alone, the benefits of this surgery are invaluable (14,17). Transplanted patients have better life expectancy, are protected from recurrent diabetic nephropathy, secondary diabetic complications can be stabilized or improved, they may become independent from insulin independence and dietary restrictions may be significantly reduced (17,18).

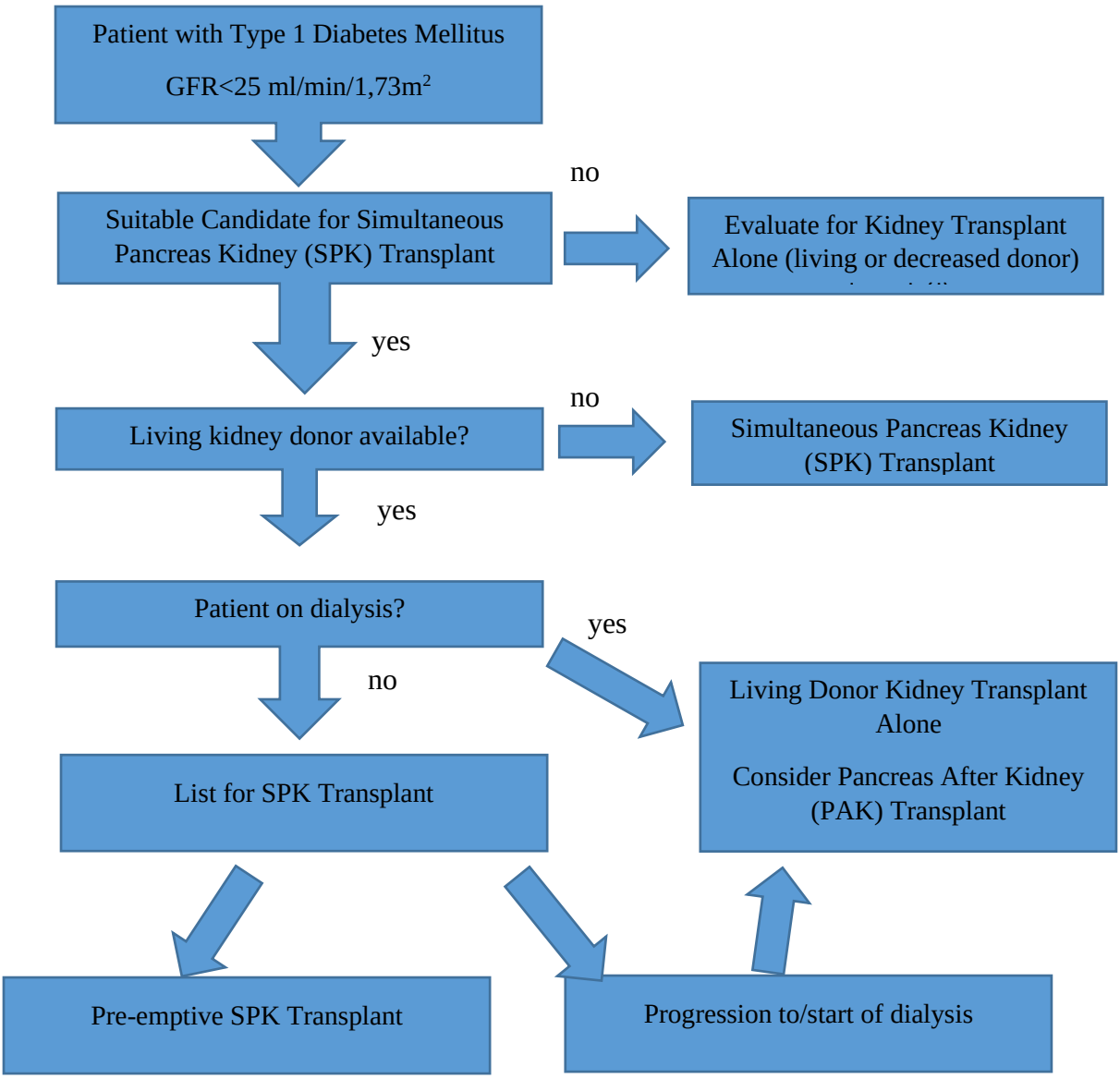


Figure 2. Therapeutic algorythm for patients with diabetic nephropathy (15).

Cardiovascular diseases are the leading cause of mortality in diabetic as well as in dialyzed patients (17,18). Despite the better CV outcome among SPK recipients, CVD has remained the most common cause of mortality (19), meaning that a significant number of patients die with a functioning graft (17,18,19). SPK transplantation normalizes glucose homeostasis, which can reduce microvascular complications such as nephropathy and neuropathy in type 1 diabetes (19). Nevertheless, SPK transplantation itself cannot prevent eventual CVD progression with definitive CVD risk factors (19). Both conventional CV risk factors (1) as well as non-traditional risk factors in chronic kidney disease such as microalbuminuria, anemia, uremic malnutrition, hyperuricemia, vitamin D metabolism,

secondary hyperparathyroidism, oxidative stress and so-called AGEs are responsible for cardiovascular complications (20). Immunosuppressive agents (steroids, cyclosporin, tacrolimus) also account for the development of CVDs in transplant recipients (21). Based on the high cardiovascular mortality among SPK patients, it is highly recommended to follow CV prevention guidelines (1,8). In addition to emphasizing proper lifestyle management (Mediterranean diet, regular physical activity, maintained metabolic parameters) antiplatelet therapy, which has an important role in the prevention of cardio- and cerebrovascular events (1), is also a well-known therapeutic option for the transplanted population (22).

Kidney transplant recipients

There are several factors involved in the progression of chronic kidney disease such as diabetes mellitus, hypertension, dyslipidemia and smoking (23). Despite the improvement of renal replacement treatments including hemodialysis and peritoneal dialysis, kidney transplantation is the most widely known therapeutic approach for patients with end-stage renal disease (24). An international study investigating survival rates after 1,5 and 10 years among kidney transplant recipients and hemodialysis patients revealed significantly higher survival rates among the transplanted population: 95.2, 88.0 and 78.8% vs. 90.6, 62.7 and 39.8% (27).

The first Hungarian kidney transplantation was carried out by Professor András Németh in 1962. Unfortunately, the patient survived only 79 days after surgery. It was only in the 1970s, when successful and safely performed kidney transplantations began in Hungary. Since then improvement of both surgical techniques and immunosuppressive therapies, the additional examinations facilitating surgical success (e.g. immunological typing) and the secure, regulated legal and ethical background of the transplantation procedure has resulted in a better survival rate and better quality of life for the recipients (26).

Today, the main danger is not acute graft rejection but the other post-transplant complications. Besides infections, malignant disorders, and bone disease, the leading cause of post-transplant complications and mortality are CV diseases (27). The improvement of long-term outcomes are based on the prevention of the above-mentioned diseases.

Association between hemorheology and CV risk factors

Well-known, classic cardiovascular risk factors were identified decades ago including male sex, smoking, advanced age, elevated cholesterol level, hypertension, diabetes mellitus, low HDL cholesterol level, elevated triglyceride level, physical inactivity, obesity, psychosocial stress, and positive family history (28). Years later, international trials discovered further risk factors such as impaired hemorheological parameters, infections, chronic inflammation, microalbuminuria, decreased GFR and enhanced oxidative stress. Impaired hemorheological parameters including enhanced fibrinogen level, whole blood viscosity (WBV), and plasma viscosity (PV), red blood cell (RBC) aggregation, and reduced RBC deformability are suggested as further cardio-, and cerebrovascular risk factors (29,30).

Hematocrit (Hct)*:*

Hematocrit, the percentage of red blood cells in whole blood, is routinely checked in everyday clinical practice and it affects all the other hemorheological parameters. Elevated Hct results in higher PV and WBV and has been determined as a CV risk factor (31).

Whole blood and plasma viscosity

Blood viscosity is the intrinsic friction of the circulating blood. Whole blood viscosity (WBV) is influenced by the hematocrit, plasma viscosity and red blood cell aggregation at low shear rates, although at high shear rates deformability becomes determinative. Elevated WBV has also been established as a CV risk factor (31). Plasma viscosity is defined by plasma proteins involving fibrinogen, certain globulins, and the triglyceride level (32).

Red blood cell aggregation

Under low shear conditions or in stasis, red blood cell aggregation develops reversibly. This process is characterized by hematocrit, the concentration of plasma macromolecules such as fibrinogen, as well as red blood cell aggregability (an intrinsic cell characteristic). It has three different phases: 1) without shear forces rouleaux formation (cells in a row like a stack of coins) develops in few minutes, then 3 dimensional aggregates appear, 2) the aggregates starts to sink with a permanent velocity, 3) sinking

slows down and then finally, stops. Increased red blood cell aggregation has been shown as a cardiovascular risk factor (33).

Red blood cell deformability

Red blood cell deformability is an essential ability of the cells to pass through the capillaries that are narrower than the cell itself. Deformability is defined by membrane viscoelastic properties, the internal viscosity of the cell, surface-volume ratio, and cell morphology (34). The impairment of RBC deformability damages tissue oxygenation, that may first manifest in the myocardium, consequently, reduced deformability has also been identified as a cardiovascular risk factor (35).

Platelet aggregation

Platelets have a key role in blood coagulation. As part of the cascade, their adhesion, activation and subsequent aggregation lead to arterial thrombus formation. Increased platelet count and increased reactivity influence both blood flow properties and microcirculation. The onset of these processes is the adhesion of platelets to the damaged endothelial wall, where free collagen releases ADP, epinephrine, serotonin and TXA2 from platelets. These substrates maintain and enhance platelet aggregation. Platelet-rich thrombus formation plays an important role in the development of atherosclerotic plaque formation and its progression (35).

Acetylsalicylic acid (ASA) is a widely used antiplatelet agent in both primary and secondary prevention of cardio-, and cerebrovascular events (1,36). The clinical efficacy of ASA therapy can be measured by how effective it is at inhibiting platelet aggregation. There are various methods that can be used in clinical practice as well as in laboratory settings to measure the effectiveness of antiplatelet therapy.

Focus and aim of the studies

Impact of home- and center- based physical training program on cardio-metabolic health and IGF-1 level in elderly women

Physically active lifestyle is essential for healthy aging and it plays a pivotal role in primary and secondary prevention of cardiovascular disease, and is associated with reduced prevalence of chronic diseases (1). Menopause is a critical state in the life of women generally accompanied by dysregulation in cardio-metabolic profile which may be modulated by an increase in physical activity level. Maintaining the adherence to a physically active lifestyle in the elderly population, especially among elderly women is challenging (37). Senior women who are physically active reported lower risks of functional limitations and a higher health-related quality of life (38). Moreover, regular PA reduces the prevalence of falls, frailty and sarcopenia among elderly women (39,40).

Data in the literature concerning the effects of physical activity on lipid and IGF-1 levels are controversial in postmenopausal women.

The aim of the present study was to determine the combined effects of a home-based walking program with the target of achieving 10 000 steps daily and a center- based aerobic exercise training on functional capacity, metabolic-, hemorheological parameters, IGF-1 level, subjective physical functioning as well as general and emotional well-being among elderly female patients.

Acetylsalicylic acid resistance after simultaneous pancreas-kidney transplantation

Simultaneous pancreas kidney transplantation is the best-known therapeutic approach for patients with type 1 diabetes (14). Due to the development of modern surgical techniques and immunosuppression, patient and graft survival has improved significantly in recent decades. Furthermore, a better quality of life has been achieved as a result of SPK transplantation (26). The leading cause of mortality after SPK transplantation has cardiovascular origin, which precedes infections, urological complications and malignancies as well (27). It is important to follow cardiovascular prevention guidelines with regard to the high CV mortality of SPK transplanted recipients (1,8). Beyond maintaining a proper lifestyle, a daily low dose (100mg) acetylsalicylic acid therapy could be recommended for these patients (1,8).

Although ASA is an extensively applied antiplatelet agent in the prevention of cardiovascular diseases (22), Aspirin resistance, non-responsiveness may occur in certain cases (41). The exact rate of ASA resistance in SPK transplanted population has not clearly been identified.

Our study aimed to determine Aspirin resistance among SPK patients and to specify the possible causes of the resistance.

Assessment of cardiovascular mortality in single center cohort analysis of 593 patients after Kidney Transplantation

Kidney transplantation is the best therapeutic option for patients with end stage renal failure, surpassing dialysis in terms of health-related quality of life and longer survival (42). Systematic data collection could be an important tool to improve the quality of patient care, integrate practice patterns and to help compare outcomes across different types of recipients. Since the first kidney transplantation performed at our Clinic in 1993, registry and data collection have not begun until now.

The present study aimed to describe kidney transplant characteristics, to estimate long-term graft survival and mortality data as well as to measure prognostic factors known to have potential effects on graft survival for the past 25 years. Determining the occurrence of CVD and CV related mortality among our recipients was also an essential goal of the study.

Impact of home- and center- based physical training program on cardio-metabolic health and IGF-1 level in elderly women

Introduction

Regular physical activity (PA) is widely recommended throughout the human lifespan to maintain health and physical fitness (1,43,44). Menopause is a critical state in the life of women generally accompanied by dysregulation in the cardio-metabolic profile resulted from critical changes in body composition such as excessive accumulation of fat at visceral level. Increase of physical activity level could modulate these negative changes both in body composition and cardio-metabolic profile. Elderly women who are physically active possess less risk of functional limitations and a higher health-related quality of life (45,46). Furthermore, osteoporosis, sarcopenia, risk of falls (40,41), dementia, depression, loss in cognitive function (40), and the risk of some type of cancers can be reduced by regular PA (47). Part of the cardio-metabolic health including physical performance, systolic/diastolic blood pressure, resting heart rate, fasting levels of plasma glucose and insulin level, abdominal visceral adipose tissue, weight, BMI, sedentary behavior are also positively influenced by PA in elderly women (44,40,49). However its effect on certain metabolic parameters, such as lipid levels are not unequivocal. Some investigations have proved that PA favorably modifies lipid parameters among elderly women (48,50), while others failed to demonstrate significant effect (49,51,52,53,54).

Insulin-like growth factor 1 (IGF-1) is a basic peptide composed of 70 amino acids, which is thought to play a central role in metabolism (55), cancer development (56), CV diseases (57) and aging (58). In adults high levels of IGF-1 are associated with increased cancer risk (59) and CV diseases. A population-based study examining the association of different IGF-1 levels with mortality, cardiovascular disease, and cancer in the elderly has found a U-shaped relationship between IGF-1 level and fatal CV diseases, which means that both high and low levels of IGF-1 were associated with increased risk of CV mortality. Significant associations of serum IGF-1 with fatal or non-fatal cancer were not observed in this elderly population (60). Serum IGF-1 level is declining with age (61) and postmenopausal women generally display even lower levels of IGF-1 compared to elderly men (58) which may in part explains increased CV mortality in postmenopausal women. Low levels of IGF-1 are associated with osteoporosis (62), disability (63), neurodegenerative illnesses such as Alzheimer dementia and brain atrophy (64) and

increased risk of CVD (65). The anti-inflammatory and anti-oxidant effects of higher IGF-1 level on blood vessels have also been investigated (66). The development of impaired glucose tolerance and type 2 diabetes is also more expected in patients with low IGF-1 levels (61,67). Regular PA has several health preserving effects and it has been examined previously how it may modulate IGF-1 level. Some investigations have demonstrated positive effect of especially resistance training on IGF-1 levels (68,69,70,71), while aerobic exercise training had no considerable effect on IGF-1 concentrations (70,72,73).

Altered hemorheological parameters including elevated hematocrit (Hct), whole blood viscosity (WBV), plasma viscosity (PV), and elevated fibrinogen levels have identified as primary CV risk factors (29) and associated with the early stage of atherogenic processes (28). Although the beneficial effects of regular PA on rheological parameters in healthy individuals have revealed (87), available data among female patients with CV risk is relatively scarce.

Elderly women usually do not report only physical but also psychological and social changes during menopause that affect their global and CV health (74). General psychological-, and emotional well-being, and optimism are related to health promoting behaviors including healthy eating and lifestyle habits and self-care, supporting CV and overall health of elderly patients (75,76,77).

The aim of our study was to investigate whether 12 weeks of an applied home- and center- based physical training program is sufficient to change functional capacity, some important cardio-metabolic, hemorheological parameters, IGF-1 level and certain psychological items of elderly female patients with moderate to high CV risk.

Methods

Ethics approval and consent to participate

The investigation was approved by the Regional Ethics Committee of the University of Pécs (No. 5829) and was conducted in accordance with the ethical principles stated in the Declaration of Helsinki. A written informed consent was obtained from all subjects.

Patients

Sixty female non-smoker patients with moderate to high CV risk (mean age: 67.4±5 years) were enrolled into our study (Table1).

Table 1. Characteristics of the study population, n=60

population characteristic	training group	control group	p value
hypertension	29 (96%)	27 (90%)	0.30
diabetes mellitus	10 (33%)	9 (30%)	0.78
dyslipidemia	19 (63%)	15 (50%)	0.29
chronic kidney disease	2 (3.3%)	0 (0%)	0.15

Patients were recruited either from primary care or from internal medicine and cardiology outpatient care by different physicians. They voluntarily agreed to participate in the study and then were randomly assigned either to the CV preventive training program or to the control group. Participants in both groups met the following inclusion criteria: ejection fraction (EF) ≥55% and metabolic equivalent (MET) ≥5. Exclusion criteria were the following: previous CV events, heart failure, inducible myocardial ischemia and arrhythmias on an exercise stress test. Medication and drug therapy were not modified during the study in either groups (Table 2). It was also suggested to the control group not to change their usual physical activity level in the next 12 weeks.

Table 2. Medication therapy during the 12 week training program, n=60.

medication	training group	control group	p value
statins	19 (63%)	15 (50%)	0.29
antiplatelet drugs	9 (30%)	7 (23%)	0.56
β-blocker	15 (50%)	14 (46%)	0.79
RAAS inhibitor	20 (66%)	14 (46%)	0.12
calcium channel blocker	8 (26%)	9 (30%)	0.77
antidiabetic drugs	10 (33%)	9 (30%)	0.78
diuretics	12 (40%)	8 (26%)	0.27

RAAS renin–angiotensin–aldosterone system

Study design

At baseline patients were examined using electrocardiography (ECG) and echocardiography to exclude unknown cardiac problems that could limit their ability to exercise. Then they were tested on treadmill according to the Bruce protocol to assess functional capacity. The intensity of the training was defined as 50-70% of the peak maximal oxygen consumption (VO2max), starting at 50% and gradually increased to 70%. Metabolic laboratory (fasting glucose, hemoglobin A1c (HgbA1c), total cholesterol (TC), low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglyceride (TG)), and IGF-1, as well as hemorheological (hematocrit (Hct), fibrinogen, whole blood viscosity (WBV), plasma viscosity (PV), red blood cell (RBC) aggregation, and deformability) measurements were performed. Three items (physical functionality, general health, emotional well-being) of SF-36 (36-Item Short Form Survey) Questionnaire were carried out. Upon reaching week 12, all tests were repeated, with the exception of echocardiography.

Home-based walking program

A daily walking program was implemented, which could be performed in a 10-15 minute workout and could be completed by the patients solely on their own. For appropriate estimation of the daily walking program our patients were asked to wear a personalized activity tracker on their wrist (78) (Figure 1). These trackers did not only registered the daily footsteps but also motivated our elderly women to achieve the daily activity goal of 10,000 footsteps based on health expert's recommendation (79,80).

Figure 1. Personalized activity tracker. https://www.trekkinn.com/f/13587/135876276/polar-loop-2.jpg

Aerobic exercise training program

The aerobic exercise training program began with warm-up exercises (breathing exercises and stretching of the large joints) for 5-10 minutes three times weekly. In the second phase, patients participated in a moderate-intensity training. The training involved static (exercises with a medicine ball, half-squats, toe raises and body flexions) and dynamic (walking, jogging, ball games e.g., basketball, football) exercise elements. The intensity of the training was defined as 50-70% of the peak maximal oxygen consumption (VO_2max), starting at 50% and gradually increased to 70%. The aerobic phase lasted 35-40 minutes. Finally, relaxation exercises were performed (stretching and breathing exercises) for 10 minutes. The exercise training was supervised by a cardiologist and conducted by a physiotherapist. Pulse and blood pressure were taken prior to, during (20 minutes after starting the training) and at the end of the training period.

Blood collecting

At baseline and after 12 weeks, blood samples were obtained from the antecubital vein in both groups. The blood was collected into one clot activator-coated and gel-containing (5ml), one potassium EDTA-coated (3ml) and one sodium fluoride and potassium oxalate-coated (2 ml) Vacutainer tubes were sent for laboratory measurements and one potassium EDTA-coated (3ml) Vacutainer tube was sent for IGF-1 measurements and two lithium heparin-coated (12 ml) Vacutainer tubes were used for hemorheological measurements.

IGF-1measurements

IGF-1 levels were measured using Human IGF-1 Quantikine ELISA Kit (R&D Systems; Cat. No.: RD-DG100). EDTA-plasma samples were collected from patients at the beginning and after the 12^{th} week, the samples were stored at -74°C until performing the assay. The assay employs a quantitative sandwich immunoassay technique. The IGF-1 assay protocol was carried out according to the manufacturer's instructions.

Hemorheological measurements

Hematocrit was measured by a micro hematocrit centrifuge (Haemofuge Heraeus Instrument, Germany) at room temperature, at 12000 g for 3 minutes. Whole blood viscosity and plasma viscosity were measured with Hevimet 40 capillary viscometer (Hemorex Ltd., Budapest, Hungary) at a shear rate of 90 s-1. Plasma was obtained by centrifugation of blood samples for 10 minutes at 1500 g at 37 °C.

Red blood cell aggregation was measured using a LORCA (Laser assisted Optical Rotational Cell Analyzer; R&R Mechatronics, Hoorn, The Netherlands) aggregometer, based on syllectometry. LORCA detects the laser backscattering from the aggregating blood, measured at 37°C, oxygenated blood was used in all performed measurements. The threshold shear rate (γ) indicates the minimal shear rate, which is compulsory for the complete disaggregation of RBCs (higher value means stronger aggregation). Other affective parameters in order to compare the samples, the aggregation index (AI, referring to the proportion of aggregation – higher value means larger aggregation), and t1/2 (referring to the swiftness of aggregation – lower value means faster aggregation) were identified.

Red blood cell deformability was measured at 37°C using a LORCA ektacytometer with a laser diffraction ellipsometry technique. Between shear stress 0.3 to 30 Pa, RBC deformability was characterized by nine values of elongation indexes (EI). The blood samples were suspended in a high viscous (32,6 mPas) polyvinylpyrrolidone solution. The results of the measurements were analyzed using the Lineweaver-Bruke nonlinear equation to calculate the maximal of the EI (EImax) value at infinite shear, and the shear stress value required half of EImax (SS1/2).

Psychological surveys

SF-36 Questionnaire was applied to examine the psychological effects of the 12 week home - and center based training program on the perception of health. It is a self-administered questionnaire measuring health over 8 dimensions (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health). Both the training- and the control group rate their health status on a scale from 0 (worst health) to 100 (best health).

Statistical analysis

A sample size and power analysis was performed for the overall population using PASS software. For the sample size of n = 28 patients (1:1 enrollment ratio of interventional and control group) needed to detect a true difference of d = 2 in MET levels with 95% power, where type I error probability is $\alpha = 0.05$.

Statistical analysis was performed using the IBM SPSS statistical software version 23. Data were shown as mean ± standard deviation (SD). Significance level was defined as $p<0.05$. To check differences in the interventional and in the control group we performed dependent-t test. For testing how the two groups varied in time the interaction of time x group effect was applied. The normality was analyzed by Kolmogorov-Smirnov test. All the studied parameters in both groups showed no significant deviation from a normal distribution ($p> 0,05$; df:56). The nonparametric Wilcoxon Rank test was applied to analyze potential changes in psychological functioning and in the number of foot-steps, since these were ordinal variables. Data were shown as median and IQR.

Results

Results - within groups

Home-based walking and center based physical training program increased patients' exercise capacity and improved metabolic parameters.

Home-based walking program resulted in a significant improvement in daily physical activity (4232 [3162-7219] vs 8455 [6757-11488] foot-steps) among our female patients ($p<0.001$). We did not register any adverse events during the trial. The combined home-based and center based physical training program improved exercise capacity, described by the significantly increased metabolic equivalent (MET) in the training group ($p=0.002$) (Figure 2). Exercise capacity did not change in the control group.

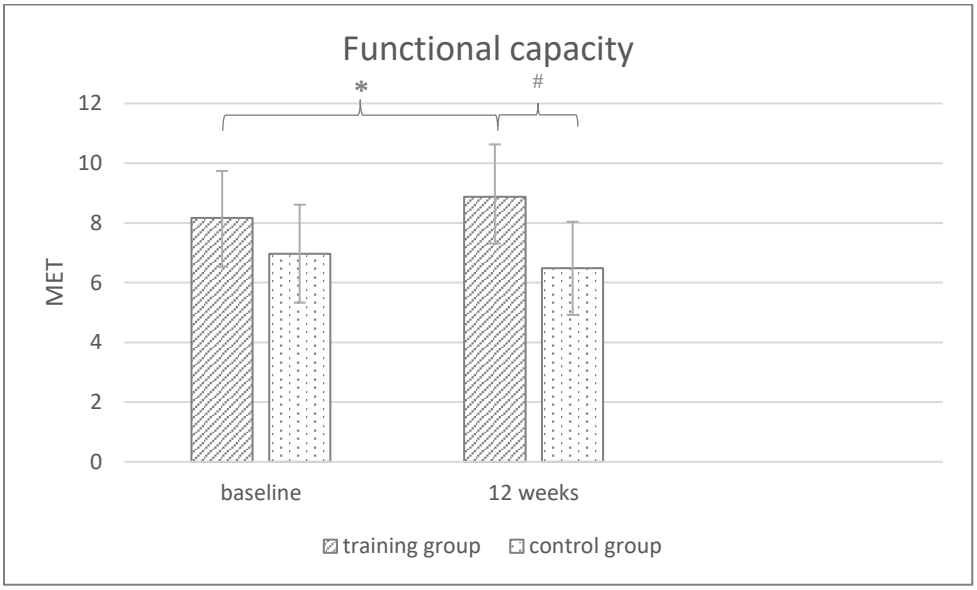


Figure 2. Significant changes in metabolic equivalent (MET) within and between the groups.
Values are baseline and 12 weeks. Levels of significance $p<0.005$.
*: $p=0.002$ regarding baseline to 12 weeks in the training group; #: $p<0.01$ regarding the training group compare to the control group after 12 weeks.

Total cholesterol, LDL cholesterol, TG, and HgbA1c level indicated a significant decrease during the investigated period ($p<0.05$), the other measured laboratory parameters did not show significant changes in the training group (Table 3). None of the laboratory parameters changed in the control group.

Body weight (BW) and body mass index (BMI) differed neither in the training group, nor in the control group after 12 weeks (data are not shown).

Table 3. Significant changes in metabolic laboratory parameters, IGF-1, and fibrinogen level after 12 weeks in the training group, n=30; values are baseline and 12 weeks (mean±SD). Level of significance: $p<0.05$

measured parameters	baseline	12 week	p value
$HgbA_{1C}$ (mmol/l)	6.24±0.67	6.06±0.58	0.007
total cholesterol (mmol/l)	5.17±1.13	4.77±1.12	0.042
LDL-cholesterol (mmol/l)	3.37±1.05	2.81±0.98	0.003
HDL-cholesterol (mmol/l)	1.46±0.39	1.51±0.46	ns
triglycerides (mmol/l)	1.68±0.71	1.28±0.71	0.002
IGF-1 (ng/ml)	59.68±27.37	66.79±22.74	0.006
Fibrinogen (g/l)	3.22±0.54	2.42±0.42	p<0.0001

Home-based walking and center-based physical training program increased IGF-1 level.

Serum IGF-1 significantly increased after 12 weeks in the training group (Table 3), while it decreased in the control group.

Home-based walking and center-based physical training program improved fibrinogen levels.

After 12 weeks, fibrinogen level demonstrated a significant decrease in the training group ($p<0.001$) (Table 3). The other measured hemorheological parameters did not show significant differences in none of the groups.

Home-based walking and center-based physical training program increased patients' physical functioning.

Participants of the training group reported significantly fewer limitations in their everyday physical functioning ($p<0.05$), however the other psychological items did not indicate significant changes following the training program. Participants in the control group did not report any changes in their psychological condition.

Results – between groups

Home-based walking and center-based physical training program increased patients' exercise capacity and IGF-1 level, and improved lipid parameters.

The interaction of time x group effect revealed, that the training group significantly differed from the control group in four parameters including MET (p=0.003) (Figure 3A), LDL-cholesterol (p=0.046) (Figure 3B), triglyceride (p=0.001) (Figure 3C) and IGF-1 levels (p<0.001) (Figure 3D) after the intervention. The training group did not differ from the control group in the other investigated cardio-metabolic parameters (total-cholesterol-, HDL-cholesterol-, and HgbA1c level) after the training program.

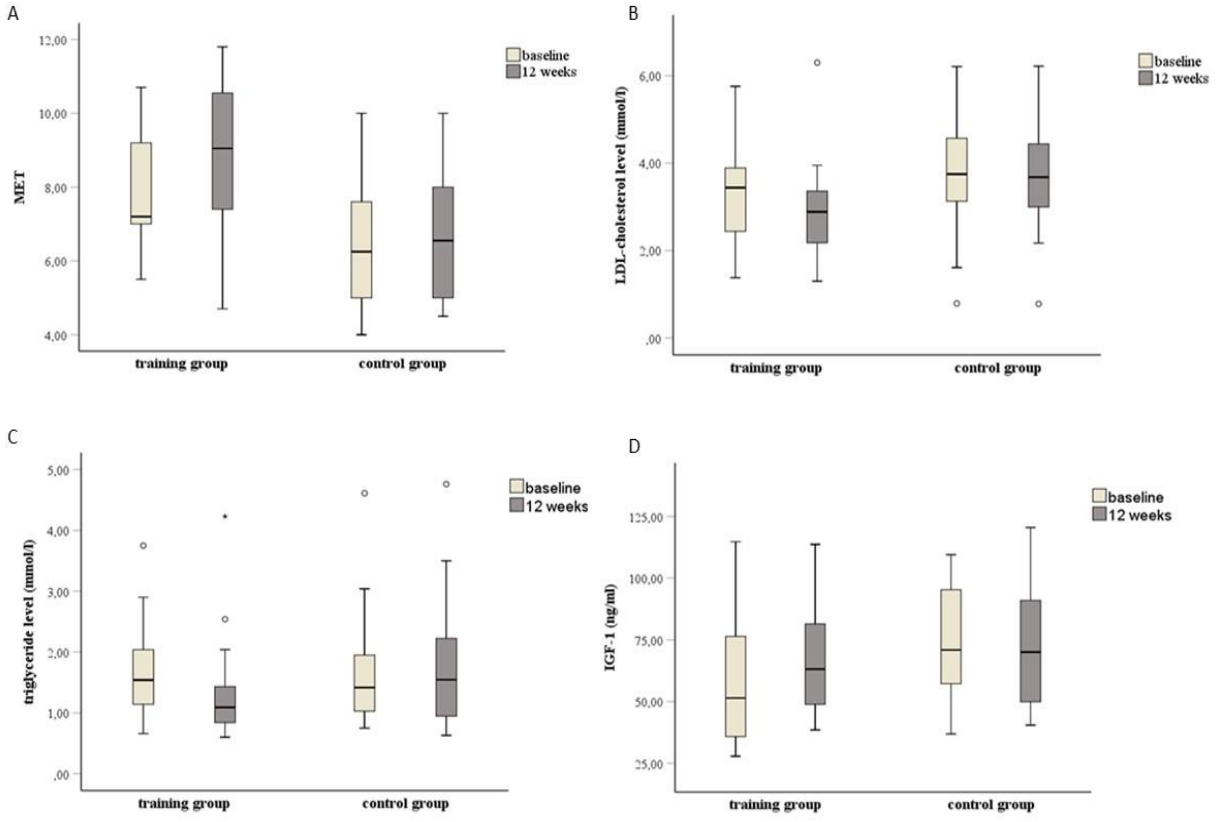


Figure 2. Box plots of cardio-metabolic parameters and IGF-1 level at baseline and after 12 weeks between the training-, and the control group. n=60. Levels of significance: p<0.05.
A. Significant difference in MET between the groups. p=0.003
B. Significant difference in LDL-cholesterol level between the groups. p= 0.046
C. Significant difference in triglyceride level between the groups. p= 0.001
D. Significant difference in IGF-1 level between the groups. p <0.001

Home-based walking and center-based physical training program improved certain hemorheological parameters.

The training group significantly differed from the control group in AI (p=0.037) and t1/2 (p=0.015) a describing parameter of RBC aggregation, as well as in PV (p=0.025) (Table 4). The other investigated hemorheological parameters did not differ between the two groups.

Table 4. Significant changes in certain hemorheological parameters after 12 weeks between the groups, n=60; values 12 weeks (mean±SD). Levels of significance: p<0.05

measured parameters	training group	control group	p value
PV (mPas)	1.23±0,05	1.26±0.06	0.025
LORCA AI	66.31±4.94	70.05±4.51	0.037
LORCA t ½ (sec)	1.81±0.51	1.50±0.4	0.015

Home-based walking and center-based physical training program and psychological status.

Psychological testing did not show significant differences between the training group and the control group.

Discussion

In our present study we investigated the effects of a home-, and center based physical training program on functional capacity, metabolic laboratory, IGF-1 levels and certain psychological parameters in elderly female patients with moderate to high CV risk. The organized training program resulted in a significantly improved functional capacity, metabolic status including LDL cholesterol, triglyceride, HgbA1c and IGF-1 level, and physical functionality.

Maintenance of a physically active lifestyle is a great challenge especially for the elderly population (81) and women are less likely to adhere physical training programs compared to men (37). We assumed that a combined, home-based walking and a center based training program fits well to the everyday life of the elderly ladies, and a center-based exercise program led by a physiotherapist might be effective and enjoyable for this special patient population. Walking is a low cost and easy way of PA for the elderly (81). Most of the studies reported that the normal daily activity of healthy adults is only 4000 to 6000 steps (82,83) and in older women it is even lower (84,85). Although in our study the elderly female patients could not completely fulfill the daily target of 10000 steps, still the achieved significant

improvement in daily PA (4232 [3162-7219] to 8455 [6757-11488] footsteps) is a great performance taking into accounts their age and co-morbidities.

After 12 weeks of our home- and center- based physical training program, we could demonstrate an average of 0.7 MET improvement in functional capacity (8.17±1.57 to 8.87±1.76). According to data in the literature an increase by 1 MET in cardiorespiratory fitness could reduce the risk of all causes and CV mortality by 13% and 15%, respectively (86). Furthermore, the training group significantly differed from the control group in MET level after the intervention, thus our results suggest that the training program significantly improved the functional capacity of our elderly female patients.

In our study we observed a significant decrease in the total cholesterol as well as in LDL cholesterol and TG levels in the training group, while in the control group no change could be observed in the metabolic parameters. In addition, the training group significantly differed from the control group in LDL cholesterol and triglyceride level after the training program, refers to the favorable effects of the home- and center-based training program on lipid status. Data in the literature regarding the effects of PA on lipid levels in general populations and also in elderly females is controversial. Examining the reasons behind this phenomenon we found some interesting observations. Fonong et al. reported that 2 months regular leisure time activity in elderly woman and men is too short to induce changes in body composition and plasma lipid levels (53). Nieman et al. could not demonstrate changes in HDL-cholesterol after 12 weeks cardiorespiratory exercise in previously sedentary elderly women. They indicated that women tend to have higher HDL-cholesterol level than men, furthermore it is harder to increase the already higher HDL-cholesterol level, and PA mostly has more favorable effects on young or middle aged than elderly women (54). Di Blasio et al. failed to report improvement in lipid levels after 13 week moderate intensity exercise program among postmenopausal women. They observed a decrease in spontaneous daily PA during the training program which may negatively affected the efficiency of the program (49). On the other hand, Fahlman et al. demonstrated favorable changes in plasma lipoprotein profile after 10 weeks endurance or resistance training among elderly women, although LDL-cholesterol level decreased significantly only in the resistance training group (50). Kemmler et al. reported decreased plasma lipid levels after 26 months intense exercise program among postmenopausal women (48). Examining our and the above described different training programs we

may realize that those physical training programs were able to induce significant changes in lipid levels in elderly females which either contained resistance training (50) or was intense and long enough (48) or could effectively increase the daily physical activity level, like the present home- and center- based exercise program.

It was previously demonstrated that regular PA improves plasma glucose level as well as plasma insulin concentration (59,87). In accordance with previous studies following the home- and center- based training program HgbA1C significantly decreased among our elderly female patients, contributing significantly to the positive metabolic effects of PA. In the control group no change could be observed in the HgbA1C level.

At baseline low levels of IGF-1 were measured in our study (Table 3). In the training group significant increase in IGF-1 levels could be observed but still remained below the average level of healthy middle-aged female adults (88). Moreover, the training group differed significantly from the control group in IGF-1 levels after the intervention, suggesting that the home- and center-based training program caused the beneficial changes in the IGF-1 levels. It is known that IGF-1 level markedly declines with aging which is also referred to as somatopause and this could be more robust around the time of menopause (89,90). It has been previously proved that resistance training improved IGF-1 levels in healthy adults (68), elderly males (69), patients with sarcopenic obesity (70), and also in postmenopausal women (71). No association has been previously reported between aerobic PA levels and IGF-1 concentrations in postmenopausal women (70,72,73). However, in a large cross-sectional study the effect of physical activity on hormone levels were examined among the postmenopausal women, a more intense PA estimated by the Cambridge Index was associated with higher IGF-1 concentrations (91). Based on previous results and our findings it seems that in the case of aerobic exercise training a more intensive PA level is needed to change IGF-1 level. The decrease in IGF-1 levels in the control group may be due to the lack of regular PA.

The triphasic phenomenon between hemorheology and exercise training has been well determined (92). Investigations have proved that short term exercise training induces hyperviscosity, resulting in an increase of Hct and WBV, while long term training leads to autohemodilution, including reduction in PV and WBV among healthy population (93). The hemorheological response to exercise is determined

by the mode and intensity of the exercise, the methods, as well as the selected individuals (93). PA could be a promising method of improving hemorheological parameters in the elderly (94), but available data among postmenopausal women with CV risk is rare. Our results have revealed significant decrease in fibrinogen levels in the training group (Table 3). The training group significantly differed from the control group in RBC aggregation (AI, t ½) and in PV after 12 weeks, suggesting that the organized training program led to beneficial hemorheological changes among our patients. These favorable changes in hemorheological status may contribute to better physical fitness by improving the microvascular perfusion and may also decrease their global CV risk.

Besides objective measurements SF36 questionnaire was applied in our study to measure the psychological well-being of our elderly female patients. The physical functionality, which is the patients' subjective judgement of their physical state has been improved after our home-, and center-based training program, meaning they have experienced fewer limitations during their everyday physical tasks, like shopping, walking or bathing. This better physical functionality was in accordance with the improved functional capacity measured by treadmill. However, no significant improvement could be measured in other examined psychological parameters. A longer follow up period may be necessary for achieving significant changes in other psychological parameters. A previous study examining 6 month exercise training in postmenopausal women attenuated the unfavorable psychological changes associated with menopause (95).

Our study indicated, that elderly women with moderate to high CV risk were able to achieve the level of physical activity necessary to result in favorable changes in cardio-metabolic profile and IGF-1 level. The subjective perception of their physical performance has also changed positively.

Conclusion

The present study demonstrated a significant improvement in several cardio-metabolic parameters such as functional capacity, physical functioning, total as well as LDL cholesterol, TG, HgbA1c as well as IGF-1 levels, and certain hemorheological parameters of elderly female patients with moderate to high CV risk after 12 weeks of complex home- and center-based training program.

Achieving significant changes in IGF-1 and lipid levels by a physical training program seems to be more difficult than in the case of other cardio-metabolic parameters. According to our findings and data in the

literature in order to improve IGF-1 level and lipid parameters in elderly women physical training programs should either contain resistance training elements or be intensive enough or effectively increase the daily physical activity level and completely change sedentary lifestyle behavior.

Funding

The authors thank all participants for their contribution to this study. The work was supported by TÁMOP-4.2.2 D-15/1/KONV-2015-0009 project of the Széchenyi 2020 program.

Acetylsalicylic acid resistance after simultaneous pancreas-kidney transplantation

Introduction

Simultaneous pancreas- kidney transplantation is one of the well-known treatment options in type 1 diabetes mellitus. Since the first simultaneous transplant in 1966, surgical techniques as well as patients care systems have improved, both short and long-term results are better. According to a study of 1000 post-transplant patients, the 1-, 10- and 20-year survival rates were 97, 80 and 58% respectively (16). Indication of SPK is stated when a type 1 diabetes patient with nephropathy needs renal replacement therapy or it will be necessary in the foreseeable future. SPK improved the patients' quality of life in several aspects compared to patients treated with conservative therapy. It renders regular dialysis unnecessary and ceases related immobility, reduces the occurrence of hypo- and hyperglycemic episodes, necessitates fewer diet restrictions and frequent blood sugar control (96). Smith et al. compared mental and physical data of pre- and post-transplantation and they registered significantly better results 2 years after the operation (97).

Besides the complications the mortality data are important to take into account for improving the results. For achieving good long-term results cardiovascular prevention is essential. According to the ESC guideline from 2012, the key points are lifestyle changes including proper nutrition, regular exercise, blood pressure and glycaemic control, as well as controlled triglyceride and cholesterol level, and effective antiplatelet therapy (1). The latter covers COX inhibitor acetylsalicylic acid, P2Y12 antagonist clopidogrel or prasugrel, alone or in combination (1,98). Resistance to platelet aggregation inhibiting therapy is a well-known phenomenon. Mani et al. in one of their reviews found ineffective platelet aggregation inhibition in 5-55% of the cases (99).

The aim of the present study was to examine ASA resistance in SPK patients as well as to identify the cause of this resistance.

Methods

Ethics statement

The research was approved by the Regional Ethics Committee of the University of Pecs (approval number: 4816) and a written informed consent was given by all participants.

Patients

The investigational period was from March 2009 to December 2013. 32 recipients were selected from the Department of Surgery in the University of Pecs (male: 22. female: 10, age: 47,4 ±8,6 years). Platelet aggregation measurements took place at the Hemorheological Research Laboratory of the 1st Department of Medicine at the University of Pecs.

Platelet aggregation measurements

Patients were routinely given 100 mg of ASA q.d. After 1 month blood samples were obtained from the cubital vein in 3.8% sodium-citrate tubes. Following multiple stages of centrifugation, platelet rich plasma (PRP), then platelet poor plasma (PPP) was separated. Platelet aggregation measurements were performed using turbidimetric Carat TX-4 (Carat Diagnostics Ltd., Budapest, Hungary) platelet aggregometer, which calculates the maximum of platelet aggregation curve via light transmission intensity changes between PRP and PPP samples. ASA therapy was considered effective as long as the maximum of platelet aggregation was under 40% respectively.

Measured factors

To determine serum- creatinine, glucose, cholesterol and triglyceride levels further laboratory tests were performed at the Department of Laboratory Medicine at the University of Pecs. Haemoglobin, haematocrit and platelet count were measured using an automated analyser. Patients' weight, height and BMI were measured in an outpatient setting. Tobacco use, medication (lipid-level lowering drugs, immunosuppressant, calcium-channel blockers, angiotensin-converting enzyme inhibitors) were assessed. The incidence of chronic allograft nephropathy and steroid resistant acute rejection was evaluated.

Statistical analysis

Linear logistic regression analysis was performed using the 21.0 version of IBM SPSS Statistics software (IBM Corporation, New York, United States).

Results

Our study revealed in 40.6% of the 32 transplant patients (13 patients) ASA resistance (Figure 3).

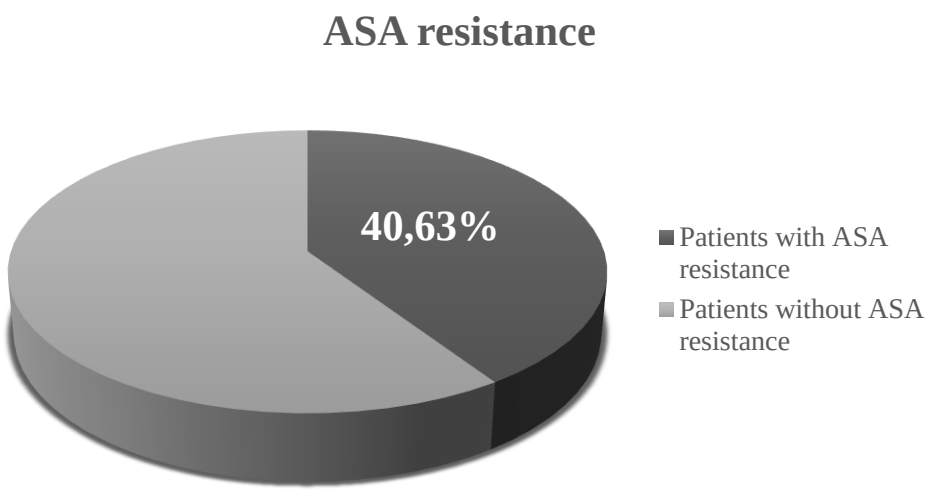


Figure 3. ASA resistance among SPK transplanted recipients

Linear logistic regression analysis with the resistance data and the above mentioned 24 investigational factors (Table 1) did not detect any statistically significant association between the variables.

Table 5. Factors which may influence ASA resistance

Age	Hemoglobin level	ACE Inhibitors
BMI	Hematocrit	Antilipid therapy
Smoking	Platelet count	Calcium channel blockers
Diabetes Mellitus	Triglyceride level	Everolimus, Sirolimus
Type of Transplantation	LDL-cholesterol level	Cyclosporine
CAN	serum glucose level	Methylprednisolone
SRAR	serum creatinine level	Mycophenolate Mofetil Mycophenolic acid

BMI: body mass index; CAN: chronic allograft nephropathy; SRAR: steroid resistance acute rejection

Discussion

The mortality of patients undergoing single kidney transplantation was studied in a large number of cases. Matas et al. followed 2202 kidney-transplant patients for 10 years: the main causes of death were cardiovascular diseases (35% and 38% cadaver, or living donor), malignancies (22% and 18%) and various kinds of infections (13% and 9%) (100). In the Biesenbach study group, five years after the operation the incidence of cerebrovascular diseases was 33%, of coronary artery diseases 41%, while peripheral vascular diseases comprised 41% (101). After 10 years the incidences increased slightly, keeping the above sequence 41, 50, 50% (101). These morbidity and mortality data originate also from underlying cardiovascular diseases, because during the uremic and hyperglycaemic periods, several vascular lesions could develop, and could influence subsequent complications. After SPK further factors could occur, and could increase the incidence of cardiovascular diseases, e.g. immunosuppressive steroid therapy, which could increase triglyceride level and blood pressure, and contributes to obesity.

ASA resistance is a widely examined phenomenon and several previous studies demonstrated that numerous factors could play a role in its development (102). The results of aggregometry can be influenced by the posture of the examined person during sampling, cholesterol level and the daytime of the test (103). Our research group examined the hemorheological background of ASA resistance. The results revealed that higher fibrinogen concentration increases RBC aggregation which can eventually increase platelet aggregation, too. Increased plasma fibrinogen level could have a role in the resistance to ASA (104). Koltai et al. found that advanced age associated with elevated fibrinogen concentration could increase platelet aggregability in ASA treated patients. The elevated platelet aggregation may contribute to higher risk of cardio- and cerebrovascular diseases, so the effectiveness of antiplatelet therapy should be more carefully controlled in the elderly (105).

Smoking is a factor causing significant increase in the incidence of ASA resistance (106), although our data discovered no association between these factors in SPK patients.

Several studies have examined the relationship between ASA resistance and diabetes, and observed increased platelet aggregation in patients with diabetes mellitus. Diabetic patients had increased susceptibility to degranulation and thromboxane A2 synthesis. In addition, due to the diabetes, micro- and macroangiopathy were also common (coronary, cerebrovascular events, peripheral vascular

diseases, nephropathy, and retinopathy) (107). Elevated lipid level and history of smoking in diabetes increased the incidence of ASA resistance (108).

74 patients undergoing coronary intervention showed significant correlation between LDL- cholesterol level, age and ASA resistance (109).

Ibuprofen significantly reduced the effectiveness of ASA, the same study demonstrated that diclofenac-containing preparations have a slightly negative effect on the inhibition of platelet aggregation (110). Another study found the following mitigation factors: female sex, low haemoglobin level, higher age and associated decreased metabolism, occurrence of cardiovascular diseases, type 2 diabetes mellitus, kidney disease and smoking (111).

Other possible factors are patient non-compliance and heart rate. Proper education and information are considered specifically important in the case of patients with antithrombotic therapy. The increased heart rate is associated with increased sympathetic tone, which could also enhance aggregation (112).

Genetic factors such as COX-1 gene polymorphism in platelet surface glycoprotein genes or COX-2 overexpression enables alternative routes of platelet activation and aggregation and simultaneous activation of multiple routes, so these could also play an important role in the development of ASA resistance (113,114).

Sandor et al. examined ASA resistance as cardiovascular risk after kidney transplantation. The results revealed that ASA resistance contributes to the elevated incidence of cardio,- and cerebrovascular events after kidney transplantation. The incidences of myocardial infarction and stroke were significantly higher in the kidney transplanted patients with ASA resistance compared to the group without ASA resistance (115).

Conclusion

The present study evaluated ASA resistance in patients with SPK. Similar data have not been reported in the literature so far. Our study found no significant correlation between the mentioned risk factors (Table 1) and ASA resistance. Nevertheless, the describing of the cause of ASA resistance would be an essential task for clinicians and researchers, and would be a cornerstone in cardiovascular prevention in SPK patients. This is on one hand a medical question and on the other hand a logistic one, because the number of kidney and pancreas donors is low, but a huge number of transplanted patients (ca. 50%) dies

with functioning grafts due to cardiovascular complications. For that reason further investigations are required to determine the cause of resistance, and hopefully the clarification of the background may reduce the cardiovascular complications and mortality after SPK.

Assessment of cardiovascular mortality in single center cohort analysis of 593 patients after Kidney Transplantation

Introduction

Kidney transplantation is the best therapeutic approach for patients with end-stage renal disease. Patient and graft survival improved significantly in recent decades due to the development of modern surgical techniques, post-transplant monitoring and immunosuppressive therapies, resulting in better quality of life and cost effectiveness (24,42,116).

Successfully performed kidney transplantations with long-term survival began in November 1973 in Hungary (117). Hungary joined the Eurotransplant with full membership in 2013 (118). Currently, four transplant centers work in Hungary and to date, more than 10,000 organ transplantations have been performed (117). The first kidney transplantation was carried out in 1993 in our surgical center at the University of Pécs. There was a slow increase in the number of transplantations performed per year between 1993-2003, reaching 20 transplantations in 2003. Since 2004 40-50 transplantations are performed each year (Figure 4).

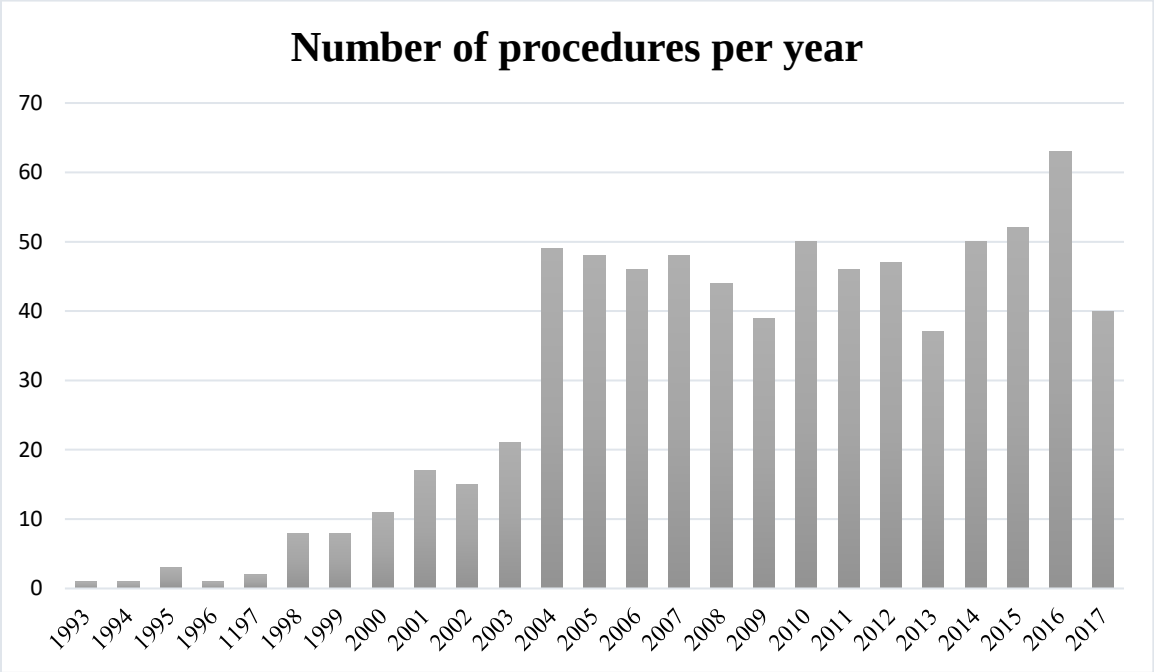


Figure 4. Number of transplantation per year

Systematic medical data collection and analysis of transplant outcomes could be an important way to improve care of transplanted patients. In several countries systematic transplant data collection and transplant registries exist and provide beneficial information for decades successfully (119,120). However, there is no renal transplant registry in Hungary at present.

This is the first paper describing kidney transplant characteristics and cardiovascular mortality in the whole cohort and the influence of Romani ethnicity on graft survival and mortality covering the past 25 years in our single center at Pécs, Hungary.

It has been revealed, that the leading cause of morbidity and mortality are CVD after kidney transplantation (27). Thus, determining the occurrence of these diseases is also crucial among our transplanted cohort.

Methods

Ethics statement

This investigation was approved by the Regional Ethics Committee (license number: 6957) of the University of Pécs. The evaluation was blinded, using the patients' registry number to protect patient privacy.

Patients

Patients, who were transplanted between 03/09/1993 and 11/07/2016 at the Department of Surgery, University of Pécs, were selected to load their data into our database between 01/02/2016 and 03/01/2017. Recipient-, donor-, and transplant procedure data were registered. Recipient data included age, sex, ethnicity, body mass index (BMI), duration of dialysis and mortality. Donor data included age, sex, donor type and creatinine level at the time of donation. Transplant procedure-related data included cold ischemia time (CIT), (all kidneys were preserved by cold storage*)*, graft function during hospitalization, early or delayed graft function, serum creatinine, serum carbamide nitrogen (CN), and hemoglobin level and thrombocyte count at discharge.

Data collection

Recipient, donor and transplant data were collected with retrospective data mining, using patient medical records and e-Medsolution program, an integrated information system of patient care at the University of Pécs. All patients were selected who underwent a single kidney transplantation in the Department of Surgery, University of Pécs between 1993 and 2016.

Assessment of ethnicity

Patients were categorized as Romani or non-Romani-Europid by two transplant coordinators independently, who were in personal contact with all patients.

Statistical analysis

Data are described as mean ± standard deviation (SD), median and interquartile range. Graft and patient survival were evaluated by Kaplan-Meier analysis with Log-Rank test. Correlations between variables were calculated by Spearman's rank correlation and chi-square test was applied in case of categorical values. To determine differences between groups independent sample t-test and analysis of variance (ANOVA) were applied. In case of the lack of normal distribution Mann-Whitney U and Kruskal-Wallis tests were carried out. Data were analyzed using SPSS version 23.0 statistical software. Recipients with functioning kidney grafts for more than 7.5 years (n=210) were compared to those with functioning grafts for less than 7.5 years (n=68) using multivariate analysis of graft survival between 1993 and 2007 (all transplants).

Results

Gender effects

The cohort's characteristics between 1993 and 2017 are shown by gender in Table 1. There was a significant difference between female and male recipients in body mass index (BMI) ($p<0.001$), creatinine (Crea; $p<0.001$), carbamide nitrogen (CN; $p=0.001$) and thrombocyte count at discharge ($p=0.009$) (Table 6). There was no significant difference between male and female recipients regarding recipient and donor age at transplantation, duration of dialysis, cold ischemia time (CIT), donor creatinine concentration at transplantation, recipient hemoglobin concentration and thrombocyte count at discharge, re-dialysis ratio, living donor vs. cadaveric donor ratio, Romani ethnicity and cardiovascular (CV) event ratio.

Table 1. Characteristics of transplant population by gender between 1993 and 2017 (n=593). (significant p-values are highlighted in bold) values are mean±SD or median and IQR

	Characteristics	Female patients (236)	Male patients (357)	p value	whole population
Donor factors	**Age at transplantation** (yrs)	46.69±13.14	48.01±12.87	0.265	47.46±12.99
	Creatinine (umol/l)	81.63 (60-98)	83.91 (57-98.75)	0.868	83.1 (57.5-98.5)
	Living donors (%)	18.4% (27)	9% (32)	0.324	9.9% (59)
Recipient factors	**Duration of dialysis** (months)	40.68 (12-48)	42.24 (12-60)	0.635	41.52 (12-48)
	Re-dialysis (%)	27.2% (64)	22.8% (80)	0.221	24.4% (145)
	Cold ischemia time (sec)	949.63 (6.14-1215.5)	969.74 (682-1297)	0.442	962.21(663-1255)
	Age at transplantation (years)	45.66±14.57	46.67±13.83	0.395	46.24±14.14
	BMI at transplantation (kg/m^2)	24.85±4.76	26.91±5.04	**0.000002**	26.09±5.03
	Creatinine at discharge (umol/l)	173.2 (95-188.75)	194.07 (118-210)	**0.000003**	186.32 (108-199)
	Carbamide nitrogen at discharge(umol/l)	14.06 (6.8315.95)	16.22(8.57-17.125)	**0.001**	15.38(8.08-16.75)
	Thrombocyte (G/l)	258.14±117.05	233.94±81.81	**0.009**	243.77±98.28
	Hemoglobine (g/l)	105.46±22.97	108.88±18.59	0.817	105.71±20.46
	New-onset cardiovascular event (%)	6.9% (16)	10.5% (37)	0.138	8.94%(53)

Primary graft function and cause of death

Primary non-function occurred in 2.7% of the recipients, whereas delayed graft function (DGF) developed in 12.2% of recipients (Figure 5A). There was no gender difference in primary graft function (p=0.357).

The leading cause of death after transplantation was cardiovascular (CV) disease (54.2%), infections (14.5%) and malignant diseases (8.4%) (Figure 5B). The cause of mortality did not differ significantly between genders (p=0.485).

There was no significant association between kidney transplant failure and CV mortality. We could not reveal higher creatinine level (p=0.794) or re-dialysis ratio (p=0.726) among patients with CV mortality compared to patients with other causes of mortality. Our results did not reveal an association between the duration of dialysis before transplantation and CV mortality (p=0.250).

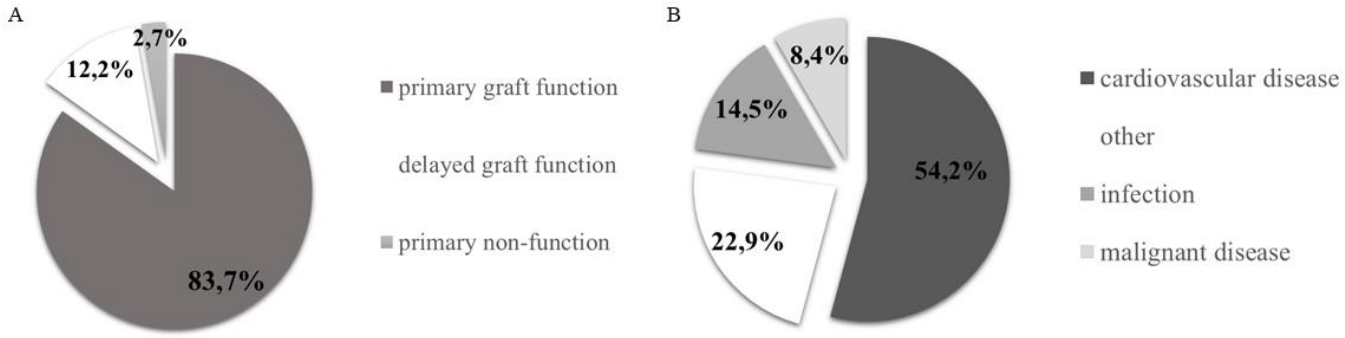


Figure 5 (A). Primary graft function and (B). Cause of death between 1993 and 2017. All transplants (n=593)

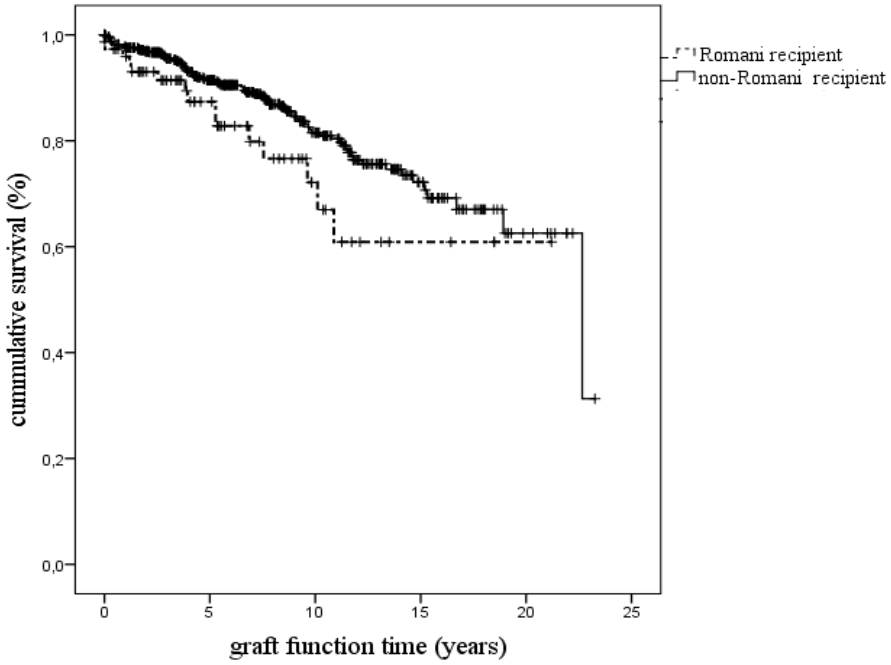
Characteristics by ethnicity

The cohort characteristics by ethnicity between 1993 and 2017 are shown in Table 7. Donor age at transplantation was significantly lower in Romani recipients (p=0.031). There were significantly fewer living donors among Romani patients (p=0.004). Romani recipients had a significantly shorter graft survival (p<0.05) (Figure 6) and higher re-dialysis ratio (p=0.026) (Table 7). Mortality and CV event ratio did not differ between ethnicities (Table 7). There was no difference between Romani and non-Romani Caucasian regarding donor creatinine concentration at transplantation, recipient age at transplantation, duration of dialysis, CIT, recipient's creatinine, CN, hemoglobin concentrations, and thrombocyte count at discharge.

Table 7. Complications in non-Romani Caucasian vs. Romani recipients (n=593); values are mean±SD or median and IQR.

	Characteristics	non-Romani Europid (n=516)	Romani (=78)	p
Donor factors	**Age at transplantation** (yrs)	47.96±13.03	44.37±12.38	**0.031**
	Creatinine at transplantation (umol/l)	75 (58-99)	79.6 (56-95)	0.75
	Living donors (%)	11% (57)	2.6% (2)	**0.02**
Recipient factors	**Duration of dialysis** (months)	24 (12-48)	36 (24-60)	0.176
	Cold ischemic time (sec)	987 (671-1259)	870 (643-1090)	0.238
	Age at transplantation (yrs)	46.51±14.27	44.42±13.14	0.226
	BMI at transplantation (kg/m^2)	26.12±4.85	25.26±4.76	0.411
	Creatinine at discharge (umol/l)	139 (108-194.5)	153 (108.5-236.5)	0.154
	Carbamide-nitrogen at discharge (umol/l)	10.89 (8-16.41)	10.4 (8.38-20.12)	0.427
	Hemoglobin level at discharge (g/l)	105.76±21.02	105.35±16.21	0.105
	Thrombocyte level at discharge (G/l)	241.12±97.07	261.93±105.02	0.105
	Mortality ratio (%)	15.14% (78)	19.2% (15)	0.132
	Re-dialysis ratio (%)	23,1% (118)	35,1% (27)	**0.024**
	CV event ratio (%)	8,4%(43)	12,8 % (10)	0.102

Figure 6 . Graft survival time between 1993 and 2016 by ethnicity. All transplants (n=593).



Factors determining long term graft function: Comparison of short- and long-term graft survival

Recipient data with functioning kidney grafts for more than 7.5 years (n=210) were compared to those with a potential graft-survival of 7.5 years but cessation of graft function earlier (n=68) using multivariate analysis (Table 8). In order to ensure statistically correct design and accurate comparability for this analysis only data of those patients were included who had a graft survival of at least 7.5 years i.e. patients who were transplanted before 2007. Longer graft survival was associated with a significantly (5 years in average) younger donor age (p=0.004) and non-Romani ethnicity (p=0.02). However, there was no significant difference in recipient age, dialysis duration, CIT, recipient BMI, renal function at discharge and CV event rates.

Graft survival time had a significant negative correlation with duration of dialysis before transplantation (δ=-0.195; p=0.000022).

Table 8: Comparison of short- (<7.5 years) and long-term (>7.5 years) graft survival between 1993 and 2007 (n=278); values are mean±SD or median and IQR.

	Characteristics	<7.5 years graft functioning time (68)	>7.5 years graft functioning time (210)	p
Ethnicity	**Romani ethnicity** (%)	22.1% (15)	11% (23)	**0.02**
Donor factors	**Age at transplantation** (yrs)	49.05±12.63	43.74±12.30	**0.004**
	Creatinine at transplantation (umol/l)	82.74 (56-105)	89.95 (64-105)	0.632
	Living donors (%)	5.9% (4)	7.6% (16)	0.79
Recipient Factors	**Duration of dialysis** (months)	38.4 (12-36)	34.8 (12-48)	0.997
	Cold ischemic time (sec)	1256.2 (1051-1455)	1216.55 (1070-1470.5)	0.728
	Age at transplantation (yrs)	44±14.99	42.37±13.02	0.392
	BMI at transplantation(kg/m^2)	24.76±4.22	25.7±5.08	0.185
	Creatinine at discharge (umol/l)	223.57 (116.75-273.25)	187.96 (119-205)	0.615
	Carbamide nitrogen at discharge (umol/l)	21.14 (8.05-17.67)	17.5 (8.45-16.92)	0.312
	Hemoglobin at discharge (g/l)	102.05±8.77	105.86±22.63	0.286
	Thrombocyte count at discharge (G/l)	238.11±98.34	254.2±93.39	0.317

Factors determining long term graft function: Immunosuppressive-treatment during the observation period

There have been a few changes in induction and maintenance immunosuppression during the investigated period (Table 9). In 1995 prednisolone was replaced by methylprednisolone and cyclosporin A with Neoral. These are drugs with similar mechanism of action but different chemical structure or formulation. Thus, the investigated first transplantation era (1993-1998) was characterized by PRED+CSA+AZA based immunosuppression. In 1998 a major change was the replacement of Azathioprine (AZA) with mycophenolate mofetil (MMF). In 2000 tacrolimus (Tac) was introduced in selected younger patients but patients already on CSA were not converted to Tac.

Table 9. Changes in Immunosuppression treatment during the observation period.

time-periods	Immunosuppressive treatment
1993-1995	PRED+CSA+AZA
1995-1998	Methyl-PRED (Medrol)+CSA-Neoral+AZA
1998-2000	Methyl-PRED+CSA-Neoral+MMF
2000-present	Methyl-PRED+Tac+MMF

PRED: Prednisolone, CSA: Cyclosporin A, AZA: Azathioprine, Methyl-PRED: Methylprednisolone, MMF: Mycophenolate mophetil, Tac: Tacrolimus

In cases of good graft function (creatinine concentration <130 mmol/l and the absence of acute rejection), steroid therapy was stopped after 3 or 12 months. Recipients remaining on methylprednisolone (Medrol) therapy had an inferior graft function in the long run. Also mortality was higher in patients receiving Medrol continuously than in patients who stopped taking steroids due to good graft function, (p=0.001). 84% (n=72) of patients received Medrol by the time of their death. Mortality was higher (p<0.003) in CSA- than in Tac-treated patients. However, CSA-patients were transplanted earlier and they were 8 years older in the CSA than in the TAC group (Table 10).

Table 10. Comparison of Tac-based vs. CSA-based Immunosuppression (n=593); values are (mean±SD).

Characteristics	Tac-based Immunosuppression (n= 247)	CSA-based Immunosuppression (n= 316)	p value
Age (yrs)	51.26±13.76	58.98±12.63	**p<0.001**
Mortality ratio (%)	10.2 (25)	19.4 (61)	**p=0.003**
Re-dialysis ratio (%)	16.2 (40)	26.6 (81)	**p=0.005**
CV event ratio (%)	8.5 (21)	9.2 (29)	p=0.733

Factors determining long term graft function: Results of 5-year quintiles analysis

The 25 years of observation (Fig 7A) was divided into 5 equal (5-year long) periods according to the time of transplantation. There was a significant increase in graft survival in all time-groups after 1998 compared to the first observation period (1993-1998). Azathioprine was replaced by mycophenolate mofetil (MMF) in 1998.

Transplant-related parameters improved over time (Fig 7B-F). CIT was the longest in the first two quintiles (1993-1998, 1998-2003) (Fig 7B.), had a decreasing tendency (Fig 7B) and it was significantly shorter in the last period (2013-2017) vs. all other periods ($p<0.001$) (Fig 7B). There was a significant association between CIT and the presence of chronic allograft nephropathy (CAN) ($p=0.00054$), creatinine concentration at discharge ($\delta=0.142$; $p=0.042$) and longer CIT was significantly associated with higher mortality ($p=0.00298$). Recipient creatinine concentration at discharge was significantly higher in the first period (1993-1998) than in the second (1998-2003) ($p=0.042$) and the fourth (2008-2013) ($p=0.039$) periods (Fig 7C). Recipient CN concentration at discharge was highest in the first period (1993-1998) and lowest in the last period (2013-2017) ($p=0.012$) (Fig 7D). Recipient BMI was significantly higher in the last period (2013-2017) than in all other periods ($p<0.05$) (Fig 7E). Donor creatinine concentration at transplantation (1998-2013) was significantly higher in the second period than in the last two periods (2008-2013,2013-2017) ($p=0.006$) (Fig 7F).

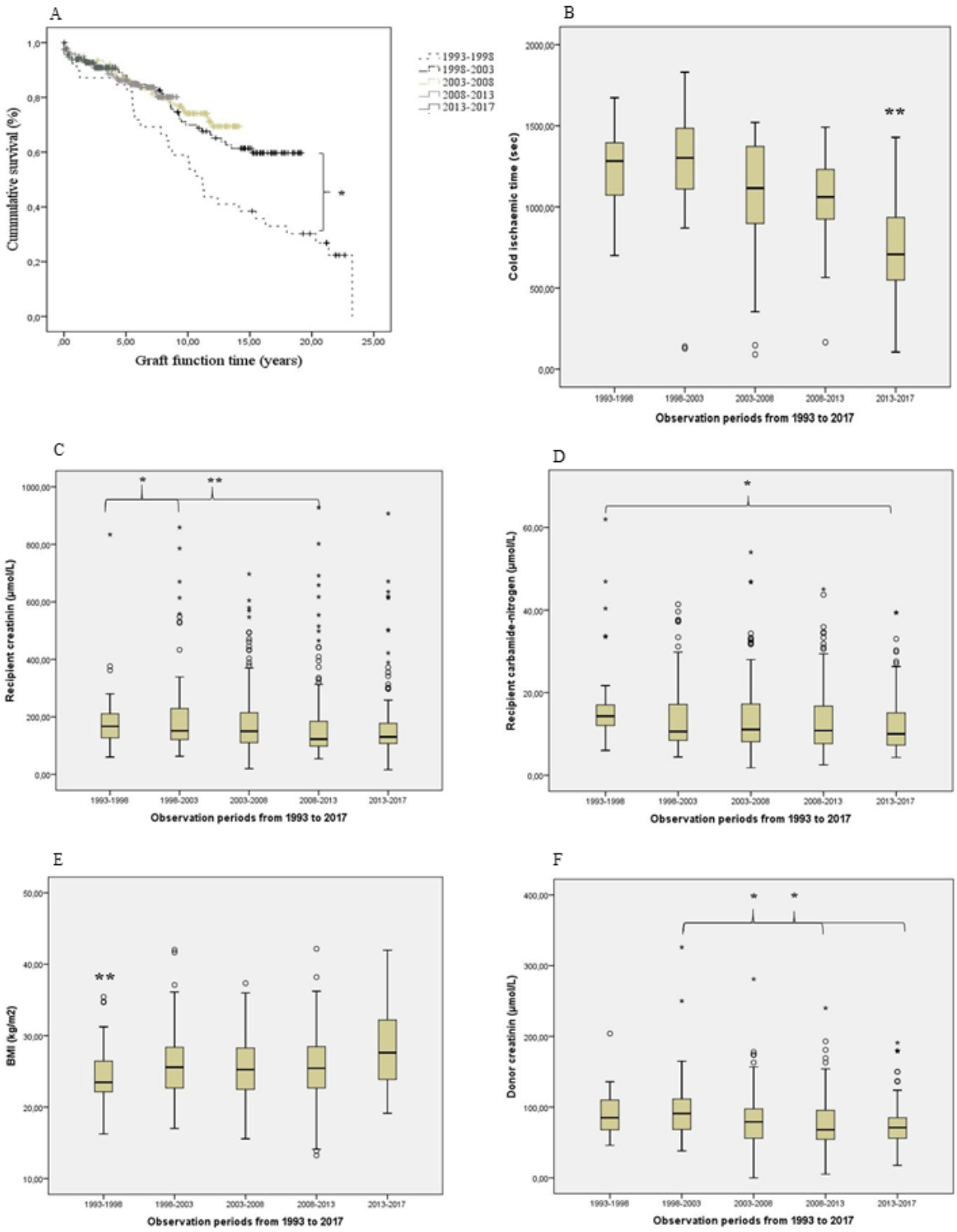


Figure 7. Factors determining long term graft function between 1993 and 2007 (n=593).
(A) Graft survival between (comparison of 5 year intervals according to time of transplantation). *: p =0.012.
(B) Cold ischemia time in the 5-year periods. **: p <0.001 vs. all previous quintiles.
(C) Differences in recipient creatinine concentration at discharge among the 5-year periods. *: p =0.042. **: p= 0.039.
(D) Differences in recipient carbamide nitrogen concentration at discharge among the 5-year periods. *: p = 0.012.
(E) Differences in recipient BMI among the 5-year periods. **: p <0.05.
(F) Differences in donor creatinine concentration at transplantation among the 5-year periods. *: p = 0.006.

Discussion

In this retrospective cohort we assessed and analyzed the outcome of kidney transplantation over 25 years at a Hungarian single center. Several international studies have been carried out to evaluate the outcomes of kidney transplantation (121,122), however, data from Hungary is scarce and there is none about the patients transplanted at the University of Pécs. The main purpose of this report was to gain insight into transplant activity and long-term outcomes from South-Hungary. The main findings of the present study are that CV mortality of transplanted patients was similar to that of the general population and was not in connection with transplant-related factors, and that graft survival significantly increased at the turn of the century.

The significant differences between male and female patients in BMI (1,123), creatinine-, CN level (124) and thrombocyte count at discharge (125) are not likely to be transplant-related issues as all the above gender differences can be observed in the general population. Furthermore, these parameters were within the reference range, thus, the clinical significance of these differences is unclear.

DGF is a well-known post-transplant complication with a prevalence of 5 to 50% in deceased donor kidney transplants (126) and is associated with unfavorable long-term graft outcome (127). In our transplanted population 12.2% of patients had DGF (similar in both genders), which was similar to that reported in the United States Renal Data System (USRDS) (128).

Internationally, the main cause of mortality after renal transplantation is CVD (30-40%) (126), similarly to USRDS reports (129). In our study the leading cause of death after renal transplantation was CVD, however, the prevalence (54%) was higher than in the US. This difference is most likely attributable to a similar difference in the general populations: according to the Hungarian Central Statistical Office database CV mortality in the general population is 55.2% (130). According to the World Health Organization (WHO) the prevalence of CV death within the general population was 34% (1,131) world-wide, and 23.4% in the United States in 2015 (132). CV mortality had no association with graft function (creatinine level or re-dialysis ratio), CSA vs. Tac based immunosuppression or with dialysis duration before transplantation. Although, graft survival time correlated negatively with the duration of dialysis before transplantation, we found no association between the duration of dialysis and CV mortality, thus, the high CV mortality in our cohort was not due to inferior dialysis. The relatively short and homogenous

dialysis duration and the number of cases in our single center may explain why we did not detect an association between dialysis duration and CV mortality. Thus, CV mortality of kidney-transplanted patients seems to correlate with CV-mortality in the general population.

According to international and USRDS data other common life-threatening causes of death are infections (18.1%) and malignancy (8.4%) in kidney transplant patients (129,133). Our transplant cohort produced similar results to USRDS with prevalence of 22.9% infections and 8.4% malignancy. The Hungarian Central Statistical Office database reported that infection-related mortality occurred at a lower rate affecting only 1.7% of the general population, thus, the transplantation procedure itself and the following immunosuppressive therapy seem to increase infection-related mortality. On the other hand, malignancy-related mortality was 10.8% in the general population – slightly higher than in our transplant cohort (130). This is lower, compared to the international statistics, as cancer is the second leading cause of mortality in the general population with a prevalence of 20.3% in WHO Europe, and 14.3% in WHO Americas (134). Thus, immunosuppression did not seem to increase malignancy in our cohort.

Romani is the largest ethnic minority with a ca. 12-15 million population worldwide (135) and about 7–9% (<1 million) of the population belong to the Romani ethnicity in Hungary (136). The occurrence of chronic kidney disease (CKD) is high (20%) in Romani (137) and it has been also observed that the risk factors for end-stage renal disease (ESRD) including CVD, diabetes, hypertension, metabolic syndrome and obesity occur more frequently among the Romani population (138). Furthermore, Romani ethnicity has been demonstrated to be associated with higher risk of graft loss and all-cause mortality (139). Our results support this, as Romani recipients had a significantly shorter graft survival time and higher prevalence of graft loss. However, we found no significant difference in mortality rates between ethnicities. There were significantly fewer living donors in the background of inferior graft survival of Romani recipients but no difference in donor creatinine concentration, recipient age, duration of dialysis, CIT, recipient's creatinine, CN, hemoglobin concentration, and thrombocyte count at discharge and donor age was even younger among Romani recipients. Factors possibly contributing to the inferior graft survival are 1) significant differences in HLA (140) and CYP2C9 (141) genetic background between Romani and non-Romani Caucasian population in Hungary reported previously. 2)

Furthermore, the poorer environmental and socioeconomic status (142,143) and higher occurrence of depression among Romani recipients may contribute to the inferior outcome. Although higher prevalence of cardiovascular disease and CV mortality has been demonstrated earlier in the general Romani vs. the majority population (138) our data do not support this in the transplanted population as a possible cause of the inferior outcomes. Better medical surveillance and better compliance of transplanted Romani patients than the general Romani population might be one reason (144).

Several investigations demonstrated that older donor age has a negative influence on long-term graft survival (145,146). Older donors are more likely to have co-morbidities (hypertension, diabetes, ischemic heart disease) which factors together with advanced age are potential risk factors for poorer graft survival (146). Our results provide supporting data, as shorter graft survival was associated with significantly older donor age.

It has been demonstrated that longer dialysis time before transplantation is associated with worse post-transplant and patient survival (147). Our results confirm previous observations, as graft survival time had a significant negative correlation with the duration of dialysis.

Induction and maintenance immunosuppression treatment changed during the investigated period in our center (Table 4). Medrol was stopped in case of good graft function (low creatinine). Continuous Medrol therapy was a prognostic factor for mortality, however this was not associated with cardiovascular morbidity or re-dialysis. Thus, the better outcome was mainly associated with better graft function.

After 2000, selected (mostly younger) people were preferentially immunosuppressed with Tac instead of cyclosporine. Tac-treated patients were significantly (8 years) younger and thus had a lower mortality and graft failure. Most probably the better outcome with Tac was related to the fact that better grafts were included in this group, as other studies have demonstrated similar outcomes with CSA or Tac (148,149). CV event ratio was similar in the CSA and Tac groups, this observation supports the above conclusion, that CV mortality was primarily determined by general CV mortality in Hungary.

Graft survival time was shorter before 1998 (in the first observation period (1993-1998) compared to all other periods. The observation that graft survival increased significantly after 1998 is corroborated by the slight decrease in discharge creatinine and the significant decrease in CN after the first observation period. The most likely explanation for the increase in graft survival and function is the replacement of

AZA with MMF in 1998. MMF is also more effective against acute rejection and supports better metabolic status than AZA (150). Further possible factors that may have contributed to the significant increase in graft survival following 1998 are the decrease in CIT and donor creatinine.

Although the effects of CIT has been extensively investigated, its impact on long-term outcomes has remained controversial. Numerous studies established that longer CIT does not have a negative effect on long-term kidney graft outcomes (151,152). In contrast, others have reported CIT as a predictor of long-term graft survival (153,154). In our experience, the steady and substantial decrease in CIT since 1998 was not translated into better graft survival. However, we observed a significant positive correlation between CIT and the presence of CAN and a significant positive correlation between CIT and discharge creatinine level. Moreover, CIT positively correlated with mortality, as it was also demonstrated by Debout et al. (154).

Elevated donor serum creatinine level was a risk factor for shorter kidney graft survival in previous studies (155). In our study, although donor creatinine level was within the normal range, there was a tendency to lower donor creatinine levels after 2003.

The worldwide prevalence of obesity (BMI ≥30 kg/m^2) has doubled recently (156). In our study, recipient's BMI was lowest in the first, and highest in the last observation period – remaining within the reference range, suggesting that most patients were not obese in our cohort at the time of transplantation. Interestingly, the significant increase in recipient BMI after 2013 did not influence graft survival – at least its effect was not obvious due to the short follow-up time. The impact of recipient obesity on long-term post-transplant outcomes is still conflicting. Some investigations revealed that increased recipient BMI (index ≥30 kg/m(2)) at the time of transplantation is a risk factor for adverse outcomes after transplantation (157,158). Others could not show a relationship between increased BMI and poorer outcomes after kidney transplantation (159,160).

Conclusion

In our single center cohort CVD was the most common cause of mortality, followed by infections and malignant disorders. CV mortality had no association with graft function or CSA vs. Tac based immunosuppression. Possible cause of the higher CV mortality in our cohort is the generally high CV mortality in Hungary. Our study revealed that elderly donor age and Romani ethnicity was associated

with shorter graft survival time, which is concordant with international findings. We did not observe higher CV event ratio among Romani recipients, contrary to that in the general Romani population in Hungary probably due to better health-care in the transplant program. Improved graft survival time in our transplant population after 1998 might be explained mainly by changes in immunosuppressive therapy. Our experience supports that longer CIT could increase the risk of graft failure and mortality.

Funding

The authors wish to thank Dr Gabor Szenasi for careful editing of the text. Peter Hamar is a recipient of the Kispál Gyula startup grant of the University of Pécs. The study was supported by the Economic Development and Innovation Operative Programme Grant (GINOP 2.3.2-15-2016-00048 to PHegyi).

Summary of the new scientific results

Impact of home- and center- based physical training program on cardio-metabolic health and IGF-1 level in elderly women

1) The originality of our study was the use of a structured home-based walking program and center-based aerobic training program in elderly postmenopausal women, which is different compared to other studies that focused only in structured exercise program (aerobic and resistance).
2) The home-, and center-based training program resulted in a significant improvement in certain cardio-metabolic parameters (physical functionality, total cholesterol, LDL cholesterol, triglyceride, HgbA1c) IGF-1 levels, hemorheological parameters (fibrinogen, PV, RBC aggregation) and a psychological item (physical functioning) among our patients.
3) Summarizing our research and data in the literature in order to improve IGF-1 level and lipid parameters in elderly postmenopausal women physical training programs should either contain resistance training elements or be intensive enough or effectively increase the daily physical activity level and completely change sedentary lifestyle behavior.

Acetylsalicylic acid resistance after simultaneous pancreas-kidney transplantation

1) Previously, no study have confirmed the very high prevalence of ASA resistance after SPK transplantation.
2) The incidence of cardiovascular disease increases after SPK transplantation, and their appearance may further increasing by the occurrence of ASA resistance, which could affect long-term patient outcomes. Based on our results, the authors presume, that the control measurements of antiplatelet therapy after SPK transplantation could be clinically useful.

Assessment of cardiovascular mortality in a single center cohort analysis of 593 patients after Kidney Transplantation

1) This is the first comprehensive report to characterize the full Pécs cohort of renal transplantations that form a basis for further studies.

2) In our study CVD is the leading cause of death, however, the prevalence (54%) was higher than world-wide (34%) and in the United States (23.4%). This difference is most likely attributable to a similar difference in the general populations in Hungary (55.2%).
3) This is the first analysis of transplantation outcomes in patients with Romani ethnicity in south Hungary. We found that, Romani ethnicity was associated with shorter graft function time, which is concordant with international findings. However, our results did not reveal higher CV event ratio among Romani patients, contrary to that in the general Romani population in Hungary, probably due to better medical-care in the transplant program.

Acknowledgements

These studies were performed at the 1st Department of Medicine and the Department of Surgery University of Pecs, School of Medicine, Pecs, Hungary.

I am grateful for the provided support to my program leader Professor Kalman Toth throughout my scientific work. I would like to express my thanks to my project leaders Dr Eszter Szabados and Dr Peter Szakaly for continuous help and the guidance in my Ph.D. research.

I am greatly thankful to Dr Barbara Sandor and Dr Adam Varga for the methodological support and useful ideas.

I express my special thanks to Dr Nelli Farkas, Professor Peter Hamar and Professor Peter Hegyi for the scientific and statistical information.

I am thankful to Dr Beata Csiszar, Dr Peter Kenyeres, Dr David Kovacs, Marianna Pesti, Peter Petrovics, Aniko Ronaky, Dr Zsolt Szekeres, Dr Szabina Szujo, Dr Andras Toth and Dr Kinga Totsimon.
I am also thankful to all the nurses and technicians for their kind help throughout the measurements, especially to Kornelia Fazekas Tapasztone.

At last but not at least, I am very grateful to my whole family especially to my mother and my husband for the patience and encouraging support.

This work could not be prepared without the financial support which was provided by „EFOP 3.6.1-16-2016-00004".

References

1. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL et al. European Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2016;37(29):2315-81.
2. Rose G. Sick individuals and sick populations. Int J Epidemiol. 1985 ;14:32-38.
3. Forman DE, Rich MW, Alexander KP, Zieman S, Maurer MS, Najjar SS et al. Cardiac care for older adults. Time for a new paradigm. J Am Coll Cardiol. 2011;57(18):1801-10.
4. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. Circulation. 2011;124(19):2145-54.
5. Gulati M, Bairey Merz CN. Cardiovascular Disease in Women. In: Zipes DP, Libby P, Bonow RO, Mann DL, Tomaselli GF. Braunwald's Heart Disease (Eleventh Edition). 2019;1767-79.
6. Gupta D, Wenger NK. Guidelines for the prevention of cardiovascular disease in women: international challenges and opportunities. Expert Rev Cardiovasc Ther. 2012;10(3):379-85.
7. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24(11):987-1003.
8. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2960-84.
9. Gulati M, Pandey DK, Arnsdorf MF, Lauderdale DS, Thisted RA, Wicklund RH et al. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. Circulation. 2003;108(13):1554-59.
10. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. JAMA. 2009;301(19):2024-35.

11. EURODIAB Study Group. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet. 2009;373(9680):2027-33.

12. Jiang AT, BHSc, Rowe N, Sener A, Luke P. Simultaneous pancreas-kidney transplantation: The role in the treatment of type 1 diabetes and end-stage renal disease. Can Urol Assoc J. 2014;8(3-4):135-8.

13. Swedish Childhood Diabetes Study Group and the Swedish Renal Register; Swedish Childhood Diabetes Study Group. Decreasing Cumulative Incidence of End-Stage Renal Disease in Young Patients With Type 1 Diabetes in Sweden: A 38-Year Prospective Nationwide Study. Diabetes Care. 2018;pii:dc181276.

14. Rayhill SC, D'Alessandro AM, Odorico JS, Knechtle SJ, Pirsch JD, Heisey DM et al. Simultaneous pancreas-kidney transplantation and living related donor renal transplantation in patients with diabetes: is there a difference in survival? Ann Surg. 2000;231(3):417-23.

15. Wiseman AC. Kidney transplant options for the diabetic patient. Transplant Rev. 2013;27(4):112-6.

16. Sollinger HW, Odorico JS, Becker YT, D'Alessandro AM, Pirsch JD. One thousand simultaneous pancreas-kidney transplants at a single center with 22-year follow-up. Ann Surg. 2009;250(4):618-30.

17. Lipshutz GS, Wilkinson AH. Pancreas-kidney and pancreas transplantation for the treatment of diabetes mellitus. Endocrinol Metab Clin North Am. 2007;36(4):1015-38.

18. Douzdjian V, Rice JC, Gugliuzza KK, Fish JC, Carson RW. Renal allograft and patient outcome after transplantation: pancreas-kidney versus kidney-alone transplants in type 1 diabetic patients versus kidney-alone transplants in nondiabetic patients. Am J Kidney Dis. 1996;27(1):106-16.

19. Larsen JL, Colling CW, Ratanasuwan T, Burkman TW, Lynch TG, Erickson JM et al. Pancreas transplantation improves vascular disease in patients with type 1 diabetes. Diabetes Care. 2004;27(7):1706-11.

20. Karthikeyan V, Karthik Ananthasubramaniam. Coronary Risk Assesment and Management Options in Kronic Kidney Disease Patients Prior to Kidney transplantation. Current Cardiology Reviews. 2009;5;177-86.

21. Małyszko J, Małyszko JS, Takada A, Myśliwiec M. Effects os immunosuppressive drugs on platelet aggregation in vitro. Ann Transplant. 2002;7(1):55-68.

22.https://kdigo.org/wp-content/uploads/2017/02/KDIGO-2009-Transplant-Recipient-Guideline-English.pdf S80 Chapter 17: Cardiovascular Disease Management.

23. Campbell RC, Sui X, Filippatos G, Love TE, Wahle C, Sanders PW et al. Association of chronic kidney disease with outcomes in chronic heart failure: a propensity-matched study. Nephrol Dial Transplant. 2009;24(1):186-93.

24. Jensen CE, Sørensen P, Petersen KD. In Denmark kidney transplantation is more cost-effective than dialysis. Dan Med J. 2014;61(3):A4796.

25. Mazzuchi N, González-Martínez F, Carbonell E, Curi L, Fernández-Cean J, Orihuela S. Comparison of survival for haemodialysis patients vs renal transplant recipients treated in Uruguay. Nephrol Dial Transplant. 1999;14(12):2849-54.

26. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group: KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009;9:1-155.

27. Grochowiecki T, Gałązka Z, Madej K, Frunze S, Nazarewski S, Jakimowicz T et al. Early complications related to the transplanted kidney after simultaneous pancreas and kidney transplantation. Transplant Proc. 2014;46(8):2815-17.

28. Kannel WB, D'Agostino RB, Belanger AJ. Fibrinogen, cigarette smoking, and risk of cardiovascular disease: insights from the Framingham study. Am Heart J. 1987;113:1006-10.

29. Lowe GDO, Smith WCS, Tunstall-Pedoe HD, Crombie IK, Lennie SE, Anderson J. Cardiovascular risk and haemorheology: Results from the Scottish Heart Health Study and the MONICA Project, Glasgow. Clin Hemorheol. 1988;8:517-24.

30. Toth K, Kesmarky G. Clinical Significance of Hemorheological Alterations. In: Baskurt OK, Hardeman MR, Rampling MW, Meiselman HJ, eds. Handbook of Hemorheology and Hemodynamics. IOS Press. 2007;392-432.

31. Sweetnam PM, Thomas HF, Yarnell JW, Beswick AD, Baker IA, Elwood PC. Fibrinogen, viscosity and the 10-year incidence of ischemic heart disease: The Caerphilly and Speedwell Studies. Eur Heart J. 1997;17:1814-20.

32. Kesmarky G, Kenyeres P, Rabai M, Toth K. Plasma viscosity: a forgotten variable. Clin Hemorheol Microcirc. 2008;39:243-6.

33. Yarnell JW, Baker IA, Sweetnam PM, Bainton D, O'brien JR, Whithead PJ, Elwood PC. Fibrinogen, viscosity, and white blood cell count are major risk factors for ischemic heart disease. The Caerphilly and Speedwell collaborative heart disease studies. Circulation. 1991;83:836-44.

34. Cooke BM, Lim CT. Mechanical and adhesive properties of healthy and diseased red blood cells. In: Baskurt OK, Hardeman MR, Rampling MW, Meiselman HJ (eds): Handbook of Hemorheology and Hemodynamics. IOS Press. 207;91-113.

35. Toth K., Kesmarky G. Clinical Significance of Hemorheological Alterations. In: Baskurt O.K., Hardeman M.R., Rampling M.W., Meiselman H.J. (eds.), Handbook of Hemorheology and Hemodynamics. IOS Press. 2007;392-432.

36. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomized trials. Lancet. 2009 ;373:1849-60.

37. Grace SL, Midence L, Oh P, Brister S, Chessex C, Arthur HM. Cardiac Rehabilitation Program Adherence and Functional Capacity Among Women: A Randomized Controlled Trial. Mayo Clin Proc. 2016;91(2):140-8.

38. Buchner DM. Physical activity and prevention of cardiovascular disease in older adults. Clin Geriatr Med. 2009;25(4):661-75.

39. Mendoza N, De Teresa C, Cano A, Godoy D, Hita-Contreras F, Lapotka M, Llaneza P, Manonelles P, Martínez-Amat A, Ocón O, Rodríguez-Alcalá L, Vélez M, Sánchez-Borrego R. Benefits of physical exercise in postmenopausal women. Maturitas. 2016;93:83-8.

40. Hita-Contreras F, Martínez-Amat A, Cruz-Díaz D, Pérez-López FR. Fall prevention in postmenopausal women: the role of Pilates exercise training. Climacteric. 2016;19(3):229-33.

41. Ivandic BT, Giannitsis E, Schlick P, Staritz P, Katus HA, Hohlfeld T. Determination of aspirin responsiveness by use of whole blood platelet aggregometry. Clin Chem. 2007;53(4):614-9.

42. Port FK, Wolfe RA, Mauger EA, Berling DP, Jiang K. Comparison of survival probabilities for dialysis patients vs cadaveric renal transplant recipients. JAMA. 1993;270(11):1339-43.

43. Vanhees L, De Sutter J, Gelada SN, Doyle F, Prescott E, Cornelissen V, Kouidi E, Dugmore D, Vanuzzo D, Börjesson M, Doherty P. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular risk factors: recommendations from the EACPR. Part II. Eur J Prev Cardiol. 2012;19(5):1005-33.

44. Church TS, Earnest CP, Skinner JS, Blair SN. Effects of different doses of physical activity on cardiorespiratory fitness among sedentary, overweight or obese postmenopausal women with elevated blood pressure: a randomized controlled trial. JAMA. 2007;297(19):2081-91.

45. Buchner DM. Physical activity and prevention of cardiovascular disease in older adults. Clin Geriatr Med. 2009;25(4):661-75.

46. Bergland A, Fougner M, Lund A, Debesay J. Ageing and exercise: building body capital in old age. Eur Rev Aging Phys Act. 2018;15:7.

47. Eliassen AH, Hankinson SE, Rosner B, Holmes MD, Willett WC. Physical activity and risk of breast cancer among postmenopausal women. Arch Intern Med. 2010;170(19):1758-64.

48. Kemmler W, Lauber D, Weineck J, Hensen J, Kalender W, Engelke K. Benefits of 2 years of intense exercise on bone density, physical fitness, and blood lipids in early postmenopausal osteopenic women: results of the Erlangen Fitness Osteoporosis Prevention Study (EFOPS). Arch Intern Med. 2004;164(10):1084-91.

49. Di Blasio A, Ripari P, Bucci I, Di Donato F, Izzicupo P, D'Angelo E, Di Nenno B, Taglieri M, Napolitano G. Walking training in postmenopause: effects on both spontaneous physical activity and training-induced body adaptations. Menopause. 2012;19(1):23-32.

50. Fahlman MM, Boardley D, Lambert CP, Flynn MG. Effects of endurance training and resistance training on plasma lipoprotein profiles in elderly women. J Gerontol A Biol Sci Med Sci. 2002;57(2):B54-60.

51. Danielson ME, Cauley JA, Rohay JM. Physical activity and its association with plasma lipids and lipoproteins in elderly women. Ann Epidemiol. 1993;3(4):351-7.

52. Shigematsu R, Tanaka K, Nho H, Nakagaichi M, Takeda M, Tomita T, Unno H, Ohkawa S. Effects of exercise conditioning on vital age in hyperlipidemic women. J Physiol Anthropol Appl Human Sci. 2000;19(6):279-85.

53. Fonong T, Toth MJ, Ades PA, Katzel LI, Calles-Escandon J, Poehlman ET. Relationship between physical activity and HDL-cholesterol in healthy older men and women: a cross-sectional and exercise intervention study. Atherosclerosis. 1996;127(2):177-83.

54. Nieman DC, Warren BJ, O'Donnell KA, Dotson RG, Butterworth DE, Henson DA. Physical activity and serum lipids and lipoproteins in elderly women. J Am Geriatr Soc. 1993;41(12):1339-44.

55. Oh KJ, Lee DS, Kim WK, Han BS, Lee SC, Bae KH. Metabolic Adaptation in Obesity and Type II Diabetes: Myokines, Adipokines and Hepatokines. Int J Mol Sci. 2016;18(1):pii: E8.

56. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-1, IGF binding protein-3, and cancer risk: systematic review and meta regression analysis. Lancet 2004;363:1346-53.

57. Juul A, Scheike T, Davidsen M, Gyllenborg J & Jorgensen T. Low serum insulin-like growth factor I is associated with increased risk of ischemic heart disease: a population-based case–control study. Circulation 2002;106(8):939-44.

58. O'Connor KG, Tobin JD, Harman SM, Plato CC, Roy TA, Sherman SS, Blackman MR. Serum levels of insulin-like growth factor-1 are related to age and not to body composition in healthy women and men. J Gerontol A Biol Sci Med Sci. 1998;53(3):M176-82.

59. Christopoulos PF, Msaouel P, Koutsilieris M. The role of the insulin-like growth factor-1 system in breast cancer. Mol Cancer. 2015;14:43.

60. van Bunderen CC, van Nieuwpoort IC, van Schoor NM, et al. The Association of Serum Insulin-Like Growth Factor-I with Mortality, Cardiovascular Disease, and Cancer in the Elderly: A Population-Based Study. J Clin Endocrinol Metab 2010; 95(10):4616-24.

61. LeRoith D, Yakar S. Mechanisms of disease: metabolic effects of growth hormone and insulin-like growth factor 1. Nat Clin Pract Endocrinol Metab. 2007;3(3):302-10.

62. Hamrick MW, McNeil PL, Patterson SL. A Role for Myokines in Muscle-Bone Interactions. Exerc Sport Sci Rev. 2011;39(1):43-7.

63. Cappola AR, Bandeen-Roche K, Wand GS, Volpato S, Fried LP. Association of IGF-I levels with muscle strength and mobility in older women. J Clin Endocrinol Metab. 2001;86:4139-46.

64. Westwood AJ, Beiser A, Decarli C, Harris TB, Chen TC, He XM., Seshadri S. Insulin-like growth factor-1 and risk of Alzheimer dementia and brain atrophy. Neurology. 2014;82(18);1613-19.

65. Boger RH, Frystyk J, Ledet T, Moller N, Flyvbjerg A, Orskov H. Low serum insulin-like growth factor I is associated with increased risk of ischemic heart disease. Circulation. 2003;27: 107(20):e193.

66. Higashi Y, Quevedo HC, Tiwari S, Sukhanov S, Shai SY, Anwar A, Delafontaine P. Interaction between insulin-like growth factor-1 and atherosclerosis and vascular aging. Front Horm Res. 2014;43:107-24.

67. Thankamony A, Capalbo D, Marcovecchio ML, Sleigh A, Jørgensen SW, Hill NR, Dunger DB. Low circulating levels of IGF-1 in healthy adults are associated with reduced β-cell function, increased intramyocellular lipid, and enhanced fat utilization during fasting. J Clin Endocrinol Metab. 2014;99(6):2198-207.

68. 27. Borst SE, De Hoyos DV, Garzarella L, Vincent K, Pollock BH, Lowenthal DT, Pollock ML. Effects of resistance training on insulin-like growth factor-I and IGF binding proteins. Med Sci Sports Exerc. 2001;33(4):648-53.

69. Tsai CL, Wang CH, Pan CY, Chen FC. The effects of long-term resistance exercise on the relationship between neurocognitive performance and GH, IGF-1, and homocysteine levels in the elderly. Front Behav Neurosci. 2015;9:23.

70. Chen HT, Chung YC, Chen YJ, Ho SY, Wu HJ. Effects of Different Types of Exercise on Body Composition, Muscle Strength, and IGF-1 in the Elderly with Sarcopenic Obesity. J Am Geriatr Soc. 2017;65(4):827-32.

71. Orsatti FL, Nahas EA, Maesta N, Nahas-Neto J, Burini RC. Plasma hormones, muscle mass and strength in resistance-trained postmenopausal women. Maturitas. 2008;59(4):394-404.

72. Vitiello MV, Wilkinson CW, Merriam GR, Moe KE, Prinz PN, Ralph DD, Colasurdo EA, Schwartz RS. Successful 6-month endurance training does not alter insulin-like growth factor-I in healthy older men and women. J Gerontol A Biol Sci Med Sci. 1997 May;52(3):M149-54.

73. Poehlman ET, Rosen CJ, Copeland KC. The influence of endurance training on insulin-like growth factor-1 in older individuals. Metabolism. 1994;43(11):1401-5.

74. Kumari M, Stafford M, Marmot M. The menopausal transition was associated in a prospective study with decreased health functioning in women who report menopausal symptoms. J Clin Epidemiol. 2005;58(7):719-27.

75. Giltay EJ, Geleijnse JM, Zitman FG, Buijsse B, Kromhout D. Lifestyle and dietary correlates of dispositional optimism in men: The Zutphen Elderly Study. J Psychosom Res. 2007;63(5):483-90.

76. Steptoe A, Gibson EL, Hamer M, Wardle J. Neuroendocrine and cardiovascular correlates of positive affect measured by ecological momentary assessment and by questionnaire. Psychoneuroendocrinology. 2007;32(1):56-64.

77. Ostir GV, Markides KS, Black SA, Goodwin JS. Emotional well-being predicts subsequent functional independence and survival. J Am Geriatr Soc. 2000;48(5):473-8.

78. Lohne-Seiler H, Hansen BH, Kolle E, Anderssen SA. Accelerometer-determined physical activity and self-reported health in a population of older adults (65-85 years): a cross-sectional study. BMC Public Health. 2014;14:284.

79. Hatano Y. Use of the pedometer for promoting daily walking exercise. ICHPER 1993;29:4-8.

80. Yamanouchi K, Takashi T, Chikada K, Nishikawa T, Ito K, Shimizu S, Ozawa N, Suzuki Y, Maeno H, Kato K, Oshida Y, Sato Y. Daily walking combined with diet therapy is a useful means for obese NIDDM patients not only to reduce body weight but also to improve insulin sensitivity. Diabetes Care. 1995;18:775-8.

81. McElrath M, Myers J, Chan K, Fonda H. Exercise adherence in the elderly: Experience with abdominal aortic aneurysm simple treatment and prevention. J Vasc Nurs. 2017;35(1):12-20.

82. Choi BC, Pak AW, Choi JC, Choi EC. Achieving the daily step goal of 10.000 steps: the experience of a Canadian family attached to pedometers. Clin Invest Med 2007;30(3):E108-13.

83. Tudor-Locke C, Ainsworth BE, Whitt MC, Thompson RW, Addy CL, Jones DA. The relationship between pedometer-determined ambulatory activity and body composition variables. Int J Obes Relat Metab Disord. 2001;25(11):1571-8.

84. Conn VS, Burks KJ, Minor MA, Mehr DR. Randomized trial of 2 interventions to increase older women's exercise. Am J Health Behav 2003;27:380-8.

85. Jensen GL, Roy MA, Buchanan AE, Berg MB: Weight loss intervention for obese older women: improvements in performance and function. Obes Res. 2004;12:1814-20.

86. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sone H. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. JAMA. 2009;301(19):2024-35.

87. Rossen J, Yngve A, Hagströmer M, Brismar K, Ainsworth BE, Iskull C, Möller P, Johansson UB. Physical activity promotion in the primary care setting in pre- and type 2 diabetes - the Sophia step study, an RCT. BMC Public Health. 2015;15:647.

88. Bidlingmaier M, Friedrich N, Emeny RT, Spranger J, Wolthers OD, Roswall J et al. Reference intervals for insulin-like growth factor-1 (igf-i) from birth to senescence: results from a multicenter study using a new automated chemiluminescence IGF-I immunoassay conforming to recent international recommendations. J Clin Endocrinol Metab. 2014;99(5):1712-21.

89. Sowers M, Zheng H, Tomey K, et al. Changes in body composition in women over sic years at midlife: ovarian and chronological aging. J Clin Endocrinol Metab 2007;92:895–901.

90. Hameed M, Harridge SD, Goldspink G. Sarcopenia and hypertrophy: a role for insulin-like growth factor-1 in aged muscle? Exerc Sport Sci Rev 2002;30(1):15-9.

91. Rinaldi S, Kaaks R, Friedenreich CM, Key TJ, Travis R, Biessy C et al. Physical activity, sex steroid, and growth factor concentrations in pre- and post-menopausal women: a cross-sectional study within the EPIC cohort. Cancer Causes Control. 2014;25(1):111-24.

92. Brun JF, Varlet-Marie E, Connes P, Aloulou I. Hemorheological alterations related to training and overtraining. Biorheology. 2010;47(2):95-115.

93. Connes P, Simmonds MJ, Brun JF, Baskurt OK. Exercise hemorheology: classical data, recent findings and unresolved issues. Clin Hemorheol Microcirc. 2013;53(1-2):187-199.

94. Sandor B, Nagy A, Toth A, Rabai M, Mezey B, Csatho A, Czuriga I, Toth K, Szabados, E. Effects of moderate aerobic exercise training on hemorheological and laboratory parameters in ischemic heart disease patients. PLoS One. 2014;9(10):e110751.

95. Villaverde Gutiérrez C, Torres Luque G, Ábalos Medina GM, Argente del Castillo MJ, Guisado IM, Guisado Barrilao R et al. Influence of exercise on mood in postmenopausal women. J Clin Nurs. 2012;21(7-8):923-8.

96. Isla Pera P, Moncho Vasallo J, Torras Rabasa A, Oppenheimer Salinas F, Fernández Cruz Pérez L, Ricart Brulles MJ. Quality of life in simultaneous pancreas-kidney transplant recipients. Clin Transplant 2009;23:600-5.

97. Smith GC, Trauer T, Kerr PG, Chadban SJ. Prospective quality-of-life monitoring of simultaneous pancreas and kidney transplant recipients using the 36-item short form health survey. Am J Kidney Dis 2010;55:698-707.

98. Easton JD. Evidence with antiplatelet therapy and ADP-receptor antagonists. Cerebrovasc Dis 2003;16:20-6.

99. Mani H, Lindhoff-Last E. Resistenz gegen Azetylsalizylsäure und Clopidogrel. Hämostaseologie 2006; 26: 229-38.

100. Matas AJ, Gillingham KJ, Humar A, Kandaswamy R, Sutherland DE, Payne WD et al. 2202 Kidney transplant recipients with 10 years of graft function: What happens next? Am J Transplant 2008;8:2410-9.

101. Biesenbach G, Königsrainer A, Gross C, Margreiter R. Progression of macrovascular diseases is reduced in type 1 diabetic patients after more than 5 years successful combined pancreas-kidney transplantation in comparison to kidney transplantation alone. Transpl Int 2005;18:1054-60.

102. Papp J, Kenyeres P, Toth K. Clinical importance of antiplatelet drugs in cardiovascular diseases. Clin Hemorheol Microcirc 2013;53:81-96.

103. Shah U, Ma AD. Tests of platelet function. Curr Opin Hematol 2007;14:432-7.

104. Feher G, Koltai K, Kesmarky G, Toth K. Hemorheologicl background of acetylsalicylic acid resistance. Clin Hemorheol Microcirc 2008;38:143-52.

105. Koltai K, Feher G, Kenyeres P, Lenart I, Alexy T, Horvath B et al. Relation of platelet aggregation and fibrinogen levels to advancing age in aspirin- and thienopyridine-treated patients. Clin Hemorheol Microcirc 2008;40:295-302.

106. Hennekens CH, Schror K, Weisman S, FitzGerald GA. Terms and conditions: semantic complexity and aspirin resistance. Circulation 2004;110:1706-8.

107. Dussaillant NG, Zapata MM, Fardella BP, Conte LG, Cuneo VM. Frequency and characteristics of aspirin resistance in Chilean cardiovascular patients. Rev Med Chil 2005; 133:409-17.

108. B. Łabuz-Roszak, K. Pierzchała, K. Tyrpień: Resistance to acetylsalicylic acid in patients with type 2 diabetes mellitus is associated with lipid disorders and history of current smoking. J Endocrinol Invest 2014;37:33-8.

109. Tasdemir E1, Toptas T, Demir C, Esen R, Atmaca M. Aspirin resistance in patients with type II diabetes mellitus. Ups J Med Sci 2014;119:25-31.

110. Schroeder WS, Ghobrial L, Gandhi PJ. Possible mechanisms of drug-induced aspirin and clopidogrel resistance. J Thromb Thrombolysis 2006;22:139-50.

111. Ferguson AD, Dokainish H, Lakkis N. Aspirin and clopidogrel response variability: review of the published literature. Tex Heart Inst J 2008;35:313-20.

112. Postuła M, Tarchalska-Kryńska B, Filipiak KJ, Kosior D, Serafin A, Huczek Z, Opolski G et al. Factors responsible for "aspirin resistance" - can we identify them? Kardiol Pol 2010;68:403-11.

113. Michos ED, Ardehali R, Blumenthal RS, Lange RA, Ardehali H. Aspirin and clopidogrel resistance. Mayo Clin Proc April 2006;81:518-26.

114. Fitzgerald DJ, Maree A. Aspirin and clopidogrel resistance. Hematology Am Soc Hematol Educ Program 2007;114-202.

115. Sandor B, Varga A, Rabai M, Toth A, Papp J, Toth K et al. Aspirin resistance as a cardiovascular risk after kidney transplantation. Korea-Australia Rheol J 2014;26:237-41.

116. Rana A, Gruessner A, Agopian VG, Khalpey Z, Riaz IB, Kaplan B et al. Survival benefit of solid-organ transplant in the United States. JAMA Surg. 2015;150(3):252-259

117. Nemes B, Szederkényi E, Nagy KK, Hartyánszky I, Ablonczy L,Vámos FR, Mihály S, Máthé Z. A Summary of Transplantation Activity in Hungary. Transplant Proc. 2019;51(4):1202-1208.

118. Szederkényi E, Szenohradszky P, Csajbók E, Perner F, Asztalos L, Kalmár N.K et al. 50-year history of kidney transplantation in Hungary. Orv Hetil. 2013;154(22):846-849.

119. McDonald SP, Russ GR. Australian registries-ANZDATA and ANZOD. Transplant Rev. 2013;27(2):46-49.

120. Terasaki PI. The UNOS scientific renal transplant registry. United Network for Organ Sharing. Clin Transpl. 1995:1-18.

121. Pruthi R, Casula A, MacPhee I. UK Renal Registry 15th annual report: Chapter 3 demographic and biochemistry profile of kidney transplant recipients in the UK in 2011: national and centre-specific analyses. Nephron Clin Pract. 2013;123 Suppl 1:55-80.

122. Matas AJ, Smith JM, Skeans MA, Thompson B, Gustafson SK, Stewart DE et al. OPTN/SRTR 2013 Annual Data Report: kidney. Am J Transplant. 2015;15 Suppl 2:1-34.

123. Jemni M, Zaman MJ, La Rocca D, Tabacchi G. Southern Italian teenagers: the older they get, the unfit they become with girls worse than boys: a cohort epidemiological study: The adolescents surveillance system for the obesity prevention project (ASSO). Medicine (Baltimore). 2017;96(51):e8810.

124. Patel SS, Molnar MZ, Tayek JA, Ix JH, Noori N, Benner D et al. Serum creatinine as a marker of muscle mass in chronic kidney disease: results of a cross-sectional study and review of literature. J Cachexia Sarcopenia Muscle. 2013;4(1):19-29.

125. Bain BJ. Platelet count and platelet size in males and females. Scand J Haematol. 1985;35(1):77-9.

126. Perico N, Cattaneo D, Sayegh MH, Remuzzi G. Delayed graft function in kidney transplantation. Lancet. 2004;364:1814-27.

127. Arlagadda S, Coca S, Formica RJ, Poggio ED, Parikh CR. Association between delayed graft function and allograft and patient survival: a systematic review and meta-analysis. Nephrol Dial Transplant. 2009;24:1039-47.

128. https://www.usrds.org/2008/pdf/V2_07_2008.pdf

129. http://images.slideplayer.com/12/3498373/slides/slide_55.jpg

130. https://www.ksh.hu/elef/archiv/2009/i/kal_jozan_2.gif

131. Moghimi M., Kianoosh Falaknazi, Nazila Bagheri: Impact of cardiovascular risk factors on the outcome of renal transplantation. Saudi J Kidney Dis Transpl. 2010;21(3);438-42.

132. https://www.ncbi.nlm.nih.gov/books/NBK453383/figure/mortality.f3/?report=objectonly

133. Silkensen JR. Long-Term Complications in Renal Transplantation. J Am Soc Nephrol. 2000;11:582-8.

134. http://gco.iarc.fr/today/online-analysis-pie.

135. Young CJ, Gaston RS. African Americans and renal transplantation: disproportionate need, limited access, and impaired outcomes. Am J Med Sci. 2002;323:94.

136. Hancock I. Romanies and the holocaust: a reevaluation and an overview. In: The historiography of the Holocaust. Palgrave-Macmillan, New York 2004.

137. Thomas JD, Doucette MM, Thomas DC, Stoeckle JD. Disease, lifestyle, and consanguinity in 58 American Gypsies. Lancet. 1987;2:377–379.

138. Vozarova de Courten B, de Courten M, Hanson RL, Zahorakova A, Egyenes HP et al. Higher prevalence of type 2 diabetes, metabolic syndrome and cardiovascular diseases in gypsies than in non-gypsies in Slovakia. Diabetes Res Clin Pract. 2003;62(2):95-103.

139. Thomas JD, Doucette MM, Thomas DC, Stoeckle JD. Disease, lifestyle, and consanguinity in 58 American Gypsies. Lancet. 1987;2(8555):377-379.

140. Inotai D, Szilvasi A, Benko S, Boros-Major A, Illes Z, Bors A et al. HLA genetic diversity in Hungarians and Hungarian Gypsies: complementary differentiation patterns and demographic signals revealed by HLA-A, -B and -DRB1 in Central Europe. Tissue Antigens. 2015;86(2):115-121.

141. Molnar MZ, Langer RM, Remport A, Czira ME, Rajczy K, Kalantar-Zadeh K et al. Roma ethnicity and clinical outcomes in kidney transplant recipients. Int Urol Nephrol. 2012;44(3):945-954.

142. Kósa K, Daragó L, Adány R. Environmental survey of segregated habitats of Roma in Hungary: a way to be empowering and reliable in minority research. Eur J Public Health. 2011;21(4):463-468.

143. Kosa Zs, Szeles G, Kardos L, Kosa K, Nemeth R, Orszagh S, Fesus G, McKee M, Adany R, Voko Z A comparative health survey of the inhabitants of Roma settlements in Hungary. Am J Public Health 2007;97:853–859.

144. Langer RM, Hidvegi M, Jaray J. Significant differences in the efficacy of kidney transplantation between Hungarian Caucasians and Gypsies. Transpl Proc. 2005;37:729–730.

145. Johnson RJ, Belger MA, Briggs JD, Fuggle SV, Morris PJ; UK Transplant Kidney and Pancreas Advisory Group. Renal transplantation in the UK and Republic of Ireland. Clin Transpl. 2000;105-13.

146. Oppenheimer F, Aljama P, Asensio Peinado C, Bustamante Bustamante J, Crespo Albiach JF, Guirado Perich L. The impact of donor age on the results of renal transplantation. Nephrol Dial Transplant. 2004;19 Suppl 3:iii11-5.

147. Meier-Kriesche HU, Port FK, Ojo AO, Rudich SM, Hanson JA, Cibrik DM et al. Effect of waiting time on renal transplant outcome. Kidney Int. 2000;58(3):1311-1317.

148. Pirsch JD, Miller J, Deierhoi MH, Vincenti F, Filo RS. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. Transplantation 1997;63:977-83.

149. Matas AJ. Chronic progressive calcineurin nephrotoxicity: an overstated concept. Am J Transplant. 2011;11(4): p. 687-92.

150. Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J et al. Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study. Health Technol Assess. 2005;9(21):1-179.

151. Kayler LK, Magliocca J, Zendejas I, Srinivas TR, Schold JD. Impact of cold ischemia time on graft survival among ECD transplant recipients: a paired kidney analysis. Am J Transplant. 2011;11(12):2647-56.

152. Summers DM, Johnson RJ, Hudson A, Collett D, Watson CJ, Bradley JA. Effect of donor age and cold storage time on outcome in recipients of kidneys donated after circulatory death in the UK: a cohort study. Lancet. 2013;381(9868):727-34.

153. Van der Vliet JA, Warlé MC, Cheung CL, Teerenstra S, Hoitsma AJ. Influence of prolonged cold ischemia in renal transplantation. Clin Transplant. 2011;25(6):E612-6.

154. Debout A, Foucher Y, Trébern-Launay K, Legendre C, Kreis H, Mourad G et al. Each additional hour of cold ischemia time significantly increases the risk of graft failure and mortality following renal transplantation. Kidney Int. 2015;87(2):343-9.

155. Roodnat JI, Mulder PG, Van Riemsdijk IC, IJzermans JN, van Gelder T, Weimar W. Ischemia times and donor serum creatinine in relation to renal graft failure. Transplantation. 2003;75:799–804.

156. Friedman AN, Miskulin DC, Rosenberg IH et al. Demographics and trends in overweight and obesity in patients at time of kidney transplantation. Am J Kidney Dis. 2003;41:480-7.

157. Curran SP, Famure O, Li Y, Kim SJ. Increased recipient body mass index is associated with acute rejection and other adverse outcomes after kidney transplantation. Transplantation. 2014;97(1):64-70.

158. Sood A, Hakim DN, Hakim NS. Consequences of Recipient Obesity on Postoperative Outcomes in a Renal Transplant: A Systematic Review and Meta-Analysis. Exp Clin Transplant. 2016;14(2):121-8.

159. Howard RJ, Thai VB, Patton PR, et al. Obesity does not portend a bad outcome for kidney transplant recipients. Transplantation. 2002;73:53.

160. Johnson DW, Isbel NM, Brown AM, Kay TD, Franzen K, Hawley CM et al. The effect of obesity on renal transplant outcomes. Transplantation. 2002;74:675.

Publications of the author

Topic related journal articles

Praksch D, Sandor B, Nagy KK, Viola M, Toth A, Toth K, Szakaly P, Varga A. Acetylsalicylic Acid Resistance After Simultaneous Pancreas-Kidney Transplantation. Transplantation Proceedings. 2016; 48(7):2555-7.

Quartile Ranking: Q2 Impact Factor: 0.908 (2016)

Praksch D, Kovacs D, Sandor B, Petrovics P, Kovacs K, Toth K, PhD, Szabados E. Impact of home- and center- based physical training program on cardio-metabolic health and IGF-1 level in elderly women. European Journal Aging and Physical Activity.

Quartile Ranking: Q2 Impact Factor: 2.65 (2017/2018)

Other articles

1. Varga A, Sandor B, Kalmar NK, **Praksch D**, Gombos K, Toth A, Toth K, Szakaly P. Clopidogrel Resistance after Renal Transplantation. In Vivo. 2015;29(2):301-3.

Quartile Ranking: Q3 Impact Factor: 1.116 (2015)

2. Kovacs D, Csiszar B, Biro K, Koltai K, Endrei D, Juricskay I, Sandor B, **Praksch D**, Toth K, Kesmarky G. Toe-brachial index and exercise test can improve the exploration of peripheral artery disease. Atherosclerosis. 2018;269:151-158.

Quartile Ranking: Q1 Impact Factor: 4.239 (2018)

3. Szakaly P, Kalmar-Nagy K, **Praksch D**, Vas T, Varga A. More than Twenty Years' Experience with "Zero-Hour" Transplant Kidney Biopsy. Clin Surg. 2018;3:2153.

Impact Factor: 1.820 (2018)

Published abstracts

1. **Praksch D**, Sándor B, Varga Á, Rábai M, Szakály P, Tóth K. Aspirin rezisztencia vizsgálata vesetranszplantáción átesett betegek körében. Magyar Haemorheologiai Társaság 21. Kongresszusa, 2014. április 4-5., Balatonkenese, Érbetegségek, 21, 42-43. (2014)

2. Kovacs D, Csiszar B, Biro K, Koltai K, **Praksch D**, Totsimon K, Endrei D, Toth K, Kesmarky G. Perifériás ütőérbetegek végtag ischaemiájának terheléses vizsgálata hemoreológiai aspektusból. Magyar Haemorheologiai Társaság XXIII. Magyar Mikrocirkulációs és Vaszkuláris Biológiai TársaságMagyar Szabadgyök-Kutató Társaság V. Közös Kongresszusa, Balatonkenese, 2016. április 22-23. Érbetegségek. 2016; 23 p. 30. (2016)

3. **Praksch D**, Kovacs D, Sandor B, Totsimon K, Mezey B, Petrovics P, Wilhelm M, Kesmarky G, Toth K, Szabados E. Ambuláns és otthoni fizikai tréning hatásának vizsgálata magas kardiovaszkulárisrizikójú nőbetegek körében. Magyar Haemorheologiai Társaság XXIII. MagyarMikrocirkulációs és Vaszkuláris Biológiai Társaság Magyar Szabadgyök-Kutató Társaság V. Közös Kongresszusa, Balatonkenese, 2016. április 22-23. Érbetegségek. 2016; 23 p. 30. (2016)

4. **Praksch D**, Kovács D, Sándor B, Tótsimon K, Mezey B, Petrovics P, Wilhelm M, Tóth K, Szabados E. Ambuláns és otthoni fizikai tréning hatásának vizsgálata magas kardiovaszkuláris rizikójú betegek körében. A Magyar Kardiológusok Társasága 2016. évi Tudományos Kongresszusa. Balatonfüred. Cardiologia Hungarica. 2016; 46: Suppl. F, p 74. (2016)

5. Kovács D, Csiszár B, Juricskay I, Bíró K, Koltai K, Endrei D, **Praksch D**, Tóth K, Késmárky G. Non-invazív módszerek és terheléses vizsgálatok szerepe perifériás ütőérbetegek végtag iszkémiájának diagnosztikájában. Magyar Angiológiai és Érsebészeti Társaság 2017. évi Kongresszusa. Szombathely, 2017 június 15-17. Érbetegségek. 2017; 2 pp. 11, p 1. (2017)

6. Kovacs D, Csiszar B, Juricskay I, Biro K, Koltai K, Endrei D, **Praksch D**, Toth K, Kesmarky G. Terheléses vizsgálatok szerepe perifériás ütőérbetegek végtag iszkémiájának diagnosztikájában. Magyar Kardiológusok Társasága 2017. évi Tudományos Kongresszusa, Balatonfüred, 2017. május 11-13. Cardiologia Hungarica. 2017; 47 Suppl. C: p. 129. (2017)

7. Halmosi R, Gal R, Deres L, Horvath O, **Praksch D**, Marton Zs, Sumegi B, Toth K, Habon T. The effect of resveratrol on non-invasive cardiologic and laboratory parameters in systolic heart failure. Heart Failure 2018 and the World Congress on Acute Heart Failure, Bécs, Ausztria, 2018. május 26-29. European Journal of Heart Failure. 2018; Supplement 20 : Suppl.S1 p. 565. (2018)

8. Gal R, Deres L, Horvath O**, Praksch D**, Marton ZS, Sumegi B, Toth K, Habon T, Halmosi R

The effect of resveratrol on non-invasive cardiologic and laboratory parameters in systolic heart failure. Magyar Kardiológusok Társasága 2018. évi Tudományos Kongresszusa, Balatonfüred, 2018. május 10-12. Cardiologica Hungarica. 2018; 48 : Suppl. C p. C 65. (2018)

9. Petrovics P, Nagy A, Palfi A, Krizsan A, **Praksch D**, Toth K, Szabados E. Életmódi szokások, tápláltsági állapot és pszichés jóllét felmérése 14-18 éves diákoknál. Cardiologia Hungarica 48 : Suppl. C pp. 89. (2018)

Poster

Praksch D, Sándor B, Varga Á, Rábai M, Szakály P, Tóth K. Vesetranszplantált betegek ASA-rezisztenciája: összehasonlítás a populációs rezisztencia adatokkal. A Magyar Kardiológusok Társasága 2014. évi Tudományos Kongresszusa, 2014. május 14-17., Balatonfüred, Cardiologia Hungarica 44, Suppl. E, E59. (2014)