

Cardiovascular risk factors in pediatric kidney transplant recipients

Margarida Cunha¹ , Ana Gusmão Palmeiro² , Ana Rita Sandes³ , Rosário Stone³ 

¹Serviço de Pediatria, Hospital de Santa Maria, Centro Hospitalar Lisboa Norte, Lisboa, Portugal

²Faculdade de Medicina da Universidade de Lisboa, Hospital de Santa Maria, Centro Hospitalar Lisboa Norte, Lisboa, Portugal

³Unidade de Nefrologia Pediátrica e Transplantação Renal, Serviço de Pediatria, Hospital de Santa Maria, Centro Hospitalar Lisboa Norte, Lisboa, Portugal

Contributions of authors:

- MC, AP, ARS: Conception and design.
- MC, AP: Acquisition of data and drafting the article.
- MC, ARS, RS: Analysis and interpretation of data, contribute with intellectual content, final approval of the version published.
- ARS, RS: Critical revision.

ABSTRACT

Introduction: Cardiovascular risk factors decrease after kidney transplantation, however cardiovascular disease remains one of the most common causes of death in children and young adults. The authors performed a comprehensive analysis of cardiovascular risk factors before and after kidney transplantation. **Methods:** Retrospective study, from 2007 to 2017, that included children and adolescents with a minimum of six months follow-up after kidney transplant. Demographic profile, chronic kidney disease characteristics and family and personal cardiovascular risk factors (hypertension, left ventricular hypertrophy, anemia, overweight/obesity, dyslipidemia, hypoalbuminemia and new onset diabetes after transplant) were assessed. Pre- and post-transplant cardiovascular risk factors were compared using the McNemar test. **Results:** We included 49 patients, with a mean age at the time of transplantation of 9.3 ± 4.2 years. Congenital anomalies of kidney and urinary tract (37.7%) and glomerulopathies (32.7%) were the most frequent causes of stage 5 chronic kidney disease. Transplantation was preemptive in five patients. Living donor transplant was performed in six cases. The immunosuppression regimen was identical in all patients and there were nine acute rejection episodes. The most frequent pre-transplant cardiovascular risk factors were dyslipidemia (90.3%), hypertension (70.8%) and anemia (61.9%). After transplant there was a decrease of all cardiovascular risk factors except for overweight/obesity. Although a better control of hypertension was granted, the decrease was not significant. Hypoalbuminemia and dyslipidemia decreased from the 6-month evaluation on ($p < 0.001$) and left ventricular hypertrophy and anemia from the second year on ($p < 0.05$). **Conclusions:** We aimed to evaluate the evolution of cardiovascular risk factors in pediatric patients before and after kidney transplant. In our cohort there was a decrease in all studied cardiovascular risk factors after kidney transplant, except for overweight/obesity. This could mean that chronic kidney disease related factors decrease with time, but traditional risk factors may persist or increase, and need active prevention.

Keywords: Cardiovascular diseases, heart disease risk factors, kidney transplantation, pediatrics

© 2022 Portuguese Journal of Nephrology & Hypertension. Published by Publicações Ciência & Vida
This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in chronic kidney disease (CKD) patients. Although this risk decreases after kidney transplantation (KT), when compared with dialysis patients, it remains one of the most common causes of death in transplanted children and young adults.⁽¹⁻⁵⁾

KT is the best therapeutic alternative in pediatric stage 5 CKD and is associated with an increase of approximately 20 years in survival when compared with chronic dialysis.⁽⁶⁾ After KT, better quality of life⁽⁷⁾, linear growth and neurocognitive development^(8,9) are reported. Even so, the average life expectancy remains lower than that of general population, which is largely due to premature CVD.⁽³⁾ When compared

with controls of the same age, these patients have 50 times the annual rate of cardiovascular events and up to 10 times the rate of cardiovascular death.⁽¹⁰⁾

In kidney transplant recipients, cardiovascular morbidity and mortality cannot be explained only by “traditional” Framingham risk factors.⁽¹¹⁻¹³⁾ Specific stage 5 CKD and also transplant-associated factors have to be taken into account.⁽¹¹⁻¹³⁾ A combination of these specific and general risk factors is responsible for CVD in children with CKD.⁽¹⁴⁾

Traditional cardiovascular risk factors include hypertension (HTN), dyslipidemia, changes in glucose metabolism, sedentary lifestyle (in relation with obesity), smoking and family history of CVD.⁽¹⁵⁾ Stage 5 CKD-related factors include anemia, disturbed lipid and calcium-phosphate

metabolism, hyperparathyroidism, hyperhomocysteinemia, hypoalbuminemia, proteinuria and chronic inflammation.^(11,12,15) Modality and age of start of kidney replacement therapy has also to be taken into account^(16–18). Transplant-associated factors include: donor characteristic (cadaver vs living donor, genetics, nephron mass, organ quality, advanced age, CVD), immunosuppressive regimen, number of acute graft rejections, viral infections and recurrence of kidney disease⁽¹⁹⁾.

Factors known to be associated with a higher mortality risk include: dialysis when compared to pre-emptive kidney transplant^(16–18), younger age at start of kidney replacement therapy⁽¹⁸⁾ and its duration⁽²⁰⁾, female sex,⁽¹⁸⁾ Asian origin⁽²¹⁾ and primary kidney disease other than congenital anomalies of kidney and urinary tract (CAKUT) or glomerulonephritis.⁽¹⁸⁾

Immunosuppressive agents also have known cardiovascular side effects.^(5,22) Calcineurin inhibitors cause HTN and predispose to insulin resistance.⁽²²⁾ Mammalian Target Of Rapamycin (mTOR) inhibitors induce dyslipidemia.⁽²²⁾ Corticosteroids have a large incremental effect on insulin resistance⁽²²⁾, arterial HTN and hyperlipidemia.⁽²³⁾

Although CVD rarely is symptomatic in pediatric age, it is known that it begins at an early age, and progresses to adulthood when most mortality occurs^(5,11,24). The etiology of this unfavorable long-term outcome is multifactorial.⁽²³⁾ In children with CKD, non-classical risk factors associated with uremia may be prominent in patients before KT, while classical risk factors (e.g. HTN, hypercholesterolemia, obesity, diabetes) seem to gain significant relevance after transplantation.⁽⁵⁾

These clinical characteristics make it difficult to extrapolate data directly from adult populations.⁽³⁾ Then again, the fact that pediatric CKD is uncommon makes it difficult to conduct large multicenter longitudinal studies to understand the true impact of cardiovascular risk in children.⁽¹¹⁾

An estimation of cardiovascular risk is important not only to identify potential modifiable risk factors, but also to evaluate the effect of treatments.^(15,17)

The aim of this study was to perform a comprehensive analysis of cardiovascular risk factors in children before and after kidney transplantation.

SUBJECTS AND METHODS

We carried out a retrospective study of all children and adolescents in follow-up during 2017 in our pediatric KT clinic, with a minimum of six months and a maximum of 10 years after KT (from 2007 to 2017). Informed consent was obtained from the legal guardians of patients. Ethics commission approval was obtained.

Data collected from clinical files and interviews included: **1)** demographics: age (at the time of transplant and current age), follow-up time, gender and ethnicity; **2)** family cardiovascular risk factors: overweight/obesity, dyslipidemia, diabetes, and HTN; **3)** CKD characteristics: CKD etiology, transplant type (pre-emptive or post-dialytic), donor type, dialysis duration, dialysis type, pre-transplant diuresis,

post-transplant glomerular filtration rate (GFR) and immunosuppression regimen; **4)** personal cardiovascular risk factors: HTN, left ventricular hypertrophy (LVH), anemia, overweight/obesity, dyslipidemia, hypoalbuminemia, new onset diabetes after transplant (NODAT); **5)** other personal comorbidities.

Chronic Kidney disease characteristics

Post-transplant GFR was calculated based on the revised Schwartz formula (2009) at the 2nd year post-transplant. Immunosuppression regimens were characterized. Rejection episodes, requiring dose escalation of immunosuppressants, were analyzed.

Cardiovascular risk factors

Personal cardiovascular risk factors were established according to a definition (Table 1). Blood pressure (BP) was measured in every appointment, in an automated oscillometric device.

Personal cardiovascular risk factors were evaluated before and after KT. We collected and analyzed data concerning the 6th month, 1st, 2nd, 5th and 10th years post-transplant and compared them with pre-transplant data. Patients were considered to have cardiovascular risk whenever they had one or more cardiovascular risk factor.

Statistical analysis was performed using IBM® SPSS® software version 24. Categorical variables were described as frequencies and percentages, and continuous variables as means and standard deviations. The minimum and maximum values were reported whenever considered relevant. The association between paired independent categorical

Table 1

Personal CV risk factors definition

Hypertension (HTN) ¹	≥ P95 and/or under pharmacologic treatment for HTN
LVH	Z-score > 2 indexed to body surface
Anemia ²	<5yrs: <11mg/dL; 5-12yrs: <11,5mg/dL; 12-15yrs: <12mg/dL; >15yrs (♀): <12mg/dL/ (♂): <13mg/dL
Overweight/obesity ¹	BMI > P85 th
Dyslipidemia ³ (at least one)	Total cholesterol: ≥ 200mg/dL LDL-c ≥ 130mg/dL Triglycerides: ≤ 9yrs > 100mg/dL; ≥ 9yrs: > 130mg/dL
Hypoalbuminemia	Serum albumin < 3 g/dL
Diabetes/ NODAT ⁴	Fasting glycaemia ≥ 126mg/dL; HbA1c ≥ 6,5% Impaired OGTT

BMI – Body mass index; CV – cardiovascular; HbA1c – glycated hemoglobin; HTN – Hypertension; LDL-c – Low density lipoprotein cholesterol; LVH – Left ventricular hypertrophy; NODAT – new onset diabetes after transplant; OGTT – oral glucose tolerance test, P – percentile

¹ National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004 Aug;114(2 Suppl 4th Report):555-76; ² KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease vol. 2, 331-5, 2012; ³ Jellinger PS, Handelsman Y, Rosenblit PD, *et al* AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE. *Endocr Pract*. 2017 Apr;23(Suppl 2):1-87. ⁴ American Diabetes Association. (2) Classification and diagnosis of diabetes. *Diabetes Care*. 2015 Jan;38 Suppl:S8-S16.

variables was tested by McNemar tests. All tests performed were two-tailed, and a *P* value of 0.05 or less was considered as statistically significant.

RESULTS

We initially enrolled 52 patients with a minimum of six months follow-up. Three were excluded, one for graft loss, one was transferred to the adult unit and one for lack of data. Forty nine children and adolescent were found eligible to participate in the study.

Demographic characteristics

Demographic characteristics of patients were collected (Table 2). The mean age at the time of transplantation was 9.3 ± 4.2 years, with a median age of 8.4 years (minimum 3.1; maximum of 17.2).

Table 2

Demographic characteristics of the population (n=49)

Characteristics	Nº patients (%)
Age at transplant (years)	
Mean \pm SD	9,3 \pm 4,2
Current Age (years)	
Mean \pm SD	14,1 \pm 3,7
Follow-up time (years)	
Mean \pm SD	4,7 \pm 3,4
Gender	
Female	26 (53.1)
Male	23 (46.9)
Origin	
Caucasian	37 (75.5)
African	12 (24.5)

Chronic Kidney disease characteristics

Patient clinical characteristics were analyzed (Table 3). Twenty-one (42.9%) had at least one comorbity and the most common were endocrine, osteoarticular and cardiac.

CAKUT (37.7%), glomerulopathy (32.7%) and vascular diseases (10.2%) were the most frequent causes of CKD. Forty four underwent dialysis, the majority peritoneal dialysis (84.4%). The minimum duration of dialysis was 3 months and the maximum of 103, with a mean of 37 ± 24.9 months. Pre-transplant anuria was present in 12/40 (30%). Transplantation was preemptive in five patients (two of which from living donor). Living donor transplant was performed in 6 (12.2%) cases.

The immunosuppression regimen was identical in all patients and included: prednisolone with starting dose of 60 mg/m², decreasing during the first six months to a dose of 10 mg/m²/day every other day, tacrolimus for a trough concentration of 10 ng/mL in the first three months and 5 ng/ml thereafter, and mycophenolate mofetil 300-600mg/m²/dose. Mycophenolate mofetil was replaced by

Table 3

Clinical characteristics of the population (n=49)

Characteristics	Nº patients (%)
Family CV risk factors	
Obesity	15/41 (36.6)
Hypertension	26/41 (63.4)
Dyslipidemia	16/39 (41)
Diabetes	15/40 (37.5)
Other Personal Comorbidities	
Endocrine	6 (12,2%)
Osteoarticular	6 (12,2%)
Cardiac	6 (12,2%)
Neurological	4 (8,2%)
Others	4 (8,2%)
CKD stage 5 etiology	
CAKUT	18 (36.7)
Glomerulopathy	16 (32.7)
Vascular disease	5 (10.2)
Hereditary disease	4 (8.2)
Other causes	3 (6.1)
Unknown	3 (6.1)
Transplant type	
Pre-emptive	5 (10.2)
Post-dialytic	44 (89.8)
Transplant donor	
Cadaver	43 (87.8)
Living	6 (12.2)
Dialysis duration (months)	
Mean \pm SD	37 \pm 24.9
Dialysis type	
Peritoneal dialysis	38/44 (86.3)
Hemodialysis	2/44 (4.5)
Both	4/44 (9)
Urine output pre-transplant	
Residual diuresis	29/40 (70)
Anuria	12/40 (30)
Post-transplant GFR (mL/min/m²)^a	
Mean \pm SD	83.5 \pm 24

CAKUT – Congenital anomalies of the kidney and urinary tract; CKD – Chronic kidney disease; SD – Standard deviation. ^aGFR measured two years post-transplant

azathioprine in one patient following an adverse skin reaction. There were nine (18.4%) acute rejection episodes (one per patient), no multiple episodes. The cardiovascular risk factors identified in the last evaluation of patients with rejection episodes were: HTN in seven (77.8%), LVH in one (11%), NODAT in one (11%), anemia in four (44%) and hypercholesterolemia in three (33%). The follow-up ranged from two to seven years, reason for why we did not perform statistical evaluation.

Personal CV risk factors

Evaluations of cardiovascular risk factors were made pre-transplant and in different moments of the follow-up with a minimum of 6 months follow-up and a maximum of 10 years (Table 4). From the forty-nine patients, forty-five had 1 year follow-up, thirty-four had 2 years follow-up, twenty had 5 years follow-up and three had 10 years follow-up.

Table 4

Evolution of CV risk factors pre and post-transplant

Characteristics	Pre-transplant CV risk factors		Post-transplant CV risk factors						
	n=49	6mth n=49		1yr n=45		2yr n=34		5yr n=20	
	n (%)	n (%)	p-value	n (%)	p-value	n (%)	p-value	n (%)	p-value
CV risk	47/49 (95.9)	47/49 (95.9)	1	41/45 (91.1)	0.625	27/32 (84.4)	0.219	15/20 (75)	0.063
HTN	34/48 (70.8)	41/49 (83.7)	0,039	33/45 (73.3)	0.508	23/34 (67.6)	0.754	11/20 (55)	0.219
LVH	17/40 (42.5)	2/10 (20)	0,5	4/20 (20)	0.219	4/27 (14.8)	0,021	0 (0)	–
Anemia	26/42 (61.9)	30/49 (61.2)	1	20/45 (44.4)	0.250	10/34 (29.4)	0,013	1/20 (5)	0,002
Hypoalbuminemia	13/38 (34.2)	1/44 (2,3)	<0,001	2/43 (4,7)	0,003	0 (0)	–	0 (0)	–
Diabetes/ NODAT	0 (0)	0 (0)	–	1/44 (2)	–	0 (0)	–	0 (0)	–
Overweight/Obesity	2/49 (4.2)	5/47 (10.2)	0.375	4/44 (9)	0.625	6/34 (17.6)	0.219	3/20 (15)	0.500
Dyslipidemia	28/31 (90.3)	16/34 (47.1)	<0,001	17/42 (40.5)	<0,001	3/31 (9.7)	<0,001	3/20 (15)	–

Pre-transplant cardiovascular risk was found in 47/49 (96%) of our patients and they are described in Table 5, with a median of 3.1 ± 1.49 cardiovascular risk factors per patient. The more frequent were dyslipidemia (90.3%) – 79% (22/28) due to hypertriglyceridemia, HTN (70.8%) and anemia (61.9%). Nutritional evaluation, based on body mass index (BMI), found 43 (87.7%) patients within normal weight range, 4 (8%) underweighted and 2 (4%) overweighted or obese.

From the 1st year follow-up onwards, there was a non-significant decrease in the cardiovascular risk ($p>0.05$), but there was a significant reduction on the median number of cardiovascular risk factors over the follow-up time: at 6 months 2.0 ± 0.98 ($p<0.001$), 1 year 1.8 ± 0.91 ($p<0.001$), 2 years 1.5 ± 0.90 ($p<0.001$) and 5 years 0.95 ± 0.75 ($p<0.001$).

Regarding the evolution of each cardiovascular risk factor, there was a significant decrease of all, except overweight/obesity. Overweight/obesity duplicated in the 6-month follow-up and had a maximum at the 2-year follow-up ($p>0.05$). There were no underweight patients after transplant. Concerning HTN, it increased 13% ($p=0.039$) at the 6-month follow-up, but decreased non-significantly in all the following evaluations. Hypoalbuminemia and dyslipidemia decreased from the 6-month evaluation on ($p<0.001$) and LVH and anemia from the 2nd year on ($p<0.05$). There was only one patient with a transient diagnosis of NODAT in the 1st year post-transplant.

At the 2nd year evaluation, hypertensin was present in 67.6%, LVH in 14.8%, anemia in 29.4%, dyslipidemia in 9.7% and the mean GFR was 83.5 ± 24 . No patient had hypoalbuminemia or NODAT. At the 5th year evaluation, HTN was present in 55%, but there was no patient with LVH, anemia was present in one patient (5%) and dyslipidemia in three (15%). No patient had hypoalbuminemia or NODAT.

DISCUSSION

The age at KT, dialysis duration and living donor KT have impact on survival and on CVD. In our cohort, the age at KT was similar to other studies^(5,25–27) reflecting the diversity of kidney disease, however the number of living donor and pre-emptive KT can still be improved. Preemptive transplantation also appears to improve graft and patient

survival, as data from the United States Kidney Data System (USRDS) show in children that underwent preemptive transplant when compared with children on dialysis for more than 12 – 18 months.⁽²⁸⁾ In our center, the mean dialysis duration was 37 months, minimum 3 months and a maximum of 103 months. Knowing that a shorter period of dialysis is associated with better outcomes, reducing the age at transplant and increasing pre-emptive transplantation are goals we aim to achieve.

Educating the general population about healthy living habits should be encouraged because family cardiovascular risk can relate to a higher prevalence of traditional cardiovascular risk factors in children and, in our study, these seem to be particularly relevant in the post-transplant.

EVOLUTION OF PERSONAL CV RISK FACTORS

Pre-Transplant

In our cohort, as reported in the literature⁽²⁹⁾, children with CKD have a high prevalence of cardiovascular risk factors (95.9%). HTN was found in a similar percentage to the one reported in the literature, ranging from 54-79% depending on dialysis modality and HTN definition.^(25,30) As for LVH, found in 40% of our population, prevalence studies are scarce but it has been reported as high as 85% in children on dialysis⁽²⁵⁾, 17% in the CKiD cohort⁽²⁹⁾. Anemia was found in 45% of children with CKD in the CKiD cohort with a decline at a rate of -0.3 g/dl per 5 ml/min/1.73 m² of GFR⁽²⁹⁾. In our population we found a higher prevalence of anemia (61.9%), likely to be related to the difference between the definition used in this study target of 11-12g/dL in CKD when under treatment with erythropoiesis stimulating agents. We also found a higher prevalence of **dyslipidemia** than the one reported in literature – 90% versus 44%, probably related to the large percentage of patients under peritoneal dialysis (86.3%) in our center and to the prevalence of glomerulopathy as the etiology for stage 5 CKD. Conversely, there was a lower percentage of **overweight/obesity** (BMI > 85th percentile) and no patient had **diabetes**. The literature reports BMI >95th percentile in 15% and abnormal glucose metabolism in 21% of patients.⁽²⁹⁾ Malnutrition is also associated with

CVD.^(31,32) A low serum albumin has been shown to be a strong predictor of cardiovascular events in adult hemodialysis patients (<3.6 g/dL)⁽³¹⁾ and associated with an increased relative risk of death and poor outcome in the pediatric population (<3.5 g/dL).⁽³²⁾ Hypoalbuminemia in our cohort was similar to other studies^(33,32).

■ Post-Transplant

Cardiovascular risk factors after KT, although found to remain higher than that of the general population,⁽¹⁵⁾ tend to decrease^(15,31,34,35). Nevertheless, recent work by the CKiD cohort study and others^(22,27,29) showed that the prevalence of cardiovascular risk factors remain even after the transplant.

HTN, as expected, remained a common finding after transplantation with a decrease and better control over time, especially from the 2nd year follow-up on. Reported prevalence of HTN following kidney transplantation ranges between 60% and 90% depending on the method used for BP measurement and diagnostic criteria for HTN.^(19,36) A lower prevalence has been reported by Sinha and the British Association for Pediatric Nephrology⁽³⁷⁾ with 66.4% at 6 months and 55.9% at 5 years after transplantation. HTN has been shown to be associated with increased cardiovascular morbidity in both the short and long term⁽³⁵⁾ and graft failure⁽¹⁹⁾. Early post-transplant HTN may be associated with uncontrolled pre-transplant HTN and with high dosages of corticosteroids and calcineurin inhibitors^(19,35). There also seems to be a positive correlation between systolic BP and BMI that could be worsened in the presence of obesity prior to transplant⁽¹⁹⁾. In our population, the low prevalence of obesity can contribute to this control.

LVH, found in less than half of our population, immediately reduces to half after 6 months of transplantation and has a statically significant decrease at the 2nd year follow-up, following the trend of better HTN control. Some authors⁽³⁴⁾ report a low prevalence (7%) of LVH after transplant despite the presence of several cardiovascular risk factors, while others⁽³⁴⁾ report a high prevalence eventually related to a higher rate of uncontrolled HTN. Left and right ventricular disfunction should be assessed in patients with end-stage kidney disease and kidney transplant recipients,⁽³⁸⁾ although its absence does not exclude the presence of occult atherosclerosis and other vascular abnormalities. The use of undirected markers of cardiac disfunction should also be considered. NT-proBNP appreciation in patients with compromised kidney function is problematic because of renal clearance, but its use with different cutoff levels⁽³⁴⁾ could be considered. Becker Cohen and colleagues demonstrated a correlation between NT-proBNP and left ventricular mass index in children and young adults.⁽³⁴⁾

Regarding **anemia**, in our cohort, we found a decrease from the 1st year post-transplant, statistically significant from the 2nd year follow-up on, although it is present in almost one third of the patients. A prevalence of anemia superior to 30% is reported by other authors^(31,34,35,39) and only one study reported a prevalence inferior to 25%⁽³⁵⁾. Anemia appears to be a major, probably multifactorial, cardiovascular risk factor. It can be associated with several post-transplant medications, parvovirus B19 infection, iron-deficiency and reduced graft function.⁽³¹⁾ Nevertheless, it remains a frequent finding,

even with reasonable graft function⁽³¹⁾ and it should be actively evaluated and treated.^(34,39)

Dyslipidemia reduced to almost half in the first 6 months, as described in most studies.^(31,35) The study of Kaidar M. et al⁽³⁵⁾ found hypercholesterolemia and hypertriglyceridemia in 22% and 12% of patients in the 2nd year post-transplant. Becker-Cohen R. and colleagues⁽³⁴⁾ also found hypercholesterolemia and elevated LDL in 10% of the studied population. Major risk factors for post-transplant dyslipidemia include the use of cyclosporine and prednisone⁽³¹⁾. The lower prevalence of dyslipidemia in our cohort can be related to the low prevalence of overweight/obesity.

Weight gain is frequent and generally more significant in the first year after transplantation,^(19,29) with obesity prevalence rising from 15% up to 29% and metabolic syndrome to 38%.⁽²⁹⁾ Steroid use was significantly associated with weight gain in several studies.⁽¹⁹⁾ Obesity leads to poorer control of dyslipidemia and HTN, and has been shown to be associated with lower graft survival rates.⁽³⁵⁾ In our cohort, **overweight/obesity** increased after transplant up to a maximum of 17.6% in the 2nd year follow-up. This has also been described by Becker Cohen R. and colleagues⁽³⁴⁾ that report a prevalence of 21% after two years of kidney transplant. Parents should be informed that children's appetite is expected to improve after KT and that appetite control combined with a balanced diet are beneficial. Parental fear in physical exercise should also be demystified.

Insulin resistance, hyperglycemia and **NODAT** are also considered major cardiovascular risk factors⁽³¹⁾ even in the general population. After KT, risk factors also include a family history of type II diabetes, the use of tacrolimus, peri-transplant hyperglycemia and growth hormone use⁽³¹⁾. Although NODAT incidence in children has been found to be much lower than in adults,⁽⁴⁰⁾ it is still much higher than the prevalence of diabetes among non-transplant children in the general population⁽⁴⁰⁾. In our cohort there was one (2%) transient NODAT in the 1st year follow-up, unlike other studies that report a prevalence between 7 and 10%.^(31,35,40) The prevalence of insulin resistance was not evaluated.

Regarding **malnutrition** and **hypoalbuminemia**, in our population there were no underweight patients after transplantation and hypoalbuminemia drastically decreased after 6 months of transplantation, remaining residual after that. It is important to bear in mind that, before transplantation, malnutrition can be underestimated by BMI because of edema.⁽³¹⁾ Perfumo et al.⁽³¹⁾ reported a normal serum albumin profile in the early post-transplant period (< 3 months). Nevertheless, the incidence and degree of malnutrition in pediatric kidney transplant recipients remains uncertain and its relation to CVD is not well studied.⁽³¹⁾

■ STUDY LIMITATIONS

This is a single center and a retrospective study. Although we enrolled 49 patients there were missing data in several, making wider statistical analyses difficult. We did not analyze other cardiovascular risk factors such as family cardiovascular events, patients' smoking habits or physical inactivity, which would also be interesting to take into account.

CONCLUSIONS

We aimed to analyze the evolution of cardiovascular risk factors in pediatric patients before and after kidney transplant. In our cohort, there was an improvement of all studied cardiovascular risk factors after transplant, except for overweight/obesity. This could mean that stage 5 CKD-related factors decrease with time, but traditional cardiovascular risk factors may persist and even increase. Because pediatric kidney transplant recipients become young adult transplant recipients, cardiovascular risk factors need to be well identified and preventive measures need to be continuously reinforced in order to reduce the precocious mortality associated with this condition.

Disclosure of potential conflicts of interest: none declared.

References

- Vella J, Lentine KL. Risk factors for cardiovascular disease in the renal transplant recipient. UpToDate [Internet]. 2017;1–22. Available from: https://www.uptodate.com/contents/risk-factors-for-cardiovascular-disease-in-the-renal-transplant-recipient/print?search=kidneytransplant%20complications&topicRef=6143&source=see_link
- Luiza M, Menezes FS, Massaoka IHT, Tavares IIV, Aron IIS. Cardiovascular risk in children and adolescents with end stage renal disease. 2019;(11):1–7.
- Becker-cohen R, Nir A, Rinat C, Feinstein S, Algur N, Farber B, et al. Risk Factors for Cardiovascular Disease in Children and Young Adults after Renal Transplantation. Clin J Am Soc Nephrol. 2006;1:1284–92.
- Schmidt BMW, Sugianto RI, Eroglu AG, Caliskan S, Doyon A, Duzova A. Early effects of renal replacement therapy on cardiovascular comorbidity in children with end-stage kidney disease: findings from the 4C-T Study. Transplantation. 2018;102(3):484–92.
- Borchert-mörlins B, Thurn D, Schmidt BMW, Büscher AK, Oh J, Kier T, et al. Factors associated with cardiovascular target organ damage in children after renal transplantation. 2017;2143–54.
- Kramer A, Pippias M, Noordzij M, Stel VS, Afentakis N, Ambu PM, et al. The European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Registry Annual Report 2015 : a summary. Clin Kidney J. 2018;11(1):108–22.
- Falger J, Landolt MA, Latal B, Rühl EM, Neuhaus TJ, Laube GF. Outcome after renal transplantation. Part II : Quality of life and psychosocial adjustment. 2008;1347–54.
- Falger J, Latal B, Landolt MA, Lehmann P, Neuhaus TJ, Laube GF. Outcome after renal transplantation. Part I : Intellectual and motor performance. 2008;1339–45.
- Chinnakotla S, Bangdiwala AS, Vock DM, Dunn TB, Finger EB, Kandaswamy R, et al. Incidence and magnitude of post-transplant cardiovascular disease after pediatric kidney transplantation : Risk factor analysis of 1058 pediatric kidney transplants at the university of Minnesota. Pediatr Transplant. 2018;(July):1–10.
- Silverstein D. Risk factors for cardiovascular disease in pediatric renal transplant recipients. Pediatr Transplant. 2004;(5):386–93.
- Shroff R, Dégi A, Kerti A. Cardiovascular risk assessment in children with chronic kidney disease. Pediatr Nephrol. 2013;28:875–84.
- García-bello JA, Gómez-díaz RA, Contreras-rodríguez A, Talavera JO, Mondragón-gonzález R, Sánchez-barbosa L, et al. Carotid intima media thickness, oxidative stress, and inflammation in children with chronic kidney disease. 2014;273–81.
- Gómez JML, Cases RJA. Factores de riesgo cardiovascular en la enfermedad renal crónica. 2002;XXII:59–67.
- Mudi A, Paed CN, Dickens C, Levy C, Bch MB, Paed CN. Cardiovascular risk factors and mortality in children with chronic kidney disease. 2017;107(8):710–4.
- Degi A, Kerti A, Kis E et al. Cardiovascular risk assessment in children following kidney transplantation. Pediatr Transplant. 2012;(6):1–13.
- Longenecker JC, Coresh J, Powe NR, Levey AS, Fink NE, Martin A, et al. Traditional Cardiovascular Disease Risk Factors in Dialysis Patients Compared with the General Population : The CHOICE Study. 2002;1918–27.
- Rinat C, Becker-cohen R, Nir A, Feinstein S, Shemesh D, Algur N, et al. A comprehensive study of cardiovascular risk factors, cardiac function and vascular disease in children with chronic renal failure. 2010;2225–9.
- Galiyeva DB, Jackson CA, Wild SH, Burns S, Hughes D, Traynor JP, et al. Long-term all-cause mortality and cardiovascular outcomes in Scottish children after initiation of renal replacement therapy : a national cohort study. 2019;
- John EG, Domingo LT. Hypertension and Obesity after Pediatric Kidney Transplantation : Management Based on Pathophysiology : A Mini Review. 2019;5(Suppl 1):1–18.
- Salmela K, Kylo L, Koskinen P, Gro C. Pretransplant Dialysis Duration and Risk of Death After Kidney Transplantation in the Current Era. 2014;98(4):458–64.
- Tjaden LA, Jager KJ, Bonthuis M, Kuehni CE, Lilien MR, Noordzij M. Racial variation in cardiovascular disease risk factors among European children on renal replacement therapy – results from the European Society for Paediatric Nephrology / European Renal Association – European Dialysis and Transplant Association Registry. 2016;(C):90–7.
- García-bello JA, Romo-Del Río E.G., Mendoza-Gómez E., Camarena-Arias P.A. S-CM. Effect of Immunosuppressive Therapy on Cardiovascular Risk Factor Prevalence in Kidney-Transplanted Children : Comparative Study. Transplant Proc. 2016;58:639–42.
- Filler G. Challenges in pediatric transplantation : The impact of chronic kidney disease and cardiovascular risk factors on long-term outcomes and recommended management strategies. Pediatr Transplant. 2011;15:25–31.
- Jr DJW, Mitsnefes M. Cardiovascular Disease in Children and Adolescents With Chronic Kidney Disease. Semin Nephrol [Internet]. 38(6):559–69. Available from: <https://doi.org/10.1016/j.semnephrol.2018.08.002>
- Pediatric renal transplantation_ Results and prognostic factors_ Elsevier Enhanced Reader.pdf. 2015.
- Sgambat K, Cheng Yi, Charnaya O. The prevalence and outcome of children with failure to thrive after pediatric kidney transplantation. Pediatr Transplant. 2018;(August).
- Cordinhã C, Rodrigues L, Carmo C, Macário F, Correia AJ, et al. Pediatric Kidney Transplantation: Experience of a Center Over 4 Decades. Transplant Proc [Internet]. 2019;51(5):1579–84. Available from: <https://doi.org/10.1016/j.transproceed.2019.05.007>
- Ruth A McDonald. Kidney transplantation in children : Outcomes. UpToDate [Internet]. 2020;1–22. Available from: <https://www.uptodate.com/contents/kidney-transplantation-in-children-outcomes>
- Bunchman TE, Bholah R, Kaspar CDW. A Review of Pediatric Chronic Kidney Disease. Blood Purif. 2016;0498:211–7.
- Maria Q, Skrzypczyk P. Advances in Medical Sciences Hypertension in children with end-stage renal disease. Adv Med Sci [Internet]. 2015;1–7. Available from: <http://dx.doi.org/10.1016/j.advms.2015.07.001>
- DM S. Risk factors for cardiovascular disease in pediatric renal transplant recipients. Pediatr Transplant. 2004;(8):386–93.
- Wong CS, Hingorani S, Gillen DL, Sherrard DJ, Watkins SL, Brandt AR, Ball A S-BC. Hypoalbuminemia and risk of death in pediatric patients with end-stage renal disease. Kidney Int. 2002;61:630–7.
- Tancredi DJ, Butani L. Pretransplant Serum Albumin Is an Independent Predictor of Graft Failure in Pediatric Renal Transplant Recipients. J Pediatr [Internet]. 2014;164(3):602–6. Available from: <http://dx.doi.org/10.1016/j.jpeds.2013.11.012>
- Becker-cohen R, Nir A, Rinat C, Feinstein S, Algur N, Farber B, et al. Risk Factors for Cardiovascular Disease in Children and Young Adults after Renal Transplantation. 2006;1284–92.
- Krauze I, Cleper R, Mor E. Cardiovascular risk factors in children after kidney transplantation – From short-term to long-term follow-up. 2014;23–8.
- Charnaya O, Moudgil A. Hypertension in the Pediatric Kidney Transplant Recipient. 2017;5(May):1–10.
- Suppl SS, Sinha MD, Kerecuk L, Gilg J, Reid CJD, Nephrology P, et al. Systemic arterial hypertension in children following renal transplantation : prevalence and risk factors. 2012;4(Suppl 8):287–94.
- Arslan A, Parmaksız G, Noyan ZA, Çalişkan K, Yıldırım S, Haberal M. Cardiac Function in Children After Kidney Transplant. 2019;2–7.
- Galutira PJ, Rio M Del. Understanding renal posttransplantation anemia in the pediatric population. 2012;1079–85.
- Burroughs TE, Swindle JP, Salvalaggio PR, Lentine L, Takemoto SK, Bunnapradist S, et al. NIH Public Access. 2010;88(3):367–73.

ORCID

Margarida Cunha  0000-0002-0090-2464

Ana Gusmão Palmeiro  0000-0002-6805-1790

Ana Rita Sandes  0000-0003-1121-1092

Rosário Stone  0000-0002-7939-836X

Correspondence to:

Margarida Cunha

E-mail: cunhamargarida@gmail.com