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Metabolic risk factors and long-term graft function after paediatric renal transplantation

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Summary

The aim of this study was to evaluate metabolic risk factors and their impact on long-term allograft function in paediatric renal transplant (RTx) patients. We reviewed the medical records of 210 RTx patients who underwent transplantation at a median age of 4.5 years (range 0.7–18.2) and a median follow-up of 7.0 years (range 1.5–18.0). Data on lipid and glucose metabolism, uric acid levels, weight and blood pressure were collected up to 13 years post-RTx, and the findings were correlated with the measured glomerular filtration rate (GFR). Beyond the first year, GFR showed gradual deterioration with a mean decline of 2.4 ml/min/1.73 m^2/year. Metabolic syndrome, overweight, hypertension and type 2 diabetes were diagnosed in 14–19%, 20–23%, 62–87% and 3–5% of the patients, respectively. These entities showed only mild association with the concomitant or long-term GFR values. Dyslipidaemia was common and hypertriglyceridaemia associated with a lower GFR at 1.5 and 5 years post-RTx ($P = 0.008$ and $P = 0.017$, respectively). Similarly, hyperuricaemia was frequent and associated significantly with GFR ($P < 0.001$). Except for hyperuricaemia and hypertriglyceridaemia, metabolic risk factors beyond the first postoperative year associated modestly with the long-term kidney graft function in paediatric RTx patients.

Introduction

Renal transplantation (RTx) is a successful treatment modality for children with end-stage renal disease. Pre- and post-transplantation care among RTx children has significantly improved the outcome, leading to a long-term patient survival over 90% [1,2]. Thus, the prevention of secondary complications and management of the adverse effects of the immunosuppressive medication are increasingly important. The long-term function of the kidney graft may be impaired by immunological and nonimmunological risk factors, such as acute and chronic rejections, infections, calcineurin inhibitor toxicity and metabolic complications [3–8].

Metabolic syndrome (MS) is a cluster of risk factors, including obesity, hypertension, dyslipidaemia and impaired glucose metabolism [9,10]. The prevalence of MS and its individual factors has been extensively studied in adult RTx patients but not in children [11–13]. The follow-up in paediatric studies has been short, and the association and impact of the metabolic risk factors for the long-term graft function is not known [14–17]. The mechanisms of the renal function impairment in MS remain speculative. Dyslipidaemia and insulin resistance may induce nephropathy by several mechanisms [18,19]. Hyperinsulinaemia may increase the synthesis of insulin-like growth factors, endothelin and transforming growth factor-β, which can lead to mesangial expansion and interstitial fibrosis. Activation of renin–angiotensin system, endothelial dysfunction, oxidative stress and glomerular hyperfiltration have also suggested to play a part in this process [20,21].

In this study, we analysed the metabolic syndrome and its components (overweight, hypertension, abnormalities in lipid and glucose metabolism) and hyperuricaemia in a national cohort of 210 paediatric RTx patients with

long-term follow-up up to 18 years. The parameters were correlated with measured glomerular filtration rate (GFR). We were especially interested in seeing which metabolic factors at the early (1.5 years) or mid-term (5 years) maintenance phase associated and predicted impaired graft function later on.

Materials and methods

Patients

Paediatric solid organ transplantations in Finland are centralized to the study centre, Children's Hospital, Helsinki University Central Hospital. The postoperative follow-up consists of visits at 3, 6, 12, 18 and 24 months post-RTx and annually thereafter until patients are transferred to adult care at the age of 18–20 years. Eleven patients had undergone a combined liver–kidney transplantation. The data on metabolic characteristics were collected at 1.5, 5, 9 and 13 years post-RTx. Seventeen patients had lost the first graft and 10 of them were included as new study patients on average 7 years (range 2–13 years) post-RTx. One was re-included after a second re-transplantation and another patient after a third RTx. The remaining seven patients were included only once (after a re-transplantation). Three patients died before transfer to adult care 4–10 years after the RTx. The graft and patient survivals at 5, 9 and 13 years post-RTx were 96.9%, 90.4% and 78.5%, and 99.4%, 98.1% and 95.4%, respectively. This study was approved by the Ethics Committee for Paediatrics, Gynaecology and Obstetrics, and Psychiatry of the Hospital District of Helsinki.

Immunosuppression

The immunosuppressive protocol consisted of triple medication, including cyclosporine A (CsA), azathioprine and methylprednisolone (MP). Basiliximab induction has been used in our centre since year 2000. Forty-five per cent (n = 94/210) of the patients had received basiliximab induction therapy at the time of the operation. The CsA dose was adjusted to obtain trough blood concentration of 300–350 μg/l during the first weeks post-RTx followed by a reduction to maintenance level of 100 μg/l at 1 year. A level of 60–100 μg/l was individually aimed thereafter. MP dosing during the first days post-RTx was 1–3 mg/kg/day after which it was tapered to 0.25 mg/kg/day at two weeks and finally to a low, alternate-day dosing at 3–6 months post-RTx (mean daily dose, 0.06 mg/kg). The MP dose was not increased along growth after the first-year post-RTx. The azathioprine dose was 2 mg/kg/day for 2 weeks after the RTx followed by a 1 mg/kg/day dosing. When MP was switched to the every other day dosing (at 3–6 months), the azathioprine dose was increased to 1.3–1.4 mg/kg/day. After the first year, doses of 1.0–1.4 mg/kg/day were used. CsA was switched to tacrolimus in case of recurrent rejections, gradually increasing creatinine, or major cosmetic problems (hypertrichosis and gum hyperplasia). Azathioprine was replaced by mycophenolate in case of recurrent rejections or gradually increasing creatinine. Also, when calcineurin inhibitor toxicity was suspected, azathioprine was switched to mycophenolate, and the dosing of CsA or tacrolimus was reduced. Over half of the patients (60%) were receiving tacrolimus or mycophenolate at some point during the follow-up.

Data collection

We analysed retrospectively the medical data on the underlying disease, age at RTx, growth, medication and laboratory measurements. Height and weight were measured and height standard deviation score and height-adjusted weight ratio in percentages of the median were used according to the Finnish growth curves for children [22,23]. Weight for height was used because a better reflection of weight changes at different ages compared with the body mass index. Short stature was defined as height <-2.0 SD and overweight as relative weight >120% of the gender and height-adjusted median (weight deviation >20%). Hypertension was defined as use of antihypertensive medication or office blood pressure (BP) levels above the 95th percentile according to the criteria of the fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents [24]. Both the systolic and diastolic BP values were indexed by dividing them by the cut-off values provided by the fourth report.

Laboratory measurements

Blood samples were drawn after an overnight fasting and analysed using standardized methods for blood glucose, insulin, glycosylated haemoglobin (GHbA1c), total cholesterol, high- and low-density lipoprotein (HDL and LDL), triglyceride and uric acid. A 2-h oral glucose tolerance test (OGTT; glucose load 1.75 g/kg up to 75 g) with the measurement of glucose and insulin levels at 0, 60 and 120-min postload was performed at 5 years post-RTx. According to the OGTT results, patients were classified as having normal glucose tolerance (fasting blood glucose <5.6 mM (100 mg/dl) and 2-h glucose value <6.7 mM (120 mg/dl)), impaired fasting glucose (IFG; fasting blood glucose 5.6–6.0 mM and 2-h glucose value <6.7 mM), impaired glucose tolerance (IGT; fasting blood glucose <6.1 mM (110 mg/dl) and 2-h glucose value 6.7–9.9 mM) or type 2 diabetes mellitus [DM; fasting blood glucose ≥6.1 mM or 2-h glucose value ≥10.0 mM (180 mg/dl)]. MS was defined according to the diagnostic criteria of the American Heart Association, based on the ATP III criteria, with the exception of

overweight used instead of waist circumference [9,25]. MS was diagnosed if a minimum of three of the five risk factors (overweight, hypertension, reduced HDL, elevated triglycerides or elevated fasting glucose) were abnormal.

Kidney function was assessed in every patient by measuring the GFR by the ^{51}Cr-EDTA clearance on every follow-up visit at 3–6 month intervals until 24 months post-RTx and annually thereafter. The measured GFR (ml/min/1.73 m^2) was corrected with a one-pool approximation model according to modified Brochner–Mortensen equation [26]. Mean annual GFR decline (ml/min/1.73 m^2/year) was calculated, starting both at 18 months and 5 years post-RTx, by dividing the difference between two subsequent GFR results by the time between the measurements until the last follow-up visit.

Statistics

Numerical results are reported as mean ± SD or median (range), as appropriate. Depending upon the variable distribution, we used Student's *t*-test or Mann–Whitney *U*-test for comparing two independent sample groups. Simple linear regression was used for assessing the ability of hypertension, relative weight, cholesterol, HDL, LDL, triglycerides, fasting glucose, fasting insulin, GHbA1c or uric acid to predict GFR at 1.5 or 5 years post-RTx or the mean annual GFR decline starting at 1.5 or 5 years post-RTx. Hierarchal multiple regression was further conducted for assessing the ability of triglycerides at 1.5 years post-RTx to predict the concomitant GFR, after controlling for the influence of uric acid. SPSS Statistics 19.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. P value <0.05 was considered statistically significant.

Results

The study cohort included 210 children and adolescents (132 males and 78 females) who received a RTx between 1984 and 2011 at the age of 0.7–18.2 years (median 4.5 years) (Table 1). Owing to the high frequency of congenital nephrotic syndrome of the Finnish type (CNF) in our country, 31% of the patients were under 2 years of age at the time of RTx. The postoperative follow-up ranged from 1.5 to 18 years with a median of 7.0 years. Seventeen patients (8.1%) lost their first graft during this time.

In the whole group, the mean GFR decreased from 62.8 ml/min/1.73 m^2 at 1.5 years to 38.0 ml/min/1.73 m^2 at 13 years post-RTx. The mean decline of GFR was 2.4 ml/min/1.73 m^2 per year (Table 1). The patients with a poor GFR (<60 ml/min/1.73 m^2) already at 1.5 years post-RTx had a worse graft function also later on (Fig. 1a).

The metabolic features were recorded at 1.5–13 years post-RTx, as shown in Table 2. We analysed the possible association of each parameter, both at 1.5 and at 5 years post-RTx, with the concomitant and long-term GFR levels as well as the annual GFR decline.

Table 1. Characteristics of 210 renal transplantation (RTx) patients included in the study.

Male/female gender, *n* (%)	132/78 (63/37)
Disease leading to first RTx, *n* (%)	
CNF	80 (38)
Urethral valve	25 (12)
Nephronophthisis	18 (9)
Polycystic kidney disease	18 (9)
Other	69 (33)
Age at RTx, years	6.9 ± 5.5 (range 0.7–18.2)
<2 years, *n* (%)	65 (31)
2–10 years, *n* (%)	74 (35)
>10 years, *n* (%)	71 (34)
Follow-up, years	8.4 ± 4.8 (range 1.5–18.0)
<5 years, *n* (%)	54 (26)
5–9 years, *n* (%)	75 (36)
>9 years, *n* (%)	81 (39)
GFR at 6 months post-RTx, ml/min/1.73 m^2	62.7 ± 18.8
1 year	61.1 ± 19.1
1.5 years	62.8 ± 20.1
5 years	54.1 ± 17.5
9 years	45.1 ± 13.4
13 years	38.0 ± 12.9
GFR decline since 1.5 years post-RTx, ml/min/1.73 m^2/year*	2.4 ± 6.8
GFR decline since 5 years post-RTx, ml/min/1.73 m^2/year*	2.2 ± 5.7

Values are number of patients (%) or mean ± SD. CNF, congenital nephrotic syndrome of the Finnish type; GFR, glomerular filtration rate. *GFR decline is the average of yearly GFR decline calculated from 1.5 or 5 years post-RTx to last control.

Metabolic syndrome

The criteria for MS were fulfilled in 28/147 (19.0%) and 18/127 (14.2%) patients at 1.5 and 5 years post-RTx, respectively. The patients with MS at 1.5 years post-RTx tended to have on average lower concomitant and long-term GFR values than the others (Table 3 and Fig. 1b), and simple regression analysis showed a more pronounced annual GFR decline in these patients (Table 4). However, at 5 years post-RTx and thereafter, no statistically significant differences in concomitant GFRs or GFR decline rates were found between the patients with or without MS (Tables 3 and 4, Fig. 2a).

Overweight

One-fifth of the patients (20–23%) were overweighed at different time points after RTx (Table 2). The trend for

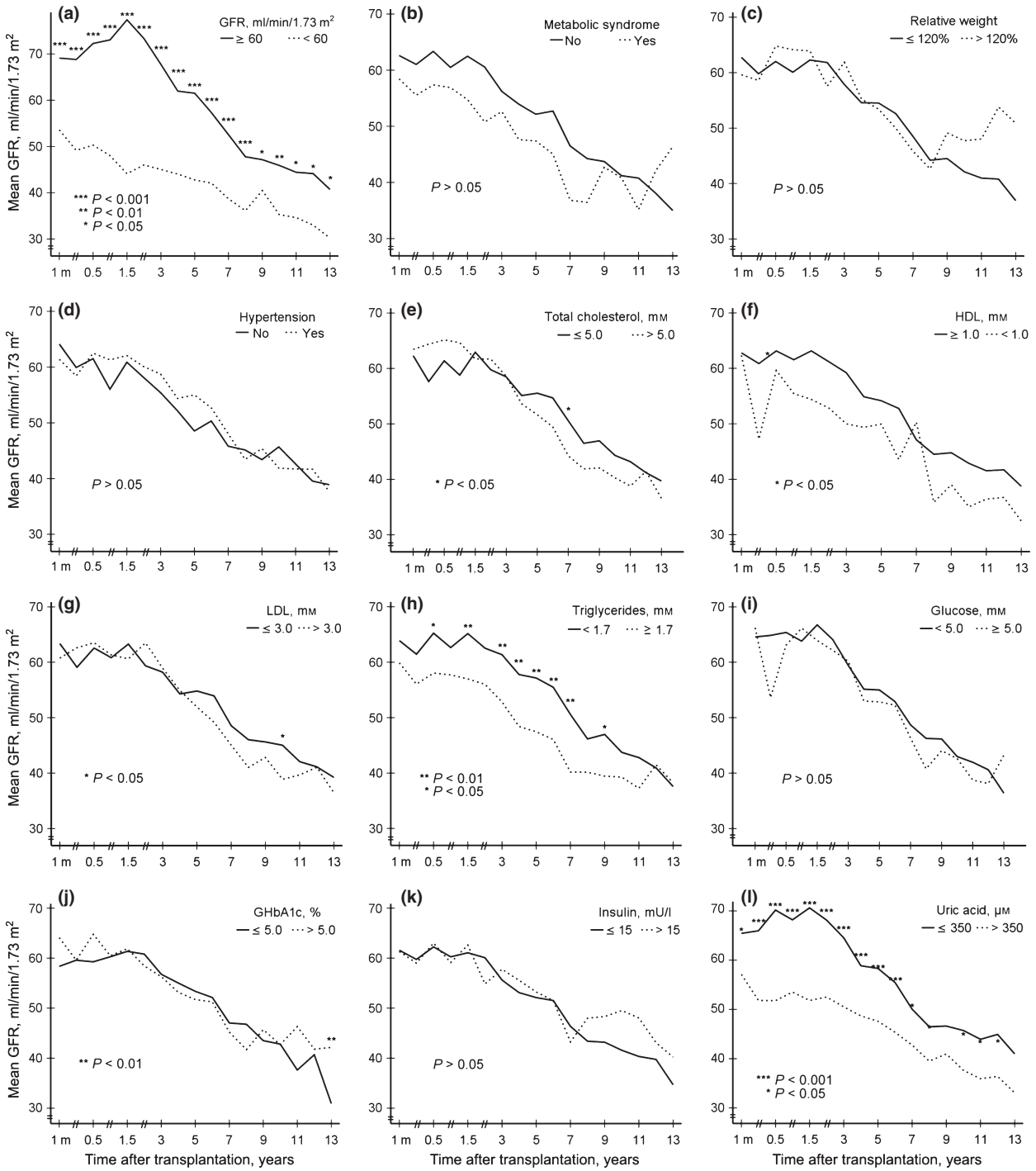

Figure 1 Mean glomerular filtration rates (GFR) during long-term follow-up in two subgroups of patients divided at 1.5 years post-transplantation according to GFR (a), metabolic syndrome (b), overweight (c), hypertension (d), cholesterol (e), HDL (f), LDL (g), triglycerides (h), fasting glucose (i), glycosylated haemoglobin (j), fasting insulin (k) and uric acid (l).

prevalence of obesity (relative weight >140% of the age and height-adjusted median) was descendent during the follow-up (12–2%). The overweighed patients at 1.5 years (43/194) or at 5 years (34/152) showed similar concomitant and long-term GFR levels, as well as subsequent annual GFR decline, compared with the normal weighed patients (Table 3, Fig. 1c). In accordance, the regression analysis showed no association between the relative weight at 1.5 or

Table 2. Metabolic characteristics of 210 patients with paediatric renal transplantation during long-term follow-up.

		1.5 years post-RTx		5 years post-RTx		9 years post-RTx		13 years post-RTx	
Variables	Normal value	Median (range)	Abnormal (%)	Median (range)	Abnormal (%)	Median (range)	Abnormal (%)	Median (range)	Abnormal (%)
Age at control (years)	NA	6.0 (2.2–19.7)	NA/206	8.7 (5.7–20.9)	NA/155	11.6 (9.6–19.6)	NA/90	15.0 (14.1–19.3)	NA/48
Height	≥−2.0 SDS	−1.5 (−5.2–1.2)	69/194 (36)	−1.1 (−4.1–1.1)	36/151 (24)	−1.2 (−4.7–1.4)	14/88 (16)	−1.5 (−5.0–1.7)	10/44 (23)
Relative weight	≤120%	3 (−21–165)	44/194 (23)	7 (−16–170)	35/152 (23)	7 (−23–78)	20/88 (23)	3.5 (22–62)	9/44 (20)
Lipid metabolism									
Total cholesterol	≤5.0 mM (≤193 mg/dl)	4.8 (2.7–11.4)	76/192 (39)	4.6 (2.6–12.5)	48/153 (31)	4.6 (2.9–7.3)	25/86 (29)	4.3 (2.7–6.6)	10/45 (22)
HDL cholesterol	≥1.0 mM (≥40 mg/dl)	1.4 (0.6–2.6)	15/192 (8)	1.5 (0.7–2.9)	8/153 (5)	1.5 (0.7–2.8)	6/86 (7)	1.5 (0.7–2.1)	6/45 (13)
LDL cholesterol	≤3.0 mM (≤116 mg/dl)	2.6 (0.7–7.2)	60/191 (31)	2.4 (1.1–8.9)	37/153 (24)	2.3 (0.9–4.6)	23/86 (27)	2.3 (0.7–4.4)	4/45 (9)
Triglycerides	<1.7 mM (<150 mg/dl)	1.3 (0.4–7.9)	64/191 (34)	1.3 (0.5–5.0)	43/153 (28)	1.3 (0.4–3.5)	27/85 (32)	1.5 (0.6–3.4)	14/45 (31)
Glucose metabolism									
Fasting blood glucose	<5.6 mM (<100 mg/dl)	4.7 (2.6–6.5)	17/171 (10)	4.8 (3.1–7.3)	16/134 (12)	5.0 (3.5–6.8)	11/87 (13)	5.1 (4.1–7.0)	9/46 (20)
2-h blood glucose	<6.7 mM (<120 mg/dl)	NR	NR	6.1 (3.5–8.0)	67/130 (52)	6.1 (4.7–10.2)	24/77 (31)	6.5 (3.2–8.5)	17/43 (40)
GHbA1c	≤6.0%	5.1 (4.0–6.5)	4/168 (2)	5.2 (4.2–6.5)	1/134 (1)	5.2 (4.1–6.0)	0/82	5.2 (4.5–6.2)	1/41 (2)
Fasting serum insulin	≤15 mU/l	8.5 (0.6–120.0)	38/166 (23)	9.4 (2.0–103.0)	35/134 (26)	10.6 (3.9–42.0)	18/82 (22)	9.0 (2.3–24.5)	6/46 (13)
2-h serum insulin	<75 mU/l	NR	NR	30.2 (0.5–137.8)	9/125 (7)	34.9 (3.9–149.0)	8/76 (11)	32.9 (9.1–80.8)	1/41 (2)
Serum uric acid	≤350 μM (≤5.9 mg/dl)	326 (144–736)	82/201 (41)	369 (177–633)	89/154 (58)	403 (250–717)	68/89 (76)	460 (308–720)	44/48 (92)

NA, not applicable; NR, not registered; GFR, glomerular filtration rate; Relative weight is the percentage of the gender and height-adjusted median weight, overweight is >20% deviation of the median; GHbA1c, glycosylated haemoglobin.

5 years and the concomitant GFR ($P = 0.362$ and $P = 0.383$, respectively) or subsequent annual GFR decline ($P = 0.127$ and $P = 0.740$, respectively) (Table 4).

Hypertension

The majority (87% and 62%) of the patients were regarded hypertensive and 60% and 35% of the patients were on antihypertensive medication at 1.5 and 5 years post-RTx, respectively. The mean systolic/diastolic BP indexes at 1.5 and 5 years post-RTx were 1.04/0.91 (117/66 mmHg) and 0.99/0.86 (116/66 mmHg), respectively. No significant differences were observed in the concomitant or long-term GFR values or the annual GFR decline between the hypertensive and normotensive patients (Tables 3 and 4, Figs 1d and 2b).

Lipid metabolism

A third of the patients had hypertriglyceridaemia at control visits (Table 2). High plasma triglyceride levels associated (P values 0.001–0.019) with worse concomitant and subsequent GFR levels (Tables 3, Figs 1h and 2e). The association between the triglyceride levels and the annual GFR decline, however, remained insignificant (Table 4).

The patients did not receive statins and elevated total cholesterol levels of >5.0 mM (193 mg/dl) and LDL levels of ≥3.0 mM (115 mg/dl) were frequent (22–39% and 9–31%, respectively) (Table 2). Low HDL levels of <1.0 mM (40 mg/dl) were detected in 8–13% of the patients. The associations between the total cholesterol or the HDL levels and the different GFR parameters were weak (Table 4). On the other hand, the LDL level at 1.5 years post-RTx associated with the annual GFR decline in the regression analysis ($P < 0.001$) (Table 4).

Glucose metabolism

Fasting glucose and insulin levels remained relatively stable during the whole follow-up and abnormal values were observed in 10–20% and 13–26%, respectively (Table 2). Type 1 DM was not diagnosed in any subject and abnormal GHbA1c values (>6.0%) were observed only in few. Furthermore, type 2 DM was detected in only 7 (5%), 3 (3%) and 2 (4%) patients at 5, 9 and 13 years post-RTx, respectively, but the prevalence of IGT increased 18%, 29% and 40% with the time being. Overall, the GFR levels and the subsequent GFR decline rates were similar in patients with normal or aberrant glucose parameters (Table 3, Figs 1i and j). The fasting glucose level did, however, associate with the concomitant GFR value (Table 4). The GFR levels or the annual decline of GFR did not differ between the patients with or without IGT at 5 years (Fig. 2c).

Table 3. Association between metabolic risk factors and concurrent GFR levels or subsequent annual GFR decline in 210 patients 1.5 and 5 years after renal transplantation (RTx).

		1.5 years post-RTx		5 years post-RTx	
Variables	Grouping value	Actual GFR, ml/min/1.73 m^2	Subsequent GFR decline, ml/min/1.73 m^2/year	Actual GFR, ml/min/1.73 m^2	Subsequent GFR decline, ml/min/1.73 m^2/year
Metabolic syndrome	No	62.5 ± 19.6 (114)	1.4 ± 5.3 (116)	54.1 ± 17.3 (108)	2.1 ± 3.9 (108)
	Yes	54.7 ± 21.2 (27)	6.1 ± 13.1 (28)	49.9 ± 16.7 (18)	1.4 ± 3.7 (18)
Relative weight	≤120%	62.3 ± 20.2 (143)	2.0 ± 6.5 (150)	54.6 ± 17.4 (116)	2.7 ± 4.9 (115)
	>120%	63.9 ± 18.9 (43)	3.4 ± 7.6 (43)	50.8 ± 17.0 (34)	1.9 ± 3.8 (34)
Hypertension (OBP)	No	60.9 ± 14.2 (23)	0.9 ± 3.8 (23)	55.4 ± 16.4 (55)	2.6 ± 5.3 (55)
	Yes	62.1 ± 21.0 (150)	2.7 ± 7.3 (156)	53.7 ± 18.0 (89)	2.3 ± 4.1 (89)
Cholesterol	≤5.0 mM (≤193 mg/dl)	62.9 ± 19.5 (114)	1.1 ± 4.7 (115)†	54.6 ± 18.2 (105)	2.1 ± 6.4 (105)
	>5.0 mM (>193 mg/dl)	61.7 ± 20.8 (74)	4.6 ± 9.2 (76)	53.7 ± 15.7 (47)	2.5 ± 3.5 (47)
HDL	≥1.0 mM (≥40 mg/dl)	63.2 ± 19.9 (173)	2.2 ± 6.3 (176)	55.2 ± 17.1 (144)†	2.2 ± 5.8 (144)
	<1.0 mM (<40 mg/dl)	54.4 ± 19.7 (15)	5.7 ± 12.9 (15)	39.6 ± 18.4 (8)	3.2 ± 4.2 (8)
LDL	≤3.0 mM (≤116 mg/dl)	63.3 ± 19.8 (128)	1.7 ± 5.0 (130)	54.1 ± 18.0 (116)	2.0 ± 6.1 (116)
	>3.0 mM (>116 mg/dl)	60.6 ± 20.5 (59)	4.1 ± 10.1 (60)	55.2 ± 15.7 (36)	2.8 ± 3.9 (36)
Triglycerides	<1.7 mM (<150 mg/dl)	65.2 ± 19.5 (125)†	1.6 ± 5.4 (126)*	56.4 ± 17.6 (110)*	2.1 ± 5.9 (110)
	≥1.7 mM (≥150 mg/dl)	57.0 ± 20.1 (62)	4.2 ± 9.4 (64)	48.9 ± 16.0 (42)	2.4 ± 5.1 (42)
Fasting glucose	<5.6 mM (<100 mg/dl)	61.8 ± 19.4 (151)	2.4 ± 7.0 (153)	53.9 ± 17.7 (117)	1.7 ± 5.5 (117)
	≥5.6 mM (≥100 mg/dl)	57.2 ± 24.6 (16)	2.4 ± 10.0 (17)	53.0 ± 13.0 (16)	1.9 ± 3.8 (8)
GHbA1c	≤6.0%	62.1 ± 19.9 (161)	1.9 ± 5.8 (163)	54.3 ± 17.7 (132)	2.1 ± 5.9 (132)
	>6.0%	44.4 ± 11.7 (4)	3.5 ± 2.1(4)	NA	2.2 ± NA (1)
Fasting insulin	≤15.0 mU/l	61.1 ± 19.9 (126)	1.9 ± 5.5 (127)	54.2 ± 17.8 (98)	1.9 ± 5.9 (98)
	>15.0 mU/l	62.6 ± 20.3 (37)	2.1 ± 6.9 (38)	50.1 ± 15.7 (35)	1.9 ± 3.4 (35)
Uric acid	≤350 μM (≤5.9 mg/dl)	70.6 ± 17.7 (115)‡	2.9 ± 5.3 (118)	62.7 ± 16.8 (65)‡	3.4 ± 5.0 (65)*
	>350 μM (>5.9 mg/dl)	51.8 ± 18.3 (80)	1.8 ± 8.7 (82)	48.1 ± 15.1 (88)	1.3 ± 6.0 (88)

GFR, glomerular filtration rate; Relative weight is the percentage of the gender and height-adjusted median weight, overweight is >20% deviation of the median; OBP, office blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GHbA1c, glycosylated haemoglobin A1c; NA, not applicable. Values are mean ± SD (number of patients) and compared with Student's *t*-test. GFR decline is the average of yearly GFR decline calculated from 1.5 or 5 years to last control post-RTx.

*$P < 0.05$.

†$P < 0.01$.

‡$P < 0.001$.

Uric acid

The frequency of elevated uric acid levels of >350 μM (5.9 mg/dl) increased from 41% to 92% between 1.5 years and 13 years post-RTx (Table 2). Hyperuricaemia, both at 1.5 and at 5 years post-RTx, was associated with lower concomitant and GFR levels and subsequent GFR levels but not with the annual GFR decline rates (Table 3, Figs 1l and 2f). Similarly, regression analyses revealed that uric acid concentrations at 1.5 and 5 years post-RTx strongly correlated with the concomitant GFRs but not with the subsequent GFR decline rates (Table 4). In the hierarchal multiple regression, uric acid at 1.5 years post-RTx explained 30% of the variance in concomitant GFR. After entry of the triglycerides, an additional 3% ($P = 0.011$) of the variance was explained, and the R squared for the final model was 0.33; $P < 0.001$ ($B = -0.11$, $P < 0.001$ and $B = -4.22$, $P < 0.001$ for uric acid and triglycerides, respectively).

Discussion

Studies on metabolic risk factors in RTx children and adolescents are important in two respects. First, these factors may adversely affect the graft function and lead to graft loss. Secondly, they present a long-term risk for the patients, especially by causing cardiovascular disease [27]. Children transplanted at a very young age, such as those with congenital nephrotic syndrome, need new grafts as young adults, and avoidance and treatment of post-transplant metabolic problems in childhood is important for the success of later therapies. Overall, the results in this work indicate that metabolic abnormalities beyond the first post-operative year are moderate and have little impact on the long-term graft function.

In our study, only 19% and 14% of the patients fulfilled the criteria for MS at 1.5 and 5 years after RTx, respectively. These numbers are lower than those reported in three previous paediatric studies. In a recent multicentre study, the

Table 4. Simple linear regression analysis of association between metabolic risk factors and concurrent GFR level or subsequent annual GFR decline 1.5 and 5 years after renal transplantation (RTx).

	1.5 years post-RTx				5 years post-RTx			
	Actual GFR, ml/min/1.73 m^2		Subsequent GFR decline, ml/min/1.73 m^2/year		Actual GFR, ml/min/1.73 m^2		Subsequent GFR decline, ml/min/1.73 m^2/year	
Variables	B (SE)	*P*	B (SE)	*P*	B (SE)	*P*	B (SE)	*P*
Metabolic syndrome	−7.75 (4.28)	0.072	4.28 (1.41)	0.003	−4.31 (4.48)	0.338	−1.08 (1.45)	0.459
Relative weight,%	−0.06 (0.06)	0.362	0.03 (0.02)	0.127	−0.06 (0.07)	0.383	−0.01 (0.02)	0.740
Hypertension (OBP)	1.21 (4.60)	0.792	1.79 (1.52)	0.242	−1.74 (3.02)	0.566	−0.38 (0.98)	0.700
Cholesterol, mM	−1.94 (1.39)	0.165	0.60 (0.39)	0.127	−1.76 (1.62)	0.280	0.03 (0.53)	0.950
HDL, mM	4.19 (3.86)	0.279	−0.52 (1.30)	0.691	0.13 (3.79)	0.973	0.19 (1.22)	0.877
LDL, mM	−0.44 (1.70)	0.795	1.63 (0.49)	0.001	−0.84 (2.00)	0.674	−0.03 (0.65)	0.966
Triglycerides, mM	−6.45 (1.82)	0.001	0.12 (0.55)	0.824	−5.42 (2.29)	0.019	−0.26 (0.76)	0.736
Fasting glucose, mM	−4.99 (2.48)	0.046	0.34 (0.84)	0.685	−5.13 (2.44)	0.037	−0.98 (0.80)	0.219
GHbA1c, %	−0.27 (3.75)	0.942	0.24 (1.26)	0.847	−5.94 (3.82)	0.122	0.13 (1.25)	0.918
Fasting insulin, mU/l	−0.05 (0.20)	0.487	0.09 (0.07)	0.163	−0.26 (0.20)	0.202	0.02 (0.07)	0.799
Uric acid, μM	−0.11 (0.01)	<0.001	−0.01 (0.01)	0.165	−0.09 (0.01)	<0.001	−0.01 (0.01)	0.240

B (SE), unstandardized coefficient beta (standard error); GFR, glomerular filtration rate; Relative weight is the percentage of the gender and height-adjusted median weight; OBP, office blood pressure; GHbA1c, glycosylated haemoglobin A1c. The variables are continuous except of metabolic syndrome and hypertension (dichotomous).

prevalence of MS at the time of RTx was 19% and 38% at 1 year post-transplant [14]. In a Mexican study, MS was detected in 25% (8/32) of the patients 2 years after RTx [15]. In a study of 58 patients at 1-year post-RTx, MS was diagnosed in 68% of patients receiving prednisone and in 15% of those without a glucocorticoid [16]. Kidney function was studied only in the third study, and the estimated GFR at 1 year was significantly lower in MS patients compared with non-MS children (65 vs. 88 ml/min/1.73 m^2). The essential difference between our study and the three previous ones is that we focused on the maintenance phase, when the immunosuppressive drug dosing was already reduced to minimum. The follow-up was also exceptionally long because of the high proportion of CNF children undergoing RTx before the age of 2 years.

Overweight is common after RTx especially during the first months when the exposure to glucocorticoids is high. In general, data on the association between obesity or overweight and graft function are contradictory in children [17,28–30]. One-fifth of our patients were moderately overweighed at 1.5 and 5 years after RTx, but it clearly was not associated with impaired concomitant or future graft function. This contrasts to the reports dealing with obesity at the time of RTx. In a report by Mitsnefes *et al.*, patients being obese at the time of RTx and 1 year thereafter had lower GFR levels than those who became obese during the first-year post-RTx [17]. In a more recent study, the opposite was found so that those who gained weight after the operation had worse graft survival at 36 months [30]. Thus, it seems that severe obesity during the early postoperative phase associates with poorer graft function, but this is not the case when overweight is moderate and appears years after RTx.

Both calcineurin inhibitors and glucocorticoids induce hypertension, which has been associated with a subsequent graft failure [31–33]. Sorof *et al.* [31] reported that hypertension is associated with higher graft failure rates, evidenced by use of antihypertensive medication predicting subsequent graft failure in children after RTx. In another study on paediatric patients, systolic hypertension at 1 year post-RTx predicted poor long-term graft survival [33]. Our results showed no clear association of hypertension with later graft function. This is in line with the result of Krmar *et al.* [34] reporting similar GFR decline rates in patients with daytime or night-time hypertension and normotension.

Post-transplant diabetes mellitus has been reported in 2–35% of children after RTx [35,36]. In our cohort, none of the patients developed type 1 diabetes and type 2 diabetes was diagnosed in only 12 patients. In oral glucose tolerance test performed at 5 years, only one of the six patients diagnosed with IFG (at 5 years post-RTx) later developed a type 2 DM. Fasting glucose or insulin levels, or GHbA1c showed no association with the GFR levels. This finding is in parallel with the previous results of both paediatric and adult studies [37–39]. Impaired glucose tolerance was quite commonly (18–40%) seen in OGTT, but, again, it did not correlate with the GFR levels. According to the results in OGTT at 5 years, the insulin level of ≥75 mU/l predicted a more rapid future GFR decline. The high fasting insulin levels and the insulin response in OGTT associated with MS (46% and 50% of the MS patients having an elevated

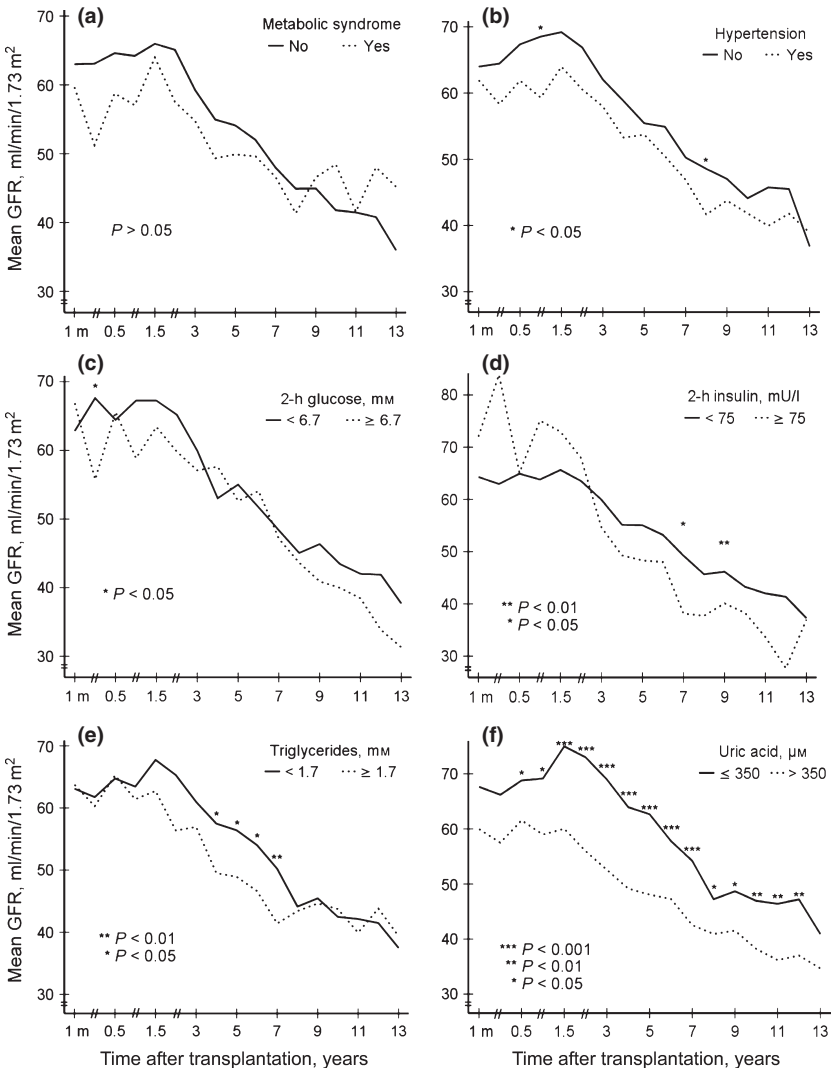

Figure 2 Mean glomerular filtration rates (GFR) during long-term follow-up in two subgroups of patients divided at 5 years post-transplantation according to metabolic syndrome (a), hypertension (b), 2-h glucose (c) and insulin (d) concentration in oral glucose tolerance test, triglycerides (e) and uric acid (f).

fasting insulin level at 1.5 and 5 years post-RTx, respectively). The low prevalence of type 1 and 2 diabetes can be partly explained by the fact that the majority of the patients received CsA instead of tacrolimus. The patients also received low-dose MP every other day, so that the glucocorticoid exposure was low.

Hypertriglyceridaemia at 1.5 post-RTx showed an association with decline in GFR. This is in accordance with the observations in adults showing an independent association of hypertriglyceridaemia with impaired renal allograft function beyond the first post-transplant year in multivariate analyses [40]. In a very recent register study, an inverse association between triglyceride levels and estimated GFR was similarly found in paediatric RTx patients [41]. Total cholesterol, HDL, or LDL did not have a comprehensive association with graft function in our patients (Fig. 1e–g). A third of the patients had hypertriglyceridaemia during the whole follow-up, while the prevalence of hypercholesterolemia (39–22%) and elevated LDL levels (17–4%) decreased over time, further emphasizing the importance of dietetic guidance of transplant children and adolescents.

Hyperuricaemia is a common complication of adult kidney recipients, and it associates with the graft function. Risk factors for post-transplant hyperuricaemia include reduced GFR, diuretic use, CsA therapy, increasing age at transplant, obesity and MS. Whether uric acid is an independent risk factor for chronic allograft dysfunction, or only a marker for reduced GFR, is not known [42–45]. A relationship between uric acid and triglyceride levels has previously been

reported [46,47], but according to our results, hypertriglyceridaemia explains the variance of GFR levels individually, even after controlling for the effect of uric acid. Hyperuricaemia was common in our patients and showed a strong negative correlation with GFR, in line with a recent Turkish study [48]. Importantly, this association was found already at 18 months after RTx, and the annual GFR decline thereafter was quite similar in patients with high and normal uric acid levels. These data favour the idea that uric acid is a marker, not a cause, of the poor kidney function.

Despite the improved results in both graft and patient survival, the kidney function declines inevitably in paediatric and adult RTx patients. This is caused by immunological and nonimmunological factors and pointing them out is important for the optimal management of the patients.

Authorship

JT, TJ and HJ: designed and performed the research/study, collected and analysed the data and wrote the manuscript. EQ, TH and MP: performed the study and wrote the manuscript.

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