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Cardiovascular effects of uremia and transplantation - non-invasive examination of target organ damage

PhD thesis

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LIST OF ABBREVATIONS

AASI	ambulatory arterial stiffness index
ABPM	ambulatory blood pressure monitoring
ACEi	angiotensin-converting enzyme inhibitor
BFM	body fat mass
BIA	multifrequency bioimpedance analysis
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
CAPD	continuous ambulatory peritoneal dialysis
CCb	calcium-channel blocker
CKD	chronic kidney disease
CV	cardiovascular
CyA	cyclosporine A
DBP	diastolic blood pressure
DM	diabetes mellitus
ECW/TBW	extracellular water, total body water ratio
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
HD	hemodialysis
HDL	high-density lipoprotein
HOMA-IR	homeostatic model assessment of insulin resistance
HR	heart rate
HT	hypertension/hypertensive
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
LDL	low-density lipoprotein
LTx	liver transplant/transplantation
MAP	mean arterial pressure
MS	metabolic syndrome
NDBPF	nocturnal diastolic blood pressure fall

NSBPF	nocturnal systolic blood pressure fall
PBF%	percent body fat %
PP	pulse pressure
PTH	parathyroid hormone
PWV	pulse wave velocity
RTx	renal transplant/transplantation
SBP	systolic blood pressure
SDS	standard deviation score
SSF	scapular skin-fold
TAC	tacrolimus
TSF	triceps skin-fold
Tx	transplantation
UAC	upper arm circumference
WaistC	waist circumference

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1. INTRODUCTION

1.1 Non-invasive cardiovascular risk assessment – pulse wave velocity and ambulatory arterial stiffness index

Increased arterial stiffness, a non-invasive indicator of arterial damage, is related to a higher risk of developing cardiovascular (CV) diseases. The lack of hard endpoints in children highlights the importance of CV risk stratification in pediatric medicine. (Aggoun et al., 2005, Morrison et al., 2010).

The parameter that is most widely used when describing arterial stiffness, characterizing arterial function, is pulse wave velocity (PWV) (Nichols, 2005).
The definition of pulse wave velocity is the path length between the wave-detecting probes divided by the pulse wave transit time:

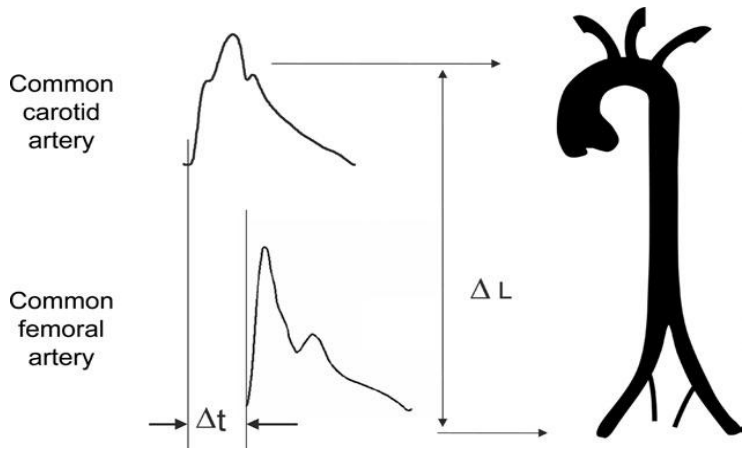

Figure 1. Carotid-femoral pulse wave velocity (Laurent et al., 2006)

PWV= ΔL/Δt (m/s)

Abbreviations: t – time; L - length

Several devices for measuring pulse wave velocity, involving applanation tonometry (SphygmoCor, PulsePen), piezoelectric mechanotransducers (Complior), and cuff-based oscillometry (Arteriograph, Vicorder) are in use (Milan et al., 2019).

The standardized measurement of pulse wave transit time is the foot-to-foot method (Millasseau et al., 2005, 2010), although various other body surface distance measurements have also been suggested (Laurent et al., 2006, Townsend et al., 2015, Reusz et al., 2020).

PWV increases with increasing arterial stiffness and vascular damage (Laurent et al., 2001). Central PWV measured as carotid-femoral PWV is a useful and accurate indicator of future cardiovascular emergencies (Laurent et al., 2006) and of long-term CV risk in adults (Nichols, 2005, Ben-Shlomo et al., 2014, Sequí-Domínguez et al., 2020). Increased PWV is associated with inflammation in patients with dyslipidemia (Aminuddin et al., 2020).

In the case of children, height-, age and sex-specific SDS values can be used (Reusz et al., 2010). PWV is higher in overweight and obese children with hypertension; the main determinant of PWV is systolic blood pressure (Stabouli et al., 2020). Chronic kidney disease is associated with higher PWV, which also increases with the stages of CKD; furthermore, it is related to an increase in aortic calcification (Kim et al., 2017).

Pulse wave velocity is known as an independent marker of cardiovascular morbidity as well as mortality following solid organ transplantation (Sidibe et al., 2017), even in pediatric populations (Schmidt et al., 2018, Cseprekál et al., 2014, Al Nasser et al., 2016).

An indirect measure of arterial stiffness calculated from data collected with 24-hour ABPM (ambulatory blood pressure monitoring) is the ambulatory arterial stiffness index or AASI. The AASI should be calculated, as defined by Dolan et al, as 1 minus the regression slope of the diastolic to systolic blood pressure over a 24 h recording period (Li et al., 2006a):

$AASI = 1 - r \times [(\text{SD of diastolic BP})/(\text{SD of systolic BP})]$

(r is the correlation coefficient).

The value of AASI varies from 0 to 1, with increasing AASI values indicating stiffer arteries.

AASI indicates the dynamic relationship between systolic and diastolic blood pressure. Calculating AASI is an easy, cost-effective method of evaluating and monitoring arterial stiffness, especially in those patients for whom ABPM is performed regularly.

AASI is recommended not only as a marker of elasticity in the arteries but also as a predictor of adult cardiovascular and cerebrovascular morbidity and mortality (Dolan et al., 2006, Li et al., 2006b). AASI predicts stroke affecting the general population (Kikuya et al., 2007, Hansen et al., 2006, Kollias et al., 2012). The value of AASI correlates with augmentation index, carotid-femoral PWV, and 24-hour pulse pressure (Li et al., 2006a, Kollias et al., 2012).

Boos et al linked AASI to the dipping of blood pressure and chronic inflammation (Boos et al., 2021).

However, AASI values in pediatric populations seem controversial (Simonetti et al., 2008a, Stergiou et al., 2010, Sulakova et al., 2012). AASI is increased in obese children (Taşdemir et al., 2020). AASI data in pediatric CKD are significantly correlated with diastolic BP and pulse pressure (Raina et al., 2020).

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1.2 Cardiovascular risk after pediatric renal transplantation

Chronic kidney disease (CKD) increases the chance of cardiovascular mortality, due to both traditional as well as non-traditional risk factors of cardiovascular origin. Risk factors specific to chronic kidney disease, such as hyperphosphatemia, hyperparathyroidism, renal osteodystrophy, and consequential vascular calcification further increase CV morbidity and mortality.

The cardiovascular risk rate decreases substantially after renal transplantation, although the risk of myocardial infarction, sudden cardiac death, and ischemic stroke remain 10 times higher than the corresponding risks characterizing the general population (Liefeldt et al., 2010).

After kidney transplantation, pre-existing or recently developed hypertension (HT), obesity, and metabolic syndrome (MS) further aggravate uremia-induced vascular dysfunction (Sorof et al., 2002). Excessive weight and obesity are highly prevalent in European children after RTx (Bonthuis et al., 2013, Dégi et al., 2014). Bárczi et al. found increased blood pressure readings and arterial stiffness in RTx children, associated with left ventricular hypertrophy and subclinical myocardial dysfunction (Bárczi et al., 2022).

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1.3 Cardiovascular risk after pediatric liver transplantation

Cardiovascular morbidity plays an important role, carrying the highest risk of death following a liver transplant (LTx) in adult recipients (Nicolau-Raducu et al., 2015). One of the most frequent complications after a transplant (with a 44% to 58% prevalence), the development of metabolic syndrome (MS), leads to a higher risk of cardiovascular morbidity and mortality in LTx patients (Jimenez-Perez et al., 2016). The side effects of immunosuppressive treatment – weight gain, new-onset diabetes, and dyslipidemia – further increase the CV risk after LTx (D'avola et al., 2017). Patients on steroids and tacrolimus have a higher risk of developing post-transplant diabetes, whereas the risk of dyslipidemia as well as of arterial hypertension is higher in patients on cyclosporine.

A five-year survival rate above 85 % makes pediatric liver transplant surgery a highly successful type of solid organ transplantation (Ng et al., 2012). However, over time children have a higher chance of developing hypertension, decreased levels of HDL (high-density lipoprotein), hypertriglyceridemia, as well as impaired glucose tolerance and diabetes. These factors predispose to increased CV risk (Kosola et al., 2014, Rothbaum Perito et al., 2012). As a complication of the immunosuppressant treatment used, the risk of developing diabetes after transplantation increases in the case of steroids and tacrolimus. Dyslipidemia and high blood pressure become more common in the case of cyclosporine use (D'avola et al., 2017, Hecking et al., 2021).

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2. OBJECTIVES

The relationships between body composition, arterial stiffness, and solid organ transplantation were examined in three studies:

1. Our first goal was to assess the presence of obesity, obesity-related metabolic changes, blood pressure disorders, and arterial stiffness (PWV) in association with obesity in pediatric patients after kidney transplantation (Dégi et al., 2014).
2. Further, we launched a cross-sectional observational research project to characterize the factors influencing AASI and examine their relationship to PWV in pediatric patients who have undergone renal transplant (Dégi et al., 2013).
3. Finally, we examined the prevalence of potential cardiovascular risk factors as well as alterations in arterial stiffness in pediatric LTx recipients. Further, we examined not only the effect of the type of immunosuppression on cardiovascular and metabolic changes, but also the presence of metabolic syndrome with its effect on arterial stiffness (Dégi et al., 2019).

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3. RESULTS

3.1 The occurrence of obesity and alterations in metabolism affecting children following renal transplant surgery

We examined 41 renal transplanted patients (aged 15.7±3.5 years, 28 males) with stage 1-3 chronic kidney disease. Patient data are presented in Table 1.

Table 1. Data referring to RTx children

	RTx recipients (n = 42)
Glomerular filtration rate (mL/min/1.73m^2)	93.2±25.5
Time spent on dialysis (months)	16 (0-60)
Time since transplantation (months)	49 (3-183)
PWV SDS	0.99±1.52

Data obtained from Dégi et al. (Dégi et al., 2014)

Data are expressed as mean±standard deviation or as median (range).

Glomerular filtration rate (GFR) was calculated according to Schwartz et al. (Schwartz et al., 2009) and with the MDRD equation used for those patients having reached 18 years of age (Levey et al., 1999).

PWV was determined by applanation tonometry (Salvi et al., 2004),

The patients with end stage renal disease had been diagnosed with renal hypoplasia, obstructive uropathy (n = 11); focal segmental glomerulosclerosis (n = 7); cystic renal disease (n = 5); nephronophtysis (n = 4); Alport syndrome (n = 3); cystinosis (n = 2); systemic lupus erythematosus (n = 1); acute tubular necrosis (n = 1); nephrocalcinosis (n = 1); other syndromes (VACTERL, Prune Belly, Noonan) (n = 3); and unknown origin (n = 3).

33 patients received tacrolimus and 8 patients received cyclosporine as basic immunosuppressive treatment. Forty patients received mycophenolate mofetil, and twenty-six patients were on a course of steroids during the research project.

Body composition was measured by body mass index (BMI), waist circumference (WaistC), skin-fold measurements (scapular skin-fold, SSF; triceps skin-fold, TSF), and multifrequency bioimpedance analysis (BIA). BIA was performed with the InBody 720 device (Biospace Co., Ltd., Seoul, Korea) (Lim et al., 2009). The device automatically displays measurements of body fat mass (BFM). Body fat percentage (PBF %) is BFM/weight x100%. We compared the received values with normal pediatric data from a database (Salvi et al., 2004, Joubert K., 2006).

Considering the various measures of obesity, we found significant correlations with the parameters measured by BIA:

BMI vs. BFM: $r = 0.94$; $p = 0.00001$

BMI vs. PBF%: $r = 0.80$; $p = 0.00001$

UAC vs. BFM: $r = 0.76$; $p < 0.05$

WaistC vs. BFM: $r = 0.75$; $p < 0.05$.

The other measures of SSF and TSF showed only loose, non-significant correlations with BFM and PBF%.

The presence of excessive weight (BMI >85%) rose from 3.2% to 24.4% at 49 (3-183) months after RTx, such as the BMI SDS (Table 2).

Table 2. Patient BMI data measured at the time of and after transplantation

	BMI SDS	**underweight/ obese+overweight (%)**
At transplantation	-0.27±0.79	3.2/3.2
After RTx	0.67±1.35*	0/24.4

Data obtained from Dégi et al. (Dégi et al., 2014)

* $p<0.05$ compared with the data at the time of transplantation

Age- and sex-dependent parameters were expressed as standard deviation scores (SDS).

Abbreviations: BMI, body mass index; SDS, standard deviation score

Underweight was defined as BMI < 5th percentile; normal weight as BMI between the 5th and 85th percentiles; overweight as BMI between the 85th and 95th percentiles; and obesity as BMI ≥95th percentile for age and sex. BMI SDS was calculated according to Hungarian standard BMI percentile curves (Joubert K, 2005).

A correlation was observed regarding the actual BMI SDS and BMI SDS at transplantation ($r = 0.63$; $p = 0.0001$).

We examined the parameters affecting BMI SDS after transplantation. We found close correlations with

- age ($r= -0.40$; $p = 0.009$)
- dialysis time ($r = -0.40$; $p =0.026$)
- PBF% and BFM ($r = 0.80$; $r = 0.94$, $p =0.0001$).

Glycemic control disturbance ($n = 14$) was correlated with body fat percentages and blood pressure readings that were higher than in children whose glucose metabolism was normal ($p < 0.05$).

The diagnosis of hypertension was established on the basis of twenty-four-hour ambulatory blood pressure monitoring (validated by the oscillometric ABPM-04 device; Meditech Kft., Budapest, Hungary) (Barna et al., 1998, Soergel et al., 1997).

Eight transplanted pediatric patients were found normotensive. 33 children were hypertensive and given antihypertensive therapy as follows:

ten of the children were on monotherapy, while the other twenty-three children were given a combination therapy involving a calcium channel blocker (amlodipine) and/or angiotensin-converting enzyme inhibitor (enalapril or ramipril) and/or b-blocker (metoprolol) and/or a1-blocker (prazosin).

BP standard deviation score (SDS) was comparatively higher in obese and overweight children (0.78 vs. 1.35 for systolic and 0.43 vs. 0.62 for diastolic BP, p = NS). Their antihypertensive treatments were similar (on average, 1.8 vs. 1.9 antihypertensive agents taken, p = NS).

Applanation tonometry, with the use of the PulsePen device (DiaTecne S.r.l., Milan, Italy), was applied to assess aortic pulse wave velocity (Salvi et al., 2004, Matthys et al., 2002). We calculated standard deviation scores (PWV SDS) specific to age, sex, and height in accordance with Reusz et al. (Reusz et al., 2010).

While no difference in PWV was observed between the obese/overweight and the lean patients (1.1 ± 1.29 vs. 0.96 ± 1.6), the patients who had undergone transplantation had higher than normal PWV standard deviations scores (Table 1).

The definition of glycemic control was based on the criteria of the American Diabetes Association (American Diabetes, 2018). The homeostasis model assessment index (HOMA-IR; fasting insulin x fasting glucose/22.5) was used to assess insulin resistance, according to the description of Matthews et al. (Matthews et al., 1985).

In our study group, 6 patients had IFG, 4 of the patients had IGT, while 4 patients had diabetes mellitus. Disturbed glucose metabolism (DM+IGT+IFG) in patients correlated with higher blood pressure as well as PBF%:

systolic BP SDS score (shown as mean±SD): 1.36± 1.26 vs. 0.73±0.75; diastolic BP SDS 0.84±0.88 vs. 0.29±0.69; PBF% 31.61±10.01 vs. 24.46±11.08; $p< 0.05$ for all values. A HOMA index higher than 2.83 (a sign of insulin resistance) was found in 13 patients, and these patients experienced a considerably greater increase in BMI SDS following RTx: 0.47±0.66 vs. 1.35±0.53, $p < 0.05$.

Regarding other laboratory parameters, we found that both uric acid and triglyceride levels were affected by the maintenance dose of steroids given after the surgical intervention. Patients receiving a prednisone dose of 0.25±0.38 mg/day had substantially lower levels of uric acid and triglyceride in comparison with patients being on an average dose of 4.39±1.98 mg/day (triglyceride, 1.52±0.94 vs. 2.49±1.76 mmol/L; uric acid, 300±63 vs. 368±107 mmol/L, $p <0.05$).

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3.2 Ambulatory arterial stiffness index in renal transplanted children

Fifty-four renal transplanted patients participated in the cross-sectional research project that we conducted. In addition, two control groups were formed, each with fifteen children, one of them included disease-free children, while the other one consisted of children diagnosed with primary (essential) hypertension. Table 3 summarizes the characteristics of patients.

Table 3. Anthropometric, blood pressure, and arterial stiffness data of the RTx children and the control groups.

Groups	**All RTx patients**	**Hypertensive RTx**	**Normotensive RTx**	**Primary hypertensive controls**	**Normotensive healthy controls**
N (males/females)	54 (38/16)	34 (26/8)	17 (9/8)	15 (10/5)	15 (8/7)
Age (years)	15.5±3.5	16.2±3.7	14.3±3.2	15.9±1.7	14.0±3.1
Height SDS †, §, *	-0.96 (-4.77-1.99)	-1.19 (-4.77-1.21)	-0.87(-3.68-0.56)	0.61 (-1.01-2.55)	0.33 (-0.89-1.74)
Weight SDS †, §, *	-0.12 (-1.99-3.58)	-0.16 (-1.99-3.58)	-0.1 (-1.37-0.56)	1.14 (-0.42-3.45)	0.79 (-0.93-3.04)
BMI SDS ¶, §, *	0.43 (-1.41-4.58)	0.50 (-1.41-4.58)	0.10 (-0.95-1.54)	1.11 (-0.25-4.56)	0.69 (-1.25-3.95)
24 h SBP SDS ¶, ‡, †, ×, *	1.1 (-1.69-3.97)	1.58 (-1.07-3.97)	-0.14 (-1.69-1.53)	2.55 (0.98-6.14)	0.19 (-2.11-1.58)
24 h DBP SDS ¶, ‡, †, ×, *	0.18 (-2.54-2.76)	0.49 (-2.42-2.76)	-0.39 (-2.54-0.87)	0.86(-1.77-5.34)	-1.13 (-2.84-0.19)
24 h Pulse PP (mmHg) ¶, ‡, †, §, *	53±8	56±8	47±6	63±9	53±7
24 h MAP (mmHg) ¶, ‡, †, ×, *	86±7	88±7	80±4	96±9	80±5
24 h HR (1/min)	79±11	76±11	81±11	75±12	79±9
Nocturnal SBP fall (mmHg) †, ×	9±6 (7%)	8±7 (6%)	11±3 (10%)	14±7 (10%)	14±6 (12%)
Nocturnal DBP fall (mmHg) ¶, †, ×	9±5 (13%)*	7±5 (10%)*	12±4 (17%)*	13±6 (16%)*	13±4 (19%)*
AASI ¶, ‡, ×, *	0.40±0.17	0.46±0.15	0.30±0.16	0.49±0.17	0.36±0.17

PWV SDS	1.24 (-4.21-5.03)	1.34 (-4.21-4.63)	0.89 (-0.75-3.02)	N.D.	N.D.

Data obtained from Dégi et al (Dégi et al., 2013)

* diastolic diurnal index

p<0.05 ¶ hypertensive transplant group vs. normotensive transplant group

‡ hypertensive control group vs. normotensive healthy control group

† hypertensive transplant group vs. hypertensive control group

§ normotensive transplant group vs. normotensive healthy control group

× hypertensive transplant group vs. normotensive healthy control group

* normotensive transplant group vs. hypertensive control group

Data are expressed as mean±standard deviation or as median (range).

Abbreviations: N - number of children; RTx - renal transplant children; SDS - standard deviation score; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; PP – pulse pressure; MAP – mean arterial pressure; HR – heart rate; AASI - ambulatory arterial stiffness index; PWV – pulse wave velocity; N.D. - no data

24-hour ambulatory blood pressure monitoring was performed with the validated oscillometric ABPM-04 device (Meditech Kft., Budapest, Hungary) (Barna et al., 1998, Lurbe et al., 2009).

AASI was calculated from 24-hour ambulatory blood pressure monitoring according to Li et al. (Li et al., 2006a).

PWV was determined by applanation tonometry (Salvi et al., 2004)

32 patients received continuous ambulatory peritoneal dialysis (CAPD) treatment, 17 patients were treated with hemodialysis (HD), and 1 patient was successively treated with both modalities before the renal transplant. In four cases, the transplantation was pre-emptive.

The conditions resulting in ESRD had been: focal segmental glomerulosclerosis (n = 10); renal hypoplasia (n = 7); obstructive uropathy (n = 6); isolated nephronophthisis (n = 6); Alport syndrome (n = 6); polycystic kidney disease (n = 5); Prune-Belly syndrome (n = 2); Bardet-Biedl syndrome (n = 2); tubulointerstitial nephritis (n = 2); cystinosis (n = 2); Joubert syndrome (n = 1); nephrocalcinosis (n = 1); VACTERL syndrome (n = 1); acute tubular necrosis (n = 1); hemolytic uremic syndrome (n = 1); and proteinuria (n = 1).

Concerning the immunosuppressive treatment, one child was on tacrolimus monotherapy; twenty-one patients received tacrolimus and mycophenolate-mofetil; cyclosporine and mycophenolate-mofetil were given to two children; one patient was

taking cyclosporine and steroids; twenty-three patients were treated with triple therapy (tacrolimus, steroids, and mycophenolate-mofetil); and six children were on cyclosporine, steroids, and mycophenolate-mofetil.

Hypertension was diagnosed on the basis of 24h ABPM after the RTx (Lurbe et al., 2009). The definition of HT that we used was daytime and/or nighttime systolic and/or diastolic blood pressure which reaches at least the 95th percentile for height according to Wuhl et al. (Wuhl et al., 2002).

Table 3 above presents the patients' anthropometric, blood pressure, and arterial stiffness data.

34 of the children suffered from established hypertension, receiving antihypertensive drugs (age: 16.2±3.7 years, 26 males). Nine of the patients received antihypertensive monotherapy with a calcium channel blocker (CCb) (n = 6), β-blocker (n = 2), or angiotensin converting enzyme inhibitor (ACEi) (n = 1); eleven patients were on a combined treatment involving CCb and β-blocker, and five on a treatment involving ACEi and CCb; while nine patients received triple medication including ACEi inhibitor, CCb, and β-blocker.

Uncontrolled hypertension (n = 14) was understood as SBP and/or DBP reaching at least the 95th percentile for height in a patient on antihypertensive treatment. Controlled hypertension (n = 20) was defined as SBP and DBP lower than the 95th percentile in patients taking antihypertensive medication. New-onset hypertension (n = 3) was understood as hypertension developed by a formerly normotensive patient (the interval of regular blood pressure controls was less than or equal to 3 months) not taking antihypertensive medication (these data are represented in the global evaluation of the RTx group but not in the comparative analysis).

Higher blood pressure readings were found in the uncontrolled hypertensive RTx patient subgroup (24 h SBP SDS, 2.37 (1.78 to 3.97) vs. 0.93 (1.07 to 1.63); 24 h DBP SDS 1.08 (0.72 to 2.76) vs. 0.16 (2.42 to 1.06), both $p < 0.0005$), and in a lesser number of patients who were on CCb medication (11/14 (79%) vs. 20/20 (100%), $p = 0.04$) than in the controlled hypertensive RTx subgroup. No differences were detected between the

two subgroups when considering laboratory and anthropometric data. These subgroups were similar with regard to AASI, BNP, and ECW/ TBW as well.

Afterwards the controlled and uncontrolled hypertensive subgroups were treated as a single hypertensive RTx group.

Both the normotensive and the hypertensive groups of RTx children showed considerably lower height and weight SDS compared to their controls of the same age. The hypertensive RTx groups showed a BMI SDS that was significantly higher than that of the normotensive RTx group.

The ECW/ TBW ratios and AASI of HT RTx patients were substantially higher than in the normotensive RTx group, and the HT RTx patients also had increased BNP values; on the other hand, no difference was observable between the PWV and PWV SDS height values of the hypertensive and normotensive groups. The time spent on dialysis by HT RTx children was longer than the time spent on dialysis by normotensive RTx children. There was no difference between the normotensive and HT RTx groups regarding data related to calcium, carbohydrate, lipid, and phosphate metabolism.

Table 4 presents laboratory data and body composition of the RTx groups.

Table 4. Laboratory data and body composition of the renal transplant children

Groups	**All RTx**	**Hypertensive RTx**	**Normotensive RTx**
se Creatinine (μmol/L)	107±32	108±31	102±36
GFR (mL/min/1.73m^2)	84±23	85±26	81±18
se Cholesterol (mmol/L)	4.4±1.2	4.6±1.4	4.1±0.7
se Triglyceride (mmol/L)	1.2 (0.3-11)	1.4 (0.3-11)	1.1 (0.6-2.6)
se Fasting glucose (mmol/L)	5.3±1.3	5.4 ±1.5	5.2 ±0.5
se Hemoglobin (g/L)	131±15	132±15	126±10
se Ca×P (mmol^2/L^2)	3.1±0.7	3.1±0.8	3.3±0.5
ECW /TBW (%) *	37.5±1.3	37.8±1.3	36.7±1.1
BNP (pg/mL) *	40 (0-340)	61 (0-340)	34 (0-104)
Time on dialysis (months) *	11 (0-74)	15 (0-54)	4 (0-74)
Time since RTx (months)	36 (1-179)	37 (1-179)	31 (5-75)

Data obtained from Dégi et al (Dégi et al., 2013)

* p<0.05 normotensive transplant group vs. hypertensive transplant group

Data are expressed as mean±standard deviation or as median (range).

Abbreviations: RTx - renal transplant children; se – serum; GFR – glomerular filtration rate; ECW/TBW - extracellular water /total body water ratio; BNP - brain natriuretic peptide

Standard laboratory parameters were measured by routine laboratory methods.

Glomerular filtration rate (GFR) was calculated according to Schwartz et al. (Schwartz et al., 2009) and with the MDRD equation used for those patients having reached 18 years of age (Levey et al., 1999).

Bioimpedance analysis was performed by the InBody 720 device (Biospace Co., Ltd., Seoul, Korea)

We compared the transplant patients' AASI with the AASI of fifteen healthy controls of identical age and with the AASI of fifteen primary HT children also of matching age. We used 24h-ABPM to assess their blood pressure; a diagnosis of primary hypertension was established after the known causes of secondary hypertension had been excluded.

An AASI value above 0.301 was found in 88 % of RTx patients, according to Simonetti et al.:

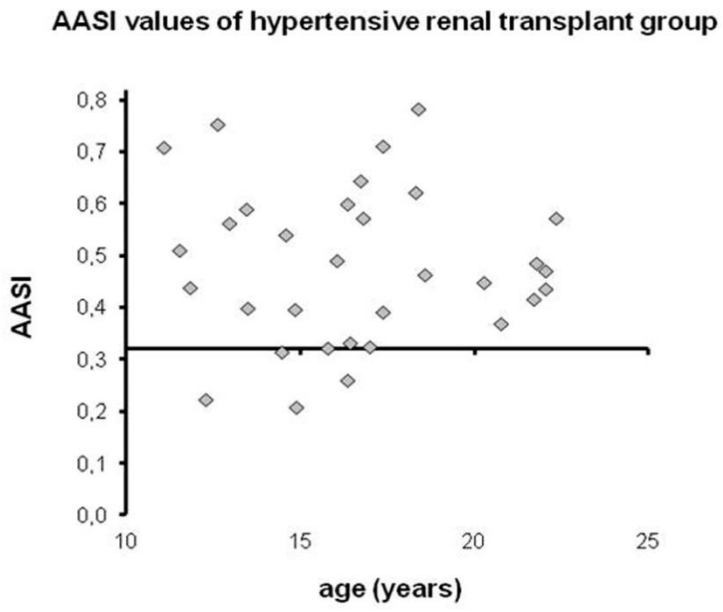

Figure 2. AASI values in hypertensive RTx children. Source: Dégi et al (Dégi et al., 2013)

The horizontal line indicates the cutoff value of AASI defined by Simonetti et al (Simonetti et al., 2008a)

AASI values were not affected by age or gender, in either the renal-transplanted or the control groups. Although, the normotensive healthy control group had considerably lower values of AASI than the hypertensive renal-transplanted group and the primary hypertensive control group, their AASI values were the same as those of the normotensive renal-transplanted children. At the same time, the AASI values presented by the hypertensive control group were similar to those of the hypertensive renal-transplanted group (Table 4). A significant positive correlation was observable between AASI and PP, time on dialysis, ECW/TBW ratio, and BMI SDS ($r > 0.30$, $p < 0.02$) in the renal-transplanted group in general. Another significant correlation existed between AASI and BNP values ($r = 0.33$, $p < 0.02$). On the other hand, there was a negative correlation between AASI and nocturnal DBP fall ($r = 0.51$, $p < 0.00007$), however, no correlation could be detected between AASI and nocturnal SBP fall.

When BP variables had been excluded from the analysis, it was ECW/TBW that remained as the single independent AASI factor in renal-transplanted pediatric patients (Table 5).

Table 5. Determinants of AASI - Univariate linear and multiple regression analysis of the whole RTx group

	Univariate linear regression analysis		**Multiple regression analysis***	
	r	**p**	**ß**	**p**
SBP SDS	0.39	0.004	N.I.	
DBP SDS	-0.005	0.97	N.I.	
HR (1/min)	-0.03	0.83	N.I.	
Nocturnal SBP fall (mmHg)	-0.18	0.18	N.I.	
Nocturnal DBP fall (mmHg)	-0.51	0.00007	N.I.	
MAP (mmHg)	0.17	0.23	N.I.	
PP (mmHg)	0.49	0.0002	N.I.	
BMI SDS	0.39	0.004	0.31	0.055
Time on dialysis (months)	0.30	0.03	0.26	0.06
ECW/TBW (%)	0.48	0.002	0.34	0.03

Data obtained from Dégi et al (Dégi et al., 2013)

* R^2 0.38 Standard error 0.15 $p<0.001$

Included parameters: BMI SDS, time on dialysis, ECW/TBW.

Abbreviations: N.I. – not included; N.S. - non significant; RTx - renal transplant children; SDS - standard deviation score; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; MAP – mean arterial pressure; PP – pulse pressure; BMI – body mass index; ECW/TBW - extracellular water /total body water ratio.

The nocturnal period was defined according to Wuhl et al. (13). A non-dipping pattern was defined as a fall of <10% of the daytime BP level. Standard deviation scores (SDS) for sex and height were calculated (13).

The renal-transplanted group presented no correlation between AASI and PWV SDS height. Nor was there any correlation of significance between PTH or proteinuria and AASI or PWV in the RTX group. In addition, we were unable to detect any connection regarding the type of immunosuppressive medication and PWV or AASI values.

We observed an elevated PWV SDS height among the transplant patients who, before the operation, had spent over a year on dialysis (1.51±1.45 vs. 0.42±1.64, $p < 0.02$). This group had both elevated cholesterol levels (4.81±1.48 vs. 4.06±0.82; $p < 0.03$) and higher BP ($p < 0.04$). Furthermore, a substantial negative correlation was found between PWV SDS and eGFR ($r = 0.43$; $p < 0.04$).

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3.3 Cardiovascular risk assessment in liver transplanted children

Forty-two liver transplant recipients (21 males) whose mean age was 9.93±3.57 years participated in the research project.

Patient characteristics and anthropometric data are presented in Table 6.

Table 6. Anthropometric data of pediatric LTx patients

Groups	**All LTx patients (n = 42)**	**Tacrolimus group (n = 30)**	**Cyclosporine group (n = 11)**
Age at examination (years)	9.9 ± 3.6	10.2 ± 3.7	9.2 ± 3.3
Age at LT (years)[*]	1.02 (0.18 – 15.04)	1.5 (0.44 – 15.04)	0.6 (0.18 – 3.6)
Time since LT (years) [#]	5.9 ± 3.6	5.2 ± 3.8	7.9 ± 2.5
Body weight SDS	0.15 ± 1.28	0.23 ± 1.48	-0.04 ± 0.5
Body height SDS	0.6 (-3.54 – 2.0)	0.52 (-3.54 – 2.0)	0.95 (-0.51 – 1.45)
BMI SDS	-0.19 (-3.22 – 5.28)	0.03 (-3.22 – 5.29)	-0.29 (-0.96 – 1.15)
BFM (kg) [#]	6.05 (1.5 – 27.6) (n = 33)	7.1 (2.1 – 27.6) (n = 23)	3.25 (1.5 – 12.2) (n = 10)
PBF (%) [#]	17.45 (5.5 – 48.2) (n = 33)	20.3 (6.2 – 48.2) (n = 23)	12.9 (5.5 – 31.7) (n = 10)
Fat mass of trunk	1.77 (0.06 – 14.32)	2.07 (0.07 – 14.32)	0.17 (0.06 – 5.65)

Data obtained from Dégi et al (Dégi et al., 2019)

[*] $p<0.006$ tacrolimus group vs. cyclosporine group

[#] $p<0.02$ tacrolimus group vs. cyclosporine group

Data are expressed as mean±standard deviation or as median (range).

Abbreviations: n - number of children; LTx - liver-transplanted children; SDS - standard deviation score; BMI - body mass index; BFM – body fat mass; PBF – percent body fat.

Body mass index SDS was calculated according to Hungarian standard BMI percentile curves (Joubert K, 2005).

Bioimpedance analysis was performed by the InBody 720 device (Biospace Co., Ltd., Seoul, Korea) (Lim et al., 2009).

Orthotopic LTx indications included the following conditions: end-stage liver disease caused by biliary atresia (n = 25); Alagille syndrome (n = 3); progressive familial intrahepatic cholestasis (n = 3; all had the low gamma-glutamyl transpeptidase phenotype); acute liver failure (n = 2); idiopathic liver cirrhosis (n = 2); and further causes (n = 7), such as alpha-1 antitrypsin deficiency, cystic fibrosis, hepatoblastoma, Ivemark syndrome, neonatal hemochromatosis, primary sclerosing cholangitis, as well as type 1 autoimmune hepatitis.

We included TAC (13 patients) and CyA (11 patients) monotherapy in the basic immunosuppressive therapy. Twelve of the patients were given a combination therapy of TAC and mycophenolate mofetil; three patients were on TAC, mycophenolate mofetil, and steroids; one patient was treated with TAC and azathioprine; another patient received TAC, steroids, and azathioprine, and sirolimus monotherapy was given to one patient.

Evaluating the potentially different effects resulting from various treatment modalities on anthropometric and selected laboratory parameters, we separately examined two further subgroups of patients who had been treated with either TAC or CyA. Patients receiving CyA therapy were younger at the time of transplantation than those receiving TAC treatment. On the other hand, in the case of the CyA group, a longer time had elapsed since the surgery. No differences of significance could be detected between these two groups with regard to height, which was in the normal range, or other basic anthropometric data (Table 6).

Eight (17.8%) of the patients were either overweight or obese. BIA measurements existed for 33 LTx patients. We found that patients treated with TAC had considerably higher BFM as well as percentage body fat than the CyA group. The data can be seen in Table 6. BIA-measured parameters (BFM, percent body fat, visceral fat area) were correlated with BMI SDS values ($p<0.01$, $r>0.57$).

The LTx patients' laboratory data are presented in Table 7.

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Table 7. Laboratory data of LTx patients

Groups	All LTx patients (n = 42)	Tacrolimus group (n = 30)	Cyclosporine group (n = 11)
se Creatinine (μmol/L)	58 (23 - 105)	57 (23 - 105)	61 (32 - 86)
GFR (mL/min/1.73m^2)	89.3 (56.9 – 170.4)	90.5 (67.6 – 170.4)	79 (56.9 – 152.9)
se Ca×P (mmol^2/L^2)	3.5 (1.2 – 4.3)	3.4 (1.2 – 4.3)	3.6 (2.4 – 4.1)
se Cholesterol (mmol/L) *	3.8 ± 0.8	3.6 ± 0.8	4.4 ± 0.6
se LDL Cholesterol (mmol/L) *	2.3 ± 0.8	2.1 ± 0.7	2.9 ± 0.6
se Triglyceride (mmol/L)	0.7 (0.4 – 1.8)	0.7 (0.5 – 1.8)	0.6 (0.4 – 1.3)
se Fasting glucose (mmol/L)	4.06 ± 0.84	4.1 ± 0.9	3.9 ± 0.8
HOMA-IR	0.69 (0.03 – 5.27)	0.71 (0.03 – 5.27)	0.53 (0.19 – 3.69)
INR	1.2 ± 0.1		
APTI	34.3 ± 5.5		
Albumin	43.4 ± 2.5		
se Bilirubin	9 (4 - 32)		
Alanine aminotransferase (ALT, SGPT)	20.5 (6 - 137)		
Aspartate aminotransferase (AST, SGOT)	31 (11 - 152)		
Alkaline phosphatase (ALP)	581.5 (90 - 1305)		
Gamma-glutamyl transpeptidase (GGT)	15 (8 - 211)		
Lactate dehydrogenase (LDH)	407.9 ± 140.3		

Data obtained from Dégi et al (Dégi et al., 2019)

* $p<0.004$ tacrolimus group vs. cyclosporine group

Data are expressed as mean±standard deviation or as median (range).
Abbreviations: n - number of children; LTx - liver-transplanted children; se - serum; GFR – glomerular filtration rate; LDL - low-density lipoprotein; HOMA-IR - homeostasis model assessment index; INR - international normalized ratio; APTI - activated partial thromboplastin time.
Standard laboratory parameters were measured by routine laboratory methods.
GFR was calculated according to Schwartz et al. (Schwartz et al., 2009) with the MDRD equation used for those patients having reached 18 years of age. (Levey et al., 1999)
Insulin resistance was assessed by the homeostasis model assessment index (HOMA-IR; fasting insulin x fasting glucose/22.5) as described by Matthews et al. (Matthews et al., 1985).

The average GFR was found normal or slightly subnormal, although twenty of the patients had GFR values of 60 to 90mL/min/1.73m^2 (14/30 in the TAC and 6/11 in the CyA group) and 1 child had <60mL/min/1.73m^2.
With the average lipid values being in the normal range, seventeen patients had borderline to high lipid values. 12%, 10%, and 12% of patients showed high serum triglyceride, total cholesterol, and low-density lipoprotein (LDL) cholesterol levels (>95th percentile), respectively. The cholesterol and LDL-cholesterol levels of CyA-treated patients were considerably higher than those of the TAC group. Only 15 patients had available serum HDL levels, all of which were found to be in the normal range.

One of the patients suffered from insulin-dependent diabetes mellitus, which had developed prior to the transplantation, and another one had IFG. None of the patients had IGT, although two patients had HOMA-IR higher than the cutoff values.
Table 8 presents the BP and PWV values of the LTx patients.

Table 8. Blood pressure and pulse wave velocity values of LTx patients

	All LTx patients (n = 42)
Casual SBP SDS	-0.15 ± 0.71
Casual DBP SDS	0.11 ± 0.69
24 h SBP SDS for age*	-0.84 ± 1.03
24 h SBP SDS for height*	-0.69 ± 0.88
24 h DBP SDS for age*	-0.99 ± 1.13
24 h DBP SDS for height*	-0.94 ± 1.09
24 h HR SDS for age*	0.64 ± 1.23
Daytime SBP SDS*	-0.96 ± 1.01
Night-time SBP SDS*	-0.29 ± 1.04
Daytime DBP SDS*	-1.19 ± 0.99
Night-time DBP SDS*	-0.07 ± 1.12
Systolic diurnal index (%)*	11 (0 – 16)
Diastolic diurnal index (%)*	14.2 ± 6.9
PWV SDS for age	0.31 ± 1.02
PWV SDS for height	0.34 ± 1.09

Data obtained from Dégi et al (Dégi et al., 2019)

*n = 19

Data are expressed as mean±standard deviation or as median (range).

Abbreviations: n - number of children; LTx - liver-transplanted children; SDS - standard deviation score; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; PWV – pulse wave velocity.

Casual blood pressure was measured according to the 2017 recommendations (Flynn et al., 2017).

24-hour ambulatory blood pressure monitoring was performed with the validated oscillometric ABPM-04 device (Meditech Kft., Budapest, Hungary) (Barna et al., 1998, Lurbe et al., 2009).

PWV was determined by applanation tonometry (Salvi et al., 2004)

Eight (19%) of the patients received antihypertensive therapy due to hypertension. 24-hour ABPM averages were available for nineteen patients, all of which were in the

normal range. Six (14%) of the patients had somewhat elevated average nighttime BP values and a non-dipping pattern.

Occasional blood pressure measurements during the investigation of PWV indicated elevated blood pressure readings in four patients and >95th percentile blood pressure in one patient.

The presence of the MS components was evaluated according to the definition of the modified Adult Treatment Panel III (ATP III) criteria (Cook et al., 2003, Sangun et al., 2011, Vanlancker et al., 2017). The patient was diagnosed with MS if ≥3 of the following disorders were detected: triglycerides >95th percentile; HDL < 5th percentile; either systolic blood pressure (SBP) or diastolic blood pressure (DBP) > 95th percentile (alternatively: treated hypertension); decreased glucose tolerance (alternatively: treated diabetes mellitus). The study population had a comparatively high presence of individual MS components (Figure 3).

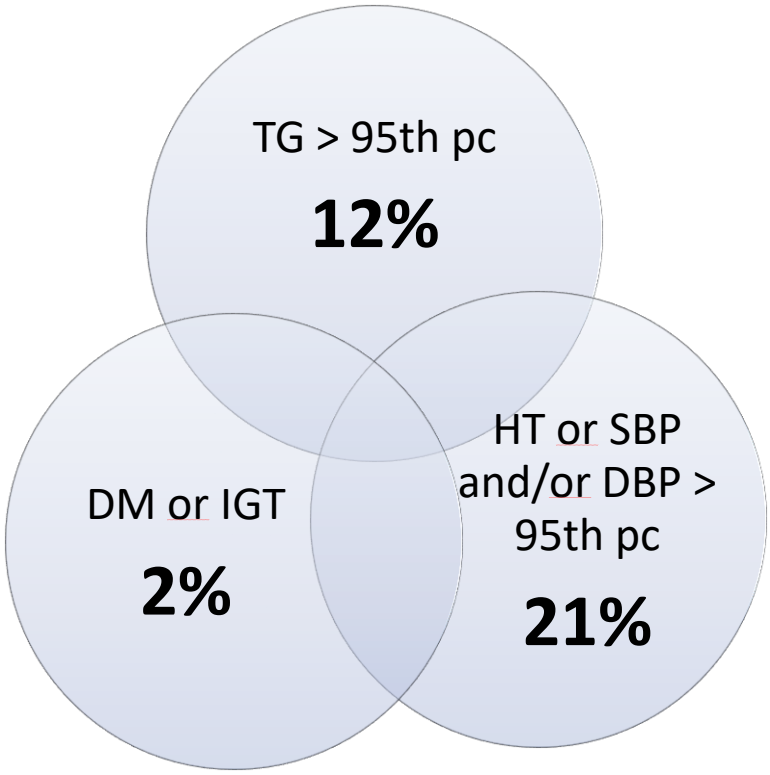

Figure 3. The prevalence of metabolic syndrome and its components

Figure obtained from Dégi et al (Dégi et al., 2019)

Abbreviations: TG – serum trigliceride; DM - diabetes mellitus; IGT – impaired glucose tolerance; HT – hypertension; SBP - systolic blood pressure; DBP - diastolic blood pressure.

There was only one patient with metabolic syndrome based on modified ATP III criteria. This patient suffered from insulin-dependent diabetes mellitus and had controlled hypertension as well. Her twenty-four-hour ABPM BP was in the normal range, albeit showing a non-dipping pattern.

PWV data are summarized in Table 8. PWV was normal in the majority of LTx patients; nevertheless, two patients showed PWV values between the 90^{th} and 95^{th} percentile, and 5 patients had PWV values in the $>95^{th}$ percentile. The 24-hour ABPM values of these patients stayed in the normal range, even though one of these patients had a non-dipping pattern. There were two patients with controlled hypertension.
Three of them presented GFR values <90 mL/min/1.73m^2. No further traditional risk factors (hyperlipidemia, impaired glucose metabolism, overweight) could be found.

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4. DISCUSSION

4.1 The prevalence of obesity and metabolic changes in children after renal transplant surgery

One of the greatest difficulties associated with transplantation in the case of children is posed by obesity. According to the NAPRTCS data (Foster et al., 2010), early development of excessive weight as well as its persistence for years following transplantation is typical. Examining data from 25 European countries between 1995 and 2010 (including nearly 4,500 children on dialysis and RTx children under 16 years of age), 3.5% of patients were characterized by insufficient weight, while 20.8% and 12.5% of them were overweight and obese, respectively (Bonthuis et al., 2013). Boschetti et al. (Boschetti et al., 2013) found 29% of patients to be overweight or obese at 1 year after transplantation. Plumb et al. found a much higher prevalence of overweight/obesity in the study cohort in comparison with the childhood population in the UK in general (Plumb et al., 2014). A meta-analysis published by Yaseri et al. found that pediatric obesity is correlated with a higher risk of short-term and long-term mortality after transplantation (Yaseri et al., 2021).

The prevalence of obesity increased from 3.2% to 24.4% after transplantation in our study group. For comparison, the frequency of pubertal pre-obesity or obesity in schoolchildren in the general population of Hungary is 15-20% (Haug et al., 2009).

The presence of excessive weight prior to the transplantation had been considerably lower than the 31.4% indicated by the data provided by Plumb et al (Plumb et al., 2014). Since there was no significant difference in the proportion of patients on peritoneal dialysis, this finding may be due to the fact that nutritional manipulation was comparatively less intensive and tube feeding was infrequently used in our group.

Gaining weight in our cohort was shown to be negatively related to the time spent on dialysis treatment while positively related to the weight at transplantation. The determining factors were similar to those described by Boschetti et al. (Boschetti et al., 2013): age at transplantation and excessive weight/obesity in the first month after transplantation.

During the first year after transplantation, weight gain is related to steroid treatment (Boschetti et al., 2013, Denburg et al., 2010). Avoidance or withdrawal of corticosteroids is linked to lower adiposity and greater height gains (Bonthuis et al., 2013, Denburg et al., 2010). Intriguingly enough, our data did not back up the above-mentioned correlation between weight gain and steroid use. This fact may be explained by the comparatively small doses of steroids administered to the patients. In our study group, higher levels of uric acid and triglyceride represented the negative metabolic effects resulting from steroid treatment.

It is possible to assess childhood adiposity with dual-energy X-ray absorptiometry (DEXA) and BIA. Sopher et al. (Sopher et al., 2004) and Lim et al. (Lim et al., 2009) found a good relationship between these two ways of measuring body composition. They concluded that it was possible to apply BIA in screening, population studies, and at the bedside.

By comparing different measures of obesity, we found that the calculated BMI and BFM and PBF% measured by BIA were closely correlated. Simple bedside measures of obesity, UAC, and WaistC were significantly correlated with BFM. The other parameters, like SSF and TSF, indicated only loose and non-significant correlations with BIA measurements.

The prevalence of hypertension was 80% in our study group, similar to the data of Denburg et al. (73%). Higher glucocorticoid dosage and increased BMI SDS were independent determinants of systolic blood pressure (Denburg et al., 2010). In our RTx group, hypertension was associated with impaired glucose metabolism. Steroid exposure did not correlate with either obesity or with hypertension.

Pediatric patients with end-stage kidney disease have increased arterial stiffness (PWV). Arterial stiffness as assessed by PWV may decrease after transplantation, suggesting improvement in arterial disease (Kis et al., 2009). The PWV SDS of our RTX children was 1 SD higher in comparison with normal standards. PWV values were the same in lean and obese RTx groups. This result suggests that other factors, like the uremic load before transplantation, are more significant determinants of arterial function than the comparatively short-term metabolic effect of excessive weight, as hypothesized by Kis et al (Kis et al., 2008). During follow-up examination of transplanted children by our

working group, neither the BMI SDS nor the PWV SDS changed significantly when comparing the data measured at 2.4 years and 9.3 years after RTX.

In many cases, the hard endpoints associated with obesity develop in adulthood (Sayin et al., 2022), while subclinical organ damage can already be detected in children (Brady et al., 2012, Karava et al., 2019). It appears essential to monitor and eliminate treatable and preventable risk factors (Stabouli et al., 2022).

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4.2 Ambulatory arterial stiffness index in kidney transplanted pediatric patients

Ambulatory arterial stiffness index has been suggested as a reliable marker of adult cardiovascular morbidity and mortality. The stiffness index is described as an early indicator of impending cardiovascular events – especially a cerebrovascular accident. It is affected by age, and is also associated with systolic blood pressure and pulse pressure, as well as with the nocturnal systolic and diastolic fall in blood pressure. A connection between AASI and PWV as well as further markers of target organ damage have been suggested by some researchers (Kollias et al., 2012).

Nevertheless, research has provided little evidence on the value of ambulatory arterial stiffness index in the case of pediatric patients. Stergiou et al. did not detect any difference between the ambulatory arterial stiffness index values of normotensive and hypertensive patients (Stergiou et al., 2010). In contrast, Simonetti et al. reported that AASI had been found to be higher in hypertensive child patients, and was also correlated with the duration of hypertension. The cutoff of AASI distinguishing hypertensive from normotensive children was established at 0.301 (8.2 odds ratio, 81% sensitivity, 65% specificity (Simonetti et al., 2008b).

Research has found that AASI depends on the dipping status of hypertension (Schillaci et al., 2007, Baumann et al., 2008). The range of diastolic blood pressure values in non-dippers is narrower throughout the day, therefore the coefficient of regression (r) of the 24-hour diastolic over systolic blood pressure has a tendency to decline, while the reciprocal of ambulatory arterial stiffness index increases. AASI can reflect the effects of both nocturnal pressure change and pulse pressure on deterioration of arterial function. (Schillaci et al., 2007, Gavish et al., 2007, Schillaci et al., 2009).

Predicting AASI on the basis of only one instance of ABPM in the case of an individual patient may be problematic due to the variability of dipping status (Chaves et al., 2005). To enable a more thorough examination of the significance and applicability of ambulatory arterial stiffness index, it is essential to standardize the method. Randomized clinical trials and follow-up evaluation are needed in this patient group (Reusz et al., 2010).

In our hypertensive RTx group, AASI values exceeding 0.301 were found in 88% of patients (Figure 2). AASI was primarily predicted by an existing condition of hypertension, dipping state and dialysis treatment time.

Normotensive RTx patients had significantly lower ECW/TBW than the hypertensive RTx group. It seems possible that the retention of fluid affects this parameter, considering the observable correlation between AASI and ECW/TBW. One explanation of this could be the antihypertensive treatment: all but three of the hypertensive recipients were taking CCbs, which can promote fluid retention and may cause a higher ECW/TBW ratio. Despite the fact that CCbs were given in the case of a few patients with uncontrolled hypertension, the ECW/TBW of these patients was identical to that of the patients with controlled hypertension.

With regard to pharmaceutical antihypertensive therapy, AASI data are controversial. A one-year treatment with atenolol or perindopril/indapamide significantly decreases pulse wave velocity, without any major alteration regarding AASI values (Jin et al., 2011). However, in the course of a 3-month research project following 188 HT subjects, Andreadis et al. provided evidence that angiotensin receptor blockers reduced AASI more than CCBs (Andreadis et al., 2010).

The fact that our hypertensive RTx patients had higher BNP values indicates the presence of an increased cardiac workload possibly resulting from decreased dipping and an increase in ECW. Hypertensive and normotensive RTx patients did not significantly differ in eGFR. One explanation may be that obesity, due to an increase in sympathetic activity and relative insulin resistance, leads to the retention of sodium. (Davy et al., 2009).

One type of evidence to support the above hypothesis is that the primary hypertensive control patients as well had a considerable increase in their BMI and showed similar AASI scores as the RTx hypertensive groups, while the BMI and AASI values of both normotensive groups, i.e., the RTx patients and the controls, were normal.

The lack of major differences in arterial stiffness markers and laboratory parameters between the controlled and the uncontrolled hypertensive renal transplanted subgroups can perhaps be due to the circumstance that an increased blood pressure led to modifications in the treatment regimen with the purpose of blood pressure

normalization. As a result, the controlled and uncontrolled status could represent temporary diagnoses of this cross-sectional study.

The relationship of AASI to PWV is contradictory. Li et al. described a significant correlation between the two markers in healthy adult volunteers (Li et al., 2006a), their finding, however, has been supported by no further studies, including ours (Stergiou et al., 2010, Schillaci et al., 2007, Wang et al., 2008, Jerrard-Dunne et al., 2008, Muxfeldt et al., 2008).

Like our previous findings, the data provided by the present research showed increased PWV in patients who had a higher uremic load before the transplantation, and also in patients who had elevated cholesterol levels and blood pressure, and decreased eGFR (Cseprekal et al., 2009).

The relation of uremic burden to AASI and to central PWV could also be due to the well-known consequence of the accelerated athero- and arteriosclerosis before transplantation, resulting in functional and structural damages of the arterial wall. Although PWV and body composition were not performed in the case of healthy controls and primary hypertensives, the results in these two groups may be helpful in interpreting the effect of calcium channel blockers on volume status and, in turn, on AASI and PWV.

Our finding indicates that it is more probably the pressure- and volume-dependent load of the arterial system that is reflected by AASI, while PWV appears to be an integrated index of vascular pathology, which marks the general burden that is gradually placed on the arteries by aging and uremia, in addition to other risk factors.

In conclusion, central PWV estimates the elastic state of the arterial wall at a single point of the pressure-volume curve, while AASI may describe the instantaneous intrinsic rigidity of the arterial wall in a dynamic circumstance caused by daily systolic and diastolic blood pressure changes, and the relationship between blood pressure values and the actual pressure-volume overload of large arteries (Wang et al., 2008). This is possibly the reason why it can be used to foretell cardiovascular complications, including cerebrovascular accidents, in the case of adults (Hansen et al., 2006). Volume overload has indeed been shown to function as an independent predictor of AASI by multiple regression analysis following the exclusion of blood pressure variables.

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4.3 Cardiovascular risk assessment in liver transplanted children

Childhood obesity and metabolic syndrome have a constantly increasing prevalence worldwide (Sgambat et al., 2018, He et al., 2017).

In the pediatric transplant population, the immunosuppression therapies (altering glucose and lipid metabolism) further aggravate the risk of obesity and hypertension (Brady et al., 2010). Individual components of MS likewise tend to be more prevalent after liver transplant surgery (Dagher et al., 2015). In addition, decreased kidney function leads to accelerated vascular aging, resulting in an elevated risk of cardiovascular morbidity and mortality. Campbell et al. (Campbell et al., 2006) reported that 32% of pediatric liver transplant recipients experienced renal dysfunction.

According to our data, patients' basic anthropometric values stayed within the normal range. However, the individual components of body composition show differences in body fat depending on the immunosuppressive therapy.

GFR values between 60-90 mL/min/1.73m^2, amounting to chronic kidney disease grade 2 (CKD 2), were found relatively frequently among the pediatric patients participating in our study, in accordance with previous reports (Kivelä et al., 2011, Campbell et al., 2010). Kidney damage in liver transplant patients is mainly caused by calcineurin inhibitors. We found that patients on cyclosporine presented somewhat lower GFR than the tacrolimus group, as described previously (Distant et al., 1993).

Dyslipidemia is more frequently associated with the use of cyclosporine (Neal et al., 2001), which can be a consequence of the inhibitory effect on bile salt synthesis (Luca et al., 2015). Despite lipid values being generally in the normal range in our cohort, we observed elevated serum lipid levels with regard to 10% of the patients. Patients treated with cyclosporine showed cholesterol and LDL-cholesterol levels that were significantly higher than those of the patients receiving tacrolimus.

Pancreatic β-cell apoptosis is the consequence of calcineurin inhibition and it causes a decline in the secretion of insulin and lower insulin sensitivity in peripheral tissues; these lead to the formation of new-onset diabetes. The diabetogenic potential of tacrolimus is higher (Luca et al., 2015). In our study, a disturbed glucose metabolism (as insulin-dependent diabetes mellitus, IFG, or higher HOMA-IR values) affects a small proportion of patients; all of them received tacrolimus.

LTx candidates generally have low peripheral vascular resistance, which shows a gradual increase following the surgical intervention. The development of high blood pressure and elevated vascular resistance following LTx is partly due to the effect of calcineurin inhibitors (Muduma et al., 2016). In our cohort, one-fifth of patients had controlled hypertension. A non-dipping pattern was detected in six patients. Elevated nighttime blood pressure is a known risk factor for left ventricular hypertrophy, and it is an early sign of developing arteriosclerosis and GFR deterioration as well (Mallamaci et al., 2016).

We have limited data concerning the development of arterial stiffness following pediatric LTx at our disposal (Al Nasser et al., 2016, Pisano et al., 2016). Memaran et al. found higher PWV values in liver transplanted children (Memaran et al., 2019).

The PWV of the LTx patients participating in our study was usually normal; nonetheless, 5 % of children showed PWV values that were between the 90^{th} and 95^{th} percentile, while the PWV values of 12% were above the 95^{th} percentile. Two of these patients had been diagnosed and treated with hypertension, while one patient had a non-dipping pattern. The GFR values of three patients were lower than 90 ml/min/1.73 m^2. Risk profiling indicates that our LTx patients already have increased body fat, CKD, components of MS, HT, and high-normal or elevated PWV. The above findings indicate the need for regular and close monitoring of these parameters in order to reduce the CV risk. Additionally, as our results are partly associated with the type of immunosuppression used, the decision, when choosing or minimizing or avoiding a calcineurin inhibitor, needs to be based on the patient's pre-transplant metabolic and vascular phenotype.

Limitations of the studies

All of the studies have several limitations. Their cross-sectional design precludes any conclusive causal relationship regarding the correlations described. The comparatively limited patient number, their heterogeneity in etiology and therapy, limited our ability to carry out an in-depth factor analysis, which prohibits any conclusion about the causal relationship of the correlations presented.

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5. CONCLUSIONS

1. The proportion of overweight or obese population in the pediatric renal cohort in Hungary is low at the time of transplantation, but increases afterwards. Excessive weight is linked to glucose metabolism disturbance and raised blood pressure; those disturbances, however, are not yet expressed by any stiffening of the arteries. There was no correlation between the obesity-related factors and PWV values.

2. In pediatric patients who have undergone kidney transplantation, AASI is associated with the volume- and pressure-dependency of arterial stiffness. AASI is a characteristic feature of the actual volume- and pressure-dependent arterial rigidity rather than the changes in the morphology of large arteries in the long term, indicated by PWV. A significant result of our present research is that it attests the effect of uremic vintage on the vasculature in this particular patient population, underlining the necessity of early transplantation in pediatric patients suffering from end-stage renal disease.

3. Elevated body fat, CKD, high lipid content, HT, and more pronounced arterial rigidity are all observed and are partly linked to the chosen immunosuppression regimen in children living with liver transplant five years after transplantation. These findings suggest that long-term follow-up evaluation is necessary to determine their influence on cardiovascular health and survival rate.

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6. SUMMARY

Cardiovascular morbidity plays a crucial part in renal and liver transplantation mortality. Given the low numbers of CV events in pediatrics, surrogate indicators should be analyzed to determine CV damage. Beyond the gold standard PWV, AASI, as an indicator of the stiffness of arteries, can be a predictor of cardio- and cerebrovascular related morbidity. We aimed at assessing the presence of obesity and related metabolic disturbances in RTx children and their effect on arterial stiffness, and at assessing the decisive factors of AASI in this population. Our further goal was to assess the occurrence of CV risk factors as well as CV impairment signs related to metabolic syndrome and immunosuppression therapy in LTx children.

The presence of obesity in the studied renal cohort of Hungarian children at the time of transplantation was 3.2%, and this rose to 24.4% at about four years after RTx. Obesity is related to disturbed glycemic control (IFG, IGT, DM, insulin resistance) and elevated blood pressure. The arterial stiffness measured by PWV is higher compared to the normal population.

Dipping status, volume overload, and dialysis time were the key predictive factors of AASI. In children with higher pre-RTx uremic burden, elevated levels of PWV as well as cholesterol and BP elevation and diminished GFR were present. Unlike AASI, PWV showed no difference between the groups of hypertensive and normotensive RTx patients. We found no correlation between PWV and AASI.

Obesity and hypertension observed was about 20% at 5 years after liver transplantation. Half of the children showed GFR values above 90 mL/min/1.73 m^2. Elevated PWV values (12%) were related with hypertension and decreased renal function. Patients on tacrolimus had higher body fat mass; children on cyclosporine had higher serum cholesterol levels.

We have established that higher AASI in hypertensive RTx children is a characteristic feature of the actual volume-dependent and pressure-dependent arterial rigidity. In contrast, PWV does reflect the changes in the morphology of the large arterial vessels in the long term. Regarding LTx patients, it was found that hypertension, obesity, hyperlipidemia, CKD, and even increased arterial stiffness are present more than 5 years after transplantation. These disturbances are partly related to the type of immunosuppression.

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