INCREASED RENAL RESISTIVE INDEX AS A MARKER OF EARLY STAGE OF DIABETIC NEPHROPATHY IN NORMOALBUMINURIC CHILDREN WITH TYPE 1 DIABETES MELLITUS

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SUMMARY – This study aimed to compare the renal resistive index (RI) as an early marker of renal damage between normoalbuminuric children with type 1 diabetes mellitus (T1D) and normal age-matched controls. A total of 76 children with T1D (aged 10-18 years) and 76 healthy age-matched controls were enrolled. Anthropometric parameters, blood pressure, glycated hemoglobin (HbA1c), serum creatinine (sCr), estimated glomerular filtration rate (eGFR), serum uric acid (SUA), urine albumin/creatinine ratio (ACR), and degree of pubertal development were determined in all participants. RI was measured using Doppler ultrasound in both groups. The T1D group had lower sCr and SUA values and higher ACR and mean RI values than the control group. Using the expectation-maximization method, 2 clusters of T1D patients were identified. Cluster 2 with higher RI values, eGFR and HDL cholesterol was more prone to albuminuria and could carry worse prognosis. In conclusion, renal RI is increased in the hyperfiltration phase of diabetic nephropathy in children with T1D. Renal RI could be helpful as a marker for diagnosing diabetic nephropathy in the early preclinical course of the disease in normoalbuminuric children with T1D.

Key words: *Doppler renal resistive index; Type 1 diabetes mellitus; Children*

Introduction

The incidence of type 1 diabetes mellitus (T1D) has significantly increased in children over the past decades[1]. Diabetic nephropathy is the leading cause of mortality in patients with T1D. Approximately 30%-40% of such patients progress to end-stage renal disease. This is the main reason for dialysis or renal transplantation[2,3]. Diabetic nephropathy is an important risk factor for coronary artery disease. Considering the increased incidence of T1D, early detection of diabetic nephropathy has a pivotal role in the prevention of end-stage renal failure in children with T1D. Recent studies have shown that in the absence of diabetic nephropathy, mortality in patients with T1D is similar to that in the general population[4]. Microalbuminuria is currently the most reliable predictor of diabetic nephropathy and is

the consequence of diabetes-induced glomerular damage. Microvascular complications may be present a few years after the onset of the disease because the pathogenic factor of T1D is microangiopathy caused by chronic hyperglycemia[2]. Doppler sonography is a noninvasive method for investigating renal hemodynamics. Renal resistive index (RI) measured by Doppler ultrasound is an indicator of increased intrarenal vascular resistance, which occurs in patients with T1D with initial renal damage[5]. Several studies in children and adults with T1D revealed an increased intrarenal RI, which could be useful as a marker of developing diabetic nephropathy. A threshold RI value of 0.70 for increased renal vascular resistance in adults is applied to children aged >6 years[6].

The aim of this study was to compare renal RI in children with T1D without microalbuminuria with that in healthy children in order to evaluate the utility of RI as an early marker in diagnosing the preclinical stage of diabetic nephropathy in normoalbuminuric children with T1D.

Patients and Methods

Study population

In this cross-sectional study, we enrolled 76 patients with T1D (39 boys and 37 girls aged 10-18 years) and 76 healthy controls (36 boys and 40 girls) who had visited the Endocrinological Division at Department of Pediatrics, Sestre milosrdnice University Hospital Center in Zagreb between December 2018 and November 2019. All patients and their parents provided informed consent, and the study protocol was approved by the Ethics Committee of the Sestre milosrdnice University Hospital Center and University of Zagreb School of Medicine.

Inclusion criteria for patients with T1D were as follows: age 10-18; pubertal development stage ≥II according to Tanner scale (for girls ≥II degrees; for boys with a testicular size ≥4 mL *per* Prader); duration of T1D ≥3 years, regardless of whether it was diagnosed before puberty; and duration of T1D ≥2 years if diagnosed during puberty, normoalbuminuria (urine albumin/creatinine ratio [ACR] <3 mg/mmol). The exclusion criteria were acute urinary tract infection, glucocorticoid therapy, other kidney diseases, orthostatic proteinuria, thyroid disease, diabetic ketoacidosis, renal artery stenosis, parvus tardus spectrum on Doppler ultrasonography, and malignant

diseases (tumors and leukemia). In the control group, there were 76 healthy age- and gender-matched children who did not have kidney disease, arterial hypertension, or acute and chronic diseases, and who neither took medicines that could affect the required parameters nor were admitted to the ward due to psychological abdominal pain, headache, or chest pain. In the study group, blood samples were obtained for the measurement of glycated hemoglobin (HbA1c), serum creatinine (sCr), serum lipids, and serum uric acid (SUA), and three first-morning urine samples were obtained for the measurement of ACR. Each subject had their systolic and diastolic arterial blood pressure measured using an auscultation method, validated by a blood pressure monitor on three separate occasions with an appropriate arm and pressure grading according to the European Society of Hypertension recommendations depending on age, sex, and body height[7]. Doppler RI was determined using an ultrasound device (Philips Affiniti 50G; Royal Philips, Amsterdam, The Netherlands) with a C6-2 convex probe.

Laboratory workup

The same laboratory procedures were performed in both patients and controls, except for HbA1c, which was determined using the DCA Vantage® Analyzer (Siemens Healthcare GmbH, Erlangen, Germany) with the monoclonal antibody agglutination method only in patients with T1D. The sample for determining HbA1c was drawn from capillary blood. Metabolic control level of the disease was evaluated based on the mean HbA1c value in the last 12 months. The Architect c8000 Automatic Biochemistry Analyzer (Abbott Laboratories, Abbott Park, IL, USA) was used to determine the following values: urine albumin (using an immunoturbidimetric method), urine creatinine (using a kinetic method with an alkaline picrate), and SUA (using spectrophotometric UV enzyme analysis), all with original reagents. The estimated glomerular filtration rate (eGFR) was evaluated using the Schwartz formula[8]. Cholesterol was determined using a colorimetric enzymatic method with cholesterol esterase and 4-aminoantipyrine, HDL-cholesterol using a homogeneous colorimetric enzyme with an accelerator (selective detergent), LDL-cholesterol using the Friedewald calculation method, and triglycerides (TG) using a colorimetric enzymatic method with lipase 4-aminoantipyrine.

Renal resistive index

Ultrasound measurements were performed using a Philips Affiniti 50G ultrasound device with a C6-2 (2 to 6 MHz) convex probe in the back or side position. Ultrasonographic examination in B-mode of both kidneys for the assessment of renal size, shape, and echogenicity was performed. The main trunk of the renal artery is displayed. Thereafter, if this examination did not reveal any renal abnormality, RI would be determined in the interlobar or arcuate arteries of both kidneys. Three measurements were made with clear spectra on three different blood vessels, i.e., upper, middle, and lower thirds of both kidneys. Based on these individual measurements, the mean RI was calculated. RI was calculated as (peak systolic velocity – end-diastolic velocity)/peak systolic velocity. All examinations were performed by the same operator.

Statistical analysis

The results were statistically processed using Statistica™ computer program (version 12) (Dell Inc., Round Rock, TX, USA). Categorical data were presented descriptively using absolute and relative frequencies, as well as numerically, depending on the distribution, arithmetic mean and standard deviation, or median and interquartile ranges. Distribution normality was analyzed using the Kolmogorov-Smirnov test. Differences between categorical variables were analyzed using χ^2-test and Fisher exact test, and among numerical variables using Student's t-test, one-way ANOVA, and Mann-Whitney U test. For detecting a possible marker for renal impairment within the group of diabetics, we used the ostensible, unsupervised machine-learning technique[9]. Using the expectation-maximization method[9], we attempted to identify clusters of patients with common characteristics. Only patients with no missing data on the selected variables were included in the expectation-maximization algorithm to avoid the potential bias of missing data and the need of imputation method. The rationale for this approach was the relatively small number of patients with missing data, which resulted in 61 patients on which expectation-maximization was performed. The level of statistical significance was set at $p < 0.05$.

Results

The study was carried out on 152 subjects, of which 76 were patients with T1D, and 76 were healthy controls. Table 1 shows general data on the subjects, with anthropometric and biochemical parameters in separate for the control and diabetic groups. With the exception of anthropometric measurements, no significant differences were found between T1D and control groups.

Table 2 presents blood pressure values and biochemical data on healthy controls and T1D patients. Patients with T1D had increased albuminuria, sCr, and lipid levels, as well as lower uric acid and eGFR ($p < 0.05$). A significant difference was found in the mean RI (mRI) value (0.58 ± 0.04 *vs.* 0.6 ± 0.04, $p < 0.001$), which was higher in the T1D group than in the control group.

Table 3 presents control parameters and diabetes treatment. The mean disease duration was 5.95 ± 3.23 years, HbA1c concentration $7.71 \pm 1.03\%$, and insulin dosage 41.96 ± 17.21 international units (IU) *per* day. With respect to insulin type, the analog type (80.52%) was most commonly used, followed by a combination of the human and analog type (12.99%), while pure human insulin was the least commonly used (6.49%). On analyzing the values of mRI for accompanying diseases in the T1D group, statistically significant differences were found only in the cluster of subjects who had autoimmune thyroiditis ($p = 0.046$). These patients had slightly lower mRI values (0.58 ± 0.04) than those who did not have thyroiditis (0.61 ± 0.04) (Table 4).

There was no gender difference in mRI values (0.60 ± 0.04 *vs.* 0.61 ± 0.04; $p = 0.702$). Correlation analysis in the T1D group revealed no positive correlation of disease duration, HbA1c values, sex, age, dosage and type of insulin with mRI.

To determine the possible marker of renal impairment in the T1D group, the ostensible, unsupervised machine learning approach was used. The expectation-maximization method was used to identify groups as proposed clusters of patients with common characteristics. Variables used to form the clusters were as follows: age, HbA1c, serum and urine creatinine, SUA, GFR, HDL, LDL, TG, cholesterol, urine albumin, urine ACR, systolic and diastolic blood pressure in centiles, body mass index in centiles, and left, right and mean RIs. Using the expectation-maximization method with ten-fold cross-validation, 2 clusters of patients were identified. They were grouped based on common characteristics. Statistically significant differences were found between the clusters

for all variables. The common characteristics are presented in Table 5. Common features of cluster 2 as compared to cluster 1 were elevated RI values, ACR in first-morning urine samples, eGFR, and HDL cholesterol, as well as lower sCr and diastolic blood pressure values. Cluster 2 with higher RI values, eGFR and HDL cholesterol is more prone to albuminuria and could carry worse prognosis.

Table 1. General and demographic data on study subjects

	Control (N=76)	T1D (N=76)	p‡
Age [years]	14.16±2.19	13.71±2.7	0.263
Gender [n (%)]			
Male	36 (47.37)	39 (51.32)	0.767
Female	40 (52.63)	37 (48.68)	
Height [cm]	167.39±11.94	161.77±13.06	**0.006**
Weight [kg]	61.47±16.24	56±15.81	**0.037**
BMI [kg/m²]	21.54±4.21	21.02±4.13	0.445
[Median (25%-75%)]	0.69 (-0.29 - +1.4)	0.33 (-0.22 - +1.1)	0.497
Tanner scale [n (%)]			
II	8 (10.53)	20 (26.32)	0.052
III	19 (25)	12 (15.79)	
IV	21 (27.63)	15 (19.74)	
V	28 (36.84)	29 (38.16)	
Family medical history [n (%)]			
No	75 (98.68)	71 (93.42)	0.201
Yes	1 (1.32)	5 (6.58)	

T1D = type 1 diabetes mellitus; BMI = body mass index

Table 2. Subject characteristics and laboratory parameters per groups (control/T1D)

	Control	T1D	p[‡]
Bood pressure [mm Hg]			
Systolic	109.47±10.57	108.22±12.24	0.501
Systolic (centile)	47.17±26.3	43.08±28.26	0.362
Diastolic	68.72±8.35	66.58±9.28	0.136
Diastolic (centile)	58.29±24.57	54.51±24.35	0.347
mRI (arithmetic mean for right and left)	0.58±0.04	0.6±0.04	**<0.001**
Urine ACR [mg/mmol]	1.06±0.92	1.68±1.56	**0.004**
Serum urea [mmol/L]	4.26±0.94	4.76±0.93	**0.001**
FT3 [pmol/L]	4.64±0.75	4.38±0.85	0.04
FT4 [pmol/L]	12.58±1.78	12.52±1.38	0.807
TSH [mIU/L]	1.76±0.68	1.83±1	0.614
Total cholesterol [mmol/L]	4.1±0.64	4.39±0.74	**0.01**
Triglycerides [mmol/L]	0.98±0.42	0.83±0.39	**0.019**
HDL [mmol/L]	1.34±0.27	1.49±0.3	**0.002**
LDL [mmol/L]	2.31±0.54	2.51±0.64	**0.036**
GFR [mL/min/1.73 m^2]	110.1±21.24	114.12±20.59	0.24
SUA [μmol/L]	285.51±77.65	257.87±58.07	**0.014**
sCr [μmol/L]	63.09±12.78	55.93±12.94	**<0.001**

T1D = type 1 diabetes mellitus; mRI = mean resistive index; ACR = albumin/creatinine ratio; HDL = high-density lipoprotein; LDL = low-density lipoprotein; GFR = glomerular filtration rate; SUA = serum uric acid; sCr = serum creatinine

Table 3. Disease control parameters and diabetes treatment

	Arithmetic mean (±SD)
HbA1C [mmol]	7.71±1.03
Duration T1D [years]	5.95±3.23
Insulin dosage [units]	41.96±17.21
Type of insulin [n (%)]	
Human	5 (6.49)
Analog insulin	62 (80.52)
Human + analog	10 (12.99)

T1D = type 1 diabetes mellitus

Table 4. Effects of comorbidities on mRI

	Arithmetic mean (±SD) mRI *per* disease		p*
	No	Yes	
Thyroiditis	0.61±0.04	0.60±0.05	0.781
Autoimmune thyroiditis	0.61±0.04	0.58±0.04	**0.046**
Celiac disease	0.60±0.04	0.65±0.02	0.066
Diagnosed in puberty	0.61±0.04	0.59±0.03	0.776

*Student's t-test; mRI = mean resistive index; SD = standard deviation

Table 5. Cluster analysis results

	Cluster 1 (N=39)	Cluster 2 (N=22)	p*
sCr [umol/L]	58.89±10.82	48.64±9.6	**<0.001**
GFR [mL/min/1.73 m²]	105.65±17.79	122.33±17.79	**<0.001**
HDL [mmol/L]	1.44±0.27	1.62±0.37	**0.033**
ACR [mg/mmol]	1.12±1.05	3.14±1.66	**<0.001**
Diastolic BP (centile)	57.22±24.29	45.59±23.73	**0.049**
mRI	0.59±0.04	0.63±0.03	**<0.001**
RI left	0.59±0.05	0.63±0.04	**0.002**
RI right	0.59±0.03	0.63±0.03	**<0.001**

*ANOVA; sCr = serum creatinine; GFR = glomerular filtration rate; HDL = high-density lipoprotein;
ACR = albumin/creatinine ratio; BP = blood pressure; mRI = mean resistive index; RI = resistive index

Discussion

In this study, it was observed that renal Doppler RI was significantly higher in diabetic children with normal renal function than in healthy age-matched control children. All RI values in both groups were smaller than 0.70, which is within the normal range for healthy adults and children aged >6 years[6]. Pelliccia *et al.* demonstrated higher RI values in children with T1D, especially among patients who were less regulated and had higher HbA1c values than in healthy subjects, concluding that Doppler method is useful in detecting early renal hemodynamic changes

and developing diabetic nephropathy[10]. Savino *et al.* report that intrarenal hemodynamic abnormalities are detectable by Doppler ultrasonography, even in early diabetic nephropathy before microalbuminuria appears[11]. In an earlier study by Okten *et al.*, no significant differences were found between diabetic and healthy children[12].

Diabetic nephropathy is defined as persistent proteinuria >500 mg/24 h or albuminuria >300 mg/24 h, usually associated with arterial hypertension and decreased GFR[4]. Currently, screening for diabetic

nephropathy is mainly based on the appearance of elevated albuminuria, with an increase in sCr and a decrease in GFR. Microalbuminuria is a commonly used parameter for the diagnosis of diabetic nephropathy and is a result of diabetes-induced glomerular damage and glomerular morphological changes such as thickening of the glomerular basement membrane and mesangial expansion[13]. Although it takes years for diabetic nephropathy to progress to its severe stages, kidney biopsies performed 1.5-2.5 years after the onset of the disease in children who remained normoalbuminuric revealed structural changes in terms of glomerular and tubular basement membrane thickening, resulting in the occurrence of albuminuria as an early indicator of diabetic nephropathy development[14]. T1D is also associated with microvascular and macrovascular complications[2]. The onset of puberty and poor glycemic control are independent risk factors for the development of microalbuminuria in children with T1D[15]. Regression to normoalbuminuria has already been observed in patients with microalbuminuria[16]. Many other factors such as physical activity and high blood pressure can affect daily excretion of albumin in urine[17]. More recent studies have revealed that children with T1D who have high normal urinary albumin levels are at a higher risk of developing diabetic nephropathy than those with low normal urinary albumin levels[18,19]. It is of paramount importance to prevent kidney disease progression in patients with T1D, especially in children with early disease onset who are mostly normoalbuminuric because they have the highest risk of developing diabetic nephropathy. Doppler sonography as a noninvasive evaluation of renal vascular resistance through the measurement of RI has provided an easily applicable and noninvasive method for investigating renal hemodynamics. Several studies have revealed that increased RI can be detected in various parenchymal kidney diseases (hemolytic-uremic syndrome, diabetic nephropathy, and autosomal-dominant polycystic disease), except for glomerulonephritis where RI values are normal[17]. Early functional and structural abnormalities that occur a few years after diabetes diagnosis may be responsible for the precocious alteration in renal hemodynamics. These can be detected by measuring RI in renal arteries, which reflects renovascular resistance. The search for alternative indicators of renal dysfunction development in children with T1D and possible noninvasive methods for the study of renal hemodynamics and determination of intrarenal vascular resistance in the renal artery and its branches led to the consideration of Doppler RI[5,20]. In patients with T1D, elevated RI has been proven to accompany diabetic nephropathy progression and correlates well with renal function parameters, elevated blood pressure, and disease duration[20].

The present study revealed significantly higher RI in cluster 2 with a higher normal range of albumin in the urine, eGFR and HDL cholesterol than in cluster 1, a phenomenon comparable with the results observed in other studies including patients with T1D[21,22].

In our study, there was no positive correlation of T1D duration and HbA1c values with mRI, which is consistent with the findings of other studies[23]. Sex, age, dosage and type of insulin did not have positive correlations with mRI values in patients with T1D in this study; however, some studies suggest a decreasing incidence of diabetic vascular complications related to improved diabetes treatment[24]. Ghaffar *et al.* report a strong positive correlation between renal RI and GFR in children with T1D[22]. In contrast, our work revealed a negative correlation between mRI and GFR values in patients with T1D, which is explained by the early phase of hyperfiltration and the consequent renal preglomerular vasodilation and lower mRI[12,22,25].

This study had the following limitations: the relatively small sample size and lack of follow-up data. However, the strength of our study is comprehensive analysis of data through cluster analysis, defining phenotype in children at an increased risk of developing renal damage. Based on this analysis, two categories of diabetic patients were identified; therefore, a new hypothesis could be extrapolated and generated, i.e., patients with higher RI values could be more prone to albuminuria. In conclusion, this cross-sectional study suggests that renal Doppler RI can be useful in detecting early changes in renal hemodynamics and diagnosing the preclinical stage of diabetic nephropathy in normoalbuminuric patients with T1D. Follow-up studies are needed to confirm these findings.

References

1. Afkarian M. Diabetic kidney disease in children and adolescents. Pediatr Nephrol. 2015;30(1)65-74. doi: 10.1007/s00467-014-2796-5.

2. Bjornstad P, Donaghue KC, Maahs DM. Macrovascular disease and risk factors in youth with type 1 diabetes: time to be more attentive to treatment? Lancet Diabetes Endocrinol. 2018;6(10):809-20. doi: 10.1016/S2213-8587(18)30035-4.

3. Bjornstad P, Cherney D, Maahs DM. Early diabetic nephropathy in type 1 diabetes: new insights. Curr Opin Endocrinol Diabetes Obes. 2014;21(4):279-86. doi: 10.1097/MED.0000000000000074.

4. Wolfsdorf JI, Glaser N, Agus M, Fritsch M, Hanas R, Rewers A, *et al*. ISPAD Clinical Practice Consensus Guidelines 2018: Microvascular and macrovascular complications in children and adolescents. Pediatr Diabetes. 2018;19;27:155-77. doi: 10.1111/pedi.12701.

5. Tublin ME, Bude RO, Platt JF. Review. The resistive index in renal Doppler sonography: where do we stand? AJR Am J Roentgenol. 2003;180(4):885-92. doi: 10.2214/ajr.180.4.1800885.

6. Kuzmić AC, Brkljačić B, Ivanković D, Galešić K. Doppler sonographic renal resistance index in healthy children. Eur Radiol. 2000;10(10):1644-8. doi: 10.1007/s003300000466.

7. Lurbe E, Agabiti-Rosei E, Cruickshank JK, Dominiczak A, Erdine S, Hirth A, *et al*. European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens. 2016;34(10):1887-920. doi: 10.1097/HJH.0000000000001039.

8. Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am. 1987;34(3):571-90. doi: 10.1016/S0031-3955(16)36251-4.

9. Dempster AP, Laird NM, Rubin DB. Maximum likelihood from incomplete data *via* the EM algorithm. J R Stat Soc Ser B Stat Method. 1977;39(1):1-22.

10. Pelliccia P, Savino A, Cecamore C, Primavera A, Schiavone C, Chiarelli F. Early changes in renal hemodynamics in children with diabetes: Doppler sonographic findings. J Clin Ultrasound. 2008;36(6):335-40. doi: 10.1002/jcu.20457.

11. Savino A, Pelliccia P, Schiavone C, Primavera A, Tumini S, Mohn A, *et al*. Serum and urinary nitrites and nitrates and Doppler sonography in children with diabetes. Diabetes Care. 2006;29(12):2676-81. doi: https://doi.org/10.2337/dc06-0346.

12. Okten A, Dinc H, Kul M, Kaya G, Can G. Renal duplex Doppler ultrasonography as a predictor of preclinical diabetes nephropathy in children. Acta Radiol. 1999;40(3):246-9. doi: 10.3109/02841859909175549.

13. Bogdanović R. Diabetic nephropathy in children and adolescents. Pediatr Nephrol. 2008;23(4):507-25. doi: 10.1007/s00467-007-0583-2.

14. Adolescent type 1 Diabetes cardio-renal Intervention Trial (AdDIT). BMC Pediatr. 2009;9(1):79. doi: 10.1186/1471-2431-9-79.

15. Papadopoulou-Marketou N, Chrousos GP, Kanaka-Gantenbein C. Diabetic nephropathy in type 1 diabetes: a review of early natural history, pathogenesis, and diagnosis. Diabetes Metab Res Rev. 2017;33(2). doi: 10.1002/dmrr.2841.

16. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. N Engl J Med. 2003;5;348(23):2285-93. doi: 10.1056/NEJMoa021835.

17. MacIsaac RJ, Ekinci EI, Jerums G. Progressive diabetic nephropathy. How useful is microalbuminuria? Kidney Int. 2014;86(1):50-7. doi: 10.1038/ki.2014.98.

18. Glassock RJ. Is the presence of microalbuminuria a relevant marker of kidney disease? Curr Hypertens Rep. 2010;12(5):364-8. doi: 10.1007/s11906-010-0133-3.

19. Thorn LM, Gordin D, Harjutsalo V, Hägg S, Masar R, Saraheimo M, *et al*. The presence and consequence of nonalbuminuric chronic kidney disease in patients with type 1 diabetes. Diabetes Care. 2015;38(11):2128-33. doi: 10.2337/dc15-0641.

20. Brkljačić B, Mrzljak V, Drinković I, Soldo D, Sabljar-Matovinović M, Hebrang A. Renal vascular resistance in diabetic nephropathy: duplex Doppler US evaluation. Radiology. 1994;192(2):549-54. doi: 10.1148/radiology.192.2.8029430.

21. Youssef DM, Fawzy FM. Value of renal resistive index as an early marker of diabetic nephropathy in children with type-1-diabetes mellitus. Saudi J Kidney Dis Transpl. 2012;23(5):985-92. doi: 10.4103/1319-2442.100880.

22. Abd El Ghaffar S, El Kaffas K, Hegazy R, Mostafa M. Renal Doppler indices in diabetic children with insulin resistance syndrome. Pediatr Diabetes. 2010;11(7):479-86. doi: 10.1111/j.1399-5448.2009.00628.x

23. Komers R, Anderson S. Paradoxes of nitric oxide in the diabetic kidney. Am J Physiol Renal Physiol. 2003;284(6):F1121-37. doi: 10.1152/ajprenal.00265.2002.

24. Amin R, Widmer B, Prevost At, Schwarze P, Cooper J, Edge J, *et al*. Risk of microalbuminuria and progression to macroalbuminuria in a cohort with childhood onset type 1 diabetes: prospective observational study. BMJ. 2008;29;336(7646):697-701. doi: 10.1136/bmj.39478.378241.BE.

25. Perkins BA, Bebu I, de Boer IH, Molitch M, Tamborlane W, Lorenzi G, *et al*. Risk factors for kidney disease in type 1 diabetes. Diabetes Care. 2019;42(5):883-90. doi: https://doi.org/10.2337/dc18-2062.

Sažetak

POVIŠENI BUBREŽNI INDEKS OTPORA KAO BILJEG RANE FAZE DIJABETIČKE NEFROPATIJE U NORMOALBUMINURIČNE DJECE SA ŠEĆERNOM BOLESTI TIPA 1

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Cilj ovog istraživanja bio je usporediti bubrežni indeks otpora (RI) kao rani biljeg bubrežnog oštećenja između normoalbuminurične djece koja boluju od šećerne bolesti tip 1 (ŠB1) i kontrolne skupine zdrave djece iste dobi. Bilo je uključeno 76 djece sa ŠB1 (u dobi od 10-18 godina) i 76 zdrave djece u kontrolnoj skupini. Antropometrijski parametri, krvni tlak, glikolizirani hemoglobin (HbA1c), serumski kreatinin (sCr), procijenjena stopa glomerularne filtracije (eGFR), mokraćna kiselina u serumu (SUA), omjer albumin/kreatinin u mokraći (ARC) i stupanj pubertetskog razvoja utvrđeni su kod svih sudionika. RI je izmjeren pomoću Dopplerova ultrazvuka u objema skupinama. Skupina ŠB1 imala je niže vrijednosti sCr i SUA i više vrijednosti ACR i prosječnog RI u odnosu na kontrolnu skupinu. Primjenom postupka maksimizacije očekivanja identificirane su dvije skupine bolesnika kod oboljelih od ŠB1. Skupina 2. s višim vrijednostima RI, eGFR i HDL kolesterola sklonija je razvoju albuminurije i mogla bi imati lošiju prognozu. U zaključku, bubrežni RI je povišen u hiperfiltracijskoj fazi dijabetičke neuropatije u djece sa ŠB1. Bubrežni RI mogao bi biti koristan biljeg u dijagnosticiranju rane pretkliničke faze dijabetičke neuropatije u normoalbuminurične djece sa ŠB1.

Ključne riječi: *Dopplerov bubrežni indeks otpora; Šećerna bolest tip 1; Djeca*