Clinical and Experimental Nephrology (2022) 26:415–423
https://doi.org/10.1007/s10157-021-02169-7

ORIGINAL ARTICLE

# Evaluation of cardiovascular risk in children with solitary functioning kidney

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Received: 2 June 2021 / Accepted: 5 December 2021 / Published online: 17 January 2022


## Abstract

**Background** The present study investigates cardiovascular risk and kidney damage in patients with solitary kidneys.

**Methods** Included in the study were 40 children with a unilateral functioning kidney and 60 healthy controls, all of whom were evaluated for carotid intima-media thickness, ischemia-modified albumin and oxidative stress parameters, and 24-h ambulatory blood pressure monitoring.

**Results** Serum creatinine and urine microalbumin levels were higher and creatinine clearance was lower in the patient group than in the control group, and serum ischemia-modified albumin, carotid intima-media thickness, aldosterone, plasma renin activity and blood pressure were all higher in the patient group than in the control group. In addition, the patient group was showed a non-dipper pattern.

**Conclusion** Children with a normal functioning solitary kidney are likely at higher risk of developing cardiovascular disease and such patients should be followed closely before marked kidney impairment occurs.

**Keywords** Solitary kidney · Cardiovascular risk · Children · Carotid intima-media thickness · Ischemia-modified albumin · 24-h ambulatory blood pressure monitoring

## Introduction

Arterial hypertension, proteinuria and kidney dysfunction are potential complications of functional solitary kidney, and the reduction of kidney mass leads to the hypertrophy of residual kidney tissue in these patients [1]. Animal studies have shown that glomerular hyperfiltration in the remaining kidney leads to systemic hypertension and microalbuminuria in the early period, and a decrease in the glomerular filtration rate (GFR) in the long term [2]. Accordingly, hypertension may be considered an important prognostic marker for the development of chronic kidney failure in children with solitary kidney. In a study, it was shown that children with solitary kidney have a risk to develop kidney injury in later life. The researchers stated that these patients should be followed closely because of the risk of chronic kidney failure that may occur in the early period [3].

As the most frequent cause of death in chronic kidney disease is cardiovascular complications, it is important to identify possible risk factors of cardiovascular disease as appropriate treatment may make it possible to reduce the risk of death [4].

In healthy adults, the elastic property of the arteries is mainly affected by aging. During growth, the thickness of the media layer increases due to the decrease in the amount of elastic fibers and the amount of increased collagen crosslinks. In addition, intima-media thickness and arterial stiffness vary with age and body size [5, 6]. Carotid intima-media thickness (CIMT) reflects structural changes as an approved morphological parameter, and increases in children with stage 2–4 chronic kidney disease [7]. Prolonged

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exposure to urea can lead to arteriosclerosis and the further deterioration of carotid intima-media thickness. Furthermore, increased carotid intima-media thickness is associated with higher blood pressure and an increased left ventricular mass index [4].

Ischemia-modified albumin (IMA) is a form of human serum albumin that is produced when circulating serum albumin comes into contact with ischemic tissue. Studies have shown IMA to be a marker of moderate myocardial ischemia in end-stage kidney disease [8]. In ischemic conditions, the formation of free radicals, the development of acidosis and the formation of free iron and copper ions occur, and modifications appear in the amino acids located on the N-terminus of the human albumin molecule, leading to the production of IMA [9].

Increased oxidation and decreased detoxification are seen in patients with chronic kidney disease [10]. There are four different oxidative stress pathways, although it has been shown that nitrous and carbonyl stress play a very important role in chronic kidney disease [11]. Uremia may thus be defined also as carbonyl overload or carbonyl stress [10].

Structural and functional changes are seen in functional solitary kidneys, with one of the main functional changes being increased filtration in the remaining glomeruli, which is generally considered beneficial. On the other hand, experimental studies have suggested that these functional changes may have also a negative effect on the remaining kidney [12]. Animal studies have shown that a decrease in kidney mass leads to sclerosis in the remaining glomeruli, and as a result, proteinuria, hypertension and progressive azotemia occur [2]. However, there are only limited data available for the assessment of long-term kidney function in children with solitary kidney [13].

Solitary kidney has been shown to be a potential risk factor for hypertension in early childhood, as blood pressure increases in these patients as a result of glomerular blood flow and hyperfiltration in the remnant kidney [1]. Although there are several approaches available for the diagnosis of hypertension, ambulatory blood pressure monitoring is a useful and accepted method in children.

In the present study, we evaluate cardiovascular risk by measuring the CIMT, IMA and oxidative stress parameters in patients with solitary kidney, and ambulatory blood pressures were measured for the determination of the effects of high blood pressure.

## Materials and methods

This study was conducted at Osmangazi University Pediatric Nephrology Clinic, Eskisehir, Turkey. A total of 40 children with solitary kidney and 60 healthy controls were included in this single-center study. The children were aged 6–18 years. Office blood pressure measurements were normal before the study in both groups, and none of the participants was using any antihypertensive drugs. There was no family history of cardiovascular and chronic kidney diseases in the patient and control groups. Renal function tests were normal and the kidneys were evaluated as normal by imaging methods in the control group. The members from control group were chosen randomly. In the statistical analysis, the age and gender characteristics of the patient and control groups showed a homogeneous distribution. Informed consent was obtained from the patient and control groups. The study protocol was approved by the Institutional Ethics Committee of Osmangazi University School of Medicine (80558721/244). The exclusion criteria were: patients aged > 18 years, diabetes mellitus, acute or chronic inflammation, abnormal kidney function and history of drug use.

The diagnosis of solitary functional kidney [congenital single kidney ($n = 17$), unilateral renal agenesis/ aplasia ($n = 14$), multicystic dysplastic kidney ($n = 3$), unilateral nephrectomy ($n = 6$)] was based on the absence of unilateral functional renal tissue on ultrasonography (USG) and renal scintigraphy. GFR was calculated separately for both kidneys scintigraphically for diagnosis. Patients with a single functioning kidney and no scar in the intact kidney were included in the study. Scintigraphically calculated GFR of one kidney was less than 5 mL/min/1.73 $m^2$ of these patients. On the other hand, creatinine clearance (CCl) was calculated for both the staging of chronic kidney disease and the comparison of groups [Urine creatinine x Volume (mL) × 1.73/ Plasma creatinine × $m^2$ × 1440 (min)].

Ambulatory blood pressure was measured in all subjects using the Medset Scanlight III Padsy RR oscillometric device (Incekaralar). A cuff of appropriate size for the arm width was placed on the non-dominant arm. Blood pressure was recorded automatically every 15 min throughout a single day and every 30 min at night. Only ambulatory blood pressure measurement (ABPM) profiles with at least 30 records were accepted, with at least eight readings between 00:00 and 06:00. The corresponding times in a study by Soergel et al. were 08:00–20:00 during the day and 00:00–06:00 at night. Blood pressure values corresponding to the 95th percentile according to gender and height were determined for each subject [14]. Hypertension was defined as systolic and/ or diastolic blood pressure in the > 95th percentile. Dipping was defined as a 10% decrease in mean systolic or diastolic blood pressure between day and night.

After placing the subjects in the supine position for 30 min, carotid intima-media thickness was evaluated using a Vivid I color Doppler ultrasonography with a 12 MHz linear probe. To measure the common carotid artery, the patient's neck was rotated 45 degrees to the opposite side, and a 10 mm segment was detected distally 20 mm proximal to the carotid bulbus.

Albumin measurement was based on its binding to the indicator dye bromocresol green of pH 4.1 to form a blue, green-colored complex, and the photometric measurement of this complex. The intensity of the blue-green color is directly proportional to the concentration of albumin in the sample.

(Albumin + BCG $\xrightarrow{pH4.1}$ Albumin-BCG complex). The albumin levels in the serum samples of all patients were measured using a Roche Kit and a Hitachi Cobas c analyzer. The results are given in g/dL.

Cobalt was added to the serum sample to measure the ischemia-modified albumin. The added cobalt binds to normal albumin, and lesser ischemia-modified albumin from the N-terminal amino region. The non-binding ischemia-modified albumin in the serum was measured using the spectrophotometric method. In the present study, ischemia-modified albumin levels were measured at the 470 nm wavelength in a spectrophotometer (Shimadzu UV-1601 UV–Vis Spectrophotometer, Shimadzu Corporation, Tokyo, Japan) following the method reported by Bar-Or et al. [15]. Ischemia-modified albumin levels were taken as Absorbance Units, and were calculated as adjusted-ischemia-modified albumin values divided by albumin levels (g/dL).

Protein–carbonyl levels were studied at a wavelength of 360 nm in the spectrophotometer device (Shimadzu UV-1601 UV–Vis Spectrophotometer, Shimadzu Corporation, Tokyo, Japan) according to the modified spectrophotometric method described by Levine et al. [16]. The results were given in micro-mols per liter (µmol/l).

Protein-sulfhydryl levels were measured using a spectrophotometer device (Shimadzu UV-1601 UV–Vis Spectrophotometer, Shimadzu Corporation, Tokyo, Japan) according to the method described by Koster et al. [17]. The results were given in micro-mols per liter (µmol/l).

## Statistical analysis

For the summary of the data, continuous variables were presented as mean ± standard deviation or median (min–max), depending on the distribution type, while categorical variables were presented as frequencies and percentages. Independent Samples *t* tests or Mann–Whitney *U* tests were used for the comparison of the groups, depending on the distribution of the data. The relationships between categorical variables were examined with Pearson Chi-Square or Fisher's Exact tests, depending on the expected value rule. The statistical analysis was carried out using IBM SPSS Statistics (Version 22.0. Armonk, NY: IBM Corp.), and the significance level was set as 0.05.

## Results

(a) Patient and Control Groups: The study sample comprised 40 patients and 60 control volunteers. There was no statistically significant difference between the average age of the patient group and the control group ($p > 0.05$). The demographic characteristics of the patients are presented in Table 1.

Hemoglobin levels were normal in the patient and the control groups (12.4 ± 2.4 vs 12.2 ± 1.9, respectively) ($p > 0.05$).

The mean systolic and mean diastolic blood pressures of the patient group were 101.75 ± 10.53 and 60.88 ± 10.68 mmHg, and 105.42 ± 9.97 and 60.75 ± 7.35 mmHg for the control group ($p > 0.05$).

Serum creatinine levels were within the normal range in both groups, although the patient group's creatinine levels were significantly higher than those of the control group ($p < 0.05$). A decreased GFR was also found in the patient group ($p = 0.001$), along with high serum alkaline phosphatase levels and low serum magnesium levels. There was no significant difference between the groups in other biochemical parameters (Table 2).

The 24-h urine sodium, chloride and creatinine levels were low in the patient group, while the daily urinary microalbumin excretion was significantly higher in the patient group than in the control group ($p = 0.003$), and the urinary density of the patient group was significantly lower than that of the control group ($p = 0.001$). Serum aldosterone, plasma renin activity (PRA) and IMA levels were also high in the patient group (Table 3).

Although the mean 24-h systolic and diastolic blood pressures were normal, blood pressure was significantly higher in the patient group than in the control group [105.90 ± 9.28;

**Table 1** The demographic characteristics of the patients

| | Patient($n = 40$) | Control ($n = 60$) | $p$ |
|---|---|---|---|
| Gender | 22 female (%55)<br>18 male (%45) | 36 female (%60)<br>24 male (%40) | 0.62 |
| Age (years) | 11.18 ± 3.46 (7–18) | 12.22 ± 3.57 (6–18) | 0.15 |
| Weight (kg) | 34.41 ± 15.89 (15.8–89) | 38.63 ± 15.9 (18.6–77.2) | 0.19 |
| Height (cm) | 136.69 ± 20.26 (109–183) | 142.31 ± 16.79 (112–171.5) | 0.13 |
| BMI | 18.4 ± 6.1 | 18.8 ± 5.7 | 0.89 |

**Table 2** Biochemical parameters of the patient and control groups

| | Patient ($n=40$) | Control ($n=60$) | $p$ |
|---|---|---|---|
| Na (mEq/L) | 140.45 ± 2.33 | 139.67 ± 2.04 | 0.07 |
| K (mEq/L) | 4.58 ± 0.32 | 4.48 ± 0.35 | 0.15 |
| Cl (mEq/L) | 102.55 ± 2.17 | 102.52 ± 2.00 | 0.93 |
| BUN (mg/dL) | 11.12 ± 3.77 | 10.26 ± 2.74 | 0.22 |
| Creatinine (mg/dL) | 0.60 ± 0.18 | 0.52 ± 0.12 | **0.015** |
| Total protein (g/dL) | 7.23 ± 0.40 | 7.32 ± 0.42 | 0.28 |
| Albumin (g/dL) | 4.54 ± 0.32 | 4.66 ± 0.22 | 0.06 |
| Calcium (mg/dL) | 9.89 ± 0.33 | 9.75 ± 0.39 | 0.06 |
| Phosphorus (mg/dL) | 4.53 ± 0.62 | 4.42 ± 0.58 | 0.36 |
| Magnesium (mg/dL) | 0.81 ± 0.08 | 0.85 ± 0.06 | **0.006** |
| ALP (U/L) | 218.90 ± 93.40 | 182.17 ± 75.52 | **0.033** |
| Uric acid (mg/dL) | 4.31 ± 1.22 | 4.05 ± 1.07 | 0.25 |
| Total cholesterol (mg/dL) | 158.61 ± 39.98 | 153.18 ± 28.31 | 0.42 |
| Triglyceride (mg/dL) | 93.39 ± 40.55 | 85.32 ± 35.62 | 0.29 |
| High-density lipoprotein (mg/dL) | 53.15 ± 12.54 | 55.08 ± 13.45 | 0.47 |
| Low-density lipoprotein (mg/dL) | 94.81 ± 40.05 | 92.35 ± 26.28 | 0.71 |

Statistically significant $p$ values are shown in bold

62.55 ± 7.29 vs 102.37 ± 4.4; 58.88 ± 4.6 ($p < 0.05$), respectively]. One remarkable finding is that a non-dipper blood pressure pattern was present in 82.5% of the patient group and 18.3% of the control group.

Significant differences were found in the $E_m$ (early diastolic mitral annular velocity), E/A Ratio (Early diastolic velocity/Late diastolic velocity), PWD (Pulse wave Doppler), $IVRT_m$ (TDI-derived isovolumetric relaxation time) and Ejection time TDI (tissue Doppler imaging) parameters between the groups (Table 3) in the echocardiographic findings, and carotid intima-media thickness was also high in the patient group ($p < 0.05$) (Table 3).

No statistically significant difference was found in the serum protein carbonyl levels of the groups [138.27 ± 20.55 in the patient group; 141.83 ± 21.85 in the control group ($p > 0.05$)]. Moreover, the free sulfhydryl group levels were similar (289.07 ± 59.80 in the patient group; 291.34 ± 52.38 in the control group), ($p > 0.05$).

(b) Primary and Secondary Groups: The patients were also evaluated in terms of their etiology, as primary (congenital) and secondary (acquired solitary kidney) groups. No significant differences were noted in the systolic and diastolic blood pressure values between the groups ($p > 0.05$). Although these values were within normal limits, potassium levels were found to be lower and calcium and phosphorus levels to be higher in the primary group. All laboratory parameters are presented in Table 4.

Potassium, creatinine and phosphorus excretions in the 24-h urine sample were significantly higher in the primary group than in the secondary group (Table 4).

The 24-h ambulatory blood pressure monitoring revealed a non-dipper pattern in 83.9% of the primary group and 77.8% of the secondary group ($p > 0.05$). There were no significant differences in the mean systolic and mean diastolic blood pressure levels of the groups (106.23 ± 10.30 vs 104.78 ± 4.41; 62.19 ± 7.56 vs 63.78 ± 6.55) ($p > 0.05$). Similarly, there was no significant difference in the echocardiographic measurements of the primary and secondary groups ($p > 0.05$).

Serum protein carbonyl and serum sulfhydryl levels were similar in both groups [(141.84 ± 16.92 vs 123.41 ± 28.84), ($p > 0.05$) and (294.41 ± 63.91 vs 266.83 ± 33.43), ($p > 0.05$), respectively].

## Discussion

To the best of our knowledge, there have been few studies to date investigating the development of cardiovascular risk and hypertension in patients with solitary kidney in childhood. In the present study, cardiovascular risk is evaluated in patients with a functional solitary kidney, in which high serum IMA, aldosterone and PRA levels, decreased GFR and high blood pressure levels, and increased microalbuminuria and impaired urinary concentrations were identified. The patients' cardiac functional disorders were also determined with an echocardiographic study.

IMA is a novel serum biomarker of myocardial ischemia. Serum albumin exhibited reduced binding to Cobalt under ischemic conditions, leading to ischemia–reperfusion injury with many different mechanisms [18]. Increased IMA levels can also be seen in chronic diseases. In a previous study, high IMA levels were identified in myocardial ischemia in patients with advanced chronic kidney disease [19]. Turedi

**Table 3** Laboratory and echocardiographic results of the groups

| | Patient group ($n=40$) | Control group ($n=60$) | $P$ |
|---|---|---|---|
| 24-h urine | | | |
| Sodium (mEq/24 h) | 99.25 ± 43.51 | 122.24 ± 56.09 | **0.03** |
| Chloride (mmol/24 h) | 92.26 ± 48.15 | 115.13 ± 52.88 | **0.03** |
| Creatinine (mg/24 h) | 51.36 ± 26.02 | 68.93 ± 31.36 | **0.004** |
| Microalbumin (mg/24 h) [median (min–max)] | 7.27 (0.07–868.78) | 4.48 (1.25–24.47) | **0.03** |
| 24-h urine abnormal values (%) | | | |
| Sodium | $8.1^{+}$ | $6.7^{+}$ | 0.17 |
| Chloride | $65.6^{+}$ | $55.9^{+}$ | 0.12 |
| Creatinine | $55.3^{-}$ | $22.6^{-}$ | **0.04** |
| Microalbumin | $12.1^{+}$ | 0 | **0.001** |
| Creatinine clearance (CCl) (mL/min/1.73 $m^2$) | 98.10 ± 43.82 | 140.85 ± 57.86 | **0.001** |
| Urine density (g/mL) | 1011.95 ± 6.11 | 1016 ± 6.25 | **0.001** |
| Serum aldosterone (ng/dL) [median (min–max)] | 187.92 (20.00–2478.20) | 20.00 (1.19–1246.00) | **0.001** |
| PRA (ng/mL/h) [median (min–max)] | 25.05 (0.80–119.50) | 3.72(0.90–83.46) | **0.001** |
| Serum IMA (g/dL) | 0.48 ± 0.06 | 0.42 ± 0.12 | **0.008** |
| Blood pressure (mean systolic/mean diastolic) (mmHg) | 101.75 ± 10.53/60.88 ± 10.68 | 105.42 ± 9.97/60.75 ± 7.35 | **0.08** |
| CIMT mean (mm) | 0.44 ± 0.03 | 0.42 ± 0.04 | **0.04** |
| Echocardiographic measurements | | | |
| EA Ratio PWD | 1.68 ± 0.29 | 1.84 ± 0.33 | **0.01** |
| IVRT TDI | 61.90 ± 33.51 | 50.90 ± 7.97 | **0.01** |
| Ejection time TDI | 261.55 ± 35.93 | 278.73 ± 25.16 | **0.006** |
| $E_m$ | 0.14 ± 0.05 | 0.15 ± 0.04 | **0.01** |
| $E/E_m$ | 8.29 ± 2.19 | 7.01 ± 2.36 | **0.01** |
| $MPI_m$ | 0.40 ± 0.06 | 0.36 ± 0.05 | **< 0.001** |
| $IVRT_m$ | 56.9 ± 8.39 | 50.9 ± 7.97 | **0.001** |
| $ET_m$ | 265.5 ± 25.26 | 278.7 ± 25.16 | **0.001** |
| $IVRT/ET_m$ | 0.21 ± 0.03 | 0.18 ± 0.03 | **< 0.001** |
| Percentage of abnormal values (%) | | | |
| EA Ratio PWD | $72.4^{-}$ | $22.6^{-}$ | **< 0.001** |
| IVRT TDI | $84.4^{+}$ | $41.7^{-}$ | **< 0.001** |
| Ejection time TDI | $76.8^{-}$ | $27.0^{-}$ | **< 0.001** |
| $E_m$ | $82.2^{-}$ | $32.1^{-}$ | **0.01** |
| $E/E_m$ | $70.5^{+}$ | $45.2^{+}$ | **< 0.001** |
| $MPI_m$ | $88.0^{+}$ | $22.0^{+}$ | **< 0.001** |
| $IVRT_m$ | $81.8^{+}$ | $16.8^{+}$ | **< 0.001** |
| $ET_m$ | $79.2^{-}$ | $20.6^{-}$ | **< 0.001** |
| $IVRT/ET_m$ | $84.6^{+}$ | $17.7^{+}$ | **< 0.001** |
| hs-CRP (mg/L) | 4.14 ± 3.94 | 3.93 ± 2.01 | **0.001** |

Statistically significant $p$ values are shown in bold

*PRA* plasma renin activity, *IMA* ischemia-modified albumin, *CIMT* carotid intima-media thickness, *EA* Ratio *PWD* early diastolic velocity/late diastolic velocity pulse wave Doppler, *IVRT TDI* tissue Doppler imaging-derived isovolumetric relaxation time, $E_m$ early diastolic mitral annular velocity, *E* early diastolic velocity, $MPI_m$ myocardial performance index, $IVRT_m$ TDI-derived isovolumetric relaxation time

+Indicates increased value, − indicates decreased value

et al. reported IMA levels to be significantly high in end-stage kidney disease, and concluded that the low hemoglobin levels associated with kidney disease increase serum IMA concentrations [20]. Sharma et al. recorded high IMA levels in non-anemic transplant patients with a dysfunctional allograft who showed an ischemic pattern in a dobutamine stress test, and reported a mean GFR of 13 mL/min in these patients. The authors concluded that IMA could be considered a moderately accurate marker of myocardial ischemia in end-stage kidney disease [8]. To date, however, no clear data on IMA levels in early-stage kidney disease have been provided in the literature. In the present study, high IMA levels were found in patients with solitary kidney. The patients had normal GFR, but relatively decreased GFR was found in our study. Although the hemoglobin levels were normal, the high IMA levels suggested that this may be an indicator of insensible tissue hypoxia. Tissue hypoxia is thought to increase IMA levels due to the associated extracardiac oxidative stress [21]. Saad et al. reported increased fractional renal tissue hypoxia to be related directly to chronically

**Table 4** Demographic and laboratory parameters of the primary and secondary groups

| | Primary group ($n=31$) | Secondary group ($n=9$) | $P$ |
|---|---|---|---|
| Gender (female/male) | 15/16 | 7/2 | 0.14 |
| Age (years) | 11.03 ± 3.40 | 11.67 ± 3.81 | 0.63 |
| Weight (kg) | 35.45 ± 16.33 | 30.82 ± 14.57 | 0.44 |
| Height (cm) | 137.90 ± 19.83 | 132.50 ± 22.36 | 0.48 |
| Na (mEq/L) | 140.61 ± 2.38 | 139.89 ± 2.20 | 0.41 |
| K (mEq/L) | 4.53 ± 0.32 | 4.78 ± 0.23 | **0.03** |
| Cl (mEq/L) | 102.42 ± 2.16 | 103.00 ± 2.29 | 0.48 |
| BUN (mg/dL) | 11.19 ± 3.97 | 10.86 ± 3.15 | 0.81 |
| Cre (mg/dL) | 0.60 ± 0.19 | 0.60 ± 0.16 | 0.92 |
| Total protein (g/dL) | 7.25 ± 0.38 | 7.17 ± 0.50 | 0.61 |
| Albumin (g/dL) | 4.58 ± 0.34 | 4.42 ± 0.22 | 0.12 |
| Ca (mg/dL) | 9.95 ± 0.30 | 9.70 ± 0.34 | **0.04** |
| P (mg/dL) | 4.64 ± 0.59 | 4.17 ± 0.62 | **0.04** |
| Mg (mg/dL) | 0.81 ± 0.09 | 0.80 ± 0.05 | 0.55 |
| ALP (U/L) | 233.81 ± 90.22 | 167.56 ± 90.44 | 0.06 |
| Uric acid (mg/dL) | 4.33 ± 1.26 | 4.26 ± 1.11 | 0.89 |
| Blood pressure (mean systolic/mean diastolic) (mmHg) | 106.23 ± 10.30/62.19 ± 7.56 | 104.78 ± 4.41/63.78 ± 6.55 | 0.61 |
| 24-h urine | | | |
| Potassium (mmol/24 h) | 40.56 ± 27.36 | 20.49 ± 11.31 | **0.04** |
| Creatinine (mg/24 h) | 57.59 ± 25.60 | 29.90 ± 13.26 | **0.001** |
| Phosphorus (g/24 h) | 53.84 ± 31.49 | 28.62 ± 14.17 | **0.02** |
| 24-h urine abnormal values (%) | | | |
| Potassium | 48.6$^{-}$ | 55.5$^{-}$ | 0.12 |
| Creatinine | 62.4$^{-}$ | 66.6$^{-}$ | 0.9 |
| Phosphorus | 61.8$^{-}$ | 55.5$^{-}$ | 0.16 |

Statistically significant $p$ values are shown in bold

*BUN* blood urea nitrogen, *Cre* creatinine, *Ca* calcium, *P* phosphorus, *Mg* magnesium, *ALP* alkaline phosphatase

+Indicates increased value, − indicates decreased value

reduced blood flow and GFR [22]. Another finding supporting data of tissue hypoxia is the high PRA and aldosterone levels identified in our patient group, although the increased uremic toxins associated with a decrease in GFR may also contribute to tissue hypoxia and high IMA levels.

Uremic toxin retention has been linked to oxidative damage in kidney disease, and the serum levels of oxidative stress markers correlate with the chronic kidney disease stage. Protein carbonyl groups and free sulfhydryl groups are important markers of oxidative stress. In advanced chronic kidney disease (CKD), while the protein carbonyl groups increase, the levels of free sulfhydryl groups decrease [23, 24]. In the present study, no change was observed in the levels of these markers, which may be related to the patients being in the early stage of chronic kidney disease. We thus concluded that as the renal failure stage progresses, the serum levels of these markers may change under the effects of uremic toxicity.

The increased urine microalbumin levels recorded were a further remarkable finding in the patient group. Microalbuminuria is known to be an important finding in renal dysfunction. In a study investigating the relationship between IMA elevation and microalbuminuria in literature, the levels of IMA were significantly higher in the microalbuminuric patients than in the normoalbuminuric patients, and the researchers suggested that IMA could be a sensitive and specific marker for micro and macroalbuminuria [25]. Furthermore, high urinary protein excretion was found as an early indicator of renal dysfunction in rats in another study, in which the highest initial level of proteinuria showed an early decrease in GFR [26]. On the other hand, kidney mass reduction is known to be an important cause of microalbuminuria, and Zucchelli et al. found that persistent hyperfiltration may lead to microalbuminuria in nephrectomized patients [27]. In a further study, high 24-h urinary microalbumin excretion levels were found in patients with 5 years or more of congenital or acquired solitary kidney. No decrease in GFR could be detected in the early period in that study, although no comparison of the patients was made according to the etiology due to the limited number of patients [28].

Similarly, microalbuminuria appeared as an early sign of kidney damage in our patients, while another indicator of kidney damage is a decrease in GFR in such patients when compared to the control group. Due to the occurrence of microalbuminuria and hypertension in childhood, patients with solitary kidney require close, regular and lifetime monitoring, including blood pressure, GFR and microalbuminuria. We, therefore, believe that it should not be left too late to start antiproteinuric and antihypertensive treatment for the avoidance of kidney damage.

In addition to microalbuminuria, a tissue Doppler examination in the present study revealed the presence of subclinical left ventricular (LV) diastolic dysfunction, and increased c-IMT, as an indicator of endothelial damage. These changes supported the finding of subclinical vascular damage, which may progress to atherosclerosis in the presence of a solitary functioning kidney. In the study cohort, the higher values of transmitral flow and early diastolic peak velocity/early diastolic mitral annular velocity ratio ($E/E_m$) were compatible with the higher LV diastolic filling pressures, as a marker of diastolic dysfunction. In addition, a longer $IVRT_m$ and TDI-derived ejection time ($ET_m$), along with a higher $IVRT/ET_m$ ratio with elevated myocardial performance index (MPI) values, were accepted as evidence of subclinical myocardial diastolic dysfunction. Decreased LV diastolic function is an early functional alteration of the heart that may progress to heart failure with preserved ejection fraction (HFpEF) [29]. The frequency of HFpEF is inversely correlated with GFR reduction. In their study, Ahmed et al. stated that renal dysfunction is one of the most common comorbidities in HFpEF, with a prevalence of 30–60% [30]. In the present study, lower estimated glomerular filtration rates (eGFR) and increased proteinuria levels were supportive of the presence of kidney damage in children with a solitary functioning kidney, and a positive correlation was identified between myocardial diastolic function and GFR (Table 5). Hence, renal dysfunction-induced cardiovascular damage can be detected especially through tissue Doppler imaging in individuals with a solitary kidney, even in childhood.

In the presence of a solitary functioning kidney, neurohormonal mechanisms such as renin, nitric oxide (NO) and vasopressin contribute to the glomerular hypertrophy and hyperfiltration processes, which may result in glomerular sclerosis, hypertension, albuminuria and end-stage kidney disease [31]. These altered neurohormonal systems induce several changes in the heart, kidneys and vasculature, and may result in hemodynamic stress and exert deleterious effects on the heart and circulation. We thus concluded that the high blood pressure profile and increased serum renin and aldosterone levels of our patients may have contributed to the development mechanism of cardiovascular remodeling.

**Table 5** Correlations between CCl or hs-CRP and echocardiographic measurements

| Variables | CCl | | hs-CRP | |
|---|---|---|---|---|
| | *r* | *p* | *r* | *p* |
| IVRT | − 0.16 | 0.199 | 0.318 | **0.001** |
| $IVRT/ET_m$ | − 0.244 | 0.048 | 0.331 | **0.001** |
| $MPI_m$ | − 0.188 | 0.13 | 0.286 | **0.004** |
| $E/E_m$ | − 0.295 | 0.016 | − 0.006 | **0.95** |

Statistically significant *p* values are shown in bold

*CCl* creatinine clearance, *IVRT* TDI-derived isovolumetric relaxation time, $ET_m$ TDI-derived ejection time, *MPI* myocardial performance index, $E/E_m$ transmitral flow early diastolic peak velocity/early diastolic mitral annular velocity ratio

Although our patients had no prior diagnosis of hypertension, high blood pressure was detected in a 24-h ABPM follow-up, which is an expected finding. Hyperfiltration in a solitary kidney is associated with an increase in the size of the tubules and glomeruli, leading, eventually, to an increase in the single nephron glomerular filtration rate. Over time, hyperfiltration and compensatory mechanisms lead to kidney damage and hypertension [32]. The presence of hypertension in the patients in the present study without overt renal failure may be associated with high renin levels, and this increase is thought to occur secondary to decreased renal perfusion pressure or renal blood flow [33]. On the other hand, the elevated renin and aldosterone levels also suggested the presence of a secondary cause, although no etiological factor was identified for hypertension in our patients. While the office measurements were normal, the high 24-h ABPM indicated that blood pressure may rise unnoticed in the early period in these patients. Another remarkable finding was the non-dipper pattern noted in most hypertensive patients, which places them at higher cardiovascular risk and more prone to target organ damage than those with dipper patterns [34]. Such patients are also at greater risk of the development and progression of chronic kidney disease [35]. The mechanism of a non-dipper pattern remains unclear, although Brotman et al. suggested that the disorder could be associated with an impairment in autonomic balance, leading to relative sympathetic overactivity at night [36]. Kaur et al. reported sympathetic overactivity to be a feature of CKD [37]. The mechanism of sympathoexcitation is not completely understood, although it is well known that renin and aldosterone activation is increased in CKD. Normally, angiotensin II (AT2) plays an important role in regulating sympathetic outflow, although high AT2 levels can cause high sympathetic discharge in kidney disease. In the present study, the non-dipper pattern suggested an

increase in AT2, and such increases cause sympathetic overactivity in early-stage kidney disease. It is thus understood that the damage starts even in the early stages of CKD in these patients.

There are some limitations to our study. First, as a cross-sectional study, only findings related to early-stage kidney disease have been revealed, while significant changes may be detected in long-term follow-up. Second, there was a lack of data on how long the patients had been living with solitary kidney, and so it could not be ascertained when the changes started to occur. Long-term studies involving larger numbers of patients are thus needed.

In conclusion, early kidney dysfunction should be considered an important risk factor in patients with solitary kidney. Early subclinical diastolic dysfunction and vascular damage findings confirmed that these patients are at greater risk of life-threatening cardiovascular diseases, as well as chronic kidney disease. Therefore, although these patients do not have complaints, they should be constantly and closely monitored. Such as diet, adequate fluid intake, prevention of obesity and the other general kidney protective factors should be applied from the moment of diagnosis.

**Acknowledgements** The authors appreciate the participation of all the volunteers of this research

**Author contributions** All the authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by NMS, PK, NC, BC, BU, OA, FA and BY. The first draft of the manuscript was written by NMS, and all the authors commented on previous versions of the manuscript. All the authors read and approved the final manuscript.

**Funding** The authors declare that they have no funding sources.

**Availability of data and material** All data generated or analyzed during this study are included in this published article [and its supplementary information files].

## Declarations

**Conflict of interest** The authors declare no competing interests and have no financial interests to declare.

**Ethical approval** All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee at which the studies were conducted) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was approved by the Institutional Ethics Committee of Osmangazi University School of Medicine (approval number: 80558721/244).

**Informed consent** Informed consent was obtained from all individual participants included in the study.

**Consent for publication** The authors agree with the publication of this manuscript in the Clinical and Experimental Nephrology and were fully involved in the study and preparation of the manuscript.

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