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Vascular and urological anomalies in children with horseshoe kidneys

Atnalı böbreği olan çocuklarda vasküler ve ürolojik anomaliler

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Abstract

Purpose: Horseshoe kidney is the most common fusion anomaly that congenital systemic and urological anomalies accompany most of the patients. In this study, we aimed to investigate its association with vascular anomalies and especially nutcracker syndrome along with accompanying urological and other systemic anomalies in children with horseshoe kidney.

Materials and methods: Twenty-six patients are diagnosed with horseshoe kidney in our clinic and 22 healthy children of the same age and sex were included in the study. All children were prospectively evaluated using Doppler ultrasonography in terms of renal artery and renal vein flow velocities, lumen diameters and vascular anomalies and presence of nutcracker syndrome.

Results: Urological anomaly was found in 50% of the children with horseshoe kidneys, and systemic anomaly in 44% of them. In Doppler ultrasonographic evaluations performed on patients to detect vascular pathologies and nutcracker syndrome; findings of nutcracker syndrome were present in 2 patients in the horseshoe kidney group, while they were detected incidentally in 1 patient in the control group. An accessory renal artery originating from the left common iliac artery was found in a case with horseshoe kidney, and a circumaortic left renal vein in one case.

Conclusions: In our study in which we investigated nutcracker syndrome based on the presence of vascular anomalies accompanying horseshoe kidneys in children, nutcracker syndrome findings were found in similar numbers in both groups.

We think that these children should be followed for a long time in terms of chronic kidney damage and vascular pathologies that may occur in adulthood.

Key words: Horseshoe kidney, child, nutcracker syndrome, vascular anomalies, urological anomalies.

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Öz

Amaç: Atnalı böbrek, konjenital sistemik ve ürolojik anomalilerin çoğu hastaya eşlik ettiği en yaygın füzyon anomalisidir. Bu çalışmada atnalı böbrek anomalisi bulunan çocuklarda eşlik eden ürolojik ve diğer sistemik anomaliler yanında vasküler anomaliler ve özellikle nutcracker sendromu ile birlikteliğinin araştırılması amaçlandı.

Gereç ve yöntem: Kliniğimizde atnalı böbrek tanısı alan 26 hasta ile aynı yaş ve cinsiyette 22 sağlıklı çocuk çalışmaya dahil edildi. Tüm çocuklar prospektif olarak renal arter ve renal ven akım hızları, lümen çapları ve vasküler anomaliler ve nutcracker sendromu varlığı açısından Doppler ultrasonografi ile değerlendirildi.

Bulgular: Atnalı böbrekli çocukların %50'sinde ürolojik anomali, %44'ünde sistemik anomali saptandı. Vasküler patolojileri ve nutcracker sendromunu saptamak için hastalarda yapılan Doppler ultrasonografik değerlendirmelerde; atnalı böbrek grubunda 2 hastada nutcracker sendromu bulguları mevcutken, kontrol grubunda 1 hastada saptandı. Atnalı böbrek anomalili bir olguda sol ana iliak arterden köken alan aksesuar renal arter ve bir olguda da sirkumaortik sol renal ven saptandı.

Sonuç: Atnalı böbrek anomalili çocuklara eşlik eden vasküler anomalilerin varlığından yola çıkarak nutcracker sendromunu araştırdığımız çalışmamızda, nutcracker sendromu bulguları her iki grupta da benzer sayıda bulundu. Bu çocukların erişkin dönemde ortaya çıkabilecek damar patolojileri ve gelişebilecek kronik böbrek hasarı açısından uzun süre takip edilmesi gerektiğini düşünmekteyiz.

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Anahtar kelimeler: Atnalı böbrek, çocuk, nutcracker sendromu, vasküler anomaliler, ürolojik anomaliler.

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Introduction

Horseshoe kidney is the most common fusion anomaly that occurs with the fusion of one pole of both kidneys, and its incidence has been reported at a rate of 1: 400 [1, 2]. In more than 90% of cases, fusion occurs between lower poles. Depending on the degree of fusion, the renal isthmus (the fused part of the kidney) may consist of a renal parenchyma or a fibrous band [3]. Most patients with horseshoe kidneys are asymptomatic and these patients are diagnosed incidentally with horseshoe kidneys. Some patients may present with flank pain and / or hematuria because anatomical abnormalities in patients with horseshoe kidneys cause urinary tract infection (UTI) and formation of stones by disrupting drainage in the collecting system. Congenital urological or systemic abnormalities are present in one third of the patients. Various arteries including aorta, iliac arteries, and rarely hypogastric and middle sacral arteries supply blood to the horseshoe kidney [4]. Although arterial and venous anomalies can be seen in fused kidneys, many studies have investigated especially arterial blood supply to the horseshoe kidneys. However, only few studies have investigated venous anomalies, and nutcracker syndrome or phenomenon in horseshoe kidneys, which is characterized by compression of the left renal vein between aorta and superior mesenteric artery (SMA) and pressure increase in the dilated left renal vein has not been investigated so far. Nutcracker syndrome may cause venous hypertension in the left kidney, leading to recurrent hematuria, orthostatic proteinuria, gonadal vein dilatation and pelvic varices due to pelvic venous congestion [5]. Awareness of this situation is of great importance in children and young adult patients, and patients may often receive delayed or erroneous diagnoses.

In this study, we aimed to investigate the accompanying urological and other systemic anomalies as well as vascular anomalies and especially their association with nutcracker syndrome in children with horseshoe kidney.

Materials and methods

Twenty-six patients diagnosed with horseshoe kidneys in our clinic between 2009-2020 and 22 healthy children of the same age and sex were included in the study. Demographic, clinical and laboratory data were recorded. This study was conducted in accordance with the Declaration of Helsinki, and it was approved by the ethics committee of Medical Faculty of Pamukkale University. At the time of diagnosis, the presence (if any) of additional urological, systemic abnormalities, UTI, hypertension, increased serum creatinine levels, decreased estimated glomerular filtration rate (eGFR), proteinuria and microalbuminuria were evaluated from their medical files. The eGFR of the cases were calculated using the Schwartz formula. An eGFR below 90ml / min / 1.73m^2 / was defined as chronic kidney injury (CKD) [6]. Protein / creatinine ratio >0.2 in the first morning urine sample was accepted as proteinuria. Calcium / creatinine and uric acid / creatinine values were estimated from spot urine samples and the results were compared with normal age-matched values [7]. UTI was determined in the presence of significant bacteriuria (>10^5 cfu / mL) in urine culture. Blood pressure was measured successively 3 times with a mercury sphygmomanometer after a 5-minute rest period and the values were averaged. Staging of blood pressures and definition of hypertension were made according to the latest consensus of the American Academy of Pediatrics [8]. Stages of vesicoureteral reflux (VUR) were determined by performing voiding cystourethrographies in patients with a history of UTI and / or hydronephrosis (HN) in patients with horseshoe kidneys [9]. The 99mTc-dimercaptosuccinic acid (DMSA) scintigraphy was performed in patients with recurrent urinary tract infection or if both kidneys of the patient differed in size as detected in urinary ultrasonography to determine renal functions and presence of scarring.

In DMSA scintigraphy, the presence of scar and a difference of more than 10% between renal functions of both kidneys was evaluated as loss

of function. The patients with hydronephrosis were investigated in terms of ureteropelvic obstruction (UPJO) by performing dynamic renal scintigraphy (MAG-3). These data were scanned from the system and recorded. Also, in patients requiring surgical operation, findings of computed tomographies performed for evaluation of vascular anatomy or renal stones were scanned from the patient files.

When the patients who were followed up with the diagnosis of a horseshoe kidney and the control group came to the clinic, they were evaluated with Doppler ultrasonography (USG) by the same two radiologists. On Doppler USG, renal artery and renal vein flow velocities were evaluated prospectively in terms of lumen diameters and variation anomalies and presence of nutcracker phenomenon. Doppler USG examination was performed after 6-8 hours of fasting. The patients were evaluated in supine position using a convex transducer operating in the 1-5 MHz frequency range and connected to an ultrasonography device (Logiq E9, GE Medical Systems, Wisconsin, USA). Left renal vein diameter was measured between the aorta and superior mesenteric artery (aortomesenteric part) and 3 cm medial from the renal hilus in the control and patient groups. In order to minimize variations in vascular diameters and flow velocity, each parameter was measured at least twice and the results averaged. During the flow velocity measurements, the Doppler angle was kept between 30°- 60°. Ultrasonographic evaluations were made by two observers in consensus. Detecting the left renal vein diameter / aorta-superior mesenteric diameter ratio above 2.25 was accepted as a nutcracker phenomenon [10]. The observers were unaware of the clinical and laboratory findings of the patients during the ultrasonographic evaluation.

Statistical methods

The data were analyzed with SPSS 25.0 package program. Continuous variables were expressed as mean ± standard deviation and categorical variables as numbers and percentages. The compatibility of the data to normal distribution was examined using the Shapiro-Wilk test. The t-test was used to examine the independent group differences, and the chi-square analysis to examine the differences between categorical variables. Spearman correlation analysis was used to examine the relationships between continuous variables. In all analyzes, $p<0.05$ was considered statistically significant.

Results

Twenty-six patients (13 girls, 13 boys) and 22 healthy children (10 girls, 12 boys) who were followed up with the diagnosis of horseshoe kidney were included in the study. The mean age of the patients during the study was 10.7±5.6 (0.8-18) years, and that of the control group it was 9.89±4.47 (2.84-17.78) years, without any statistically significant difference between the two groups in terms of gender and age. Kidney fusion anomaly with cross ectopia was detected in two patients (7.7%) with horseshoe kidneys, and lower poles of both kidneys were fused and localized in the abdomen of 24 cases (92.3%). Eleven patients (42.3%) were diagnosed incidentally, 3 patients were diagnosed during antenatal period, other patients received the diagnosis of horseshoe kidney while investigating for the presence of urinary incontinence (n=6) or recurrent urinary tract infection (UTI) (n=6). Urinary system anomaly was present in 50% of the patients. Hydronephrosis was detected in 8 patients, 3 of which were isolated, and VUR in 5 patients (the highest VUR grade was grade IV, 2 patients bilateral and 3 had unilateral VUR). Other urological anomalies are given in Table 1. A total of 3 patients underwent surgical intervention for urological anomalies. Nephropyelolithotomy operation was performed in a patient with UPJO + duplicated collecting system + kidney stones, subureteric deflux injection was performed in a patient with VUR due to proteinuria and recurrent UTI history, and one patient with UPJO underwent bilateral pyeloplasty.

Additional systemic anomalies were detected including a cardiac anomaly in 4, gastrointestinal system (GIS) anomaly in 3, genital anomaly in 1, skeletal anomaly in 2 patients, spinal dysraphism in 1 patient and Turner syndrome in 1 patient (Table 1).

Table 1. Demographic data and accompanying urinary system symptoms in patients with horseshoe kidneys

Characteristics	**n (%)**
Mean (± SD) age (years)	10.7±5.65 (0.8-18)
Sex	
Male	13 (50)
Female	13 (50)
Types of diagnosis	
Incidental	11 (42.3)
Bladder dysfunction	6 (23.1)
Recurrent UTI	6 (23.1)
Antenatal	3 (11.5)
Urinary system anomaly	
VUR	5 (19.2)
Isolated Hydronephrosis	3 (11.5)
UPJ obstruction	3 (11.5)
Extrarenal pelvis	1 (3.8)
Duplicated collecting system	2 (7.7)
Neurogenic bladder	2 (7.7)
Bladder diverticulum	1 (3.8)
Systemic anomaly	
Cardiac anomaly	4 (15.4)
Mitral insufficiency, mitral valve prolapsus	
Persistent anomalous pulmonary venous return	
Atrial septal defect	
Patent ductus arteriosus	
GIS anomaly	3 (11.5)
Anus imperforatus	
Ileal atresia	
Tracheoesophageal fistula	
Genital anomaly	1 (3.8)
Hypospadias	
Skeletal abnormalities	2 (7.7)
Scoliosis	
Spinal deformity	1 (3.8)
Meningomyelocele, hydrocephalus	
Turner Syndrome	1 (3.8)

UTI: Urinary tract infection, VUR: Vesicoureteral reflux, GIS: Gastrointestinal system

Eight patients (30.8%) had recurrent UTI, 6 patients who were diagnosed with horseshoe while being examined for UTI, and the other 2 patients suffered from urinary tract infection during follow-up. Kidney stones were detected in 5 patients (19.2%), hypercalciuria and hyperuricosuria were detected in one of these patients, and metabolic examinations of the other 4 patients were within normal limits.

Renal scar was detected in 2 patients (7.7%) in DMSA scintigraphy, the difference in renal functions of both kidneys in 7 patients (38.9%) was over 10% and ultrasonographic examinations of these patients revealed a significant difference between dimensions of both kidneys Proteinuria was present in 3 (11.5%), CKD in 1 (3.8%), and hypertension in 1 (3.8%) patient.

In renal Doppler USG examinations of both groups, any significant difference was not found between the patient and the control groups in terms of renal vein diameters at the aorta level and left para-aortic areas, and the highest and lowest flow velocities *(p*>0.05) (Table 2).

Table 2. Doppler Ultrasonographic data concerning diameters of hilar part the left renal vein, and aortomesenteric left renal vein with the patient examined in the supine position. Comparison between the patient, and the control groups

	Horseshoe kidney group (n=26)	**Control group (n=22)**	***P***
Diameter of the proximal renal vein (mm)	4.58±1.35 (2-6.3)	4.86±0.99 (3.5-7.40)	0.433
Diameter of left renal vein between aorta and superior mesenteric artery (SMA) (mm)	3.6±1.63 (1.8-8.2)	3.44±0.77 (2.5-6)	0.682
A/SMA	1.5±0.58 (1-3.15)	1.44±0.29 (1.12-2.5)	0.672
Number (%) of patients with A/SMA >2.25	2 (7.7)	1 (4.5)	0.607
VMAX/VMIN	1.99±0.39	1.79±0.22	0.051

A/SMA: The ratio between diameters of aorta and superior mesenteric artery, V MAX: Left renal vein peak blood flow velocity
V MIN: Left renal vein the lowest blood flow velocity

The ratio between the highest and the lowest flow rates in the left renal vein was higher in children with horseshoe kidneys compared to the healthy group without any statistically significant intergroup difference (*p*=0.052). In all children, renal vein diameters at the level of the abdominal aorta and the left para-aortic area were significantly correlated with age (*p*=0.001 for both, *r*=0.580, *r*=0.509, respectively). In the horseshoe kidney group, findings of nutcracker syndrome were present in 2 patients, while in the control group, they were detected incidentally in only 1 patient. Accessory renal artery originating from the left common iliac artery was detected in a case with horseshoe kidney and in another case the presence of a circumaortic left renal vein was revealed.

Discussion

In our study, at least one accompanying urological anomaly was found in 50% of the patients with horseshoe kidneys, and one concomitant systemic anomaly was detected in 35% of the patients. Nutcracker phenomenon was detected in 1 case in the control group, but in 2 of the cases evaluated for nutcracker anomaly in the disease group known to be accompanied with vascular anomalies. In addition, accessory renal artery originating from the left common iliac artery in a case with horseshoe kidney and in another patient circumaortic left renal vein were found. Nutcracker syndrome in horseshoe kidney has not been investigated to date. Since the horseshoe kidney is a fusion anomaly, a vascular anomaly such as nutcracker syndrome can theoretically be expected to be common. However, in our study, it was found that there was no significant increase in horseshoe kidney patients compared to control patients.

Horseshoe kidney is the most common fusion anomaly, and it is known to be twice as common in boys than in girls [11, 12]. In our study, the number of male and female patients were equal. Fusion between the lower poles

of both kidneys is known as the most common (>90%) fusion type in the horseshoe kidneys [11]. In accordance with the literature findings, in our study, fusion of the lower poles of both kidneys was seen in our 24 patients.

Most patients with horseshoe kidneys are asymptomatic. In these patients, horseshoe kidneys are diagnosed incidentally. Similarly, in our study, 11 patients (42.3%) were incidentally diagnosed as a result of ultrasonographic examinations performed for other indications, and 11.5% of the cases were diagnosed during antenatal period. Anatomical abnormalities in patients with horseshoe kidneys disrupt the drainage in the collecting system, causing infection and stones. Generally, symptomatic patients present with flank or abdominal pain due to stones or urinary tract infections [3, 12]. In some studies, while 9.8%-23.5% of the patients presented with urinary tract infection, 6.1%-17.1% of them with complaints of urinary incontinence [3, 13, 14]. In our study, the most common indications for presentation among symptomatic patients diagnosed with horseshoe kidneys were urinary incontinence and urinary tract infections (23.1% and 23.1% of the patients, respectively).

It is known that between one third and half of the patients with horseshoe kidneys have other congenital anomalies [3, 15]. In our study, 13 (50%) patients had additional urinary system anomalies. Hydronephrosis, VUR and UPJO are among the urinary system anomalies which are frequently seen in patients with horseshoe kidneys. In some studies, the incidence of concomitant hydronephrosis has been reported between 21-80% [1, 3, 16, 17]. In our study, a total of 8 patients had hydronephrosis, 3 of whom had only hydronephrosis without any comorbidities. Causes of hydronephrosis include VUR, UPJO, kidney stone, or external compression on ureters by an abnormal vessel. In some studies, incidence rates of VUR have been reported as 5.2-25%, respectively [1, 3, 15, 16]. Similarly, the incidence of VUR in our study was 19.2%. UPJO has been reported between 19.5% and 35% in patients with horseshoe kidneys in the literature [3, 15, 18]. UPJO in horseshoe kidneys is associated with high and lateral insertion of ureters into the renal pelvis, displacement of the fused isthmus, and the vascular support of the isthmus [19]. We recorded a lower incidence of UPJ obstruction in our study (11.5%).

Horseshoe kidney is an anomaly that specifically facilitates urinary tract infection. Infection is seen in one third of the patients [4]. According to the data obtained from 13 articles including 825 patients with horseshoe kidneys, Weizer et al. [16] found the incidence of UTI as 22.9%. In another study, the incidence of UTI was reported to be 42% [3]. Similar to the literature, 8 patients (30.8%) had UTI in our study, and 6 of them were diagnosed during the examination carried out with this indication. Ascending infection is the most common form of infection and VUR is a common underlying cause [15]. In our study, in half of the patients, UTI was accompanied by VUR.

The coexistence of horseshoe kidney with extrarenal diseases or syndromes has been reported in the literatüre [1, 3, 14]. Nine (34.6%) of our patients had 12 extrarenal diseases and syndromes. Patients with horseshoe kidneys had cardiac (n=4), genital (n=1), gastrointestinal (n=3,) skeletal (n=2), spinal pathologies (n=1), and Turner Syndrome (n=1). In our study, the most common extrarenal anomaly was also cardiac anomaly. Horseshoe kidney can coexist with many syndromes, including genetic disorders such as Turner syndrome and trisomy 13, 18, and 21 [20]. Our patient had mosaic Turner syndrome.

The prevalence of stones in the horseshoe kidney varies between 20 and 60% [16, 21, 22]. Although it is known that anatomical abnormality in horseshoe kidney causes stasis and stone formation, the results of studies investigating the contribution of metabolic abnormality to stone formation is contradictory. In one study, metabolic scanning was performed in patients with horseshoe kidneys and kidney stones, and at least one metabolic abnormality (most commonly hypercalciuria and hypocitraturia) was found in 30% of the patients [23]. In another study, 75% of metabolic abnormalities were found in patients with horseshoe kidneys and stones [24]. In contrast to these studies, in a study, the researchers could not find any difference in the frequency of metabolic abnormalities associated with kidney stones between patients with horseshoe kidneys and the general population [21]. In our study, 19.2% of the patients had stone disease without any significant difference

with the control group (9.1%) (p>0.05). In the study by Weizer et al. [16] 9 (39%) patients had nephrolithiasis, and 4 of them were operated. In our study, nephropyelolithotomy operation was performed on a patient with kidney stones. In our study, only one of the patients with stones had hypercalciuria and hyperuricosuria. When compared with the healthy control group, no significant difference was found in terms of the presence of hypercalciuria and hyperuricosuria (p:0.609, p:0.247).

Vascularization (in the arteries and veins) of the horseshoe kidney can be variable. There may be accessory and aberrant vessels and accompanying malformations [25]. While the kidneys are normally supplied by the renal arteries originating from the aorta, it has been shown that the isthmus can be supplied by the iliac, inferior mesenteric artery, sacral and lumbar arteries, especially in cases with rotation anomalies and ectopy accompanying the horseshoe kidney [18, 26]. This condition may cause problems especially regarding triage among patients with urological anomalies that require operation, and advanced examinations such as computed tomography and angiography are required to demonstrate vascularization to guide the surgical operation [25, 26]. In our study, CT imaging was performed for anatomical and vascular evaluation of the patients who would undergo bilateral pyeloplasty for UPJ obstruction, injection for VUR and nephropyelolithotomy for stone disease, and any intraoperative complication was not encountered. As could be seen in Doppler USG performed on our patients, accessory renal artery originating from common iliac artery was detected in only one patient. Coexistence of horseshoe kidney with abdominal aortic aneurysm has been reported in the literature with a rate of 0.12%. In a retrospective study of 25 patients with horseshoe kidneys operated for aortic aneurysm rupture; 16 patients were operated for aortic aneurysm rupture and 9 patients due to aortailiac stenosis [27]. Horseshoe kidneys in these patients were detected in preoperative imagings performed, and four of 16 patients with ruptured aneurysms were urgently operated. In the literature, arteriovenous fistula and related bleeding in adult patients, and in another case, obstruction in the vena cava inferior due to compression of the isthmus of the horseshoe kidney were reported [28, 29]. Although pathologies such as fistula and aneurysm were not detected in our patient group, we think that these patients should be followed up especially in terms of vascular complications that may develop in adulthood.

Nutcracker phenomenon is an anatomical disorder that does not show symptoms due to compression of the paraaortic part of the left renal vein between the aorta and the superior mesenteric artery. Nutcracker syndrome is due to this anatomical disorder; It is accompanied by symptoms such as flank pain, hematuria, pelvic congestion, and menstrual disorders [30]. In our study we searched for the possibility of nutcracker phenomenon in patients with horseshoe kidneys where concomitant vascular anomalies are frequently seen, we radiologically observed findings of nutcracker syndrome in 2 patients in the patient group and in 1 patient in the control group (aorta/superior mesenteric artery diameter ratio >2.25). However, in patients with nutcracker phenomenon in both groups, accompanying findings and symptoms such as hematuria, proteinuria, and left flank pain were not encountered. Any difference was not detected between the renal vein diameters and flow rates in the aorta and left paraaortic areas of both groups. The peak blood flow velocities in the left renal vein were –though mot statistically significant -higher in patients with horseshoe kidneys than in control patients. It is known that the incidence of malignancy increases in patients with horseshoe kidneys.

Although the cause is not known exactly, it has been suggested that the risk is higher especially in cases with fibrous isthmus during migration (ascent) of the kidney in the embryonic period. Wilms tumor is the most frequently seen tumor in children with horseshoe kidneys and is detected twice as much as the normal population [1, 31, 32]. Again in the literature, although rare, cases of extrarenal Willms tumor have been encountered in pediatric patients with horseshoe kidneys. It has been suggested that metanephric blastema cells remaining in the abdomen after metanephric blastema fusion in the intrauterine period cause development of extrarenal Wilms tumor [33]. The most common tumor seen in adult patients with horseshoe kidneys is renal cell carcinoma which is seen in an incidence similar to the normal population [34, 35]. In our cases horseshoe kidneys did not

accompany by tumors, and we think that patients with horseshoe kidneys not accompanied by tumors should be followed up by USG in terms of tumors that may develop in the future.

Small number of patients is one of the limitations of our study. Although renal Doppler USG is an adequate examination for the diagnosis of nutcracker syndrome, USG may be insufficient for detecting other vascular anomalies. However, computed tomography (CT), which is a successful method for detecting vascular anomalies could not be performed due to radiation risk.

In conclusion, studies on long-term follow-up results of patients with horseshoe kidneys are limited in number. In a study conducted in our country, after a 10-year follow-up of these patients, the rates of hypertension, proteinuria, and chronic kidney damage were found to be 10, 15, and 7%, respectively [3]. In our study, these rates were 3.8%, 11.5 and 3.8%, respectively. In our study, malignancy was not found in cases with horseshoe kidneys, but the frequency of vascular anomalies or nutcracker phenomenon was comparable to the control group. We think that annual lifelong controls of these patients for chronic kidney damage and vascular pathologies should be performed.

Conflict of interest: No conflict of interest was declared by the authors.

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Authors' contributions to the article

I.G. and S.Y. have constructed the main idea and hypothesis of the study. H.K.Z. and A.R.U. developed the theory and arranged/edited the material and method section. T.B. and F.U. have done the evaluation of the data in the Results section. Discussion section of the article written by I.G., H.K.Z. and S.Y. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.