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The Association Between *Sodium Citrate Cotransporter (NaDC-1)* Gene Polymorphism and Urinary Citrate Excretion in Patients with Calcium-containing Kidney Stone

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What's known on the subject? and What does the study add?

The I550V single-nucleotide polymorphism (SNP-rs11567842) has been associated with hypocitraturia and calcium kidney stones. Previous studies have reported that the rs11567842 mutation may be protective against hypocitraturia and kidney stones. However, in these studies, urine levels of oxalate, uric acid, and calcium in stone formers were higher those in healthy individuals in the control group. This indicates that hypocitraturia cannot be the main factor in those who form stones. The current study investigated the relationship between patients with calcium-containing kidney stones and those with normal and low citrate excretion.

Abstract

Objective: To evaluate the relationship between *sodium citrate cotransporter (NaDC-1)* gene polymorphism and urinary citrate excretion in patients with kidney stones containing calcium.

Materials and Methods: Between June 2009 and August 2011, stone materials obtained from patients treated for nephrolithiasis at the Urology Clinic were examined using X-ray diffraction, and patients with calcium-containing stones (calcium oxalate and calcium phosphate) were identified. Patients were divided into two groups based on their 24-hour urine citrate levels: (1) those with normal urine citrate levels and (2) hypocitraturia. To analyze the rs11567842 mutation in the *NaDC-1* gene, their blood was collected in a Na-EDTA hemogram tube and stored at -40 °C. The genotypes of the cases were determined by analyzing the obtained genomic DNAs in real-time polymerase chain reaction.

Results: Ninety-six patients with calcium-containing nephrolithiasis were eligible for this study, 40 with normal urine citrate levels and 56 with hypocitraturia. The mean 24-hour urine citrate levels in the normal- and hypo-citraturia groups were 773 mg/1.73 m^2/24 hours and 152 mg/1.73 m^2/24 hours, respectively. Citrate measurements revealed a statistically significant difference between the two groups ($p<0.001$). Twenty-four-hour urine oxalate, magnesium, calcium, and uric acid levels did not differ significantly between the groups (all $p>0.05$). *NaDC-1* gene rs11567842 homozygous mutation (GG genotypes) was detected in 4 (10%) of normocitraturia and 4 (7%) of hypocitraturia. The normocitraturia group had a higher mutation rate than the hypocitraturia group, but this difference was insignificant ($p=0.618$).

Conclusion: This study suggests that the *NaDC-1* gene polymorphism does not cause hypocitraturia in calcium-containing kidney stones. Larger studies are needed to understand genetic disorders' impact on low urinary citrate excretion, with patient groups and healthy controls, and a standard diet.

Keywords: Citrate, hypocitraturia, NaDC-1, polymorphism, kidney stone, urolithiasis

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Introduction

Urinary citrate prevents the formation of calcium-containing kidney stones by inhibiting the crystallization and precipitation of calcium, so hypocitraturia, or low urinary citrate excretion, is an essential metabolic risk factor for the formation and recurrence of urinary stones (1). Hypocitraturia ranges from 20% to 60% among patients with calcium-containing kidney stones (2). The mechanisms underlying hypocitraturia in calcium-containing kidney stones still need to be fully clarified. Citrate's intestinal transportation, serum concentration, and filtered load do not differ between patients with kidney stones and healthy volunteers (3-5). But, metabolic abnormalities or a diet high in acid-producing foods affect the renal handling of citrate, resulting in alterations in citrate excretion levels in the urine (6-9). However, hypocitraturia can be observed in patients with calcium-containing kidney stones without any metabolic abnormalities, and despite urine collection being performed with fixed diets to minimize dietary factors in the studies, kidney stone formers still have lower citrate excretion compared to controls (4,5,10). These reports suggest that genetic predispositions play a role in the formation of kidney stones in patients with hypocitraturia (2).

Citrate is reabsorbed in the proximal tubule apical membrane by the Na^+/$citrate^{2-}$ cotransporter, also known as Na^+/dicarboxylate cotransporter (NaDC-1). Therefore, NaDC-1 is a significant determinant of citrate excretion in the urine. The cDNA of the human *NaDC-1* gene contains 12 exons with 1.953 base pairs and encodes 593 amino acids (11-13). The genetic polymorphism of NaDC-1 (I550V or rs11567842) has been reported to be associated with urinary citrate excretion in Japanese patients with calcium stone formation (14). An *in vitro* experiment revealed that the single nucleotide polymorphisms (SNP) - rs11567842 in *NaDC-1* gene affects the function of NaDC-1, as it causes a decrease in protein expression and transport activity (15). Although the effect of the SNP - rs11567842 on citrate excretion has been demonstrated, its association with calcium stone formation remains unclear. In the current study, the relationship between *NaDC-1* gene SNP (I550V/rs11567842) and stone formation was evaluated by analyzing *NaDC-1* gene polymorphism in two separate patient groups with calcium-containing kidney stones and normal or low citrate excretion.

Materials and Methods

Between June 2009 and August 2011, stone materials obtained from patients treated for kidney stones at the Düzce University Faculty of Medicine Hospital Urology Clinic were examined using X-ray diffraction, and patients with calcium-containing kidney stones (calcium oxalate and calcium phosphate) were identified. The patients' weight and height were measured, a detailed medical history was obtained, and they were questioned about familial stone formation, recurrent stone formation, receiving treatment for the urolithiasis (surgical or medical), and systemic or metabolic disease. Excluded from the study were patients with any systemic disease (except hypertension), non-calcium component kidney stones, any treatment that could affect acid-base balance, diuretic treatment, and calcium or vitamin C supplements. For metabolic evaluation, serum creatinine, sodium, potassium, calcium, and uric acid levels were measured in each patient, as well as 24-hour urine citrate, oxalate, magnesium, calcium, and uric acid levels. In addition, a urinalysis and culture of the urine were conducted. Patients were instructed to avoid excessive consumption of red meat, salty foods, chocolate, leafy greens, tea, and coffee prior to the 24-hour urine test. Solute excretion in 24-hour urine samples were measured using the photometric method with Ben Biochemical Enterprise™ (CI8820, Milan, Italy) kits in the biochemistry laboratory of Düzce University Faculty of Medicine Hospital. Patients were divided into two groups based on their 24-hour urine citrate levels: normal and low. To analyze the rs11567842 mutation in the *NaDC-1* gene, their blood was collected in a Na-EDTA hemogram tube and stored at -40 °C.

The study was conducted in line with the principles of the Declaration of Helsinki and was approved by the local ethics committee of Düzce University, Turkiye (approval no: 2010/102, date: 30.12.2010).

Real-Time Polymerase Chain Reaction (PCR)

DNA isolation and PCR studies were conducted in the Molecular Genetics Laboratory of the Medical Genetics Department at the Abant Izzet Baysal University Faculty of Medicine Hospital. Genomic DNA was isolated and obtained using the High Pure PCR Template Preparation Kit-Roche™ kit. The genotypes of the cases were determined by analyzing the obtained genomic DNAs in real-time PCR (Light Cycler480 II™) using primers and probes covering the relevant polymorphism. Each sample was classified as wild type (AA), heterozygous type (AG), or homozygous type (GG) based on the results of the analysis

Statistical Analysis

Statistical analyses were performed using SPSS Statistics 15 (IBM, Chicago, IL, USA). A $p<0.05$ indicated statistical significance. The Kolmogorov-Smirnov test was used to determine the normality of the numeric data. The two groups were compared using the Student's t-test for numerical variables and the Pearson chi-square test for nominal and ordinal variables, including genetic analysis results, gender, family history, and positive urine culture.

Results

Ninety-six patients with calcium-containing kidney stones were eligible for this study. Within the scope of the study, patients

were evaluated: 40 patients with normal 24-hour urine citrate levels and 56 patients with low levels. Twenty-four men and 16 women comprised the normocitraturia group, whereas 33 men and 23 women comprised the hypocitraturia group. The mean ages of the normocitraturia and hypocitraturia groups were 44.0 (9-72) and 43.3 (3-70) years, respectively (p=0.84). There were no statistically significant differences between the groups concerning age, gender, body mass index, or positive family history (all p>0.05, Table 1). The normocitraturia group had mean serum creatinine levels of 0.84 mg/dL, while the hypocitraturia group had mean serum creatinine levels of 0.88 mg/dL (p=0.417). Serum calcium and urine pH and density exhibited no statistically significant differences between groups (all p>0.05).

The mean 24-hour urine citrate level in the normocitraturia group was 773 mg/1.73 m^2/24 hours; in the hypocitraturia group, it was 152 mg/1.73 m^2/24 hours. Citrate measurements revealed a statistically significant difference between the two groups (p<0.001). The normocitraturia group had an average 24-hour urine oxalate concentration of 39.2 mg/1.73 m^2/24 hours, while the hypocitraturia group had an average 24-hour urine oxalate concentration of 33.3 mg/1.73 m^2/24 hours. Regarding oxalate measurement, there was no statistically significant difference between the groups (p=0.130). In addition, 24-hour urine magnesium, calcium and uric acid levels did not differ significantly between the groups (all p>0.05). The results of a 24-hour urine analysis (urine volume, oxalate, magnesium, calcium, and uric acid) are shown in Table 2.

Comparing the urine culture results of the normocitraturia and hypocitraturia groups, urine culture positivity was detected in 2 (5%) normocitraturia and 4 (7.2%) hypocitraturia patients. In terms of urine culture positivity, there was no statistically significant difference between the two groups (p=0.665). In 4 (10%) normocitraturia patients and 4 (7%) hypocitraturia

Table 1. Patient characteristics and familial stone formation rates

		Nephrolithiasis with normal citraturia (n=40)	Nephrolithiasis with hypocitraturia (n=56)	p-value*
Age (years)		44.0±15.0	43.3±15.0	0.839
Height (cm)		168.8±7.7	166.9±13.2	0.425
Weight (kg)		75.1±11.1	74.7±13.4	0.903
BMI (kg/m^2)		26.3±3.9	26.9±4.0	0.820
Gender	Male	24 (60)	33 (59)	0.916
	Female	16 (40)	23 (41)	
Familial stone formation	Yes	22 (55)	21 (38)	0.089
	No	18 (45)	35 (63)	

*: To compare mean values, the Student's t-test was used, and Pearson's chi-squared test was used to compare proportional values

Table 2. The outcomes of serum, spot urine, and 24-hour urine collection tests

	Nephrolithiasis with normal citraturia (n=40)	Nephrolithiasis with hypocitraturia (n=56)	p-value
Serum (blood)			
Creatinine (mg/dL)	0.84±0.1	0.88±0.2	0.417
Calcium (mg/dL)	10.1±3.8	9.5±0.5	0.224
Urinalysis			
pH	5.2±0.7	5.1±0.8	0.308
Density	1017±6.0	1016±6.0	0.377
24-hour urine collection			
Volume (mL)	2276±758	2075±925	0.264
Citrate (mg/1.73 m^2/24 hours)	773±301	152±87	**<0.001**
Oxalate (mg/1.73 m^2/24 hours)	39.2±19.5	33.3±18.0	0.130
Magnesium (mg/dL)	4.7±2.2	5.0±2.2	0.527
Calcium (mg/dL)	9.6±5.2	9.9±6.0	0.810
Uric Acid (mg/dL)	23.4±9.6	23.8±12.5	0.859

Bold values denote statistical significance at the p<0.05

Table 3. Genotype frequencies of *NaDC-1 (SLC13A2/I550V)* gene polymorphism			
Genotypes, n, (%)	**Nephrolithiasis with normal citraturia n=40**	**Nephrolithiasis with hypocitraturia n=56**	**p-value**
AA genotype	20 (50)	29 (51.8)	0.618
AG genotype	16 (40)	23 (41.1)	
GG genotype (rs11567842 mutation)	4 (10)	4 (7.1)	

patients, the *NaDC-1* gene rs11567842 homozygous mutation (AA) was found. The hypocitraturia group had a higher mutation rate than the normocitraturia group, but this difference was not statistically significant (p=0.618, Table 3).

Discussion

The approximately 23.8 kb human *NaDC-1* gene is located on chromosome 17 p11.1-q11.1 and comprises 12 exons (16). The *NaDC-1* gene encodes the 592-residue NaDC-1 protein, which shares 54% and 43% sequence identity with the human NaCT and NaDC-3 proteins (17). The kidney and small intestine express NaDC-1 predominately. More specifically, NaDC-1 is localized on the apical membrane of renal proximal tubular and small intestine cells where it reabsorbs tricarboxylic acid cycle intermediates from urine and diet, respectively (18). According to *in vivo* and *in vitro* studies, acidosis stimulates both NaDC-1 function (citrate transport activity) and expression (mRNA and protein levels), whereas alkalosis only affects its citrate transport function (9,19). The primary physiological function attributed to NaDC-1 is citrate elimination in the kidneys. Urinary citrate is essential for preventing the formation of kidney stones by complexing Ca^{2+} ions, thereby preventing urine supersaturation and precipitation of Ca^{2+} salts-based calculi. This suggests that NaDC-1 is involved in the pathophysiology of kidney stones (18). Furthermore, the human *NaDC-1* gene I550V-SNP has been genetically related to hypocitraturia and kidney stones (14). Since citrate reabsorption by NaDC-1 determines urinary citrate concentration, inhibition of NaDC-1 is expected to increase urinary citrate excretion. However, potent specific NaDC-1 inhibitors are not yet available. A specific inhibitor could clarify the connection between NaDC-1-mediated urinary citrate excretion and calcium nephrolithiasis, and it could have been used as a treatment agent today. Therefore, additional research and evidence are required to conclude that NaDC-1-mediated hypocitraturia is a fundamental mechanism underlying calcium-containing kidney stones.

A SNP (pI550V/rs11567842) in the *NaDC-1* gene causes a change from isoleucine (I) to valine (V) at amino acid 550th. Three genotypes have been identified in SNP. These are AA (wild type), AG (heterozygous mutant), and GG (homozygous mutant) genotypes. In the present study, 51.8%, 41.1%, and 7.1% of individuals with hypocitraturia had the AA, AG, and GG genotypes, respectively. Stone formers with normal citrate levels comprised 50% AA, 40% AG, and 10% GG genotypes. There was no statistical difference in the frequency of genotypes between groups.

Okamoto et al. (14) evaluated the effect of I550V-SNP on hypocitraturia and calcium stone formation and found that those with AA genotype had lower urinary citrate levels than other genotypes. They also detected AA genotypes at a higher rate in stone-forming patients than in healthy individuals. They demonstrated that the I550V polymorphism is associated with hypocitraturia and kidney stones and that having the AA genotype may be a risk factor for hypocitraturia and kidney stones. However, according to this study's 24-hour urine examination results, stone-forming groups had lower pH and citrate levels and higher calcium, oxalate, and uric acid levels than stone-free groups. The presence of these values, which may be a risk factor for the formation of kidney stones, makes it difficult to interpret the findings correctly, and it may not be accurate to state that stone formation is only due to low citrate levels.

Udomsilp et al. (20) evaluated the impact of the I550V polymorphism on hypocitraturia and recurrent calcium stone formation. They discovered that individuals with the AA genotype had lower urinary citrate levels than those with other genotypes. However, there was no noticeable distinction in the frequency of genotypes between stone-forming individuals and healthy individuals. They concluded that having the AA genotype is associated with hypocitraturia and may be a risk factor for kidney stone formation. This study did not report urinary levels of calcium, oxalate, and uric acid. In the present study, all I550V polymorphism-examined patients had calcium-containing kidney stones. In addition, pH, calcium, oxalate, and uric acid levels in urine were similar between groups. The current study design minimizes the influence of confounding variables and lacks the limitations of previous research.

Pajor and Sun examined the effect of SNPs on NaDC-1 expression and function using the COS-7 cell heterologous expression system (15). They showed that the I550V variant had an increased sensitivity to lithium inhibition, although there was no significant effect on protein expression. They also concluded that all SNP mutations reduced the transport activity or expression of NaDC-1, leading to reduced intestinal

and renal absorption of citric acid cycle intermediates. In the current study, although those with *NaDC-1* gene rs11567842 mutation (GG genotype) were detected less frequently in the hypocitraturia group than those with normal urine citrate levels, this difference was not statistically significant. However, when evaluating the findings of our study, it must be kept in mind that no strict diet was adhered to during the research. As is well known, environmental factors, particularly foods that make the urine more acidic, also influence the urinary citrate excretion of individuals with normal renal function. Consequently, environmental factors cannot be ruled out as a cause of hypocitraturia in these patients.

Study Limitations

This study's most significant limitations are its small sample size and lack of a healthy control group. Comprehensive studies with larger patient groups, healthy controls, and a strict diet are required to clarify this relationship.

Conclusion

These results do not support a role for *NaDC-1* gene polymorphism in the etiopathogenesis of hypocitraturia in calcium-containing idiopathic kidney stones. Important limitations of this study include the absence of healthy control subjects and a standard diet. To further elucidate the role of genetic disorders in low urinary citrate excretion, comparative studies with larger patient groups and healthy controls, excluding environmental effects (with a standard diet), should be conducted.

Ethics

Ethics Committee Approval: The study was conducted in line with the principles of the Declaration of Helsinki and was approved by the local ethics committee of Düzce University, Turkiye (approval no: 2010/102, date: 30.12.2010).

Informed Consent: The authors declare that they have no relevant financial.

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Authorship Contributions

Surgical and Medical Practices: A.Ç., Ö.M., A.T., S.D., Concept: A.Ç., Ö.M., A.T., S.D., Design: A.Ç., A.T., Data Collection or Processing: A.Ç., Ö.M., A.T., Analysis or Interpretation: A.Ç., Ö.M., AT., S.D., Literature Search: A.Ç., Ö.M., A.T., Writing: A.Ç., Ö.M., A.T.

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Apparent Diffusion Coefficient of Variation (ADCcv): A New Biomarker for Aggressiveness in Prostate Cancer

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What's known on the subject? and What does the study add?

Apparent diffusion coefficient (ADC) cv could be benefical in improving future prostate cancer imaging. The validation of ADC cv as an imaging biomarker may have important consequences for the detection and assessment of aggressiveness of prostate cancer.

Abstract

Objective: The purpose of this study was to evaluate which apparent diffusion coefficient (ADC) parameter can predict the aggressiveness of prostate cancer in patients confirmed by radical prostatectomy specimens.

Materials and Methods: Patients who underwent radical prostatectomy for prostate cancer between October 2019 and June 2023 were retrospectively reviewed. Patients were separated into two groups based on the International Society of Urological Pathology (ISUP) classification, and the correlation between ADC metrics and ADC parameters, including ADC_{mean}, $ADC_{coefficient\ of\ variation}$ (ADC_{cv}), and ISUP classification the aggressiveness of prostate cancer was studied.

Results: Fifty-seven patients were included in the study. Patients were evaluated as low-risk (group 1) (n=40), and high-risk (group) (n=17). ADC_{mean} values for the two groups were not significantly different (p=0.218). ADC_{cv} values that can demonstrate tumour heterogeneity index were higher in group 2 than in group 1 (p<0.001). Multivariate analysis revealed that extracapsular extension, positive surgical margin, and ADC_{cv} values indicated tumour proliferation, whereas seminal vesicle invasion, prostate-specific antigen levels, and body mass index were not correlated with ISUP grade groups.

Conclusion: ADC cv is a promising new biomarker for tumour aggressiveness in prostate cancer.

Keywords: Diffusion weighted imaging, apparent diffusion coefficient, ISUP grade group, prostate cancer, prostatectomy

Introduction

Prostate cancer is a leading cause of disease and death among men, with 1.6 million men being diagnosed annually and 366.000 men dying from the disease (1). In recent years, imaging has taken on more significance in the detection, staging, posttreatment evaluation, and detection of prostate cancer recurrence. Magnetic resonance imaging (MRI) offers the most exact representation of zonal anatomy and the highest soft tissue resolution of any imaging technique to date, allowing for a thorough anatomic evaluation of the prostate. The most effective MRI approach is multiparametric MRI (MpMRI). MpMRI combines T1-weighted and multiplanar T2-weighted images and functional diffusion-weighted imaging with apparent diffusion coefficient (ADC) maps and dynamic contrast-enhanced imaging sequences that can provide information about anatomy and function. Diffusion-weighted imaging (DWI), which uses the random mobility of water molecules to construct ADC maps, allows for both qualitative and quantitative assessments of prostate cancer (2,3). ADC is the net movement of molecules

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over a tissue area per second (mm^2/s) (4). In fact, the typical glandular morphology is changed in prostate cancer, with nests of cancer cells and fibrous stroma displacing the large interstitial gaps and glandular lumens, resulting in a decrease in unrestricted water circulation. Consequently, a high-signal-intensity zone on DWI pictures indicates clinically severe malignancy. In the monoexponential model, the ADC has a mean value that is connected to diffusion. The ADC value has proven to be an effective indicator of cancer aggressiveness, providing quantitative information on tumor characteristics (5). Many studies in the current literature indicate that the mean value of ADC reflects the degree of aggressiveness of prostate cancer (6-8). In contrast, a study that examined the ADC_{mean} and ADC_{ratio} values revealed no association with the aggressiveness of prostate cancer (9). However, there is still some uncertainty in this area, and no agreement has been achieved (6,10). This notion is related to some challenges. First, the ADC can differ greatly due to various factors. These are the b-values employed, MR scanner field strength, patient and coil geometry, temporal fluctuations in the magnetic field, and measurement differences between different readers. Furthermore, non-cancerous tumours, such as benign prostatic enlargement, may have lower ADC values. Consequently, various options beyond ADC_{mean} are needed to determine the aggressiveness of prostate cancer. Therefore, we intended to investigate the efficacy of $ADC_{coefficient\ of\ variation}$ (ADC_{cv}) measurement, a new biomarker of tumour heterogeneity index, in prostate cancer and examine, in a cohort of consecutive patients, the correlation between absolute ADC_{mean} and ADC_{cv} and ISUP grade following robot-assisted laparoscopic prostatectomy (RALP).

Materials and Methods

Patient Selection

The local ethics committee accepted this single-center retrospective study conducted between October 2019 and June 2023 and waived the requirement for informed consent (Approval ID:2023/13466) because of the retrospective evaluation of anonymized medical data. The following were the criteria for inclusion: (1) prostate mpMRI collected on a 3Tesla unit and (2) accessible serum prostate-specific antigen (PSA) levels at the time of prostate mpMRI. Patients with motion artifacts and inadequate imagesand a history of androgen deprivation therapy, radiation, or transurethral resection were also excluded. The cohort in our study was divided into two distinct groups based on the final whole prostate specimen obtained following radical prostatectomy. Group 1 was classified as the low-risk group, whereas Group 2 was categorized as the high-risk group. This classification was determined on the basis of theInternational Society of Urological Pathology) grading system related to the pathology findings of the excised prostate specimen.

•-grade Group 1: Very low-grade cancer with well-formed glands (corresponding to Gleason Score 6)

• Grade Group 2: Low-grade cancer with slightly irregular glands (corresponding to Gleason Score 3 + 4 = 7)

•-grade Group 3: Intermediate-grade cancer with irregular and fuzed glands (corresponding to Gleason Score 4 + 3 = 7)

• Grade Group 4: High-grade cancer with fused and poorly formed glands (corresponding to Gleason Score 8)

• Grade Group 5: Very high-grade cancer with no gland formation, characterized by sheets of tumor cells (corresponding to Gleason Score 9-10)

Specifically, Grade 1 and Grade 2 are considered low risk and assigned to Group 1, whereas Grade 3, Grade 4, and Grade 5 are categorized as high risk and assigned to Group 2. This classification allows for the differentiation of prostate cancer cases based on their perceived risk levels according to the ISUP grading system. Table 1 shows patient distribution according to the ISUP grade

MRI Protocol

All patients underwent prostate mpMRI using a Siemens Medical Systems Skyra 3.0 Tesla MRI scanner with an 18-channel phased-array coil (Skyra, Siemens Medical Systems, Erlangen, Germany). Butylscopolamine bromide (Buscopan, Boehringer Ingelheim) was administered before all exams to reduce bowel motions, which could cause motion artifacts. The index lesion was assessed using prostate mpMRI by an abdominal radiologist with 10 years of experience. Our institution's mpMRI protocol for prostate imaging included tri-planar T2-weighted imaging, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE) imaging. Echo-planar imaging in axial planes with b-values of 50, 500, 1.000, and 1.400 s/mm^2 was used for DWI. This was accomplished by merging data from all accessible b-values and fitting them using a least-squares monoexponential fitting technique. This approach represents the diffusion properties of prostate tissue.

Table 1. Patient distribution according to ISUP Grade Groups.

ISUP Grade Groups	Number Of Patients	Percentage (%)
1	16	28.1
2	24	42.1
3	10	17.5
4	2	3.5
5	5	8.8

Image Analysis

To accurately evaluate prostate cancer lesions with true-positive findings, a free-form region of interest (ROI) was constructed. The ADC maps were generated automatically using the software (Syngo Via, Siemens Medical Systems) used in our facility. The radiologist evaluated the ADC maps and manually delineated an ROI on the tumour visible on the ADC map. Where ROI was entered, the software automatically calculated ADC_{mean} and standard deviation.This ROI, known as $ADC_{mean,}$ corresponded to the interior margin of the entire tumour outline. On the tumour segment with the greatest cross-sectional area, ROIs were carefully established. ADC_{cv} was computed using the formula Standard Deviation/ADC_{mean} on the ADC map, according to a previous study (11). The measurements of ADC_{mean} and ADC_{cv} are depicted in Figure 1. To ensure that only the tumor region was examined, normal tissue outside the borders of the lesion was excluded.

Statistical Analysis

To determine the normality of variable distribution, the Kolmogorov– Smirnov test was used. The chi-square test for categorical data was used to evaluate patient characteristics and postoperative pathological outcomes. For regularly distributed data, the Student 's t-test was employed, whereas for non-normally distributed data, the Mann– Whitney U test was used. Variables less than 0.05 in the univariate analysis were investigated further in a multivariate logistic regression analysis to identify high-grade prostate cancer. In addition, receiver operating characteristic curve (ROC) analysis was performed on ADC_{cv} to determine its sensitivity, specificity, area under the curve (AUC), and cutoff value (Figure 2).

The data were analyzed using SPSS 22.0 (IBM SPSS Corp., USA). Variables less than 0.05 were accepted as statistically significant.

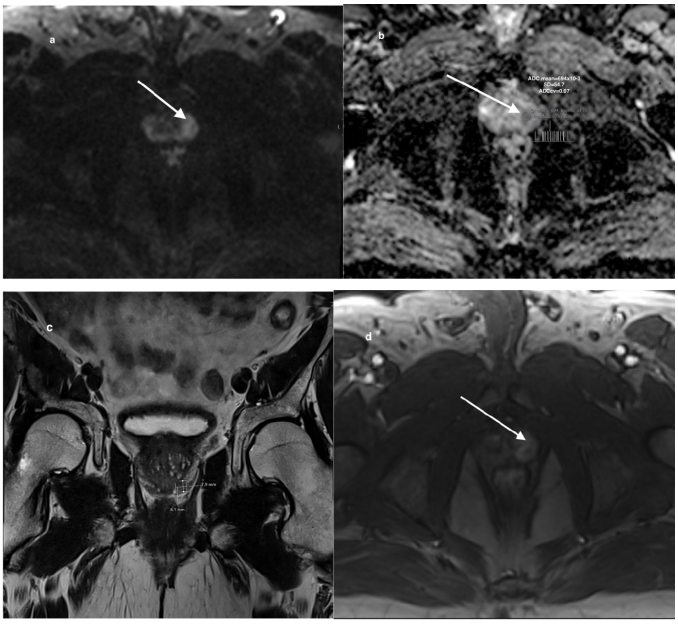

Figure 1. A 65-year-old patient with ISUP Grade Group 2 (Gleason Score 3+4) prostate cancer. On diffusion-weighted image (a) the tumour has hyperintensity signal. The apparent diffusion coefficient (ADC) map (b) demonstrates ADC_{mean} ($694x10^{-6}$) ADC_{cv} (54,7/694= 0.07) (white arrows). T2-weighted coronal (c) and post-contrast T1-weighted axial (d) images (white arrow) depict 8 mm diameter tumour.

Results

Overall, 57 men with prostate cancer were enrolled in our dataset (age, 62,2 ± 6,5; range, 51–76 years). The detailed patient distribution according to ISUP Grade Groups is shown in Table 1.

ADC_{mean} inverse correlation with ISUP (p=0.218) while ADC_{cv} showed a strong positive correlation with ISUP grade groups (p=0.041). Detailed information regarding the ADC metrics of the study sample is shown in Table 3. When ROC analysis was performed by evaluating ADC_{cv}, the threshold value was defined as 0.081 with 55% sensitivity and 82% specificity (p=0.010, AUC: 0.716).

However, bladder invasion, extracapsular extension (ECE), and positive surgical margin were correlated with ISUP grade groups, whereas seminal vesicle invasion, prostate-specific antigen (PSA) levels, and body mass index (BMI) were not correlated with ISUP grade groups. Table 2 demonstrates the laboratory and pathological findings of patients.

ADC_{cv} value of low grade group and high-grade groups were 0.099 0.099±0.06 and 0.174±0.12 respectively (p=0.041***). Figure 3 depicts the ADC metrics of a patient categorized as ISUP Grade Group 3. ADC_{mean} value of low grade group and high grade group was $760.6±201.8×10^{-6}$ mm^2/s and

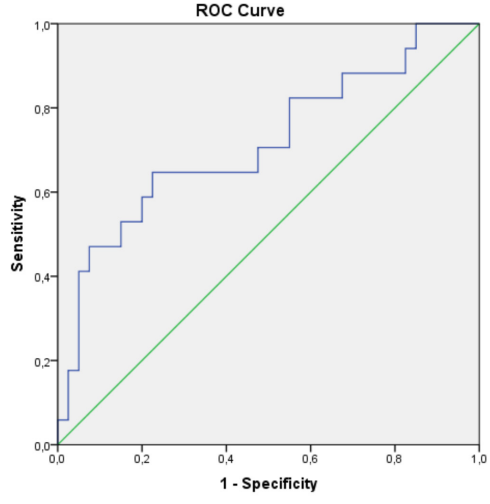

Figure 2: Receiver operating characteristic (ROC) analysis curve of high risk prostate cancer detection with ADC_{cv}, AUC: 0.716 (p<0.010).

633.4±182.3×10^{-6} mm^2/s, respectively (p=0.218). In 13 patients (22.8%), surgical margins were positive. Seminal vesicle invasion was detected in 16 patients (28.1%), whereas bladder neck invasion was observed in 8 patients (14%). Extraprostatic extension was in 22 patients (38.6%). The ADC results for the two groups are shown in Table 3.

Discussion

In the present study, we validated the utility of two ADC parameters (ADC_{mean} and ADC_{cv}) as imaging biomarkers in patients who underwent 3-T mpMRI and radical prostatectomy with WM histopathologic analysis correlation.

Indeed, multiple previous studies with different cohorts have compared ADC_{min}, ADC_{mean}, and ADC_{ratios} in prostate imaging and reported conflicting results with varying endpoints. These studies have evaluated different clinical outcomes or endpoints, such as tumor detection, differentiation of malignant and benign lesions, and prediction of tumor aggressiveness or treatment response (10,11-13). The inconsistency of these studies' conclusions highlights the intricacy and diverse nature of prostate imaging, as well as the difficulties in establishing a clear superiority of one ADC parameter over another.

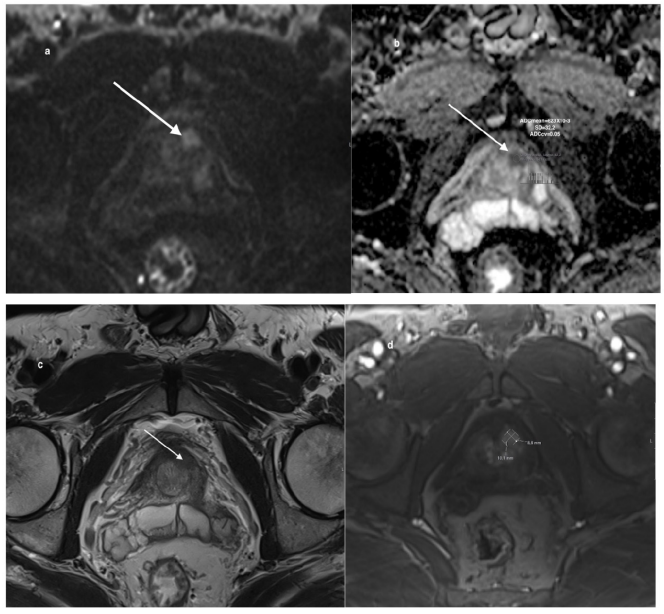

Figure 3. Prostate cancer ISUP Grade Group (Gleason Score 4+3). The diffusion-weighted image (a) and ADC map (b) reveal an ADC_{mean} of 623 X 10^{-6} and an ADC_{cv} of 32/623 = 0.05 (white arrow). T2-weighted axial (c) and post-contrast T1-weighted axial (d) images depict a tumour with a 10 mm diameter.

Table 2. Laboratory and pathological findings of patients according to ISUP Grade groups.

Parameters	ISUP 1-2	ISUP 3-4-5	P*	P**
	N=40	N=17		
Age (years)	61.47±6.18	63.94±7.2	0.202	
PSA (ng/ml)	8.31±5.83	13.72±15.84	0.120	
BMI (kg/m^2)	28.2±3.9	29.55±5.3	0.543	
Blood loss (cc)	318.7±178.1	288.2±182.4	0.539	
Seminal vesicle invasion	9 (22.5%)	7(41.2%)	0.201	
Bladder neck invasion	1(2.5%)	7(41.2%)	**<0.001**	0.237
Extraprostatic extension	8(20%)	14(82.4%)	**<0.001**	**0.004**
Positive surgical margin	3(7.5%)	10(58.8%)	**<0.001**	**0.019**

*Univariate analyses
** Multivariate analyses
PSA: Prostate-specific antigen
BMI: Body mass index
ISUP: International Society of Urological Pathology

Table 3. ADC parameters according to ISUP Grade groups

ADC Parameters	ISUP 1-2 N=40	ISUP 3-4-5 N=17	P*	P**
ADC_{cv}	0.099±0.06	0.174±0.12	**0.010**	**0.041**
ADC_{mean}	760.6±201.8	633.4±182.3	**0.009**	0.218
SD	72.02±43.44	101.56±56.48	0.052	

ADC_{cv}: apparent diffusion coefficient $_{coefficient\ of\ variation,}$ SD: standart deviation

Recent publications have compared conventional ADC parameters with ADC $_{ratios}$. Many new studies have shown that ADC $_{ratios}$, particularly the ADC_{mean} ratio concerning the conventional parameter, exhibit the strongest negative correlation with prostate cancer aggressiveness (14).

Variability in study designs, patient populations, imaging protocols, and analysis methodologies may have contributed to the disparate findings. The inherent heterogeneity of prostate cancer, with its diverse histological subtypes and varying degrees of aggressiveness, further complicates the interpretation of ADC measurements.

Given the contradictory findings in the literature, additional research involving larger and more diverse cohorts is required to determine the clinical significance and optimal use of $ADC_{minimum}$ ($ADC_{min)}$ and ADC_{mean} in prostate imaging applications.

These studies should aim to address the limitations of prior research and establish robust correlations between these ADC parameters and clinically relevant endpoints, with the goal of improving diagnostic accuracy and patient management in prostate cancer. ADC_{min} and ADC_{ratio} (reported as the ratio of tumour and nontumour ADC values) are two of the metrics that have been investigated. According to studies, all of these variations have a substantial connection with the Gleason score; however, there are gaps in clinical relevance and aggressiveness. In the current study, we used 3-T mpMRI metrics and histopathological results acquired after radical prostatectomy to validate the usefulness of ADC_{cv} as an imaging biomarker.

The ADC_{cv} value represents a novel texture parameter that is utilized in cancer. Tissue heterogeneity has been proposed as a basis for a tumour biomarker in cancer investigations. Tissue heterogeneity is an emerging hallmark of tumour. Although numerous methods for measuring tissue heterogeneity using textural analysis tools have been described, they are frequently complicated and require sophisticated software (15). Stein et al. (11) reported that ADC_{cv} is a simple-to-calculate statistical parameter that indicates related variation. They evaluated the ADC_{cv} and SUV_{max} values using positron emission tomography MRI of liver metastases. As the outcome of this investigation, it was discovered that the SUV_{max} value and the ADC_{cv} value have a positive link. Overall, the study findings suggest that the ADC_{cv} value obtained from diffusion-weighted MRI can serve as a usef biomarker for predicting tumor aggressiveness in liver metastases. This information could aid in cancer investigations and treatment planning for patients with liver metastases. Sokmen et al. confirmed with MRI fusion prostatic biopsy that ADC_{cv} is a tissue texture parameter in prostate cancer (16). However, our difference from their study is that our study was conducted after radical prostatectomy.

The multivariate analysis conducted in our study revealed that the ADC_{cv} parameter effectively predicts tumor aggressiveness. According to our findings, the ADC_{cv} parameter was suitable for regular inclusion in mpMRI reports. This parameter was considered easy to measure, facilitating its integration into radiology reports. Furthermore, integrating ADC_{cv} measurements into routine practice did not significantly increase the workload of radiologists. Throughout our investigation, ADC_{cv} demonstrated the highest efficacy in predicting tumor aggressiveness. Considering the ADC $_{cv}$ cutoff value, it should be noted that prostate cancer may be highly aggressive with ADC $_{cv}$ values higher than 0.081. Resection and lymph node dissection should be performed more carefully in these patients.

Nevertheless, it is important to note that other factors such as bladder invasion, extracapsular extension (ECE), and positive surgical margins were also correlated with ISUP grade groups. Formun ÜstüFormun Alt

Study Limitations

Our research has a few limitations. First, this is a retrospective study, and the data were collected from past medical records and imaging reports. This design has inherent limitations compared with prospective studies, where data are collected in real time. The study was conducted with a limited number of participants, which can impact the generalizability and statistical power of the findings. Due to the small sample size and retrospective nature of the study, there might be biases in the selection of participants, leading to a non-representative sample.

Overall, this study emphasizes the need for further research to enhance the understanding of ADC measurements in prostate cancer and their potential clinical applications. By addressing the study limitations and establishing stronger correlations, ADC values could be used more effectively for diagnostic accuracy and patient management in prostate cancer.

Conclusion

The statement suggests that the speed and accuracy of ADC_{cv} could be advantageous in enhancing future prostate cancer screening methods. The validation of ADC_{cv} as an imaging biomarker may have significant implications for the detection and assessment of prostate cancer aggressiveness, potentially aiding in more accurate diagnosis and treatment planning for patients. Our findings suggest that the ADC_{cv} parameter holds promise as a valuable tool for characterizing prostate cancer aggressiveness. Its simplicity of use and potential to provide clinically meaningful information make it a compelling candidate for integration into routine clinical practice.

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Long-Term Outcomes of Pyeloplasty in Children with Poorly Functioning Kidneys

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What's known on the subject? and What does the study add?

The studies of poorly functioning kidneys in children are limited. This article adds to the literature, long-term results on the renal function and parenchymal thickness of patients with poorly functioning kidneys in children, and details on those patients according to age.

Abstract

Objective: This study aimed to determine the efficacy and long-term outcomes of pyeloplasty in children with poorly functioning kidneys.

Materials and Methods: Twenty-six patient charts were reviewed who underwent pyeloplasty with poorly functioning kidneys from 2008 to 2020. Patients were divided into two groups based on DRF; Group 1: 0-10%, and Group 2: between 10-30%. Patient demographics, preoperative and postoperative anteroposterior diameter (APD), parenchymal renal thickness (PT) ratio, and differential renal function (DF) were analyzed to confirm the postoperative benefits and potential predictors of renal functional recoverability. The parameters of patients younger than one year of age were also compared to those of older patients.

Results: The renal function of 12 of 26 patients' was <10% (mean DF 4.9±3,8%)(Group I). The DF of the other 14 patients was between 10-30% (mean DF 22,6%) (Group II). Sex, age at operation, antenatal diagnosis, preoperative APD, DF, PT ratio, and UTI were also evaluated using multivariate analysis, but none of the parameters were found to be predictable for renal function improvement (p>0.0001). The postoperative PT ratio and postoperative DF were increased in Group II, but not in Group I. DF and PT ratios also improved in Group II in patients younger than 1 year of age (p:0,014, p:0,032 respectively). Hypertension was detected in 5 patients (41.6%) during follow-up in Group I.

Conclusion: Pyeloplasty is recommended considering parenchymal and DF recovery in patients younger than 1 year of age with a DF of 10–30%. However, in patients with <10%, parenchymal or DF improvement was unsatisfactory, even in the late renogram.

Keywords: Differential renal function, poorly functioning kidney, parenchymal renal thickness, pyeloplasty, ureteropelvic junction obstruction

Introduction

Management of children with ureteropelvic junction obstruction (UPJO) and poorly functioning kidneys remains controversial. However, the definition of poorly functioning kidneys remains unclear. Some investigators consider a DF below 30% as poorly functioning (1), while others believe a DF of 20% (2,3). Stock et al. concluded that patients with UPJO with a differential function of less than 35% have significant histological changes on biopsy and a low probability of postoperative improvement in DF (4). Ortapamuk et al. reported no improvement in adult patients with DF <30% (5). Thus, we included patients with a kidney function of less than 30% in our study.

Poorly functioning renal units directly underwent pyeloplasty without prior placement of a PCN in our center for nearly

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15 years. In the present study, we reviewed this decision and determined the long-term efficacy of pyeloplasty in patients with poorly functioning kidneys as well as the factors that could predict improvement in DF after pyeloplasty.

Materials and Methods

We retrospectively reviewed the medical records of patients with UPJO and poorly functioning kidneys between 2008 and 2020. Patients with DF >30%, bilateral UPJO, solitary kidney, vesicoureteral reflux, ureterocele, megaureter, distal ureteral obstruction, bladder outlet obstruction, multicystic dysplastic kidney, or patients with less than 1 year follow-up period and incomplete investigations were excluded from the study. A diagnosis of UPJO was made with increased APD and thinning in parenchymal thickness on ultrasonography (USG) and the presence of an obstructive pattern (poor response to frusemide with a plateau and an up-raising curve with no response) on 99mTc-MAG3 scintigraphy. AP diameters were measured by a pediatric radiologist at the parenchymal edge in the transverse plane. The last imaging before surgery was included in the study.

Patients were divided into two groups: split renal function <10% (Group I) and 10-30%(Group II). Patient demographics, anteroposterior diameter, PT ratio (the ratio of the PT of the involved side to that of the contralateral side was measured as follows: involved side PT/contralateral side PT) on USG and postoperative drainage pattern on the 99mTc-MAG3 renogram were analyzed retrospectively and compared among the groups. The parameters that may affect recovery (sex, age at operation, antenatal diagnosis, preoperative APD, DF, PT ratio, and UTI) were also evaluated using multivariate analysis. Preoperative and postoperative parameters were compared between the groups to clarify operative benefits. Patients were grouped by age (younger than one year of age and older than one year of age) to reveal the role of age in DF and PT recovery.

Percutaneous nephrostomy (PCN) was performed only to treat pyonephrosis or a huge renal pelvis before the operation. Open Anderson Hynes' pyeloplasty with a mini-incision was performed in all patients. Postoperative renal ultrasonography and clinical visits were performed at 1, 3, 6, and 12 months. A Tc-99m MAG3 renogram was routinely performed in all patients one year after surgery. The results of the cases in which scintigraphy was repeated for various reasons in the late follow-up period (2-8 years) were evaluated and compared with the postoperative results to determine whether there was any long-term improvement in DF. Since this was a retrospective study, the reasons for requesting late Mag III scintigraphy could not be determined.

Statistical Analysis

Data are presented as frequencies and percentages for categorical variables and medians for continuous variables. Comparisons between groups were performed using the chi-square test for qualitative variables and the Mann-Whitney U test for quantitative variables. Spearman's correlation analysis used coefficients for those with a skewed distribution. Binary logistic regression analysis was used for multivariate analysis. All reported P-values were 2-sided, and $p<0.05$ was considered to be statistically significant. Statistical analyses were performed using SPSS Statistics 20.0

Results

The case records of the 26 patients were analyzed (Table 1). 12 of the 26 patients' DF was <10% (Group I). The median age of the operation was 72.5 (4 -156 months) months, the

Table 1. Comparison of the group's demographics, preoperative parameters and complications

	Group I	Group II	P value
Number of the patients	12	14	
Age (month)	72,5	16	**0,009**
<1 year of age	4	10	
Laterality (L/R)	9/3	8/6	0,340
Antenatal diagnosis	3	9	**0,045***
PCN	2	1	
Preop DF(%)	4,9±3,8%	22,6±5,6	**<0,001**
Preoperative APD	30,7±16	43,7±17,2	0,076
Preoperative PT ratio	0,31±0,16	0,36±0,18	0,487
Complication(reop)	-	1	
Hypertension	5	0	**0,007***
UTI	8	4	0,052*
Follow up (year)	9,8±2,8	6,5±3,8	

Mann-Whitney U test was used.* A chi-square test was used (a significance level of p<0.05)

mean DF was 4.96±3.8%, and the mean follow-up was 9.8±2.8 years (6-13 years). In the other 14 patients (Group II), DF was-10-30% (median age 16 months, mean DF 22.6±5.6%), and mean follow-up was 5.2±2.11 years (2-10 years). In Group I, the presenting symptoms were ANHN in 3 patients, abdominal pain in 4, palpable mass in 1, and UTI in 2. In Group II, the presenting symptoms were ANHN in 9, minor abdominal pain in 3, abdominal trauma in 1, and UTI in 2 cases.

99mTc-MAG3 scintigraphies of all patients before the operation showed a poor response to frusemide with a plateau and an up-raising curve with no response. After the operation, good drainage or moderately delayed drainage after frusemide was observed in all patients, except one who underwent redo pyeloplasty.

Three patients underwent percutaneous nephrostomy before the operation (pyonephrosis in 2, giant hydronephrosis in one). One patient was admitted to the hospital with a grade 4 renal injury due to minor trauma. A double-J stent was first inserted in this patient, and he underwent pyeloplasty three months later.

Preoperative APD and preoperative PT ratios were not statistically significant among the groups (Table 1), and parameters that may affect recovery (sex, age at operation, antenatal diagnosis, preoperative APD, DF, PT, PT ratio, and UTI) were also evaluated, but none of the parameters were found to be significant (p>0.0001). However, a negative correlation was found between operative age and postoperative DF (Figure).

In Group I, the postoperative drainage pattern and APD of the patients improved, but DF and PT did not (Table 2). In Group II, PT ratios, APD, and DF were significantly improved during follow-up, in addition to the drainage patterns on 99mTc-MAG3 scintigraphy (Table 2).

Late 99mTc-MAG3 scintigraphy (2-8 years) was present in six patients in Group I and 11 patients in Group II. In Group II, DF remained the same in three of the cases with late 99mTc-MAG3 scintigraphy, while a slight decrease was found in eight of them compared to those performed in the postoperative 1st year. There was no long-term improvement in the DF (mean 6.7±4.7%) of the patients in Group I, as in the postoperative scans.

The patients in Group I were older (p=0.009). 75% of the patients in Group II were diagnosed antenatally (p=0.045) (Table 1). When the cases in Group II were classified according to age, the DF and PT ratios improved significantly in patients younger than 1 year of age (p=0.014, p=0.032 respectively) (Table 3). This improvement was not observed in older cases. On the contrary, although there was no significant increase in parenchymal thickness in patients older than 1 year of age in Group I (p=0.932), an improvement in DF was detected (p=0.012) (Table 3).

The perioperative and early postoperative course was uneventful. Anesthesia-related complications, including infantile age, were not observed. None of the patients had acute obstruction, urinary leakage, or unexpected readmissions. The success rate

Table 2: Comparison of preoperative and postoperative DF, APD, and PT ratios in Group I and Group II.

		Preoperative mean ± sd	Postopertavite mean ± sd	P value
Group I	DF(%)	4,96±3,8	6,9±4,7	0,247
	PT ratio	0,31±0,16	0,27±0,20	0,875
	APD	30,7±16,0	12,2±11,4	**0,019**
Group II	DF(%)	22,6±5,6	27,5±10,9	**0,022**
	PT ratio	0,36±0,18	0,62±0,23	**0,007**
	APD	43,7±17,2	9,7±4,3	**0,001**

Table 3: Distribution of preoperative, postoperative DF and PT ratios by age among groups

	Age (year)		Preoperative mean±sd	Postoperative mean±sd	P value
Group I	< 1	DF(%)	6,0±4,8	3,25±2,7	0,109
		PT ratio	0,25±0,05	0,21±0,15	0,715
	>1	DF(%)	4,4± 3,5	8,75±4,5	**0,012**
		PT ratio	0,34±0,18	0,31±0,22	1,000
Group II	< 1	DF(%)	24,3±4,7	31,0±10,3	**0,014**
		PT ratio	0,39±0,17	0,66±0,24	**0,032**
	>1	DF(%)	18,3 ±5,9	19,0±7,8	0,715
		PT ratio	0,29±0,21	0,51±0,18	0,144

of the pyeloplasty was 96.1%. Except for one patient in Group II who underwent redo pyeloplasty, the obstruction resolved postoperatively in all patients, as evidenced by a better drainage pattern on 99mTc- MAG3 renogram and a reduction in APD. The obstruction was relieved after the second operation in this patient, and DF improved during follow-up. Five patients in Group I developed hypertension that required medication after the operation; in Group II, no patient developed hypertension (p=0.007) (Table 1). Recurrent postoperative urinary tract infections (more than two) were less common in Group II but were not statistically significant.

Renal function improvement >5% was detected in two patients in Group I (16.6%) and in six patients (42.8%) in Group II postoperatively. DF improved by >5% in only 30.7% of the patients. The mean improvement in DF in Group I and Group II was 4.18% (0.5-13%), and 8.05% (2-20%), respectively.

Discussion

Several studies have been conducted both in favor of and against the preservation of poorly functioning kidneys. Early reports favored nephrectomy, especially if DF was <10%. Gupta recommended most of the poorly functioning UPJO kidneys show improvement in function and that not all such kidneys should be removed without a trial of PCN (6). Singh reported renal function improvement in only 24.1%, no improvement in 44.8%, and deterioration in 31.0% of older children after PCN replacement (7). However, PCN can cause infection, risk dislodgement, and require secondary scintigraphy.

In recent years, many authors have recommended renal salvage over nephrectomy even if DF <10% (1,2,8). Therefore, in the last decade, especially in infants, most pediatric urologists have preferred to perform pyeloplasty (1). Lone recommended performing a pyeloplasty straightaway to preserve the kidney, which is much easier and feasible without prior PCN (9). In this study, renal units with <30% split function directly underwent pyeloplasty without prior placement of a PCN, except in three patients because of pyonephrosis in two patients and giant hydronephrosis in one patient.

Grimsby et al. claimed that the pyeloplasty success rate is low in patients with poorly functioning kidneys(10). However, impaired DF was not associated with a high incidence of complications or failure rates in this study, similar to those in the literatüre (9). Anesthesia-related complications were not observed, including infantile age in our series. There were no patients with acute obstruction, urinary leakage, or unexpected readmissions. The absence of these complications in the early postoperative period may be related to the routine use of intraureteral stents. However, urinary infections after pyeloplasty were not uncommon, and five patients in Group I experienced hypertension, although they could be controlled with medication (Table 1).

Recent reports seem to agree that DF can markedly improve in patients with poorly functioning kidneys (2,11-14) after pyeloplasty. Bansal et al. reported a 14% mean increase in DF in patients with DF <30%, and a 13,9% mean increase in DF in patients with DF <10% after pyeloplasty (1). Wagner et al. reported that a DF of less than 10% was associated with the greatest degree of improvement, but their series included only four patients with less than 10% DF (8). The DF and PT ratios improved significantly in patients with DF between 10 and 30% in our study. However, our results are not as optimistic as those of previous reports in patients with DF <10%. Similarly, Nayyar et al. reported that pyeloplasty was followed by an improvement in DF in only one-third of the cases(15). The overall improvement of poorly functioning kidneys' function >5% was found in 30,7% of the patients in our series too, only two patients in Group I (16.6%), and six patients in Group II (42.8 %). The mean improvements in Group I and Group II were found 4.18% (0.5-13%), and 8.05% (2-20%), respectively.

Many factors have been studied regarding the degree of improvement after pyeloplasty, such as age, sex, antenatal diagnosis, APD, and PT on USG and preoperative DF (16). In our study, sex, age at operation, antenatal diagnosis, preoperative APD, DF, PT, PT ratio, and UTI were not predictive of DF improvement. Thus, based on our study and published data, it is not possible to predict which patients' PT or DF will improve after pyeloplasty. On the other hand, five of six patients in whom DF improved by >5% were under one year of age in Group II. The patients in Group II were younger than those in Group I and were mostly diagnosed antenatally (Table 1); a negative correlation was found between operative age and postoperative DF (Figure 1).

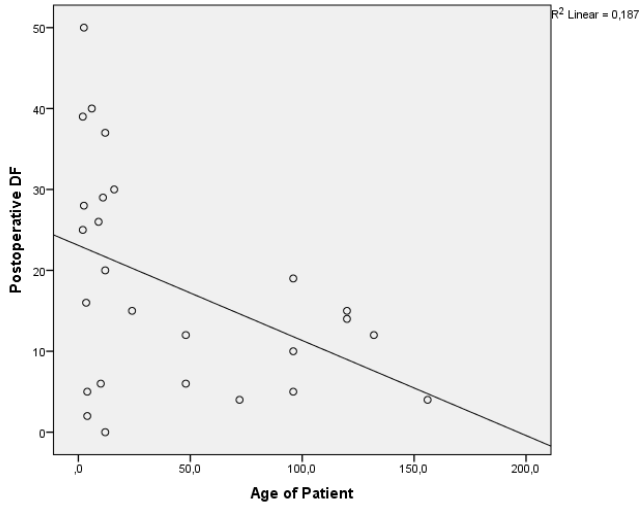

Figure 1. Postoperative DF and the age of the patients (months) have a negative correlation

Gench reported better improvement in DF of the patients with poorly functioning kidneys who were postnatally diagnosed (3). Chandrasekharam et al. reported that infants aged <1 year showed a significant improvement in renal function after pyeloplasty compared with older children (17). They suggested that the potential recovery of renal function is dependent on the timing of the surgery. When patients were grouped according to their age in our study, it was found that older patients in Group I had significant DF improvement after the operation (Table 3). However, parenchymal improvement was not observed in these patients. In older patients with a DF improvement >5%, infection at the time of diagnosis may have caused false DF impairment. Perhaps after infection treatment and surgery, the actual DF of the patients was measured. DF or PT improvement was not detected in four patients younger than one year of age in Group I (Table 3). Mennon's series, comparing different age groups consistent with our results, showed a significant increase in mean DF in infants with preoperative 10-20%, in older patients with 0-9% DF, but not in infants (2). This finding, evident in both series, suggests that some infants with DF below 10% may have congenital dysplastic kidneys. In contrast, in patients with DF 10-30% and younger than one year of age, DF and PT improvements were found to be significant. In patients with 10-30% DF and older than one year of age, DF improvement was not observed, and PT improvement was not significant (Table 3). Therefore, considering that there is a negative relationship between age and postoperative DF according to our study, early diagnosis is important in patients with 10-30% DF.

Late scintigraphy was not routinely performed in UPJO patients at our institution and was available in only 61% of cases in this series. In most cases, DF decreased slightly in the late scintigraphies compared to the postoperative values. Mennon et al reported a minor fall in DF with time in their series too and attributed this result to better growth of the opposite kidney and a reduction in the size of the baggy kidney (2).

Song et al. showed that PT might be useful for distinguishing between the true and false estimation of differential renal function in a study that investigated the changes in DF before and after pyeloplasty in renal units with unilateral UPJO and supranormal function (18). Kim et al. reported that pyeloplasty performed at <1 year of age was a significant factor for recovery of PT (17). However, PT was not mostly reported in studies on low-functioning kidneys (1,2,8,14). PT varied significantly with the age of the children at the time of surgical repair. For this reason, we also evaluated the PT ratios in our study which were defined by Kim et al. (19). Our study showed parenchymal improvement in patients with DF 10-30% and younger than one year of age, and parenchymal thickness may be a better parameter for demonstrating kidney recovery (20,21).

A third treatment option for patients with very poorly functioning kidneys (DF <10%) is to leave the kidney in situ if the patient does not suffer from infection or pain. However, no series or comparative studies support this option. In the pediatric age group, the risk of trauma or developing hypertension must be considered. Minor trauma may threaten the life of the patient and complicate surgery in these patients, as in one patient in our series.

Study Limitations

The limitations of the present study are its retrospective design and the small number of cases. However, considering that patients with low-functioning kidneys comprise a small group of UPJO patients, we believe that our series of patients treated in a single center with long-term follow-up is valuable.

Conclusion

The surgical outcomes of pyeloplasty in poorly functioning kidneys have been satisfactory. In our study, a significant improvement was found in PT and DF in patients with 10-30% DF and younger than 1 year of age after pyeloplasty, and a negative correlation was found between postoperative DF and age at surgery. Antenatal and postnatal USG needs to become widespread for the early diagnosis of these patients. Based on our results and recent literature, we recommend pyeloplasty in infants with 10-30% DF. However, in infants with 0-10% DF, our results and the literature are more confusing. Unfortunately, PT and DF did not improve significantly in the early and late terms in kidneys functioning below 10%, especially in infants, even though the obstruction was resolved. It should be kept in mind that have a risk of hypertension in these patients and postoperative renal recovery may not always be as good as desired, and parents should be informed accordingly.

Ethics

Ethics Committee Approval: The study was approved by the ethics committee of the hospital with the decision number 746, 2022/15-05 (University of Health Sciences Turkiye, Dr. Behçet Uz Training and Research Hospital Clinical Research Ethics Committee, date: 15.09.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.B.U., G.Y., M.Ş., Ö.O., A.Ş., Concept: A.B.U., A.Ş., Design: A.B.U., G.Y., Data Collection or Processing: A.B.U., M.Ş., Ö.O., Analysis or Interpretation: A.B.U., G.Y., Literature Search: A.B.U., Ö.O., Writing: A.B.U., A.Ş.,

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