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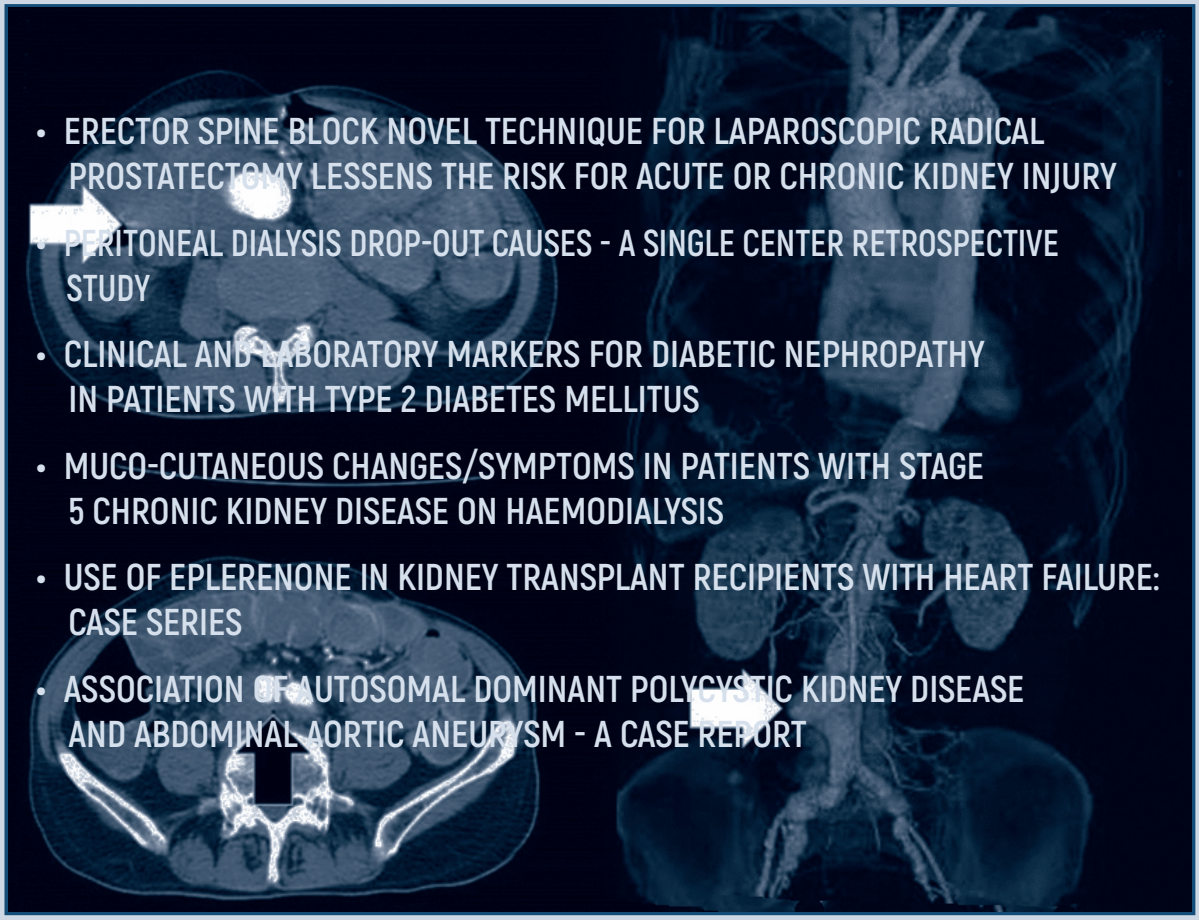

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Original article

Erector Spine Block Novel Technique for Laparoscopic Radical Prostatectomy Lessens the Risk for Acute or Chronic Kidney Injury

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Abstract

Introduction. Prostate cancer, the second most common cancer in males globally, frequently requires radical prostatectomy. Laparoscopic radical prostatectomy, a common approach, has uncertainties regarding pain reduction. This study investigates ultrasonography-guided erector spinae plane block for pain management in laparoscopic radical prostatectomy.

Methods. This one-year prospective study involved 50 American Society of Anesthesiology classification I-III male patients (age 40-78) undergoing laparoscopic radical prostatectomy. An ultrasonography-guided erector spinae plane block was performed before surgery after induction of anesthesia. Postoperatively, pain was assessed using a numerical rating scale. Postoperative nausea and vomiting were evaluated using a verbal descriptive scale. Total time for block performance, anesthesia and surgery time, and any complications was noted as well.

Results. The study demonstrated that erector spine block improved pain management in laparoscopic radical prostatectomy patients. At different times after surgery, numerical rating scale scores, rescue analgesia needs, postoperative nausea and vomiting scores were reduced with no adverse effects on the kidney function.

Conclusion. This evaluation supports the beneficial role of ultrasonography-guided erector spine block in enhancing pain control during laparoscopic radical prostatectomy preventing any acute or chronic kidney injury.

Keywords: erector spinae plane block, laparoscopy, radical prostatectomy, pain management, acute kidney injury

Introduction

Globally, prostate cancer ranks as the second most frequent cancer in men [1]. Since it has been demonstrated that radical prostatectomy (RP) improves overall survival, RP is the usual course of action for the majority of patients who have chosen to have surgery as part of their treatment. There are three possible ways to carry out this surgery: open, laparoscopic, or robotic [2]. Laparoscopic radical prostatectomy has higher costs, a longer recovery period, a steeper learning curve, and a larger operating room staffing requirement, and there is no evidence that laparoscopic radical prostatectomy reduces pain [3,4].

The ultrasonography-guided erector spinae plane (ESP) block is a relatively recent trunk block, first described by Forero *et al.* [5]. Areas between the bones are the spots where the local anesthetic (LA) is injected. These are the erector spinae muscles and the thoracic transverse processes. One idea for how the LA works is that it blocks the dorsal-ventral rami of spinal nerves and the sympathetic ganglia by spreading in a straight line from the skull to the tailbone and to the paravertebral area. Consequently, it is possible to induce visceral and somatic sensory blockages [5-9]. When ESP block is applied at the lower thoracic vertebral levels (T7-T9), it has been demonstrated in the literature it produces abdominal analgesia [8]. To our knowledge, ESP is not described in the literature for LRP pain management [10]. Thus, this evaluation sought to determine how ESP block affected perioperative pain management in RP patients, who experience both physical and visceral pain.

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Material and methods

This prospective study was conducted at the University Clinic for Anesthesiology, Reanimation, and Intensive Care and the University Clinic for Urology at the Clinical Center, Mother Theresa, after obtaining the internal Ethical Committee's permission and signed informed consent from all patients. It has been finished for a period of nine months with 50 patients, American Association of Anesthesiology physical status (ASA) I-III patients, ranging in age from 40 to 78, who had laparoscopic radical prostatectomy. The study did not include patients with coagulopathy, allergies to local anesthetic drugs, advanced organ failure, vertebral abnormalities, or mental retardation.

Prior to surgery, all patients underwent standard protocol procedures, which included a complete medical and surgical history, laboratory assessments, a cardiac examination (echocardiography, EKG), and a chest X-ray. All patients underwent standard anesthesia procedures, which included non-invasive blood pressure monitoring, pulse oximetry, and regular non-invasive EKG monitoring with five leads prior to anesthesia induction.

For inducing anesthesia, each patient got the following: 0.01 mg/kg of midazolam, 1 mcg/kg of fentanyl, and 2 mg/kg of propofol. Rocuronium bromide 0.6 mg/kg IV was used to induce muscle relaxation and facilitate endotracheal intubation with a proper endotracheal tube size. EtCO2 was maintained between 35 and 45 mmHg using pressure-controlled volume-guaranteed mechanical ventilation (Datex-Ohmeda S/5 Advance GE Healthcare, Madison, USA) with a tidal volume of 6-8 mL/kg, a frequency of 10-12/min, and 50% FiO2 oxygen in the air. Maintenance of anesthesia was achieved by administering a 0.01-0.03 mcg/kg/min infusion of remifentanil and adjusting the MAC to 0.8-1. For fluid replacement therapy, crystalloid fluids were administered in accordance with urine output, blood loss, and fluid deficits.

After induction of anesthesia before the initiation of surgery, all patients were placed in the lateral decubitus position, and an ESP block was administered. Following the placement of the patient in the lateral position, the transverse processes of the T11 vertebra were seen using a linear probe and an ultrasound machine (Samsung Ultrasound H60; Hampshire, Korea) (Figure 1). A Stimuplex B, 21-gauge 100 mm, Braun R, Melsungen, AG, Germany needle was used to inject bupivacaine 0.5% 20 ml bilaterally above the erector spinae muscles. Afterward, patients were placed back in the supine position, and dexamethasone 4 to 8 mg was administered with gastric protective therapy, and surgery was started. During the procedure, the total amount of remifentanil used was noted. Time for block

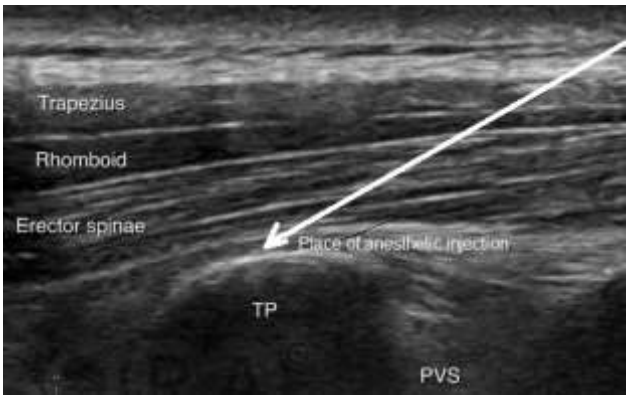

Fig. 1. Ultrasound visualization of the place of hneedle positioning and local anesthetic injection

performance was noted as well. The patients' postoperative pain was assessed using the numerical rating scale (NRS), where 0 represents no pain and 10 represents the most severe pain. Patients who had an NRS of ≤4 in the recovery room were moved to the ward. As a rescue analgesic, patients with an NRS score of 4 or above were scheduled to receive 1 g IV of paracetamol. The verbal descriptive scale (0=none, 1=mild nausea, 2=moderate nausea, 3=vomiting once, 4=multiple vomiting) and metoclopramide were used to assess postoperative nausea and vomiting (PONV). Receiving 10 mg IV was scheduled for when the PONV score was greater than 2.

NRS scores, the requirement for rescue analgesia, and nausea-vomiting scores were noted at the time of the postoperative transfer to the recovery room, as well as at the 1st, 6th, 12th, 18th, and 24th hours. Every patient's postoperative 24-hour tramadol use was noted. Time of anesthesia, surgery and block performance were noted as well.

IBM SPSS 22 (Statistical Package for Social Sciences 22) was used to statistically evaluate the study's data. Numbers and percentages for descriptive statistical categorical variables and mean ± standard deviation (SD) for normally distributed continuous variables were provided throughout the evaluation of the study data.

Results

Fifty male patients who had laparoscopic radical prostatectomy procedures performed at our university clinical center between January and September 2023 were included in our analysis. Table 1 shows the demographic data of the patients, clinical characteristics, analgesia scores and requirements, and PONV scores.

The patient's HR, MAP, and SpO_2 % readings are shown in Table 2. Baseline laboratory findings preoperative and postoperative are shown in Table 3.

Table 1. Patient demographic and clinical characteristics, analgesia scores and requirements, and PONV scores

Parameter		Value
Age (years)		**67±8.7 mean±SD**
BMI	underweight	3(6%)
	normal	37(74%)
	overweight	7(14%)
	obesity	3(6%)
ASA	I	10(20%)
	II	20(40%)
	III	20(40%)
Anesthesia time (min)		320±45.6
Block performance time (min)		7±5
Surgery time (min)		280±40.8
NRS scores	≤4	47(94%)
	>4	3(6%)
Remifentanyl consumption rate (mcg/kg/min)		0.01±0.005
Tramadol consumption (mg)		200±50
PONV scores	≤2	40(80%)
	>2	10(20%)

*BMI – Body mass index; NRS –Numerical rating scale; PONV –Postoperative nausea and vomitus; min- minutes; mcg-micrograms; kg-kilograms; mg-milligrams

Table 2. Hemodynamic parameters of the patient'

Parameter		Value (mean±SD)
HR	baseline	88±35
	perioperative	60±34
MAP	baseline	84±30 mmHg
	perioperative	70±27 mmHg
SaO_2%	baseline	95±2%
	perioperative	98±2%

*HR: heart rate; MAP: mean artery pressure; SaO2: peripheral oxygen saturation; mmHg- millimeters of mercury

Table 3. Laboratory findings

Parameter		Value (mean±SD)
Urea	baseline	4.8±2.7 mmol/L
	postoperative	5.1±3.0 mmol/L
Creatinin	baseline	78±42 umol/L
	postoperative	81±44 umol/L
K^+	baseline	4.2±1.7 mmol/L
	postoperative	3.9±2.0 mmol/L
Na+	baseline	140±4.7 mmol/L
	postoperative	142±4.0 mmol/L

NRS scores were ≤4 in 47 patients (94%); only 3 patients (6%) had a numerical rating score in pain assessment >4 and received rescue analgesia. All three patients received 1 gram of paracetamol in the post-anesthesia care unit. Two patients received tramadol on the ward in the 6^{th} and 18^{th} hours.

Discussion

Regional anesthesia, a component of the multimodal strategy in perioperative pain treatment, is very successful at treating visceral and somatic pain [11]. The ESP block, also known as a field block, has gained popularity in pain management in recent years since it is simple to use and has fewer side effects [6]. ESP block offers the essential benefits of effective analgesia with a single injection and fewer intrusive procedures required over time. A study showed that the local anesthetic used in ESP block can reach the paravertebral area and the ventral branches of the spinal branches through the costa transfer foramen [12,13]. A single spinal level can be the starting point for an ESP block that works at at least five levels [13]. Applying extra volume in the ESP block, like in other volume-dependent area blocks, can result in increased dermatomal spread and block efficiency [9,12].

Literature search: reviled publications on the ESP block for open RP. To our knowledge, this is the first study evaluating his usefulness in LRP. Since no research has been done on the impact of ESP block on LRP in the literature, we compared our results with open RP and abdominal surgery [14-18]. Dost *et al*. carried out a study on open radical prostatectomy procedures [15]. They discovered that ESP block at the T11 level lowered postoperative NRS scores in the first hour, but it had no effect on the amount of morphine taken over the course of a day. Additionally, patients who had block needed less rescue analgesia in the first hour following surgery. These findings are in correlation with the results presented in our investigation. With ESP block at the T9 level, efficient and long-lasting postoperative analgesia for radical retropubic prostatectomy patients was created [9]. According to reports, patients who had laparoscopic cholecystectomy with an ESP block added to the rectus sheath block consumed fewer opioids during and after surgery [16]. In a different study, paravertebral block, a type of field block, was used at T10-11-12 levels during radical retropubic prostatectomy procedures. It effectively relieved pain after surgery [17]. In a study by Beverly *et al*.

ESP block decreased the need for rescue analgesics during laparoscopic cholecystectomy procedures, in addition to lowering 24-hour NRS ratings and tramadol use. Similar findings are presented in our evaluation, showing that patients who have ESP block consume fewer intraoperative and postoperative opioids and analgesics. The side effects of opioid nephrotoxicity are well documented [18]. This evaluation shows that the levels of electrolytes and nitrogenous metabolic products were normal before and after surgery in this group of patients who used fewer opioids and painkillers. This is another benefit of ESP block for people with acute or chronic kidney injury. According to a meta-analysis, there is moderate evidence that ESP block can lower opiate usage, surgical pain, and postnatal pain [19]. Our study demonstrated that postoperative NRS is lower in patients with ESP block, as were intraoperative total remifentanil and postoperative tramadol use. These findings are consistent with other studies in the literature [17,19]. In our group of patients with ESP blocks, fewer patients overall underwent rescue therapy consisting of paracetamol and tramadol. Only three patients needed rescue analgesia, although all of them had an NRS score of 5, and since this is a subjective method, we can conclude that the average pain score was reduced.

The groups' MAP values stayed stable, and their HR values were lower during the surgery. This suggests that ESP block may help in controlling the heart's response to a surgical stimulus and improving hemodynamic stability. Similar results are presented in the study of Turan and coauthors [14].

There are several restrictions on our investigation. Standardization is impossible to achieve because pain is a subjective concept and treatment must be customized for each patient. Furthermore, because the patients were only monitored for the first twenty-four hours, it was not possible to assess the long-term impact of ESP block on pain levels.

Conclusion

As far as we are aware, this is the first study assessing ESP block analgesic effects in LRP surgery. Our evaluation has shown that ultrasound-guided ESP block, as a form of multimodal analgesia, improves pain control by lowering pain scores and the amount of intraoperative and postoperative analgesics used in LRP while at the same time providing hemodynamic stability preventing any acute or chronic kidney injury. Its growing popularity can be attributed to its relative safety and convenience.

Conflict of interest statement. None declared.

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Original article

Peritoneal Dialysis Drop-Out Causes - A Single Center Retrospective Study

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Abstract

Introduction. Peritoneal dialysis (PD) offers a greater rate of patient comfort and better survival at lower costs than other forms of kidney replacement therapy (KRT). However, long-term therapy appears to be exceedingly challenging because of peritonitis, mechanical issues, and possibly dialysis failure. It is possible to take the proper steps for treatment and prevention if the precise causes of PD discontinuation are known. In this study, we looked into the causes of PD treatment termination in our facility.

Method. A retrospective study was done on the data of PD patients who were monitored in our facility between 2012 and 2023. Data included the etiology, comorbidities of the patients, catheter placement technique, duration of PD, reasons for stopping therapy, and types of mechanical problems.

Results. Of the 132 PD patients treated between 2012 and 2023, 83 stopped their treatment. Male patients made up 50.6% of the population, with a mean age of 54.4 years and a PD duration of 33.5 months. The causes of end-stage kidney disease were identified as diabetic nephropathy in 39.8%, nephrosclerosis in 16.9%, autosomal dominant polycystic kidney disease in 12%, and chronic glomerulonephritis in 13.3%. Only one patient had cancer, and 59% of the patients had diabetes mellitus. A nephrologist placed 12% of the PD catheters, whereas the surgeon laparoscopically implanted 37.3% of them. The primary causes of stopping PD therapy between 2020 and 2022 were death (10 out of 27 patients), dialysis failure (20 patients), peritonitis (19 patients), and kidney transplant (7 patients). In 10 of the cases, mechanical difficulties occurred; one had hydrothorax, two had hernias, and seven had leaks. Patients who had a catheter placed by a nephrologist experienced no difficulties, underwent PD treatment for a longer duration of time (35.6+-33.3 months), and the most frequent cause of treatment termination was dialysis failure. Catheters implanted through open surgery were more likely to cause mechanical issues and peritonitis.

Conclusion. PD is a reliable alternative to KRT. Only a few of our patients experienced mechanical issues. The widespread death rate was attributed to the Covid-19 epidemic. The third reason for stopping treatment was peritonitis. In order to diagnose and treat peritonitis, it is evident that closer monitoring and quicker action are needed. Most likely because the surgical technique was favored in more problematic patients, there were less problems in those who had a catheter put by the nephrologist.

Keywords: peritoneal dialysis, drop-out, catheter replacement, peritonitis

Introduction

The number of persons with chronic kidney disease is rising too quickly in recent years. According to The Global Kidney Health Atlas, almost 850 million people globally suffer from chronic kidney disease (CKD) [1]. Patients who require kidney replacement therapy (KRT) to survive, such as kidney transplants or some type of dialysis, are growing along with this number.

As a result of its affordability, ease of use, low need for technical assistance, ability to enhance life satisfaction, and independency, peritoneal dialysis (PD) has become an important KRT modality. Despite major technological advancements in dialysis therapy, a large number of patients discontinue their PD treatment. Depending on the demographic and study period, rates of PD drop-out varied from 19.8 to 54.8% [2]. Among these difficulties, dialysis failure accounts to up to 35% of patients' transfer from PD to hemodialysis (HD) each year [2]. Also, death and transplantation account for a significant number of the reasons why people drop out of PD. The main cause of PD withdrawal during the first three-month period is problems linked to the catheter [2]. In the first year, the primary causes

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of the switch to HD are reported to be psychological issues and infectious concerns [2]. Finding the factors causing withdrawals is crucial for optimizing the dialysis planning and implementation programs, optimizing the peritoneal catheter implantation process, and wisely allocating resources.
In this retrospective cohort study, we aim to pinpoint the root causes of this manifestation and explore ways to enhance them.

Material and method

Participant

This is a retrospective study based on data from PD patients who were followed at the Dialysis Center at Bezmialem Vakif University between 2012 and 2023. Patients who were over the age of eighteen and who had not undergone PD treatment for a period of three months or longer were not eligible for the study. Since the examination of the electronic medical record was done retrospectively, informed consent at the individual level was not requested.

Data collection

The demographic characteristics, date of catheter placement, catheter replacement technique, primary disease, number of peritonitis, peritonitis in the first three months, comorbidities of the patients, PD dialysis vintage, PD solution types, drop-out causes, and types of mechanical complication were all gathered from the electronic medical system.

Statistical analysis

Version 22.0 of the IBM Statistical Package for the Social Sciences was used to compute all statistical analyses. The study population was evaluated using a descriptive analysis utilizing the percent distribution for categorical variables, mean ± SD continues normally distributed variables. To find statistically significant differences across groups, the Anova test was used. Statistics were considered statistically significant when $p<0.05$.

Results

Between 2012 and 2023, 83 patients discontinued their treatment. 50.6% of the patients were male (Table 1), the average age was 54.4±14.4 years, and the average duration of PD treatment was 33.5±27.5 months (Table 2). The causes of end-stage kidney damage were diabetic nephropathy in 39.8%, nephrosclerosis in 16.9%,

Table 1. Baseline Characteristics

		No of patients 83
Gender	Male	42(50.6%)
	Female	41(49.4%)
DM	No	49(59%)
	Yes	34(41%)
Etiology	Diabetic Nephropathy	33(39.8%)
	ADPKD	10(12%)
	Nephroangiosclerosis	14(16.9%)
	Unknown	11(13.3%)
	GN	9(10.8%)
	Nephrolithiasis	6(7.2%)
Chronic Heart Failure	No	73(88%)
	Yes	10(12%)
COPD	No	78(94%)
	Yes	5(6%)
Malignancy	No	78(94%)
	Yes	5(6%)
Ischemic Heart Disease	No	63(75.9%)
	Yes	20(24.1%)
Hepatomegaly	No	82(98.8%)
	Yes	1(1.2%)
Obesity	No	54(65.1%)
	Yes	29(34.9%)
Drop Out Causes	Death	27(32.5%)
	Dialysis Failure	20(24.1%)
	Mechanical Complication	10(12%)
	Peritonitis	19(22.9%)
	Transplant	7(8.4%)
Mechanical Complication	Hernia	2(2.4%)
	Leakage	7(8.4%)
	Hydrothorax	1(1.2%)

ADPKD in 12%, and chronic glomerulonephritis in 13.3%. In terms of comorbidities, only five patients had COPD and cancer, 41% of patients had diabetes mellitus (DM), 10% had chronic heart failure, 20% had ischemic heart disease, and 29% had a body mass index (BMI) of more than 30 kg/m2. PD catheter placement was performed by a nephrologist in 12% and by a surgeon in 37.3% laparoscopically. Only 3 patients were stratified as early discontinuation (defined as discontinuation occurring within the first 6 months on PD) and this was due to mechanical complications (leakage and hydrothorax). The main reason for late discontinuing PD treatment was death (10 of 27 cases died between 2020 and 2022), followed by dialysis failure (20 cases), peritonitis (19 cases), kidney transplantation (7 cases) and mechanical complications in 10 of the cases; hernia in two, and leakage in seven and only one patient had hydrothorax. There was no significant difference between a nephrologist and a surgeon in the Anova test when comparing the rate of peritonitis and the vintage of dialysis across the three groups in the catheter placement procedure (p=0.963 and p=0.137, respectively) (Table 3 and 4). Although there was no statistically significant difference between the groups, it was noted that patients who underwent nephrologist-inserted catheters did not experience any mechanical complications, they continued on PD treatment for a longer duration (35.6+-33.3 months) (Table 3), and dialysis failure was the most frequent cause of treatment discontinuation (Table 5). Patients who had open surgery to place a catheter were more likely to experience mechanical issues and peritonitis (Table 5).

Table 2. Baseline Characteristics

	N	Minimum	Maximum	Mean	Std. Deviation
Age	83	23	85	54.43	14.007
Dialysis Vintage	83	3	132	33.54	27.384
No of Peritonitis	83	0	6	.95	1.239
First 3 Months Peritonitis	83	0	2	.14	.417

Table 3. Comparison of dialysis vintage according to technique of catheter placement

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	Sig.
					Lower Bound	Upper Bound			
Percutaneous	10	35.60	33.331	10.540	11.76	59.44	10	96	
Surgery	42	32.95	28.442	4.389	24.09	41.82	3	132	**.963**
Laparoscopic	31	33.68	24.677	4.432	24.63	42.73	7	120	

Table 4. Peritonitis according to technique of catheter placement

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	Sig.
					Lower Bound	Upper Bound			
Percutaneous	10	.40	.699	.221	-.10	.90	0	2	
Surgery	42	1.19	1.452	.224	.74	1.64	0	6	**.137**
Laparoscopic	31	.81	.980	.176	.45	1.17	0	4	

Table 5. Catheter placement and drop-out causes

			DROP-OUT CAUSES					Total
			Death	Dialysis failure	Mechanical Complication	Peritonitis	Transplant	
Catheter Placement	Percutaneous	Count	2_a	5_a	0_a	2_a	1_a	10
		% of Total	2.4%	6.0%	0.0%	2.4%	1.2%	12.0%
	Surgery	Count	11_a	9_a	7_a	11_a	4_a	42
		% of Total	13.3%	10.8%	8.4%	13.3%	4.8%	50.6%
	Laparoscopic	Count	14_a	6_a	3_a	6_a	2_a	31
		% of Total	16.9%	7.2%	3.6%	7.2%	2.4%	37.3%
Total		Count	27	20	10	19	7	83
		% of Total	32.5%	24.1%	12.0%	22.9%	8.4%	100.0%

Discussion

The main objectives of this study were to identify the risk factors for PD discontinuation. This could help nephrologist to more effectively select patients for PD therapy, identify prospective problems, and mitigate them so the patient can benefit from the treatment for as long as possible.

As the primary outcome we investigated the causes of discontinuation of PD treatment, and revealed that the most common reasons were death and dialysis failure. Only few patients had mechanical complication. Fac-

tors associated with the most common reasons were presence of comorbid conditions such as ischemic heart diseases, diabetes mellitus and dialysis vintage. Moreover, most of the cases died in the period of Covid-19 pandemia. It is well known that diabetes mellitus has a strong impact on survival. Patients treated with PD are subjected to high glucose absorption from dialysate solution; consequently, prolonged dialysate exposure may result in alteration of glycemic blood levels, which due to the production of advanced glycosylation end products (AGEs) may result in accelerating peritoneal aging in DM patients [3].

A study carried out in the Netherlands between 2012 and 2016 found that the most common reason for discontinuation was death, followed by infections like peritonitis and exit-site infections [4]. The factors indicating an increase in the incidence of death are cardiovascular disorders and the vintage of dialysis [4]. In contrast with the findings we observed, mechanical issues like leaks had a significant role in PD failure over the first six months [4]. A two-year study cohort examined the causes of death for individuals with PD between 2014 and 2015 using information from the Japanese Society for Dialysis Therapy (JSDT) registry [5]. Older age, vintage of dialysis, diabetes mellitus, atherosclerosis and ischemic heart diseases, use of dialysate with high glucose levels, higher levels of inflammatory and mineral bone diseases markers were found to be independently associated with an increased in mortality risk [5].

The majority of the deaths in our analysis occurred between 2020 and 2022, during the COVID-19 pandemic. Despite the fact that PD treatment gained popularity during the COVID-19 pandemic and was strongly advised as a first option for KRT by the International Society for Peritoneal Dialysis (ISPD) due to its safety, some researches [6,7] have found that the mortality rate was still quite high. The incidence of mortality in the PD group was higher than that of the HD population in two retrospective cohort studies, where data were taken from the ERA registry and published in 2021 and 2023. In the 2021 ERA Registry report, the adjusted risk of death at day 28 was greater in PD patients (21.6%) than in HD patients (18.0%), despite the fact that there was no statistically significant difference between PD and HD patients [6]. In contrast to HD patients, PD patients had greater mortality (crude HR: 1.49; 95% CI: 1.33-1.66) in the 2023 ERACODA study [7]. This difference persisted even after clinical presentation and comorbidities were taken into account (adjusted HR: 1.56; 95% CI: 1.39-1.75) [7]. Given the lack of data indicating a distinction in immune function between individuals with PD and those with HD, one possible reason for the differences could be the fact that PD patients arrived at the hospital much later than HD patients. Furthermore, research has demonstrated that they typically exhibit a prolonged clearance of viruses following Covid-19 recovery [7].

Telemedicine use is another factor that could have a significant impact on the rise in mortality. A retrospective study including 103 participants in Brazil revealed that the number of hospitalization episodes during the post-pandemic period rose from three to fifteen [8]. Our lack of preparation for the COVID-19 pandemic was evident in a number of ways, such as insufficient training for PD nurses, nephrologists, and patients during telemedicine, difficulties identifying patients who would benefit from consultations as outpatients, the inability to conduct a physical examination of patients-particularly those with peritoneal catheters-using a phone or video call, and patients' reluctance to seek medical attention when something went wrong out of fear being infected with the virus [8].

The second result is that we look into the differences in catheter placement techniques, such as laparoscopic, percutaneous, and surgical techniques. In the study we conducted, there was no statistically significant difference between these three groups with regard to mechanical problems, dropout reasons, or peritonitis. Nevertheless, it was observed that patients who had nephrologist-inserted catheters did not have any mechanical issues, they continued on PD treatment for a longer period of time (35.6+-33.3 months), and the most common reason for treatment discontinuation was dialysis failure. On the other hand, mechanical problems and peritonitis were more common in patients who underwent open surgery to implant a catheter. Similar to our results, a meta-analysis conducted by Esagian *et al*., showed that percutaneous placement was linked to a significantly lower incidence of catheter issues, like migration or removal, and tunnel/exit-site infections [9]. In the subgroup analysis, the percutaneous group had a lower catheter removal rate than both the laparoscopic and open surgery groups. Regarding mechanical issues and hernias, the subgroup analysis did not reveal any statistically significant differences between the percutaneous and laparoscopic groups. Compared to the open surgical group, the percutaneous group had a significantly greater leakage rate, as reported in 28 studies, which is in contradiction to our findings. Additionally, the rate of peritonitis was documented in 24 investigations, and there was no statistically significant difference observed between the groups that underwent open surgery or laparoscopic procedures and the percutaneous group [9].

This study has several shortcomings. It is retrospective, single center study. Data presented were not compared with survived patient or patients on HD. Also, risk factors for patients' outcome were not performed by proper statistical analysis.

Conclusion

PD is a reliable alternative to KRT. Only a few of our patients experienced mechanical issues. The widespread death rate was attributed to the Covid-19 epidemic. The third reason for stopping treatment was peritonitis. In order to diagnose and treat peritonitis, it is evident that closer monitoring and quicker action are needed. Most likely because the surgical technique was favored in more problematic patients, there were less problems in those who had a catheter put by the nephrologist.

Conflict of interest statement. None declared.

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Original article

Clinical and Laboratory Markers for Diabetic Nephropathy in Patients with Type 2 Diabetes Mellitus

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Abstract

Introduction. Diabetic nephropathy (DN) is a leading cause of ESRD worldwide and an independent risk factor for cardio-vascular mortality in diabetic patients. The multifactorial pathogenesis of DN is illustrated by many scientific researches. Nevertheless, there are no affirmed biomarkers of its presence, except albuminuria and kidney biopsy still stays the only method that confirms the diagnosis. The aim of our study is to reveal a relationship between certain biomarkers and the development of DN in patients with type 2 Diabetes Mellitus (DM).

Methods. Eighty-one patients are studied (49 males and 32 females), age 22 to 75 years. All of them are with CKD and histologically proven nephropathies, regardless of the kidney function. Forty-eight of subjects are with T2DM and the rest (33) are without DM. The patients are divided into 3 groups, according to histological findings: 1-st group (n=30): patients with DM and DN; 2-nd group (n=18): diabetic patients with other nephropathies but non DN and 3-rd group: patients without DM. Kidney function, lipid profile, IL-6, CRP, fibrinogen, D-dimer, homocysteine, folic acid, methylenetetrahydrofolate reductase gene polymerphism (MTHFR A1289C and C677T) are tested in the three groups.

Results. Serum homocysteine is significantly increased in patients with DN (p=0,034), compared to diabetic patients without DN. Also, there is a significantly increased level of serum IL-6 (p=0,019) and serum fibrinogen (p=0,012) in all diabetic patients, compared to non-diabetic patients. There is no significant difference between the rest of biomarkers among the three groups.

Conclusion. No single biomarker can be a predictor of DN, but a combination of biomarkers should be searched in larger studies.

Keywords: biomarkers, chronic kidney disease, diabetes mellitus type 2, diabetic nephropathy, predictors

Introduction

Microvascular complications of Diabetes mellitus (DM) are of major health and social importance. Diabetic nephropathy (DN) is a leading cause of end-stage renal disease (ESRD) worldwide and also an independent risk factor of cardio-vascular mortality in diabetic patients [1]. Approximately 90% of all diabetic patients are with type 2 DM. The rest 10% are with type 1 DM and some other rare types, as MODY (Maturity-onset diabetes of the young) and secondary types in pancreatitis, Cushing syndrome, and corticosteroid treatment [2,3]. It is found that nearly 50% of all patients with type 2 DM have also a chronic kidney disease (CKD), which is more common in certain populations as elderly patients, obese, some ethnic groups, low social and economic status [4]. The problem is not only the large number of diabetic patients, but also the late diagnosis in an advanced stage with minimal or no therapeutic options. The early diagnostics of CKD in patients with type 2 DM includes clinical and laboratory tests, as well as a histological verification with percutaneous puncture kidney biopsy [5]. The latter shows the presence of DN and other non-diabetic nephropathies (primary glomerulonephritis, autoimmune diseases and etc.) which is crucial for the treatment. Percutaneous puncture kidney biopsy is an invasive procedure and is not applicable in all patients. The restrictions of its performance are associated with the presence of advanced parenchymal changes, small kidneys, renal asymmetry, comorbidity, uncontrolled hypertension, severe anemia, concomitant anticoagulant and antiplatelet medication [6]. This provoke investigators to search for non-invasive methods with a high predictive value of presence of diabetic kidney injury and its prognosis.

The aim of our study was to reveal a relationship between certain clinical and laboratory biomarkers which are routine for the clinical practice and development of DN in patients with type 2 DM.

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Material and methods

The study enrolled 81 biopsied patients between the age of 22 and 75 years with histologically proven nephropathies, hospitalized at Nephrology Department, Clinic of Internal Diseases, Acibadem CityClinic University Hospital Tokuda in Sofia, Bulgaria from 2018-2023. Forty-nine of them were male (60,5%) and 32(39,5%) - female. Forty-eight of all patients (59,3%) were with type 2 DM and the rest 33(40,7%) were without diabetes. Patients were divided into 3 groups according to the presence of DM and DN in renal histology: I group: Patients with type 2 DM and DN (n=30); male 22(73,3%) and female 8(26,7%). II group: Patients with type 2 DM without DN in the biopsy (n=18); male 11(61,1%) and female 7(38,9%). III group: Non-diabetic patients (n=33); male 16(48,5%); female 17 (51,5%).

Indications for performing renal biopsy were: a presence of albuminuria or proteinuria of different range or impaired renal function.

Patients were assessed for having arterial hypertension and diabetic complications: diabetic retinopathy, polyneuropathy, macroangiopathy (for the I and II group). The presence of diabetic retinopathy was confirmed after fundoscopy by ophthalmologist. Diabetic neuropathy was accepted on the basis of neurological consultation and in some cases- electromyography test. Diabetic macroangiopathy involved cases with a history of ischemic heart disease or peripheral artery disease.

In all 3 groups the following parameters were measured: serum creatinine and e-GFR (CKD-EPI), cystatin C, BMI, lipid status (Low density lipoproteins-LDL, High density lipoproteins-HDL, Triglycerides), uric acid, glycated hemoglobin, inflammatory markers (CRP, IL-6), indexes of blood clotting and vessel damage (fibrinogen, D-dimer), homocysteine, folic acid, genetic factors (methylenetetrahydrofolate reductase gene polymorphism MTHFR A1289C and MTHFR C677T) as well as the thyroid function (TSH, FT4, Antithyroid microsomal antibody - MAT, Antithyroglobulin antibody - TAT). All laboratory tests were performed at the Clinical Laboratory of Acibadem CityClinic University Hospital Tokuda, Sofia.

From the statistical point of view the results are presented as number and proportion of patients in each group as well as the mean± standard deviation for normally distributed variables. The shape of the distribution was assessed by Kolmogorov-Smirnov and Shapiro-Wilk tests. Pearson Chi-Square test (Fisher Exact test when applicable) was performed to check the relationship of categorical variables.

Results

The mean age of patients in the 3 groups was as follows: group (diabetic patients with DN) - 62±8; II group (diabetic patients without DN) - 61±9; III group (non-diabetic patients) 46±14.

There was no significant difference regarding duration of DM between I and II group. In the I group the duration was 13±8 years and in the II group - 12±5 years, respectively (p=0,505).

Patients from the 3 groups were at different stages of CKD. Distribution of patients according to the stages of CKD (KDIGO Classification) is presented in Table 1.

Table 1. Distribution of patients according to the stages of CKD (KDIGO Classification)

	I group	II group	III group
CKD 1	n=6(20.0%)	n=2(11.1%)	n=10(30.3%)
CKD 2	n=3(10.0%)	n=7(38.9%)	n=4(12.1%)
CKD 3a	n=4(13.3%)	n=1(5.6%)	n=5(15.2%)
CKD 3b	n=0(0.0%)	n=0(0.0%)	n=0(0.0%)
CKD 4	n=12(40.0%)	n=8(44.4%)	n=13(39.4%)
CKD 5	n=5(16.7%)	n=0(0.0%)	n=1(3.0%)

Data presented as number of patients and percent.
Abbreviation: CKD – Chronic kidney disease.

Histological findings in the 3 groups are as follows:

In the I group, despite DN, 3(10.0%) of patients have hypertensive nephropathy; 5(16.7%) have tubulointerstitial changes; 1(3.3%) has FSGS; 1(3.3%) has membranous nephropathy; 1(3.3%) has C3- Glomerulonephritis. So, 11(36.6%) out of 30 patients with DN have another co-existing non-diabetic disease.

In the II group of diabetic patients with CKD, renal histology didn`t show DN, but we found the following diagnosis: predominant number of patients-10(55.5%) have a combination of hypertensive vascular changes and tubulointerstitial lesions; 3(16.6%) of patients have only hypertensive nephropathy and 1(5.5%) patient has tubulointerstitial nephritis alone; 2(11.1%) have membranous nephropathy; 1(5.6%)-membranoproliferative nephropathy; 1(5.6%)-mesangioproliferative glomerulonephritis with deposition of C3.

In the III group non-diabetic patients, we found: 7(21.2%) patients have chronic tubulointerstitial nephritis, 7(21.2%) have FSGS; 6(18.2%) have IgA nephropathy; 4(12.1%) have lupus nephrites; 3(9.1%) have membranous nephropathy; 3(9.1%) have membranoproliferative glomerulonephritis; 2(6.1%) have idiopathic nephrotic syndrome and 2(6.1%) - other.

Regarding diabetic complication, the comparison between the two diabetic groups revealed a significant difference in the presence of diabetic retinopathy. Fifty percent of patients with DN have a kind of retinopathy, whereas no one from diabetic patients without DN has it. There was no significant difference between the two groups in respect of other diabetic complications (Table 2).

Table 2. Comparison of diabetic complications between groups I and II

		I group-DM with DN	II group-DM without DN	P for groups 1 and 2
Diabetic retinopathy	Yes	n=15(50.0%)	n=0(0.0%)	<0.001
	No	n=15(50.0%)	n=18(100.0%)	
Diabetic polyneuropathy	Yes	n=20(66.7%)	n=10(55.6%)	0.441
	No	n=10(33.3%)	n=8(44.4%)	
Diabetic macroangiopathy	Yes	n=10(33.3%)	n=7(38.9%)	0.697
	No	n=20(66.7%)	n=11(61.1%)	
Diabetic gangrene	Yes	n=2(6.7%)	n=0(0.0%)	0.263
	No	n=28(93.3%)	n=18(100.0%)	

Data presented as number of patients and percent.
Abbreviation: DM - Diabetes Mellitus, DN – Diabetic Nephropathy.

Table 3. Comparison of clinical parameters between the 3 groups

		I group-DM with DN	II group-DM without DN	III group-Non-diabetics	P for groups 1 and 2	P for groups 1 and 3	P for groups 2 and 3	P for groups (1+2) and 3
BMI	18.0-24.9	n=1 (3.3%)	n=1 (5.6%)	n=11 (33.3%)	0.747	<0.001	0.013	<0.001
	25.0-29.0	n=6 (20.0%)	n=5 (27.8%)	n=13 (39.4%)				
	>30.0	n=23 (76.7%)	n=12 (66.7%)	n=9 (27.3%)				
Arterial hypertension	Yes	n=30 (100.0%)	n=18 (100.0%)	n=28 (84.8%)		0.054	0.148	0.009
	No	n=0 (0.0%)	n=0 (0.0%)	n=5 (15.0%)				

Data presented as number of patients and percent.
Abbreviation: DM - Diabetes Mellitus, DN – Diabetic Nephropathy, BMI – Body Mass Index.

Table 4. Comparison of metabolic parameters between the 3 groups

		I group – DM with DN	II group DM without DN	III group non-diabetics	P for groups 1 and 2	P for groups 1 and 3	P for groups 2 and 3	P for groups (1+2) and 3
LDL	Low	n=4 (14.3%)	n=5 (27.8%)	n=1 (3.3%)	0.307	0.322	0.024	0.092
	Normal	n=22 (78.6%)	n=13 (72.2%)	n=26 (86.7%)				
	High	n=2 (7.1%)	n=0 (0.0%)	n=3 (10.0%)				
HDL	Low	n=19 (67.9%)	n=11 (61.1%)	n=9 (30.0%)	0.639	0.013	0.093	0.007
	Normal	n=9 (32.1%)	n=7 (38.9%)	n=20 (66.7%)				
	High	n=0 (0.0%)	n=0 (0.0%)	n=1 (3.3%)				
Triglycerides	Normal	n=15 (50.0%)	n=10 (55.6%)	n=24 (72.7%)	0.709	0.064	0.214	0.062
	High	n=15 (50.0%)	n=8 (44.4%)	n=9 (27.3%)				
Uric acid	Normal	n=24 (80.0%)	n=11 (61.1%)	n=28 (61.1%)	0.154	0.613	0.085	0.204
	High	n=6 (20.0%)	n=7 (38.9%)	n=5 (15.2%)				
HbA1C	Normal	n=14 (46.7%)	n=9 (50.0%)		0.823			
	>6.5%	n=16 (53.3%)	n=9 (50.0%)					

Data presented as number of patients and percent.
Abbreviation: DM - Diabetes Mellitus, DN – Diabetic Nephropathy.

Other clinical features that we compared between the 3 groups are the presence of obesity and arterial hypertension. The results are presented in the table 3.
There was a significant prevalence of obesity (BMI >30.0) in diabetic patients, regardless the presence of DN, compared to non-diabetic patients. Everybody with diabetes in our study has arterial hypertension and most patients without DM have arterial hypertension as well.

Table 5. Comparison of inflammatory and coagulation factors between the 3 groups

		I group DM with DN	II group DM without DN	III group Non-diabetics	P for groups 1 and 2	P for groups 1 and 3	P for groups 2 and 3	P for groups (1+2) and 3
CRP	Normal	n=17 (56.7%)	n=13 (72.2%)	n=26 (78.8%)	0.281	0.060	0.732	0.119
	High	n=13 (43.3%)	n=5 (27.8%)	n=7 (21.2%)				
IL-6	Normal	n=17 (56.7%)	n=14 (77.8%)	n=29 (87.9%)	0.139	0.005	0.430	0.019
	High	n=13 (43.3%)	n=4 (22.2%)	n=4 (12.1%)				
D-dimer	Normal	n=13 (43.3%)	n=10 (55.6%)	n=22 (66.7%)	0.412	0.063	0.433	0.095
	High	n=17 (56.7%)	n=8 (44.4%)	n=11 (33.3%)				
	Low	n=1 (3.3%)	n=0 (0.0%)	n=0 (0.0%)				
Fibrinogen	Normal	n=14 (46.7%)	n=11 (61.1%)	n=27 (81.8%)	0.508	0.012	0.177	0.021
	High	n=15 (50.0%)	n=7 (38.9%)	n=6 (18.2%)				

Data presented as number of patients and percent.
Abbreviation: DM - Diabetes Mellitus, DN – Diabetic Nephropathy.

Table 6. Comparison of homocysteine, folic acid and thyroid function between the 3 groups

		I group DM with DN	II group DM without DN	III group non-diabetics	P for groups 1 and 2	P for groups 1 and 3	P for groups 2 and 3	P for groups (1+2) and 3
Homocysteine	Normal	n=9 (30.0%)	n=11 (61.1%)	n=11 (33.3%)	0.034	0.777	0.056	0.448
	High	n=21 (70.0%)	n=7 (38.9%)	n=22 (66.7%)				
Folic acid	Normal	n=20 (87.0%)	n=13 (100.0%)	n=27 (81.8%)	0.323	0.338	0.219	0.242
	High	n=3 (13.0%)	n=0 (0.0%)	n=6 (18.2%)				
	Low	n=1 (3.3%)	n=0 (0.0%)	n=3 (9.1%)				
TSH	Normal	n=29 (96.7%)	n=16 (88.9%)	n=27 (81.8%)	0.135	0.140	0.416	0.220
	High	n=0 (0.0%)	n=2 (11.1%)	n=3 (9.1%)				
	Low	n=2 (6.9%)	n=0 (0.0%)	n=1 (3.0%)				
FT4	Normal	n=27 (93.1%)	n=17 (94.4%)	n=30 (90.9%)	0.240	0.326	0.753	0.640
	High	n=0 (0.0%)	n=1 (5.6%)	n=2 (6.1%)				
TAT Ab	Normal	n=26 (86.7%)	n=15 (83.3%)	n=29 (87.9%)	0.999	0.885	0.686	0.751
	High	n=4 (13.3%)	n=3 (16.7%)	n=4 (12.1%)				
MAT Ab	Normal	n=29 (96.7%)	n=15 (83.3%)	n=26 (78.8%)	0.142	0.033	0.999	0.096
	High	n=1 (3.3%)	n=3 (16.7%)	n=7 (21.2%)				

Data presented as number of patients and percent.
Abbreviation: DM - Diabetes Mellitus, DN – Diabetic Nephropathy.

With respect of the metabolic status, we didn`t find any significant difference between diabetic patients with DN and those without DN. We only found that HDL is significantly lower in patients with DN compared to non-diabetic patients (p=0.013). Also, it is significantly lower in two diabetic groups, as compared to the non-diabetic patients (p=0.007). Glycemic control didn`t show any difference between diabetic patients with DN and those without DN. Glycated hemoglobin (HbA1C) was above 7.5% in almost half of the patients from the two groups (Table 4).

We compared the presence of some inflammatory markers (CRP, IL-6) and coagulation factors (fibrinogen, D-dimers) between the 3 groups. We didn`t find any significant difference between diabetic patients with and without DN, but there were a significantly higher levels of IL-6 in diabetic patients with nephropathy compared to non-diabetic patients (p 0.005). In addition, levels of fibrinogen appeared to be higher in diabetic patients with nephropathy than in non-diabetic patients (p 0.012) (Table 5).

We found that the levels of homocysteine are signifycantly elevated in diabetic patients with DN compared to DM patients without DN (p 0.034), although there was no significant difference between patients with DM and those without DM. There was no difference in the levels of folic acid and thyroid function between the 3 groups (Table 6).

In our study we investigated the carriage of mutations of methylenetetrahydrofolate reductase gene (MTHFR A1289C and C677T) as genetic factors for development of diabetic nephropathy. We found out that the carriage of pathological alleles is widespread and it doesn`t play any role for the manifestation of DN (Table 7).

Table 7. Carriage of pathological alleles of methylenetetrahydrofolate gene (MTHFR A1289C and C677T) among the 3 groups

		I group DM with DN	II group DM without DN	III group non-diabetics	P for groups 1 and 2	P for groups 1 and 3	P for groups 2 and 3	P for groups (1+2) and 3
MTHFR A1289C	Homozygous AA normal	n=16 (53.5%)	n=10 (55.6%)	n=15 (45.5%)	0.982	0.794	0.785	0.721
	Heterozygous	n=12 (40.0%)	n=7 (38.9%)	n=16 (48.5%)				
	Homozygous CC mutation	n=2 (6.7%)	n=1 (5.6%)	n=2 (6.1%)				
MTHFR C677T	Homozygous AA normal	n=13 (43.3%)	n=6 (33.3%)	n=7 (21.2%)	0.770	0.094	0.300	0.084
	Heterozygous	n=12 (40.0%)	n=8 (44.4%)	n=22 (66.7%)				
	Homozygous CC mutation	n=5 (8.7%)	n=4 (22,2%)	n=4 (12.1%)				

Data presented as number of patients and percent.
Abbreviation: DM - Diabetes Mellitus, DN – Diabetic Nephropathy.

Discussion

Diagnosing etiology of CKD in patients with DM is a challenge for the clinicians. Kidney biopsy is seldom considered, except in cases with atypical presentation as: lack of diabetic retinopathy, short duration of diabetes (under 5 years), presence of micro- or macrohematuria, active urinary sediment, sudden onset of gross proteinuria or nephrotic syndrome, acute kidney injury, suspicion of an autoimmune disease and markers of hepatitis B or C [7]. As in many trials in the literature, in our study approximately 1/3 of diabetic patients (37.5%) have non-diabetic kidney injury, 1/3 (36.6%) have a combination of diabetic and non-diabetic lesions and the rest 39.5% - diabetic nephropathy alone [8].

In our study, the group of diabetic patients without DN showed a similar duration of DM as those with DN and suggests that the predictive value of duration is not a strong one.

Diabetic retinopathy (DR) is present significantly in 50% of patients with DN, whereas no one in the II group has it. So, the existence of DR might be of a high predictive value for the presence of DN. It has been confirmed by large studies [9,10]. Severity of DR could be a marker of progression of CKD [11]. If DR is established, a screening for Diabetic Kidney Disease (DKD) should be performed regularly.

In our study, diabetic polyneuropathy (DPN) is found in most of the patients with DN (66.7%) and in more than half of diabetic patients without DN (55.6%). It indicates a high prevalence of polyneuropathy among diabetic patients with CKD and its predictive value should be an object of further research. In the literature there are publications, stating a relationship between DPN and DKD [12,13].

As it is observed in our study, the predominant number of patients from the 3 groups are at CKD 4, which might indicate a progressive course of the kidney disease.

Regarding histological findings it is worth mentioning that a significant number of patients with DN (36.6%) have another co-existing non-diabetic injury. At the same time, most of the patients from the II group

(77.7%) have hypertensive and/or tubulointerstitial lesions. That states the question if these vascular or tubulointerstitial changes could be associated with DM and/or if they could be a manifestation of DKD. The role of tubulointerstitial damage in DKD has been recently researched by many authors [14-16]. That explains the fact that many diabetic patients reach ESRD without a significant albuminuria [17-19].

Obesity and arterial hypertension presented significantly in all diabetic patients in our study, compared to non-diabetic patients. Although they don`t show an existence of DN, they could deteriorate the course of CKD in patients with DM [20].

We studied the role of IL-6 as a marker of DN and found that it was significantly higher in patients with DN compared to the non-diabetic patients, although there was no significant difference between the two diabetic groups. IL-6 is an inflammatory cytokine with a pleiotropic action. It is involved in the mechanisms of obesity and insulin resistance [21,22]. The mechanism of its action is impairing phosphorylation of the insulin receptor and inhibition of insulin signaling to the cells [21]. Also, IL-6 unlocks molecular mechanisms (gp-130-STAT 3 dependent mechanisms) that lead to an adaptive immune response, cellular infiltration and inflammatory process [23]. Several studies in literature demonstrate the role of IL-6 for developing DN [24,25]. Shikano *et al*. found a significant elevation of serum IL-6 in patients with microalbuminuria and overt proteinuria, compared to normoalbuminuric patients, as well as a significant correlation with fibrinogen [26].

Fibrinogen is a 340kD plasma protein, containing two sets of α-, β- and γ-chains. At the beginning of coagulation process thrombin cuts off fibrin-peptides from the N-end of α and β chains, which leads to polymerrization of fibrin monomers in insoluble fibrin set [27]. Mechanisms of microvascular injury are due to changes of blood viscosity, activation of thrombogenesis and erythrocyte aggregation in the terrain of impaired endothelial function and vascular reactivity [28]. Several studies in the literature demonstrate elevated levels of fibrinogen in patients with DM and DN [29-31]. In our trial, levels of IL-6 and fibrinogen were significantly higher in diabetic patients, compared to non-diabetic patients. It is not sufficient to accept the role of these biomarkers as single predictors of DN, but they could also be indicators of renal injury in diabetic patients.

We investigated the role of homocysteine, folic acid and methylenetetrahydrofolate reductase gene polymerphism (MTHFR A1289C and C677T) in patients from the 3 groups. Methylenetetrahydrofolate reductase (MTHFR) is an enzyme, which takes part in the process of remethylation of homocysteine to methionine. Inadequate enzyme activity causes elevation of homocysteine serum levels. MTHFR is encoded by MHTFR -gene, which is located in humans in chromosome 1, locus p36.3 [32]. Different sequences in the DNA molecule determine so called genetic polymorphism, which has 24 genetic variants [33]. The most investigated ones are C677T and A1289C. In 1998 Neugebauer *et al*. established the role of MTHFR gene polymorphism as a risk factor for DN in DM type 2 [34]. In our study, we found that carriage of pathological alleles 677T and 1289C is widespread among the studied population and it couldn`t be used as a biomarker of DN.

Interestingly, in our trial homocysteine appeared to be significantly higher in patients with DN, than diabetic patients without DN, although there was no significant difference between diabetic and non-diabetic patients. Homocysteine is a sulfur containing amino acid, which is formed as a result of intracellular metabolism of methionine [35]. Its unfavorable action in the kidneys and vascular system is associated with an endothelial dysfunction, increased formation of reactive oxygen species (ROS), activation of vasoconstrictor and depression of vasodilator substances, increased extracellular matrix deposition. The relationship between elevated plasma concentration of homocysteine and the level of albumin excretion in diabetics has been described in some trials [36,37]. Wang *et al*. demonstrated a positive correlation between homocysteine, albumin excretion and the degree of reduction of e-GFR for a 4 years period of follow-up [38]. Some authors consider homocysteinemia as an independent predictor of kidney injury in early stages of kidney disease [38,39]. The small number of patients in our study does not allow us to accept homocysteine as a single biomarker of DN, but its high levels might predict a progressive course of renal disease.

Conclusion

Multifactorial pathogenesis of DN reveals different metabolic disorders in diabetic patients with CKD. That`s why it is so difficult to determine a particular biomarker, except albuminuria, as a hallmark of DN. None of the studied biomarkers in our trial could be a single predictor of DN and a combination of biomarkers should be searched in larger studies. Since renal biopsy stays the only method that determines diagnosis and prognosis, we recommend to perform it in each patient with elevated albumin or protein excretion or impaired renal function, if there are not contraindications for it.

Conflict of interest statement. None declared.

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Original article

Use of Eplerenone in Kidney Transplant Recipients with Heart Failure: Case Series

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Abstract

Introduction. Despite their potential benefits, mineralocorticoid receptor antagonists are rarely used in kidney transplant recipients due to the fear of complications. We aim to describe epidemiological, clinical and laboratory characteristics, treatment, and outcomes of kidney transplant patients treated with eplerenone.
Methods. Kidney transplant recipients who received eplerenone were included in this single-center retrospective study. Serum electrolytes, uric acid, estimated glomerular filtration rate (eGFR), and proteinuria were recorded.
Results. Ten kidney transplant recipients (6 male) received eplerenone for treatment of heart failure. With the median follow-up of 16 months (range 6-78 months), nine were alive with the functioning kidney allograft. Eplerenone was well tolerated. Only one patient developed mildly elevated potassium and one developed severe symptomatic hyponatremia, requiring hospitalization. The glomerular filtration rate decreased after eplerenone's introduction from 47.5(42-54) to 40 (35-48) ml/min/1.73m^2 at three months ($p<0.01$) and remained stable in follow-up. Proteinuria decreased from 303 mg/24h to 185 mg/24h without a statistically significant difference. Eplerenone did not influence cyclosporine or tacrolimus trough levels. Uric acid increased after the introduction of eplerenone, requiring increased doses of allopurinol.
Conclusions. Eplerenone may be used with caution in kidney transplant recipients. Careful monitoring of all electrolytes and not only of potassium is mandatory. In our cohort, eplerenone increased uric acid levels. Further studies are required to elucidate the clinical benefits and safety of eplerenone in this patient population.

Key words: eplerenone, heart failure, kidney transplant, hyperuricemia, hyponatremia, mineralocorticoid receptor antagonist

Introduction

Cardiovascular diseases are the leading cause of death, accounting for up to 60% of all lethal outcomes after kidney transplantation [1]. All major phenotypes of cardiovascular diseases are present in kidney transplant recipients, including heart failure, coronary artery disease, valvular heart disease, peripheral vascular disease, cerebrovascular diseases, arrhythmias, and pulmonary hypertension. The shared risk factors between kidney failure and cardiovascular disease, such as diabetes and hypertension, can partially explain this phenomenon. However, end-stage kidney disease (ESKD) can additionally exacerbate cardiac problems due to anemia, fluid overload, uremic toxins, and secondary hyperparathyroidism with vascular calcifications that contribute to the development and exacerbation of atherosclerosis, coronary artery disease, and left ventricular hypertrophy. Finally, mineralocorticoid excess, which is present in ESKD, significantly contributes to the risk of cardiac disease. Mineralocorticoid receptor (MR) activation is involved in inflammation, fibrosis, and progression of chronic kidney disease. Besides the kidneys, MR is expressed in many other organs, including the colon, heart, central nervous system, and brown adipose tissue, which are responsive to aldosterone signaling. Aldosterone contributes to blood pressure control and maintains extracellular volume homeostasis by provoking renal sodium reabsorption and potassium excretion [2].
Eplerenone is a second-generation steroidal mineralocorticoid receptor antagonist (MRA) that selectively binds to the MR, blocking aldosterone binding and inhibiting sodium reabsorption and other aldosterone-mediated mechanisms. It is more selective in the MRA effect and devoid of androgen antagonism and progesterone agonism than spironolactone. Additionally, the absence of its long-acting metabolites could be associated with less frequent adverse events. However, the use of eplerenone still carries a risk of hyperkalemia [3]. Thus, despite the potential benefits, MRAs are ra-

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rely used in kidney transplant recipients (KTR) due to the fear of complications. Herein, we report our experience with the use of eplerenone after kidney transplantation.

Material and methods

We conducted a retrospective, observational cohort study that included patients who underwent kidney transplantation at the University Hospital Centre Zagreb, Croatia, and received eplerenone therapy. The patient's electronic medical records were used to extract the relevant data. Data extracted from the patients' database included their age, gender, primary kidney disease, dialysis vintage, posttransplant complications, and laboratory data before the introduction of eplerenone, three months after the start of treatment, and at the last follow-up. Laboratory measurements included estimated glomerular filtration rate (eGFR), uric acid, potassium, sodium, and 24-h proteinuria. Patients were advised to limit their potassium-rich food intake. The research was conducted in accordance with the Declaration of Helsinki. The University Hospital Center Zagreb Ethics Committee reviewed and approved this study protocol.

The primary endpoint was the tolerance to eplerenone, assessed by the occurrence of the adverse events: occurrence of hyperkalemia (>5.1 mmol/L), decrease in eGFR >30% from baseline, or any adverse event that required discontinuation of eplerenone. Efficacy outcomes of the present analysis included a CV composite outcome of nonfatal myocardial infarction, stroke, or hospitalization for heart failure. Changes in proteinuria, uric acid, and electrolytes from baseline to the end of the study were also analyzed.

Categorical data were presented by absolute and relative frequencies. The Shapiro-Wilk test tested the normality of the continuous variable distribution. The median and the interquartile range described continuous data. Logistic regression analysis was used to analyze the independent factors associated with decreased eGFR and increased serum uric acid. The level of significance was set at an Alpha of 0.05. Considering the relatively small sample size and the possibility of overfitting in the multivariate logistic regression model, we adopted a forward stepwise method (probability for stepwise: entry $p<0.05$, removal $p>0.1$) for logistic regression analysis to reduce the number of independent variables entering the model. There was no substitution for the missing data. The statistical analysis was performed using MedCalc® Statistical Software version 20.023 (MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org; 2021) and the IBM SPSS Stat. 23 (IBM Corp. Released 2015., Ver. 23.0. IBM Corp; Armonk, NY, USA).

Results

Out of 2226 KTRs who underwent kidney transplantation at our institution, ten patients were treated with eplerenone. There were 6 male and 4 female patients, with a median age of 75 (range 61 to 84). The immunosuppressive protocol was based on calcineurin inhibitors (tacrolimus in 2, cyclosporine in 5 patients) or mTORi (everolimus in 3 patients). Eight patients received mycophenolate.

All patients had arterial hypertension, four had a history of myocardial infarction, 3 had a stroke, seven had peripheral arterial disease, and seven had cardiac arrhythmia. Their characteristics are presented in Table 1.

Table 1. Characteristics of patients treated with eplerenone

	n=10
Age (years)	75(61-84)
Gender ratio (M/F)	6/4
Dialysis vintage (years)	3(1-8)
Time from transplantation (years)	13(8-27)
Primary kidney disease, n / Total	
Diabetic nephropathy	1/10
Glomerulonephritis	2/10
ADPKD	3/10
Nefroangiosclerosis	1/10
Endemic nephropathy	2/10
Analgetic nephropathy	1/10
CNI, n / Total	
Tacrolimus	2/7
Cyclosporine	5/7
Mycophenolate, n / Total	8/10
mTORi, n / Total	3/10
Steroid dose (n = 9)	5(2.5-10)
Myocardial infarction, n / Total	4/10
Stroke(n = 3) , n /Total	
1 episode	2/3
2 episodes	1/3
Peripheral vascular disease, n / Total	7/10
Arrhythmia, n / Total	7/10
Acute rejection, n / Total	1/10
CMV reactivation, n / Total	1/10
Malignant tumor, n / Total	5/10
Hypertension, n / Total	10/10
Number of antihypertensive drugs, n/Total	
2	2/10
3	3/10
4	2/10
5	3/10
Posttransplant diabetes, n / Total	2/10
Heart echo, n / Total	
EF (%)	65(22-65)
Pulmonary artery pressure	45(40-90)
Valvular disease, n / Total	3/10
NTproBNP 0	5539(2235-118070)
NTproBNP final	2740(1500-4596)

Data are expressed by median (range)

At the last outpatient visit, with the median follow-up of 16 months (range 6-78 months), nine patients were alive with functioning kidney allograft. One of them died from heart failure 26 months after the introduction

of eplerenone.

The glomerular filtration rate decreased from 47.5 (IQR, 42-54) ml/min/1.73m^2 after eplerenone's introduction to 40.0 (IQR, 35-48) ml/min/1.73m^2 and remained stable in follow-up. Proteinuria decreased from 303 mg/24h to 185 mg/24h without a statistically significant difference (Table 2).

Table 2. Estimated glomerular filtration rate significantly decreased after introduction of eplerenone. Uric acid levels increased during the treatment, not reaching the statistical significance (p=0.06). Data are represented as median and range. *p<0.05 vs. baseline

	Median (IQR)			*P**
	At baseline	**3 months**	**Last follow-up**	
Body weight	80(67-88)	81.5(68-88)	76.5(69-89)	0.91
eGFR	47.5(42-54)	40.0(35-48)	39.0(33-48)	**0.01**†
SBP	138(128-167)	132(125-158)	137(122-160)	0.72
DBP	87(76-108)	82(74-105)	84(72-103)	0.58
Proteinuria	303(219-378)	241(128-263)	185(118-407)	0.64
Potassium	4.3(4.1-4.7)	4.3(4.0-4.5)	4.1(3.8-4.6)	0.76
Sodium	140.5(139-141)	141(137-142)	140(139-142)	0.97
Calcium	2.35(2.32-2.43)	2.43(2.36-2.47)	2.43(2.34-2.51)	0.28
Uric acid	380(364-450)	442(389-521)	430(421-471)	0.06

IQR-interquartil range, *Friedman's Test, †at the level of P<0,05 significantly higher values at baseline compared to other measurements

Only one patient developed mild hyperkaliemia (serum potassium increased from 4.9 to 5.2 mmol/L). Other patients had potassium levels within the normal range, including those with mildly elevated potassium at the baseline. Uric acid increased in all but one patient, requiring either the introduction or increase of the existing dose of allopurinol or febuxostat.

Calcium levels were stable after the introduction of eplerenone.

Two patients required hospitalizations after the introduction of eplerenone. One patient developed severe hyponatremia one month after the start of treatment with 25 mg eplerenone. She was admitted to the hospital with mental deterioration and a serum sodium level of 113 mmol/L. On physical examination, she was dysponoic, with a heart rate of 99 bpm, blood pressure of 136/69 mmHg, with edema and hyperemia of the lower extremities. Heart auscultation revealed an ejection systolic murmur without radiation to the carotids. The electrocardiogram (ECG) showed atrial fibrillation with a normal ventricular response. A chest radiograph showed an increased cardiothoracic index with cranial vascular redistribution-the transthoracic echocardiogram calcification of the mitral valve, with moderate MV regurgitation. There was also a severe tricuspid valve (TV) regurgitation, secondary to TV annulus dilation. The left ventricular ejection fraction (LVEF) was preserved (60%), and the left ventricle was not dilated. Eplerenone was immediately omitted, and hyponatremia was conservatively treated. The patient recovered within five days and was discharged with stable kidney allograft function. The other patient was hospitalized due to the heart failure. He died with a functioning kidney allograft.

There were no significant changes in blood pressure during the follow-up, and we did not perform continuous ambulatory blood pressure monitoring. All patients required at least two antihypertensive drugs to control arterial hypertension.

Tacrolimus and cyclosporine trough levels were stable, without significant oscillations after the introduction of eplerenone. There was no need to change the dose of everolimus after the introduction of eplerenone.

Discussion

This study showed an acceptable safety profile of eplerenone in KTR with heart failure. Nine out of ten patients were alive at the last outpatient visit. Eplerenone was associated with a decline in eGFR at three months, which remained stable after that, and increased uric acid levels in follow-up. A decline in proteinuria was recorded but did not reach statistical significance. One patient developed severe symptomatic hyponatremia, requiring hospitalization. Only one patient developed mild hyperkaliemia.

Cardiovascular diseases are the leading cause of death in patients with ESKD. Despite detailed cardiac evaluation in kidney transplant candidates, different cardiovascular complications, including heart failure, remain the most common cause of death after kidney transplantation [4]. All other cardiovascular conditions, including coronary artery disease, valvular heart disease, peripheral vascular disease, cerebrovascular diseases, arrhythmias, and pulmonary hypertension, significantly affect posttransplant outcomes. Additionally, kidney transplantation is increasingly accessible to elderly recipients with a more pronounced burden of different comorbidities, including diabetes, coronary heart disease, or heart failure. All these conditions have been associated with the upregulation of mineralocorticoid receptors [5]. Mineralocorticoid receptor upregulation results with increased transcription of profibrotic genes, including TGF-beta1, plasminogen acti-

vator inhibitor 1, connective tissue growth factor, and extracellular matrix proteins, which are linked to renal and cardiac fibrosis, adding to the risk of cardiovascular disease [2]. In different clinical settings, mineralocorticoid receptor antagonists (MRA) may have antihypertensive and antiproteinuric effects. However, they also prevent ischemia-reperfusion injury, the transition from acute, chronic injury to chronic kidney disease (CKD), the progression of CKD, and the prevention of cardiovascular outcomes [6]. Mineralocorticoid receptor knockout in smooth muscle cells, but not in the endothelium, prevented cyclosporine-induced nephrotoxicity [7]. In experimental models, MR blockade efficiently ameliorated calcineurin toxicity, possibly by preventing increased renal vascular resistance in acute CIN [8]. The majority of these conditions already develop in kidney transplant recipients before transplantation or evolve during the posttransplant follow-up period.

For this reason, MRAs may represent an essential therapeutic option in kidney transplant patients [9], hypothetically protecting transplanted organs from different injuries. Mineralocorticoid receptor antagonists were found to be effective in patients with resistant hypertension [10], heart failure, or myocardial infarction [11,12], presenting an attractive and additive treatment after kidney transplantation. However, despite the obvious multiple potential benefits of MRA in this particular group of patients, which carries a heavy burden of cardiovascular problems, they are rarely prescribed due to the fear of complications.

Hyperkaliemia is most frequently considered a problem after the introduction of MRAs. A recent clinical trial investigated the safety of eplerenone 25 mg/day in 31 kidney-transplanted patients receiving cyclosporine. Patients with serum potassium levels ≥5 mmol/L or a history of severe hyperkalemia (≥6 mmol/L) were excluded from the trial, whereas 61% of patients were treated with angiotensin convertase enzyme inhibitor or angiotensin receptor blocker. Eight patients experienced mild hyperkalemia (>5 mmol/L) while treated with eplerenone, and one had moderate hyperkalemia (>5.5 mmol/L) and received potassium-exchange resin. One patient developed acute kidney allograft failure that was attributed to diarrhea [13]. In our cohort, only one patient developed mild hyperkaliemia. It is important to stress that all patients from our cohort were educated about the risk of hyperkaliemia before introducing eplerenone. They were advised to avoid potassium-rich food.

Serum sodium changes frequently complicate cardiovascular diseases. Sodium balance is fine-tuned in the distal parts of the nephron, where eplerenone exhibits some of its pleiotropic effects. Out of a total of 6632 patients with myocardial infarction and heart failure included in the EPHESUS trial randomized to either eplerenone or placebo, 6221 had a post-baseline sodium measurement. Seven hundred ninety-seven patients developed hyponatremia, and 1476 developed hypernatremia. Patients treated with eplerenone had lower mean serum sodium over the follow-up (140 vs. 141 mmol/L; $p<0.0001$) and more often developed hyponatremia episodes (15 vs. 11% $p=0.0001$) and less often hypernatremia episodes (22 vs. 26% $p=0.0003$) [14). In our study, only one patient developed hyponatremia, but a severe form with neurological presentation requiring hospitalization. This case indicates that sodium should be regularly checked along with other electrolytes after the introduction of eplerenone.

Hyperuricaemia is a common problem after kidney transplantation. Diuretics are one of the most important and frequent causes of secondary hyperuricemia that may either increase uric acid reabsorption and/or decrease uric acid secretion. Serum uric acid was found to be an independent predictor of all-cause and cardiovascular mortality but also acute coronary syndrome, stroke, and heart failure [15]. However, the threshold levels of serum uric acid that can contribute to cardiovascular risk significantly are not defined [16].

The association of spironolactone with increased serum uric acid levels is controversial. Previous results suggested that spironolactone does not increase serum uric acid levels [17]. Later, Cabrera et al. showed that low-dose spironolactone increases serum uric acid levels in patients with chronic kidney disease [18]. In Ohta *et al*.'s study, eplerenone treatment increased serum uric acid levels while indapamide decreased them [19]. In our group, uric acid increased from the median 380 to 430 umol/L, not reaching the statistical significance ($p=0.06$), probably due to the small sample size.

In our study, eplerenone decreased proteinuria over the follow-up; however, it was without statistical significance. Proteinuria is a specific problem in the kidney transplant population associated with numerous etiologic factors. Early use of MRA may prevent kidney allograft deterioration in patients with proteinuria and non-immunological lesions on kidney biopsies. Additionally, it may have a beneficial effect on other forms of proteinuria. However, this hypothesis needs to be evaluated.

The use of eplerenone did not significantly alter our patients' blood pressure. However, we did not have continuous ambulatory blood pressure monitoring, so we may have missed the beneficial effect of eplerenone on 24-hour blood pressure control.

Solid organ recipients are usually not included in randomized clinical studies due to the potential risk of interactions with immunosuppressive medications. Eplerenone does not inhibit or induce CYP3A4, which results in a neutral effect on calcineurin inhibitor levels. There is also no drug–drug interaction between mycophenolic acid and eplerenone [13].

Current data suggest that finerenone, a novel, more selective MRA, protects against kidney disease progre-

ssion and cardiovascular events in patients with type 2 diabetes and chronic kidney disease [20]. Finerenone has been shown to reduce the urinary albumin-to-creatinine ratio in patients with chronic kidney disease receiving a renin-angiotensin antagonist but with less pronounced effects on serum potassium levels than spironolactone [21-25]. Other non-steroidal MRAs (esaxerenone and apararenone) have also been shown to significantly reduce albuminuria in CKD patients in phase 2 clinical trials [26]. In the recently published European Renal Association (ERA) synopsis for nephrology practice of the 2023 European Society of Hypertension (ESH) Guidelines for the Management of Arterial Hypertension, MRAs have not been commented as a potential treatment for KTR [27].

The current data add to the body of information regarding the safety of eplerenone in the kidney transplant population. However, the present study had certain limitations, which should be mentioned. It is a retrospective and observational study, providing associations rather than causation. Given the small sample size and cardiac indication for using eplerenone, we could not precisely evaluate the potential renoprotective effect. Selecting patients from a single transplant center could reduce our findings' generalizability.

In conclusion, eplerenone may be used cautiously in kidney transplant recipients with eGFR>35 ml/m2/1.73m2. Careful monitoring of all electrolytes and not only of potassium is mandatory. In our cohort, eplerenone increased uric acid levels. Further studies are required to elucidate eplerenone's and other MRA's clinical benefits and safety in this patient population.

Conflict of interest statement. None declared.

Reference

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Case report

Association of Autosomal Dominant Polycystic Kidney Disease and Abdominal Aortic Aneurysm - A Case Report

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Abstract

Introduction. Autosomal dominant polycystic kidney disease (ADPKD) is a systemic disease with multiple cysts in several organs. Formation of aneurysms of: the aorta, coronary and cerebral arteries are increasingly reported in the literature as extra-renal manifestations.

Case report. We report a 77-year-old male with ADPKD and long-standing hypertension, admitted to our ward due to an extreme weakness, malaise and abdominal pain with severe anemia and elevated serum levels of creatinine and urea. The treatment with hemodialysis and blood substitution was initiated. Abdominal echo-sonography showed hepatic cysts and polycystic kidneys. The cysts were filled with a clear content, in the right kidney toward the upper pole, two larger cysts were noted and an adjacent pulsatile cystic lesion with a hemorrhagically-filled content, highly suspicious for an aneurismatically dilated abdominal aorta. CT angiography of the aorta showed dilated, tortuous aorta with advanced atherosclerosis along its entire length. The dilatation was evident in the descending part of the aorta, with an infrarenal saccular dilatation before the bifurcation, that seemed to be thrombosed and a denser content was observed next to it, probably an older hemorrhagy, without imaging signs of acute extravasation of the contrast. Cardiovascular surgeon recommended coronography and coronary artery aneurisms were excluded. Unfortunately, the patient started to alternate with his consciousness and brain CT angiography showed corticoreductive changes, without any aneurism, or extra-or intra-axial hemorrhage. Due to the severe general condition, clinical assessment and advanced age of the patient, the case was declared as inoperable.

Conclusion. Due to a hypertension and associated connective tissue disorders patients with ADPKD are prone to develop aortic aneurysms, that should be questioned as a frequent feature in such patients. Hence, an early diagnosis and treatment decision based on a risk-benefit analysis, remain the cornerstone of management.

Keywords: Autosomal dominant polycystic kidney disease, arterial hypertension, abdominal aortic aneurysm

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic, progressive, systemic disease characterrized by the formation and growth of cysts primarily in the kidneys and other organs such as liver, pancreas and spleen, leading to an kidney enlargement and often progressive loss of renal function [1]. Another extra-renal maknifestations associated with this condition that are increasingly reported in the literature are: formation of aneurysms of the aorta, coronary and cerebral arteries [2,3].

The exact mechanisms underlying the association between ADPKD and aortic aneurysms are not fully understood, but it is believed to involve mutations in one of two genes PKD1 and PKD2, which encode polycystin-1 and -2, respectively. These proteins that contribute to the integrity of blood vessel walls are expressed in smooth muscle cells and myofibroblasts of the tunica media and in the endothelial layer of vessels, so that when they are mutated, they lead to abnormalities in connective tissue proteins, such as collagen, causing vascular wall weakness and formation of aneurysms [4].

The signs and symptoms of ADPKD can vary greatly from person to person and can range from mild to severe. Here are some common signs and symptoms associated with ADPKD: abdominal pain, hypertension, urinary tract infections, gross hematuria and nephrolithiasis. Hypertension is considered to be one of the most common early signs of ADPKD and it occurs in 50-75% of the patients, prior to loss of kidney function [5]. There are two main assumptions about the cause of hypertension in ADPKD: a primary vasculopathy secondary to mutations in the PKD1 and PKD2 genes

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that encode polycystine; and secondary to activation of the rennin-angiotensin-aldosterone system by cyst expansion and intrarenal ischemia. Which mechanism prevails, remains unknown [6].

Case report

We report a 77-year-old male with ADPKD and long-standing hypertension, with poor blood pressure control, admitted to our ward due to an extreme weakness, malaise and abdominal pain. Laboratory findings showed anemia with haemoglobin levels 65g/l and an elevated serum levels of creatinine 514 umol/L, urea 41 mmol/l, with elevated inflammatory markers C-reactive protein (CRP) 251 mg/l and leukocytosis $26x10^9$ /l. Treatments with hemodialysis and blood substitution were started, simultaneously administering a double, parenteral antibiotic. Abdominal echo-sonography showed hepatic cysts and polycystic kidneys. The cysts were fulfilled with a clear content, in the right kidney toward the upper pole, two larger cysts were noted and an adjacent pulsatile cystic lesion with hemorrhagically-filled content highly suspicious for an aneurismatically dilated abdominal aorta. The echo- cardiography showed: dilated aortic bulbus diameter 34 mm, arcus aortae dimensions- 25mm, descending aorta at left ventricle (LV) level with diameter 41mm. At 10 cm above the umbilicus, dilatation of the abdominal aorta was noticed, with maximum dimensions of 51x56 mm, and thrombosed section in the lumen with a dimension of 21-23 mm, with signs for recanalization. Aortic cusps were atheromatously changed, with normal function. Mild mitral and tricuspid regurgitation was present, without hemodynamic significance. Dimensions of the left cavities were slightly enlarged, with a moderate reduction of the global LV systolic function, and an ejection fraction (EF) of 48%, impaired diastolic function and a worsened LV relaxation (E/e 9.87). Computed tomography angiography (CTA) of the thoracic and abdominal aorta showed dilated, tortuous aorta with advanced atherosclerosis and significant atheromatous plaques presenting in concentric form, and a mixed character of calcifying plaques and intramural hematomas almost along its entire length (Figure 1 and 2). The dilatation was evident at the level of the descendenting aorta with diameter: 46 mm, thoracic aorta with diameter: 60 mm and aneurismatically expanded infrarenal aorta with diameter: 58 mm (Figure 3, 4 and 5). Infra- renal, at the level just before the bifurcation of the common iliac artery, a larger saccular aortic aneurysm with dimensions: cranio- caudal (CC)-8.5cm, latero- lateral (LL)-8.4cm and anterio- posterior(AP) - 10.5cm was observed, filled-up with a denser content and different zones of hemorrhage in organization. (Figure 6 and 7) Marked green arrows on (Figure 8) showed an anterior part around the aneurysm with a denser liquid collection highly suspicious for hemorrhage in organization and no signs of an active extravasation of the contrast.

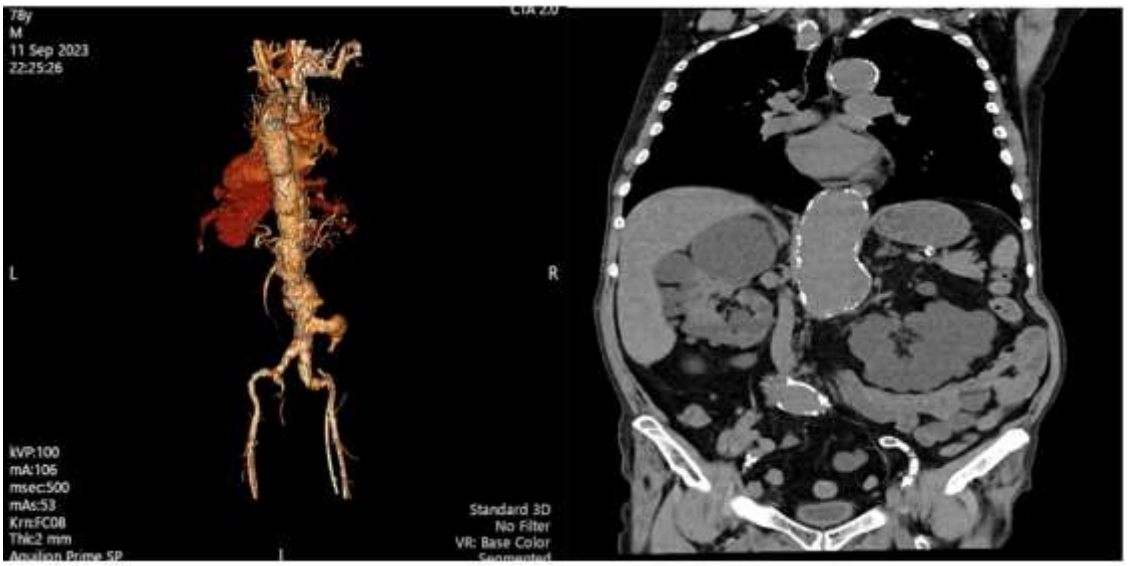

Fig. 1. and Fig. 2. Computed tomography angiography (CTA) of the thoracic and abdominal aorta showing dilated, tortuous aorta with advanced atherosclerosis along and significant atheromatous plaques, presenting in concentric form and mixed caracter of calcifying plaques and intramural hematomas almost along its entire length.

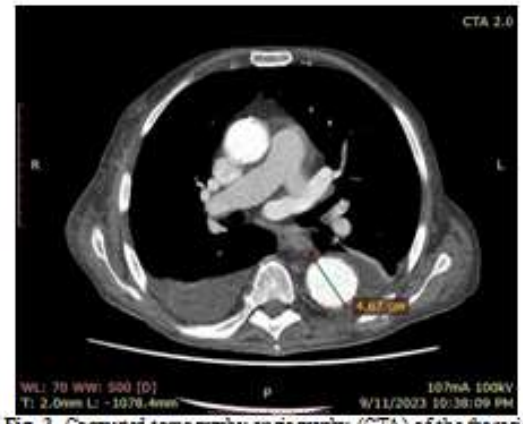

Fig. 3. Computed tomography angiography (CTA) of the thoracic aorta showing aneurismatically expanded descending aorta with diameter: 46 mm.

Fig. 4. Computed tomography angiography (CTA) of the thoracic aorta showing aneurismatically expanded thoracic aorta with diameter: 60 mm.

Fig. 5. Computed tomography angiography (CTA) of the aorta showing aneurismatically expanded infrarenal aorta with diameter: 58 mm.

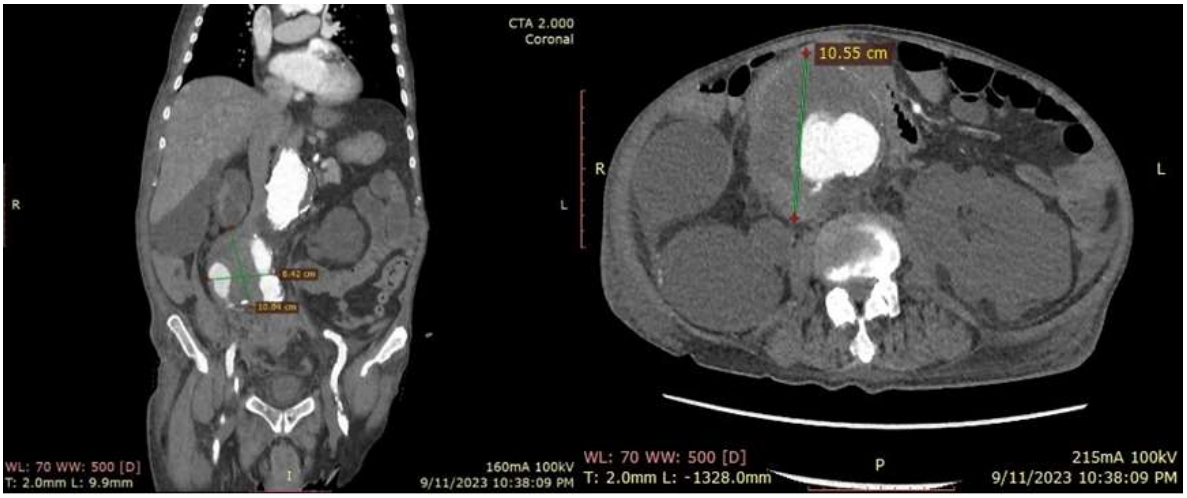

Fig. 6. and Fig. 7. Computed tomography angiography (CTA) of the abdominal aorta showing just before the bifurcation of the common iliac artery, a larger saccular aneurysm with dimensions CC - 8.5cm, LL - 8.4cm and AP - 10.5cm, filled with a denser content and different zones of hemorrhage in organisation.

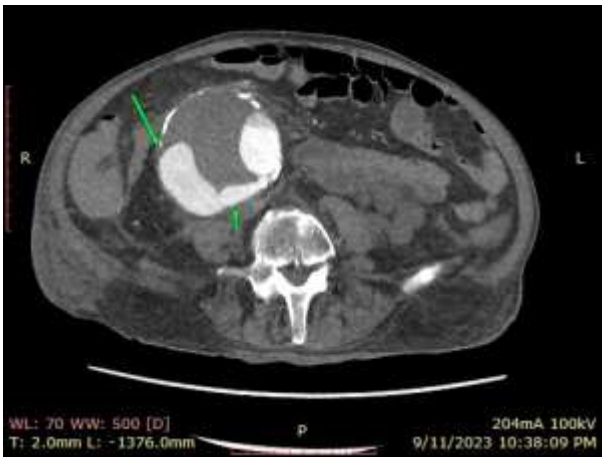

Fig. 8. Computed tomography angiography (CTA) of the abdominal aorta: green arrows showing anteriorly around the aneurysm a denser liquid collection highly suspicious for hemorrhage in organization and no signs of an active extravasation of the contrast.

The cardiovascular surgeon recommended coronary angiography and the finding was with plaques on the RCA and LAD, excluding coronary artery aneurisms. Unfortunately, the patient started to alternate with his consciousness and the brain CT angiography showed corticoreductive changes, without an aneurysm, or extra-or intra-axial hemorrhage. Due to the severe general condition, clinical assessment and advanced age of the patient, the case was declared as inoperable.

Discussion

Multiple renal and extra- renal cystic formation and growth is the core feature of ADPKD, due to the hereditary disruption of the PKD1 and PKD2 genes, resulting in a disturbance of the structure of polycystin 1 and polycystin 2 proteins in vascular smooth muscle, which in return causes further expansion of the vascular architecture and ultimately leads to extensive thoracic and abdominal aneurysm formation [7].

Original Ravine PKD1 diagnostic Criteria are: two or more cysts, unilateral or bilateral at the age from 15 to 29 years, two or more cysts in each kidney at the age of 30 to 59 years and four or more cysts in each kidney at the age of 60 years or older. These criteria are less accurate for diagnosing PKD2, and two notable characteristics are: Three or more total cysts in those aged 15 to 39 years have a positive predictive value of 100%, two or fewer cysts in those older than 40 years have a negative predictive value of 100% [8].

Due to the history of previous myocardial infarction and implanted coronary stent to RCA, coronary angiography was indicated to rule out an aneurysm dilatation of the coronary vessels. Neves *et al*., showed in their systematic review that 6 out of 23 patients with ADPKD (40%) had multiple coronary aneurysms, which is why this complication should be considered more often, although in the general population their occurrence is rare [9]. Jiang *et al*., in their systematic review reported that out of 76 patients with CAA, 3% of cases described the etiology of the aneurysm as ADPKD [3].

The most dramatic cardiovascular complication in patients with ADPKD is the rupture of an intracranial aneurysm (ICA). A family history of ICA rupture was a significant predictor identified in a retrospective study of 608 adults from 199 ADPKD families [10]. Due to a sudden alteration in level of the consciousness and movement difficulties in our case, a neurologist and psychiatrist were consulted, CTA of the brain was performed and corticoreductive changes were noted, without an aneurysm or an extra- or intraaxial bleeding. Kataoka *et al*., study showed that ICA in patients with ADPKD were associated with general risk factors such as: female sex, increased age, subarachnoid hemorrhage (SAH) history, but also with declining kidney function and increased kidney volume. The factors observed to be associated with ICA may contribute to an effective ICA screening and treatment planning in patients with ADPKD [11].

According to the National Institute for Health and Care Excellence (NICE) recommendations, all men aged 66 or more and women aged 70 or more should be screened especially for abdominal aortic aneurysm (AAA) if they have one of the risk factors such as: COPD, coronary, cerebrovascular or peripheral arterial disease, family history of AAA, hyperlipidemia, they smoke or used to smoke, including hypertension [12].

Another cohort study of Sung PH *et al*., concluded that ADPKD is a risk factor for developing AA and aortic aneurysm dissection (AAD), and hypertension, advanced age, and male gender were mentioned as independent risk factors for developing AA/AAD in ADPKD. Also, the ADPKD patients had more comorbidities than the general population, and those patients with coexistence of ADPKD and hypertension had much higher risk to develop AAD in the future [13]. Therefore, a strict blood pressure control in ADPKD patients is considered to be an important clinical issue for prevention of any vascular complication, especially for AA/AAD. This concept is also supported by current available consensus guidelines for most patients with ADPKD, with the goal of blood pressure to be at 120 to 125/<80 mmHg-using the non-routine [preferred] measurement methods including standardized office blood pressure monitoring (OBPM), home blood pressure monitoring (HBPM), and daytime ambulatory blood pressure monitoring (ABPM) or 125 to 130/<80 mmHg (using routine OBPM) [14].

According to NICE recommendations, aneurysm repair is considered for people with an unruptured AAA in case of symptomatic aneurysm, asymptomatic and larger than 4.0 cm with a growth by more than 1 cm in 1 year, or asymptomatic measuring ≥5.5 cm [12]. Our case was declared to be inoperable due to a severe ge-

neral condition, the clinical assessment and the advanced age of the patient.

Conclusion

Due to a hypertension and associated connective tissue disorders patients with ADPKD are prone to develop aortic aneurysms, that should be questioned as a frequent feature in such patients. A careful preventive monitorring with periodic clinical and ultrasound check-up, as well as a rigorous BP control could reduce the risk of AA and improve the outcome of these patients, hence early diagnosis and treatment decisions based on a risk-benefit analysis, remain the cornerstone of the management.

Conflict of interest statement. None declared.

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