



Endothelin-1 Level in Patients with Simple Renal Cyst

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Abstract

Introduction: Endothelin-1 (ET-1) is potent vasoconstrictive peptide and elevated ET-1 levels are associated with hypertension, endothelial dysfunction and atherosclerosis. Research on (ET-1) has demonstrated that elevated ET-1 levels in autosomal dominant polycystic kidney disease leads to systemic hypertension. The prevalence of simple renal cysts increases with age and the association with simple renal cyst and hypertension is not clear. The aim of this study was to investigate the ET-1 levels in patients with simple renal cyst and compare them with those in healthy adults.

Materials and methods: The study included patients that underwent laparoscopic renal cyst decortication in the Department of Urology and healthy controls. Serum and urinary ET-1 levels were measured before surgery and one month after it in the patients with simple renal cyst. Serum ET-1 levels were measured in healthy adult patients. Ambulatory blood pressure was measured in all patients. Glomerular filtration rate was measured according to the chronic kidney disease epidemiology collaboration formula.

Results: Thirty-two patients were included in the present study. Of these, 16 patients with simple renal cyst were allocated into group 1 and 16 healthy patients - in group 2. There was no significant difference between systolic and diastolic blood pressure between the groups ($p=0.820$ and $p=0.618$, respectively). Serum EL-1 levels were significantly lower in group 1 than those in group 2 ($p=0.036$). Interestingly, serum EL-1 levels were increased after laparoscopic cyst decortication and there was no significant difference with healthy patients ($p=0.429$).

Conclusions: The present study demonstrated that serum EL-1 level in patients with simple renal cyst was lower than that in healthy people. Further studies are needed to investigate the EL-1 levels in simple renal cyst patients.

Key words

Bosniak, decortication, endothelin-1, simple renal cyst, laparoscopy

INTRODUCTION

Hickey et al. were the first to describe an endothelium derived factor which was thought to be a peptide hormone

after analyzing the bovine aorta in 1985.¹ Three years later, Yanagisawa et al.² identified a new factor called endothelin (ET) from the porcine aortic endothelial cells. There are three forms of ET in human tissues called ET-1, ET-2,

and ET-3 and two receptors including ET_A and ET_B.³ While ET-1 and ET-2 were more potent than ET-3 (ET-1 = ET-2 > ET-3) for ET_A, all three isoforms were equally effective (ET-1=ET-2=ET-3) for ET_B.

Endothelin-1 is a 21-amino-acid peptide which is converted from 39 amino-acid (big endothelin described by Yanagisawa) by endothelin converting enzymes.³ Endothelin-1 is vasoconstrictive, inflammatory and mitogenic peptide and elevated ET-1 levels are associated with hypertension, endothelial dysfunction and atherosclerosis.⁴ In addition, ET-1 directly promotes mesangial cell proliferation and involves in matrix protein biosynthesis in kidney.⁵

The progressive cyst enlargement causes the stimulation of intrarenal renin-angiotensin-aldosterone system thus resulting in the increased sympathetic activity and ET-1 levels in autosomal dominant polycystic kidney disease (PKD) leading to systemic hypertension.⁶ In the mouse model of congenital PKD, the authors found the renal ET-1 mRNA levels were 3.2- and 10-fold greater than controls at 1 week and 3 weeks when cystic disease was at its highest.⁷

The prevalence of simple renal cyst is more than 5% at the age of 40 and 36% at 80 and increases with age.⁸ The relationship between simple renal cysts and hypertension is not clear and there are contradictory results in the literature. The aim of this study was to measure the ET-1 levels in patients with renal cyst and to compare these with healthy population.

MATERIALS AND METHODS

This study included the patients who underwent laparoscopic renal cyst decortication (LRCD) between January 2016 and March 2017 and some healthy adult patients. The patients with renal cysts were included in group 1 and the healthy people (controls) were in group 2. The present prospective study was approved by the Ethics Committee of Hitit University (2016-50) and written informed consents were obtained from the participants.

Fasting venous blood and 24-hour urinary samples were collected from all patients. The same samples were taken from the patients in the group after 1 month from the LRCD. After centrifuging the blood samples, all samples (blood and urine) were stored at -80°C.

Laboratory tests included serum creatinine, C reactive protein, complete blood counts, 24-hour sodium, creatinine, albumin levels. The glomerular filtration rate (GFR) was calculated using the chronic kidney disease epidemiology collaboration formula. Medical histories (diabetes, hypertension) were taken and lifestyle factors (smoking and alcohol) were recorded. The antihypertensive drugs were changed in the patients using angiotensin II antagonists and angiotensin converting enzyme blocker drugs before the operation. The ambulatory blood pressure was taken in all patients and 1 month after the LRCD. Concentrations of ET-1 were measured by ELISA using commercially available kits, in accordance with the manufacturers' instructions.

The cysts were diagnosed using ultrasonography and contrast enhanced computed tomography was performed for the differential diagnosis of cystic renal malignancies (Fig. 1). The patients in group 2 were controlled with ultrasonography for renal cyst. The volume (V) of the cyst was calculated using the formula $V = (l \times w \times d) \times 0.523$ where l is length, w is width, and d is depth.

Surgical techniques

Laparoscopic renal cyst decortication was performed with transperitoneal and retroperitoneal techniques by one and same surgeons (SÇ, MS). The bladder catheterization was performed with the patients in lateral decubitus position under general anaesthesia. Transperitoneal approach: CO₂ was used for pneumoperitoneum using mini laparotomy technique through a 1-cm incision in the periumbilical area. After 11-mm port was inserted for the laparoscopic 30° lens, the intra-abdominal pressure was set between 12-14 mm Hg. After the other two ports were inserted under direct vision, the lateral peritoneal line of the Toldt fascia was cut and the colon was reflected medially. The cyst was dissected from the fat and other tissues and opened using L-hook monopolar device (Figs 2, 3).

Retroperitoneal approach: 1-cm transverse skin incision was made over the mid-axillary line, 1 cm inferior the 12 rib. The musculature was spared by blunt dissection and a balloon dissection trocar. After the camera was inserted, two 5-mm trocars were inserted under direct vision in the anterior and posterior axillary lines below the ribs. The Gerota's fascia was opened to reach the kidney and the cyst wall was recognized. The cyst was dissected from adjacent fat tissues.

The fluid was aspirated and cyst wall excised by monopolar and bipolar scissors in two techniques. A surgical drain was routinely placed and removed one day after the operation.

Exclusion criteria

Patients with autosomal dominant polycystic kidneys, asymptomatic simple cysts, history of previous open or laparoscopic surgery, radiologic diagnosis of Bosniak type IIF, III, and IV, and history of any malignancy were excluded from the study.

Statistical analysis

All statistical analyses were performed using MedCalc Statistical Software demo version 17.6 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2017). Kolmogorov-Smirnoff analysis was used to verify the data as normal distribution or not. The mean ± standard deviation and median values (IQR) were used for data which had normal distribution or not. Mann-Whitney U-test, Wilcoxon signed rank test and t test were used to compare the results of the groups. The chi-squared test was used to compare categorical variables.



Figure 1. Image of the cyst on computed tomography.

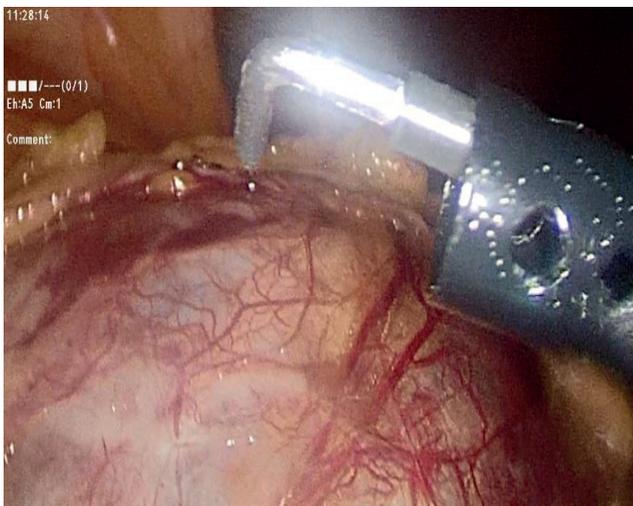


Figure 2. Laparoscopic cyst image after dissection from fat and the other tissues.

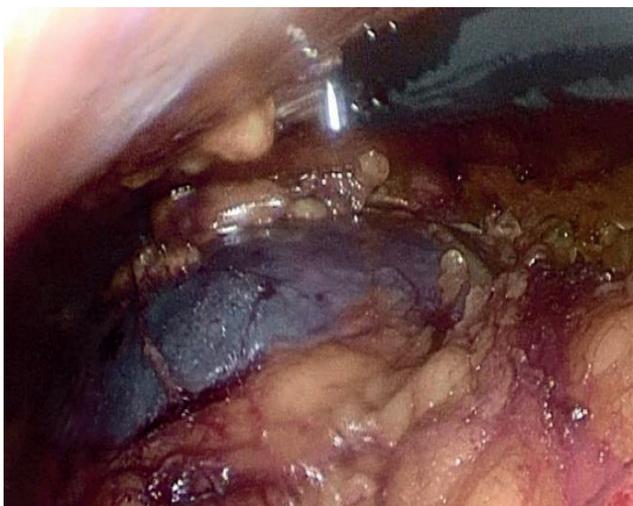


Figure 3. The L-hook monopolar device was used to open the cyst wall.

RESULTS

There were 32 patients in the present study divided into two groups each of 16 patients. The median age of the patients in the two groups was 59.5 yrs and 56.68 yrs, respectively. There was no significant difference between groups in their systolic and diastolic blood pressure ($p=0.820$ and 0.618). Diagnosis of hypertension was reported in 6 patients in group 1. The patient characteristics are shown in **Table 1**.

Serum ET-1 levels were significantly higher in group 2 ($p=0.036$). There was no significant difference between the patients in group 1 a month after surgery. Although serum ET-1 levels increased after surgery, there was no significant difference between the patients with renal cyst after 1 month from surgery and healthy patients ($p=0.429$). The median level of urinary ET-1 was 137 ng/ml and increased to 193 ng/ml one month after operation. The difference did not reach statistical significance ($p=0.216$) as seen in **Table 2**. Although some of the parameters such as GFR, serum and urinary ET-1s were increased there was no significant difference between the results.

No complication occurred in the patients who underwent laparoscopic surgery. Transperitoneal and retroperitoneal techniques were used in 13 and 3 patients, respectively. Cyst localization was 8 in low, 5 in middle and 3 in the upper pole of the kidney. The cyst laterality: 10 was right and 6 was left kidney.

DISCUSSION

The prevalence of simple renal cyst (SRC) is between 20-50% in the general population and the incidence of the condition increases with age.⁹ Researchers from Korea reported that the renal cyst prevalence was 2.5% and 1.4% under the age of 40 and increased to 30.1% and 18.3% aged more than 70 years in male and female patients respectively.¹⁰ The general prevalence of renal cyst was 7.8% in all participants. Özveren et al.¹¹ found the renal cyst prevalence to be 7.7%. The patients with SRC usually present with hematuria, infection, obstruction, and hypertension.¹²

The relation between hypertension and SRC has been described in many studies.^{8,10,12} The authors showed that the prevalence of hypertension, systolic, diastolic and mean blood pressures were higher in patients with renal cyst than in the control group.¹⁰ In addition, the patients with multiple cysts, large cysts and peripheral cysts had higher hypertension prevalence than the patients with single, small cyst and perihilar cyst. The GFR of the patients with multiple cysts had lower than single cyst and control groups. Kim et al.⁸ reported that incidence of hypertension was higher in the newly diagnosed simple renal cyst group with odds ratio of 1.53. However, there is no significant risk of hypertension when one simple cyst and unilateral cyst, but bilateral cyst and ≥ 2 or 3 cysts, larger than 1 cm increase the hypertension risk significantly. Afsar et al.¹² found that the patients with multiple cysts had higher ambulatory di-

Table 1. Patients' characteristics and lab results before laparoscopic surgery

	Group 1	Group 2	p value
Number of patients, n	16	16	
Age, yrs	58 (52-69)	56 (52-62)	0.32
Gender			
Male, (%)	5 (31)	8 (50)	0.28
Female, n (%)	11 (69)	8 (50)	
Hypertension, n (%)	6 (37.5)	0 (0)	<0.05*
Diabetes mellitus, n (%)	3 (19)	0 (0)	0.07
Systolic BP, mmHg	118 (108-133)	120 (115-130)	0.82
Diastolic BP, mmHg	80 (71-85)	80 (77.5-80)	0.61
Blood urea nitrogen, mg/dL	14 (11-15)	14.5 (11-19)	0.55
Creatinine, mg/dL	0.76 (0.67-0.86)	0.73 (0.62-0.8)	0.38
White blood cell*, 10 ⁶ /L	6595 (5215-8370)	7999 (6515-9565)	0.14
Glucose, mg/dL	103 (92-115)	90 (85-97)	0.01*
Na, mEq/L	138(137-139)	140 (138-141)	0.02*
Uric acid, mg/dL	5.9 (4.8-6.6)	4.70 (3.82-5.64)	0.02*
HDL, mg/dL	44 (38-50)	58(53-65.5)	<0.05*
LDL, mg/dL	103 (97-109)	143 (116-155)	<0.05*
Cholesterol, mg/dL	168 (155.5-184)	234 (208-244)	<0.05*
Triglyceride, mg/dL	116 (82-157.5)	125 (90-187)	0.43
CRP, mg/dL	3.3 (3.15-3.5)	3.16 (3.14-3.9)	0.42
GFR, ml/dk/1.73m ²	95 (91-105)	101 (93-109)	0.32
Proteinuria, mg/day	99 (90-180)	75 (70-94)	0.02*
Serum endothelin-1, ng/L	63 (32-101)	85 (72-137)	0.03*

Data are expressed as median (IQR) values. Mann Whitney U and chi-squared tests were used for comparisons.

BP: blood pressure; GFR: glomerular filtration rate; * statistically significant

astolic blood pressure, ambulatory arterial blood pressure and ambulatory heart rate when compared to the patients with a solitary cyst. They also found that the ambulatory systolic blood pressure, office systolic blood pressure and ambulatory heart rate were higher and creatinine clearance was lower of the patients with bilateral renal cyst than the patients with unilateral cyst. Chin et al.¹⁰ reported that the hypertension and blood pressures were higher in patients with renal cyst than the others. On the contrary the authors described that there was no association between renal cyst and hypertension.^{13,14} The mechanisms between SRC and hypertension is not clear, but activation of renin-angiotensin system, loss of nephrons are hypothetical theories.⁸

Endothelin-1 is a peptide which has vasoconstrictive,

inflammatory, and mitogenic activities.⁴ The pathophysiological pathways of autosomal dominant polycystic renal disease; compression of the renal vasculature leads to ischemia, hypoxia and activation of renin-angiotensin system increases the ET-1 synthesis.⁶ Endothelin-1 stimulate cyst growth and interstitial fibrosis through ET-A and ET-B receptors with vasopressin dependent and independent mechanisms. Increased ET-1 concentrations lead to systemic hypertension.⁶ The authors reported that plasma ET-1 levels were higher by 42% in hypertensive patients than in control patients.¹⁵ The effect of endothelin-1 on blood pressure occurs via tubular water and salt excretion, constriction of smooth muscle cells, modulating sympathetic nerve activity and vasodilatation with nitric oxide. The articles

Table 2. Renal functions of the patients with simple renal cysts in the preoperative period and 1 month after surgery

	Before operation	1 month after operation	<i>p</i>
Number of patients, n	16	16	
Systolic BP, mmHg	119±16	123±14	0.469
Diastolic BP, mmHg	78±12	80±11	0.584
Creatinine, mg/dl	0.76(0.7-0.9)	0.71(0.6-0.8)	0.063
CRP, mg/L	3.3(3.15-3.5)	3.3(3.1-3.3)	0.733
Serum endothelin, ng/L	63(32-101)	85.8(37.3-123.9)	0.325
Urinary endothelin, ng/day	139(59.7-246)	193(107.2-333)	0.216
GFR, ml/dk/1.73m ²	95(91.5-105)	97.5(92.2-109.5)	0.934

Data are expressed as mean ± standard deviation and median (IQR) values. Wilcoxon signed rank test and t test were used for statistical analysis.

about ET-1 are about autosomal dominant PKD in the literature. To the best of our knowledge, this is the first study investigating the relationship between SRC and ET-1 levels.

Although SRCs are common in the general population they are diagnosed incidentally and the clinical presentations include pain, hematuria, hypertension and urinary system obstruction.⁹ Surgical treatment is needed when the patients are symptomatic. Percutaneous aspiration, open surgery and laparoscopic techniques are the treatment modalities. Laparoscopic decortication is the gold standard and advantages for minimal invasiveness and high success rate when comparing the open surgery and percutaneous aspiration.¹⁶ The authors investigated the efficacy of LRCD and percutaneous aspiration with sclerosing agent and found that LRCD is more successful than percutaneous intervention for recurrence. The other advantage of laparoscopic technique is minimal invasiveness which play important role for analgesic use, short hospital stay and small incision.¹⁷

The present study has some limitations among which are the small number of studied patients and the short follow-up. The histopathological and molecular studies could be more objective than serum levels for evaluating the ET-1 for cyst pathogenesis.

CONCLUSIONS

The current study showed that serum ET-1 levels were lower in patients with simple renal cyst. After laparoscopic cyst decortication, the level of ET-1 increased. Further studies are needed to define the relationship between ET-1 and renal cystic disease.

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Уровни эндотелина-1 у пациентов с простыми кистами почек

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Абстракт

Введение: Эндотелин-1 (ЭТ-1) является мощным вазоконстриктивным пептидом, а повышенные уровни ЭТ-1 связаны с гипертензией, эндотелиальной дисфункцией и атеросклерозом. Исследование ЭТ-1 показывает, что повышенные уровни ЭТ-1 при аутосомно-доминантной поликистозной болезни почек приводят к системной гипертензии. Частота возникновения простых кист почек увеличивается с возрастом, и связь между простыми кистами почек и гипертензией неясна. Цель этого исследования состояла в том, чтобы изучить уровни ЭТ-1 у пациентов с простыми кистами почек и сравнить их с таковыми у здоровых лиц.

Материалы и методы: В исследование были включены пациенты, перенёвшие лапароскопическую декортикацию почечной кисты в отделении урологии и контрольная группа из здоровых лиц. Уровни ЭТ-1 в сыворотке и уровни его в моче были исследованы до операции и через месяц у пациентов с простыми кистами почек. Уровни ЭТ-1 в сыворотке также измеряли у здоровых взрослых пациентов. Амбулаторно артериальное давление измерялось у всех пациентов. Скорость клубочковой фильтрации была измерена с использованием формулы СКД-ЕПИ (*the Chronic Kidney Disease Epidemiology Collaboration*).

Результаты: В исследование было включено 32 пациента. Из них 16 пациентов с простой кистой почек были отнесены к группе 1, а 16 здоровых пациентов - к группе 2. Не было значимого различия между систолическим и диастолическим давлением между группами ($p = 0,820$ и $p = 0,618$ соответственно). Уровни сывороточного ЭЛ-1 были значительно ниже в группе 1, по сравнению с группой 2 ($p = 0,036$). Интересно, что уровни ЭЛ-1 в сыворотке увеличивались после лапароскопической декортикации кисты и не отличались значительно от уровней у здоровых пациентов ($p = 0,429$).

Выводы: Настоящее исследование показало, что уровни ЭЛ-1 в сыворотке были ниже у пациентов с простыми кистами почек, чем у здоровых пациентов. Необходимы дальнейшие исследования для изучения уровня ЭЛ-1 у пациентов с простыми кистами почек.

Ключевые слова

Bosniak, декортикация, лапароскопия, простая киста почки, эндотелин-1