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Renal Resistive Index and Renin-Angiotensin-Aldosterone System Components as Early Indicators of Kidney Damage in Persian Cat Polycystic Kidney Disease

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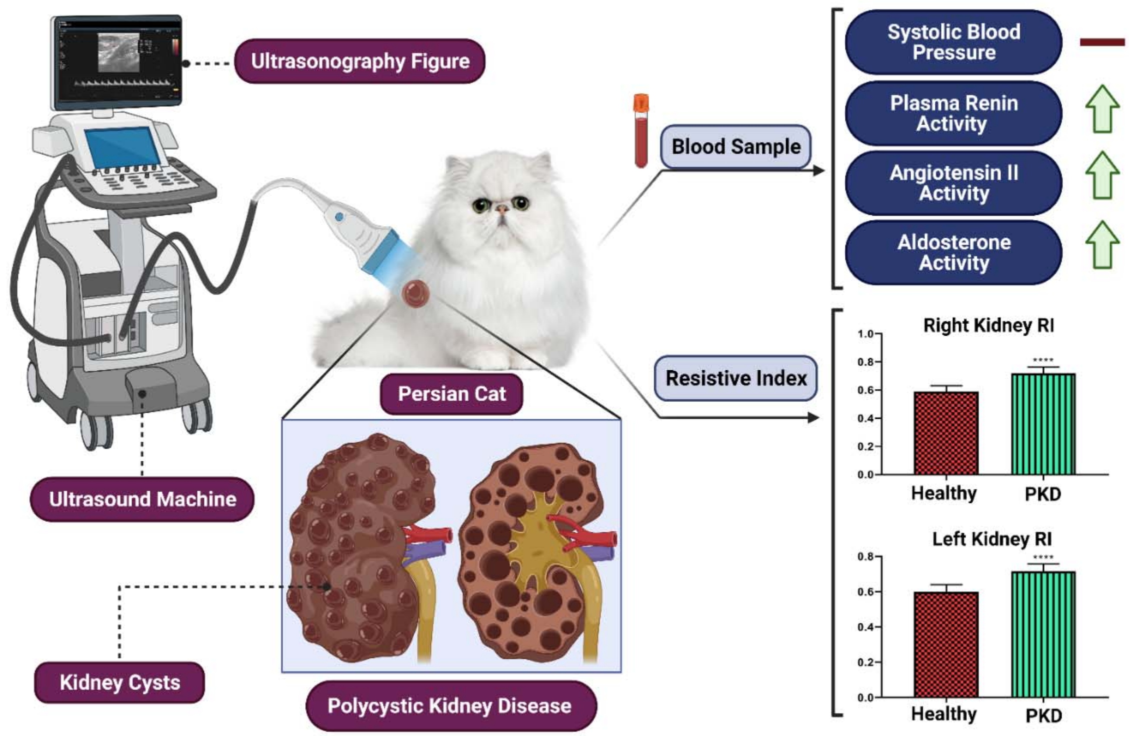

Abstract

Background: Polycystic kidney disease (PKD) in Persian cats is a common genetic disorder that accounts for 10% of chronic renal failures.

Objectives: This study aimed to assess the effect of PKD progression on renal resistive index (RI), plasma renin activity (PRA), angiotensin II (ANG II), aldosterone levels and systolic blood pressure in Persian cats.

Methods: Fifty Persian cats (25 PKD and 25 healthy) were included in the present study. The blood pressure of each cat was measured, and then PRA, ANG II, and aldosterone enzymes were evaluated by ELISA test. Additionally, B-Mode ultrasonography was performed in PKD group to evaluate and calculate the diameter and overall volume of cysts (OVC). Furthermore, the RI was computed by pulsed-wave Doppler in all cats.

Results: There were no significant differences in the systolic blood pressure between healthy and PKD cats (138.84±2.89 mmHg and 140.92±2.35 mmHg). PRA, aldosterone, and ANG II were significantly higher in the PKD group compared to the healthy group; 3.64±0.36 vs 2.26±0.029 ng/ml ($p<0.01$), 80.45±2.35 vs 30.98±1.75 pg/ml ($p<0.0001$), and 53.54±3.22 vs. 30.08±3.06 pg/ml ($p<0.0001$), respectively. Statistically significant increases ($p<0.0001$) were detected in RIs of right and left kidneys in PKD cats (0.72±0.01 and 0.71±0.008, respectively) compared with healthy cats (0.59±0.008 and 0.60±0.008). The statistical analysis showed a strong direct correlation between RI changes and the right or left kidney OVC ($p<0.001$), in which manifest the correlation between RI increase and renal disease progression.

Conclusion: Increase in renin-angiotensin-aldosterone activity, and RI in Persian cats diagnosed with PKD can be valuable diagnostic tools for their renal disease progression. However, our results showed that the systemic blood pressure is maintained and stays in its normal ranges.

Keywords: Aldosterone, angiotensin II, Persian cat, polycystic kidney disease, resistive index, renin

1. Introduction

Polycystic kidney disease (PKD) is a prevalent genetic disorder in felines, affecting Persian cats and outcrossed breeds. The condition is characterized by the formation of cysts in the kidneys, liver, and occasionally, the pancreas. According to a previous report, PKD is responsible for 10% of chronic kidney failure in cats and has been reported with a prevalence of 37-49% in long-hair cats, including Persian cats associated with PKD-1 gene mutation (Vidiastuti et al., 2020). As seen in pathophysiology, the kidney tubules become cyst-like in PKD, which results in the gradual destruction of the renal parenchyma, and renal failure (Bosje et al., 1998). In humans during manifestation and progression of PKD, increased blood pressure is found to complicate the clinical condition and leads to end-stage renal disease (ESRD) (Pedersen et al., 2003). Also, an increase in blood pressure seems to be related to the rate of renal cystic involvement in the autosomal dominant polycystic kidney disease (ADPKD) and also the increase in the activity of the renin-angiotensin-aldosterone system (RAAS), caused by hypoperfusion and renal ischemia due to the development of renal cysts (Pedersen et al., 2003). Increase in blood pressure also reported to be associated with overall renomegaly as a consequent of higher number of cysts. Due to the increase in blood pressure, cardiac blood perfusion increases, and subsequently hypertrophy of the left ventricle will be seen (Philips et al., 2007; Chapman et al., 1991).

In feline physiology, RAAS is pivotal in the modulation of arterial blood pressure. Post renal injury, a surge in angiotensin II levels could theoretically exert effects on both local and systemic hemodynamics (Lourenço et al., 2022). Contrarily, empirical studies demonstrate that exogenous aldosterone administration in rats precipitates an elevation in blood pressure and consequent renal pathology (Lourenço et al., 2022). A myriad of nephropathic alterations in rodent models are postulated to be induced and exacerbated by aldosterone re-administration, irrespective of the pharmacological attenuation of angiotensin II activity (Navar et al., 1994). Furthermore, adrenalectomy subsequent to partial nephrectomy in rodent subjects has been evidenced to mitigate the ensuing hypertensive response (Navar et al., 1994). Investigations into PKD in murine models have underscored the preeminence of the RAAS in hemodynamic regulation, noting anomalously elevated levels of angiotensin I and II in both circulatory assays and immunohistochemical analyses of polycystic renal tissues (Philips et al., 2007). Moreover, there is a marked upregulation in the expression of intrarenal renin, angiotensin II, and angiotensin-converting enzyme (ACE) in these pathological contexts (Philips et al., 2007).

Diagnostic imaging is also an essential tool to evaluate renal diseases, especially for diagnosing feline PKD (Paepe et al., 2013). Radiography and excretory urography can be used in more advanced cases to estimate renal function, but their findings will not necessarily benefit patient management; thus, ultrasonography is preferential (Guerra et al., 2019). Moreover, ultrasound can be used to evaluate renal morphology and detect renal cysts and is a non-invasive, safe, and inexpensive method widely available in veterinary practices (Guerra et al., 2019). Cysts are anechoic to hypoechoic spheres with thin walls in ultrasonography, ranging from a few to over ten millimeters. In cats older than six months old, ultrasound's sensitivity, specificity, and reproducibility are reported approximately 91-96.2%, 91-100%, and 100% in the diagnosis of PKD, respectively (Yu et al., 2019; Schirrer et al., 2021). Also, doppler ultrasonography measures the blood flow velocity in renal arteries during systole and diastole, enabling calculation of the resistive index (RI) as an indicator of renal blood flow resistance (Tipisca et al., 2016). RI assessment is useful for diagnosing feline kidney disease and detecting renal vascular damage. Elevated RI levels in cats with kidney disease are associated with unfavorable outcomes such as renal failure and cardiovascular events (Lai et al., 2018).

The current investigation sought to assess the prognostic implications of plasma concentrations of renin, angiotensin II, and aldosterone as indicators of disease severity in Persian cats diagnosed with PKD during its incipient phases. Furthermore, the research aimed to elucidate the potential correlation between the RI and the severity of PKD within this specific feline cohort.

Materials and Methods

2.1. Experimental Animals

Fifty Persian cats (25 PKD and 25 healthy) were included in the present study. Animal care and the practical steps were performed in full accordance with the criteria of care and use of institutional animals, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran (Ethical code: 76/268178, 1400/9/22). The Persian cats with age more than six months old, without considering their gender, which were referred to the small animal teaching hospital of faculty of veterinary medicine of Tehran University from December 2021 to November 2022, were all considered as potential participants in the present study.

2.2. Study Design

After general examination, auscultation, electrocardiogram (ECG), and echocardiography were performed to check the cardiac condition. Complete blood count (CBC) and biochemistry tests (CBT) were done. Additionally, thyroid factors (T3-T4-TSH), urinary tract infections (in which checked with urinalysis and culture), and urine protein to creatinine ratio were evaluated. If the Persian cats were normal in all the mentioned criteria, then underwent fast screening abdominal ultrasonography to check whether they have polycystic or healthy kidneys. Finally, 25 PKD and 25 healthy cats were included to the study for further investigations such as systolic blood pressure measurement, hormone analysis and abdominal ultrasonography.

2.3. Systolic Blood Pressure Measurement

A non-invasive cuff using an integrated sensor (SunTech Vet25, USA) was used to measure blood pressure. An inflatable 2.5cm cuff was tied on the animal's left clipped antebrachium, and blood pressure was measured. Blood pressure was calculated five times in a row, and the average record was submitted. Blood pressure was recorded before any other intervention interfering with blood pressure, including blood collection, which was done for hormone analysis (Henik et al., 2005)

2.4. Blood Collection and Hormone Analysis

After the blood pressure evaluation, blood was collected by superficial veins to reduce stress in the animal. The Enzyme Immunoassay (EIA) Kit was used to determine plasma renin activity (ELH-Renin; RayBiotech; UK), angiotensin II (EIA-ANG II; Raybiotech; UK), and aldosterone (EU2580; Fine Test; China) levels. Blood samples were collected in prechilled tubes containing EDTA to measure these factors and stored on the ice at 4°C. The samples were centrifuged at 3,000×g for 20 min at 4°C and kept at −80°C until extraction. Within four months after blood sampling, the hormonal determination was performed in one ELISA run (Ward et al., 2022).

2.5. Kidney Ultrasonography

The cat's abdominal hair was clipped and after environmental adaptation (10 minutes) they have been restrained physically in lateral recumbency on the table then the skin was cleaned with alcohol. Ultrasound was performed by an expert veterinary radiologist using a high-resolution ultrasound device (Phillips Affinity 70g, Netherlands) with a 5-12 MHz multi-frequency linear transducer. The volume of each kidney in both PKD and healthy Persian cats groups was calculated. The diameter (d) of each cyst was measured, and the volume of each cyst was derived with the sphere volume formula ($V= \frac{1}{6}\pi d^3$), then overall volumes of all cysts in each kidney were calculated. Then the occupying percentage of each kidney was calculated based on the total volume of all cysts of the same kidney (Debruyn et al., 2012).

Color Doppler was used to visualizing the intrarenal vasculature. The RI was determined for each kidney based on three to five waveform averages of the interlobar arteries automatically (**Figure 1**). To measure the value of RI of the renal arteries branches, first the interlobar artery was identified with color Doppler ultrasound. A less than one millimeter gate of pulsed-wave Doppler was placed on the interlobar artery. The wall filter and the pulse repetition frequency were set to the lowest values to allow the best assessment of the flow shown. Resistive indices were calculated automatically from the average of 3 to 5 waves recorded for each kidney based on the following **formula 1** (Debruyn et al., 2012; Heine et al., 2007).

Formula 1: Resistive index = (peak systolic velocity – end-diastolic velocity) / (peak systolic velocity)

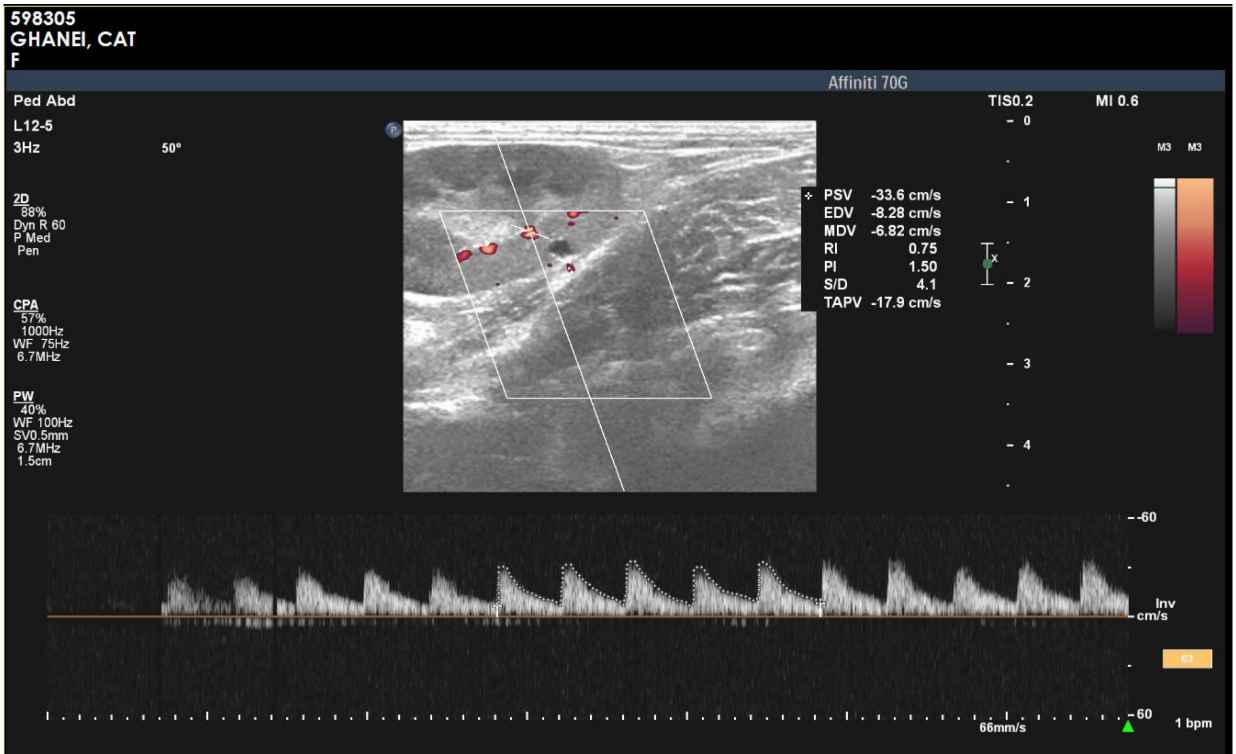

Figure 1. Color Doppler ultrasound image and measurement of the resistive index of an interlobar artery in a PKD Persian cat

2.6. Statistical analysis

Statistical analysis was performed using SPSS version 26 software. Descriptive data were expressed as mean ± standard error (Mean ± SEM). An Independent t-test was used to analyze indices in cystic and non-cystic groups. Pearson and Spearman correlation coefficients were used to measure the correlation between variables. A p-value less than 0.05 were statistically considered significant.

3. Results

3.1. Systolic Blood Pressure

The systolic blood pressure values were (140.92±2.35 mmHg) in PKD and (138.84±2.89 mmHg) in healthy Persian cats. No statistically significant difference was detected between PKD and healthy groups (*p>0.05*) (**Figure 2**).

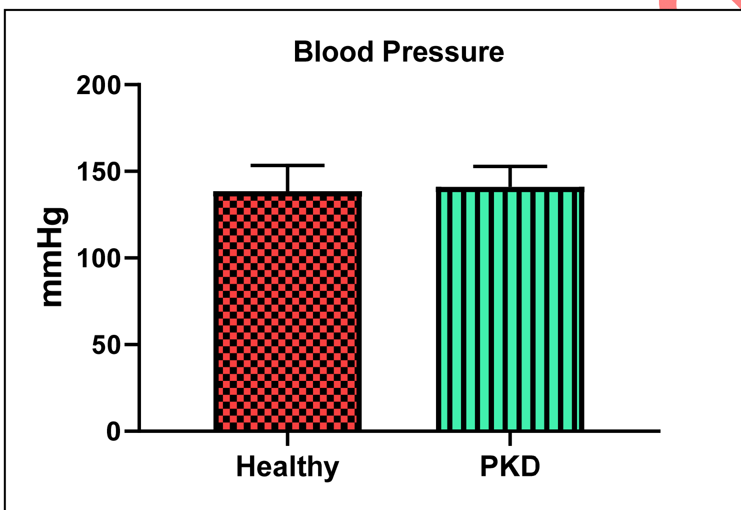

Figure 2. Systolic blood pressure in the polycystic kidney disease (PKD) and healthy groups. Data are shown as the mean ± SD, n = 25.

3.2. Plasma Renin, Angiotensin II, and Aldosterone Activity

The results of hormones analysis including: plasma renin, angiotensin II, and aldosterone activity changes in PKD and healthy Persian cats are shown in **figure 3.** The amount of renin, angiotensin II, and aldosterone showed a statistically significant increase in the PKD group compared to the healthy group respectively (*p<0.01, p<0.0001, and p<0.0001*).

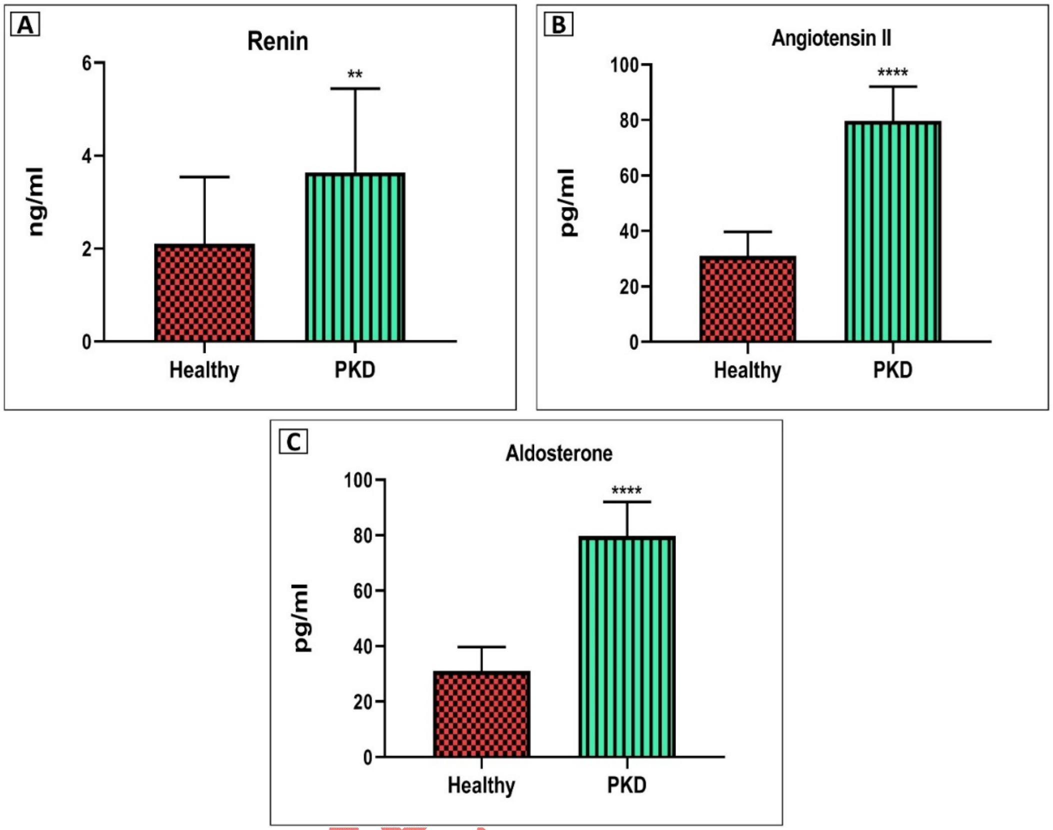

Figure 3. Renin (**A**), angiotensin II (**B**), and aldosterone (**C**) activity in the polycystic kidney disease (PKD) and healthy groups. Data are shown as the mean ± SD, n = 25. The mean values with asterisks are significantly different (*p≤ 0.05*).

3.3. Resistive Indices Analysis

The mean values for RI in healthy and PKD cats were 0.59 ±0.008 and 0.71 ±0.01, respectively. The RI of the right and left kidneys were compared separately in the PKD and healthy groups and showed statistically significant differences (**Figure 4**). As it is shown in figure 4, the amount of RI in PKD showed a significant increase in both sides of the kidneys compared to the healthy group (*p<0.0001*).

Using Pearson's correlation coefficient, an incomplete, direct, strong, and significant correlation was observed between the percentage of right and left kidney occupation with cysts and right and left kidney RI (R=0.872, *p<0.001* and R=0.858, *p<0.001*, respectively) (**Figure 5**).

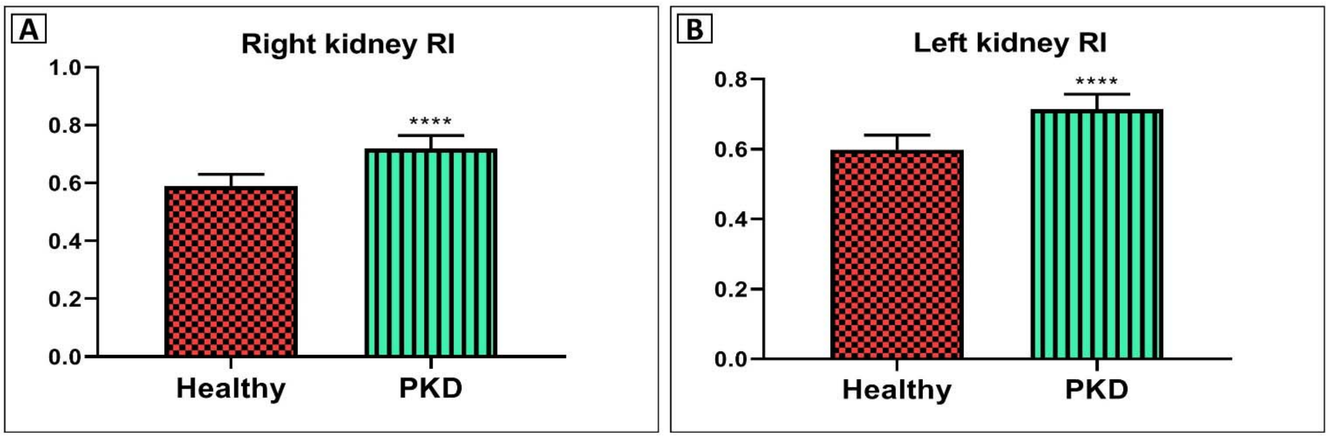

Figure 4. Resistive indices in the polycystic kidney disease (PKD) and healthy groups. Data are shown as the mean ± SD, n = 25. The mean values with asterisks are significantly different (*p≤ 0.05*).

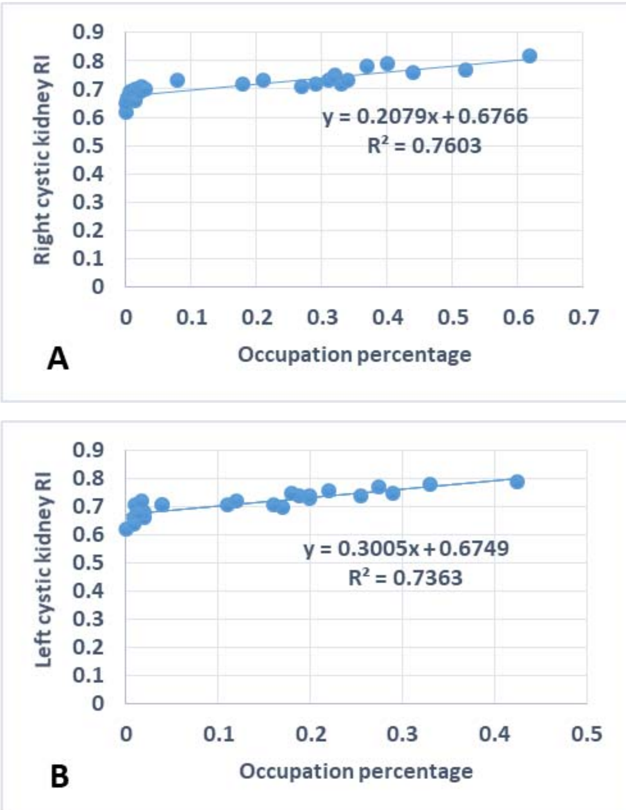

Figure 5. Scatter plot presenting the correlation between RI in right and left kidney and kidney occupation percentage with cysts in PKD group.

4. Discussion

The present investigation has provided insights into the potential utility of certain markers for the identification of subclinical renal damage and progression in Persian cats' PKD patients. Specifically, our data demonstrated a significant elevation in renin, angiotensin II, and aldosterone levels in Persian cats with PKD, while no significant increase in mean blood pressure was observed in comparison to controls. The ultrasound Doppler examination in PKD Persian cats revealed significantly higher RI values (0.71 ±0.01) comparing to healthy Persian cats (0.59 ±0.008) and also, this is the first reported instance of a positive correlation between RI values and the percentage of cyst occupancy in both the right and left kidneys. This study did not find any significant correlation between RI values and systemic blood pressure, renin, angiotensin II, and aldosterone levels in the Persian cats' participants.

Recently, there has been increasing focus on markers of subclinical renal damage. These markers can provide vital information for early detection and management of kidney disease, especially in relation to assessing the risk of cardiovascular and renal failure (Kuo et al., 2019). In human studies, endothelial dysfunction, inflammation, and insulin resistance have emerged as the most commonly encountered risk factors in the pathogenesis of cardiovascular disease in patients with PKD (Miller et al., 1999). Notably, these risk factors have been observed in the early stages of the disease, emphasizing the importance of early detection and intervention to mitigate the development of cardiovascular complications. The most significant finding from these studies is the early appearance of inflammatory indexes, endothelial dysfunction, atherosclerotic and metabolic markers, which are associated with a reduction in parameters of exercise tolerance and metabolic response indexes in PKD patients compared to healthy controls (Kuo et al., 2019). These observations highlight the need for improved risk stratification and management strategies in PKD patients to prevent the progression of cardiovascular disease and improve overall health outcomes, which may be translated in the veterinary medicine as well. Accordingly, the primary objective of this study was to bridge the gap in knowledge regarding the impact of PKD on systemic blood pressure in Persian cats. By conducting this research, we aimed to address the existing lack of information in this specific area and gain a better understanding of the relationship between PKD and blood pressure regulation in these Persian cats.

The existing literatures pertaining to potential prognostic markers in Persian cats with PKD is limited. In 1999, Miller and colleagues conducted a study that failed to demonstrate any significant differences in baseline blood pressure, heart rate, motor activity, RAAS status, and renal function between cats with PKD and control subjects. Moreover, hypertension was not observed in PKD-afflicted cats (Miller et al., 1999). Five years later, Pedersen et al. conducted a follow-up study on 21 cats, which showed that patients with PKD had elevated mean arterial pressure and often had high angiotensin/renin ratios compared to the control group. However, no significant differences were found in serum aldosterone and plasma renin activity between the cats with PKD and the control cats (Pedersen et al., 2003). Our current study corroborates the previous findings that PKD cats do not exhibit a significant increase in systolic blood pressure (SBP). However, we observed a significant increase in the levels of major RAAS components in Persian cats with PKD. These inconsistencies in results may be attributed to variations in age, sex, breeds and blood pressure device among the studies. Additionally, it is plausible that the disease was not severe enough to exhibit changes in the investigated indices. These observations suggest that heightened levels of RAAS components or systolic blood pressure may not necessarily indicate systemic hypertension. As related studies have been suggested, the relationship between serum concentrations of RAAS components and the development of systemic hypertension is multifaceted and not strictly linear, owing to the existence of counter-regulatory mechanisms, paracrine RAAS functions, and receptor dynamics. Various extraneous factors, such as dietary sodium intake, sympathetic nervous system activity, and compensatory renal responses, further modulate the physiological impact of RAAS components. Thereby underscoring the need for alternative markers to assess cardiovascular and mortality risk in PKD patients

In recent scientific inquiries, RI has been employed as a metric to evaluate renal function in felines. Notably, while there's an accumulating body of research on RI values in cats diagnosed with renal diseases, specific investigations into PKD in the feline domain, with a particular emphasis on Persian cats, appear to be sparse. A seminal study in 2007 by Novellas et al. delved into the assessment of RI in a cohort of 10 healthy cats, arriving at a mean RI value of 0.62 ±0.04 (Novellas et al., 2007). Advancing the field, a subsequent study by Carvalho et al., more specialized in its approach, ascertained a mean RI of 0.52 ±0.06 in a sample of 25 healthy Persian cats (Carvalho et al., 2011). Crucially, a consistent finding spanning these studies is the absence of any significant variation in RI values between the right and left renal structures, a consistency that resonates with observations from our own study.

In further attempts, a 2010 study by Novellas et al. discerned a comparative RI analysis involving 20 healthy cats and 20 cats diagnosed with various renal disorders, of which 15 had chronic kidney disease (CKD) and 5 had PKD (Novellas et al., 2010). This study elucidated that cats with renal pathologies had a discernibly elevated RI of 0.72 ±0.10, in contrast to the 0.62±0.04 value in their healthy counterparts. Substantiating these findings, Tipisca et al. delineated that cats suffering from CKD and acute kidney injury (AKI) exhibited significantly amplified RI values of 0.73 ± 0.12 and 0.72 ± 0.08, respectively, in comparison to healthy subjects (Tipisca et al., 2016).

In a pivotal 2018 research endeavor, Matos et al. posited an RI threshold of 0.639 as a preliminary indicator for CKD diagnosis in felines, applicable to both kidneys (Matos et al., 2018). Intriguingly, this benchmark closely aligns with our PKD cat study, where the lower RI limit for the PKD cohort was 0.62. Moreover, it is noteworthy that our research is the pioneering study to establish a substantial association between RI values and the extent of renal cyst occupancy. Such findings insinuate the potential of the RI as a non-invasive metric to gauge renal parenchymal damage and cyst-induced ischemia, thus underscoring its promise as a prognostic instrument.

Nonetheless, it is imperative to recognize the inherent limitations of our investigation. Constrained by a modest sample size and an absence of age and gender data, the robustness of our conclusions and the capacity to monitor disease evolution may be compromised. Future endeavors should contemplate more expansive and varied sample sizes, coupled with longitudinal methodologies, to corroborate and refine our insights. There remains a pressing exigency to explore alternative biomarkers that could facilitate the timely identification and therapeutic management of PKD in Persian cats, thereby enabling a more holistic understanding of disease trajectories and informing the conceptualization of enhanced therapeutic interventions.

Subsequently, studies focused on the possible correlation between RI values and kidney diseases. In 2010 Novellas *et al*. compared RI values between 20 healthy cats and 20 cats with different renal diseases which conclude 15 cats with CKD and 5 cats with PKD diagnosis (Novellas et al., 2010). Their findings indicated that healthy cats exhibited a mean RI of 0.62±0.04, whereas the group with renal anomalies showed a higher value of 0.72 ±0.10. This emphasized that cats with renal anomalies tend to have an elevated RI in comparison to their healthy peers.

Another study by Tipisca *et al.* confirmed the previous study's findings, reporting that RI was significantly higher in cats CKD (0.73 ± 0.12) and AKI (0.72 ± 0.08) compared to healthy cats (Tipisca et al., 2016). Finally, in 2018, Matos *et al.* established an acceptable cut-off for the RI value of 0.639 for a preliminary diagnosis of CKD for both kidneys (Matos et al., 2018). Interestingly, this value is almost valid for our study on PKD cats, where the minimum RI value in the PKD group was 0.62, and none of the RI values from healthy cats exceeded this value except in a small number of animals. Moreover, our study is the first to demonstrate a significant correlation RI values and cyst occupancy. This suggests that RI could be utilized as a non-invasive measure of renal parenchymal damage and ischemia induced by the cysts, thereby serving as a novel prognostic tool. Despite these promising findings, it's important to acknowledge the limitations of this study. The study was limited by its relatively small sample size and the lack of age and sexuality data, which may have affected the robustness of the findings and the ability to track disease progression over time. In light of these limitations, future research should consider larger, diverse cohorts and longitudinal study designs to validate these findings. There is also a need to explore the potential of other biomarkers for early detection and management of PKD in Persian cats. This could provide more comprehensive insights into the disease progression and help in the development of more effective treatment strategies.

Conclusion

Our results suggest RI, OVC and RAAS components as promising candidates for risk stratification and monitoring of kidney injury in this condition. Our data demonstrated a significant elevation in renin, angiotensin II, and aldosterone levels in Persian cats with PKD, while no significant increase in mean blood pressure was observed in comparison to controls. The ultrasound Doppler examination in PKD Persian cats revealed significantly higher RI values comparing to healthy Persian cats and also, this is the first reported instance of a positive correlation between RI values and the percentage of cyst occupancy in both the right and left kidney. These markers will help inform therapeutic strategies to slow disease progression and improve renal outcomes in Persian cats with PKD.

Declarations

- **Ethics approval and consent to participate**

  There are no "human subjects" in this study

- **Availability of data and materials**

All data analyzed during this study are included in this published article.

- **Competing interests**

The authors declare that they have no competing interests

- **Funding**

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- **Authors' contributions**

Y.V developed the idea and designed the experiments. M.GH.SH conducted the experiments. M.GH.SH, D.SH, SH.J, S.M.N, M.M, M.M, S.B and Y.V analyzed the data. M.GH.SH wrote the manuscript. All authors confirmed the final manuscript before submission.

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بررسی تغییرات شاخص مقاومت کلیوی و سیستم رنین-آنژیوتانسین-آلدوسترون به عنوان شاخص های اولیه آسیب کلیه در بیماری کلیه پلی کیستیک گربه ایرانی

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پیشینه مطالعه: بیماری کلیه پلی کیستیک (PKD) در گربه ایرانی یک اختلال ژنتیکی شایع است که 10 درصد از نارسایی های مزمن کلیه را تشکیل می دهد

هدف: این مطالعه با هدف بررسی تأثیر پیشرفت PKD بر شاخص مقاومت کلیوی (RI)، فعالیت رنین پلاسما (PRA)، آنژیوتانسین II (ANG II)، سطوح آلدوسترون و فشار خون سیستولیک در گربه ایرانی انجام شد.

روش کار: 50 گربه ایرانی (25 PKD و 25 سالم) در مطالعه حاضر وارد شدند. فشار خون هر گربه اندازه‌گیری شد و سپس آنزیم‌های PRA، ANG II و آلدوسترون با آزمون الایزا ارزیابی شدند. علاوه بر این، سونوگرافی B-Mode در گروه PKD برای ارزیابی و محاسبه قطر و حجم کلی کیست (OVC) انجام شد. علاوه بر این، RI توسط داپلر موج پالسی در همه گربه‌ها محاسبه شد.

نتایج: اختلاف معنی‌داری در فشار خون سیستولیک بین گربه‌های سالم و PKD وجود نداشت (138.84±2.89 میلی‌متر جیوه و 140.92±2.35 میلی‌متر جیوه). PRA، آلدوسترون، و ANG II در گروه PKD در مقایسه با گروه سالم به طور قابل توجهی بالاتر بود. 3.64±0.36 در مقابل 2.26±0.029 (*p<0.01*) ng/ml،

2.35±80.45 در مقابل 30.95±1.75 (*p<0.0001*) pg/ml، و 53.54±3.22 در مقابل 30.08±3.06 pg/ml. به ترتیب. افزایش معنی‌دار آماری (*p<0.0001*) در RIهای کلیه راست و چپ در گربه‌های PKD (به ترتیب 0.72±0.01 و 0.71±0.008) در مقایسه با گربه‌های سالم (0.59±0.008 و 0.60±0.008) مشاهده شد. تجزیه و تحلیل آماری همبستگی مستقیم قوی بین تغییرات RI و OVC کلیه راست یا چپ را نشان داد (*p<0.001*)، که در آن ارتباط بین افزایش RI و پیشرفت بیماری کلیوی آشکار شد.

نتیجه‌گیری نهایی: افزایش فعالیت رنین-آنژیوتانسین-آلدوسترون و RI در گربه‌های ایرانی با تشخیص PKD می‌تواند ابزار تشخیصی ارزشمندی برای پیشرفت بیماری کلیوی آنها باشد. با این حال، نتایج ما نشان داد که فشار خون سیستمیک حفظ شده و در محدوده طبیعی خود باقی می‌ماند.

واژه های کلیدی:

آلدوسترون - آنژیوتانسین II - بیماری کلیه پلی کیستیک - رنین - شاخص مقاومتی - گربه پرشین