

# Renal resistive index in obese and non-obese cats

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## Keywords

Body condition score,  
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Kidney,  
Resistive index.

## Summary

This study aimed to compare renal function between obese and normal-weight healthy cats, using intrarenal resistive index (RI), serum symmetric dimethylarginine (SDMA), and serum creatinine, and to identify the variables that might influence intrarenal RI. Thirty crossbred client-owned cats met the inclusion criteria and were allocated into two groups: Control and Obese. Body weight, body mass index (BMI), body condition score (BCS), SAP, serum SDMA, urea, and creatinine were evaluated. B-mode and Doppler ultrasound of the kidneys were done. RI evaluation was in the interlobar artery. SDMA and intrarenal RI were compared between groups, also considering the gender of the cats. A correlation analysis between intrarenal RI with the other parameters was performed. SDMA was higher in the Obese group. Intrarenal RI was higher in females than males in the Obese group. Obese females presented higher RI and SDMA than Control females. A positive correlation was observed between RI, age, body weight, and BMI. Six obese cats (40%) showed increased RI. The increase in body weight, BCS, and BMI resulted in a simultaneous increase in RI and SDMA. The RI may assist in monitoring renal function, and may be associated with preclinical kidney changes in obese cats.

## Introduction

Obesity represents an important health problem for people worldwide (Mayer *et al.* 2009). Feline obesity is considered one of the most important chronic diseases, related to several comorbidities and reduced lifespans (Larsen and Villaverde 2016). Excess body fat has been associated with kidney diseases in mice (Deji *et al.* 2009), as well as heart diseases, high arterial pressure and dyslipidemia in cats (Rowe *et al.* 2015). Obese people are susceptible to renal alterations (Ninomiya *et al.* 2006) due to comorbidities, such as diabetes mellitus and high blood pressure, risk factors for renal diseases (Salama 2011). In humans, obesity induces complex metabolic abnormalities that may affect the kidneys (Kovesdy *et al.* 2017) and, consequently, represents

a factor for Chronic Kidney Disease (CKD) (Salama 2011). On the other hand, kidney diseases are important causes of morbidity and mortality in cats (Rivers *et al.* 1996), but the association with obesity need to be investigated (Pérez-López *et al.* 2020).

Renal biopsy classifies the etiology of the kidney disease and severity of kidney injury, but the procedure is invasive, requires anesthesia, and has some potential complications (Vaden *et al.* 2005). Therefore, non-invasive methods that aid in the diagnosis and prognosis of kidney injuries are highly beneficial (Rivers *et al.* 1996).

B-mode and Doppler ultrasound is an important non-invasive tool for assessing the urinary system in cats since the reduction in renal perfusion may be the first clinical finding pointing towards dysfunction

(Carvalho and Chamas 2011). The kidneys are highly vascularized organs, and several nephropathies have an important vascular component (Novellas *et al.* 2010). Since the blood supply plays a role in renal function, the use of the Doppler-derived intrarenal Resistive Index (RI) may be suitable in the diagnosis (Nelson and Pretorius 1988, Tipisca *et al.* 2016), treatment, and prognosis of kidney diseases (Park *et al.* 2008). However, RI may be influenced by age, patency of the urinary tract, and the circulatory status of the cat (Park *et al.* 2008).

Additionally, symmetric dimethylarginine (SDMA) is a kidney biomarker and permits earlier diagnosis of kidney disease (Reldford *et al.* 2016). In cats, the renal function has been correlated with serum concentration of SDMA, which compared to serum creatinine was considered more reliable and allowed earlier detection of CKD (Hall *et al.* 2014).

Therefore, this study aimed to compare renal function between obese cats and normal-weight healthy cats by using intrarenal RI, serum SDMA, and serum creatinine, and to identify the variables (systolic arterial pressure, body weight, body condition score, body mass index, serum SDMA, and serum creatinine) that might influence intrarenal RI.

## Materials and methods

This study was approved by the Institutional Ethics Committee on Animal Use (n. 0176/2016-CEUA). Permission for the participation of cats in the study was obtained from their owners by signing an informed consent form.

### Animal selection

Thirty crossbred client-owned cats were evaluated and allocated into two groups based on a 9-point body condition score (BCS) (LUND *et al.* 2005): Control Group, cats with a BCS of 5; Obese Group, cats with a BCS of 8 or 9. In the 9-point BCS scale, cats with a BCS of 6 or 7 are overweight, and cats with a BCS of 8 or 9 are obese.

The cats were selected aleatorily during a routine of a Veterinary Medical Teaching Hospital, over years. The inclusion criteria for the Control group were healthy cats through complete physical examination, CBC, biochemical profile, and urinalysis. Inclusion criteria for the Obese Group were obese cats with no other abnormalities on complete physical examination, or history of medication administration for at least two months. The exclusion criteria in both groups included a history of chronic diseases, previous kidney or heart diseases, changes in heart rhythm observed on the electrocardiogram, and proteinuria.

## Evaluation methods

All cats were weighed on the same digital weighing scale (kg). The Body Mass Index (BMI) was calculated with the following equation (Hawthorne and Butterwick 2000):

$$[(\text{rib cage}/0.7062)\text{-LIM}/0.9156]\text{-Lim}$$

where:

LIM (Leg Index Measurement) = length from top of the patella to end of calcaneus;

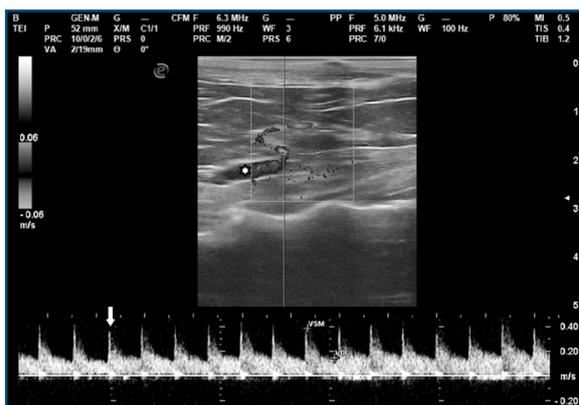
rib cage = circumference of the rib cage at the 9<sup>th</sup> rib level (cm).

The body fat content was considered ideal between 15 and 30%, overweight between 30 and 42%, and obesity above 42%.

The Systolic Arterial Pressure (SAP) was measured by Doppler ultrasound. The cats were gently restrained in a comfortable position in lateral recumbency. A cuff with adequate size (approximately 30-40% of the cuff site circumference) was positioned in the middle third of the antebrachium (Brown *et al.* 2007). Five measurements were taken for each cat and the average values were recorded. Outliers were excluded from the final calculation.

For kidney function tests, blood samples were collected via jugular venipuncture in a silicone-coated tube containing no anticoagulant, and centrifuged immediately after removal. Then, the serum samples were frozen at - 20 °C for later analysis. Serum creatinine and urea were determined by enzymatic colorimetric method and kinetic method, respectively, using a semi-automatic analyzer (Cobas Mira Plus, Roche Diagnostic Systems, Rotkreuz, Switzerland). SDMA concentrations were determined using liquid chromatography-mass spectroscopy (IDEXX Laboratories) as previously described (Hall *et al.* 2014).

B-mode and Doppler ultrasound of the kidneys were done with the cats fasted for 8 hours to minimize imaging artifacts. The non-sedated animals were placed in the right or left lateral recumbency for scanning the left and right kidneys, respectively. After renal echotexture, architecture, shape and size, and vessels have been assessed, the RI was measured using color Doppler at the interlobar artery. Doppler measurements were repeated three times (Figure 1). Intrarenal RI was calculated by the built-in software as follows: (peak systolic velocity – end-diastolic velocity)/peak systolic velocity (Tipisca *et al.* 2016). All ultrasonography examinations were performed by a Doppler ultrasonography machine (Mylab Alpha, Esaote Healthcare do Brasil, São Paulo/SP, Brazil) equipped with a 3-13 MHz linear transducer, and 5-8 MHz convex transducer. Ultrasonography was carried out by an experienced evaluator.



**Figure 1.** Ultrasonographic representation of color Doppler of renal vasculature (asterisk) and renal artery wave spectra to calculate resistivity index in the cat. The arrow indicates the systolic wave peak.

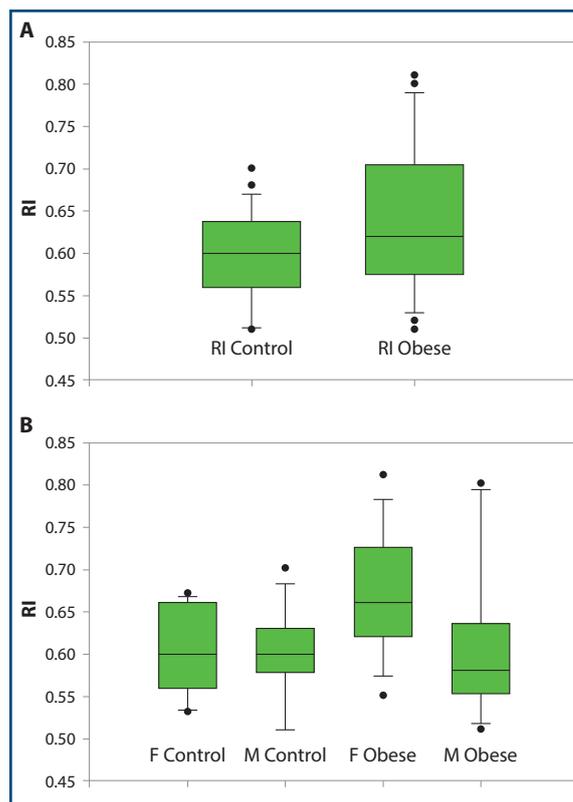
### Statistical analysis

To compare the intrarenal RI between groups, both right and left kidney values were considered, totalizing 30 RI values per group. Both kidney values were also used to compare RI values between males and females within each group and between groups. The Control group included 18 RI for nine males and 12 RI for six females. The Obese group included 16 RI for eight males and 14 RI for seven females. The data were analyzed in commercially-available software (Prism 5; GraphPad software). The PROCMEANS procedure of the SAS System (SAS System version 9.12, SAS Institute) was used to represent the Box plot figures (Figures 2A and 2B). The Scatter plot (Figure 3) was created using Microsoft Excel®.

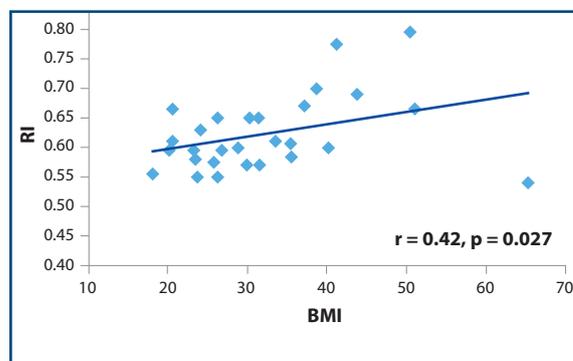
The normal distribution of variables was tested using the Kolmogorov-Smirnov test. Non-paired Student's t-test for parametric data or Mann-Whitney test for non-parametric data were used to compare the data (age, RI, SDMA, SAP, Body Weight, BMI, BCS, serum urea and creatinine) between groups, as well as assess the influence of gender in the Obese and Control groups, and to compare intrarenal RI in adult (two to six years old) and more aged cats (seven to 12 years). Fisher's exact test was performed to assess increases in the intrarenal RI (right and left kidneys) when comparing the Obese and Control groups. Pearson's test was performed to establish a correlation between intrarenal RI with Body Weight, BMI, age, SDMA, creatinine, and SAP. The Spearman's test evaluated a correlation between RI and BCS. Statistical significance was defined as  $p < 0.05$ .

### Results

A total of 30 crossbred cats met the inclusion criteria. The Control group ( $n = 15$ ) was composed of six spayed females (40%) and nine males (60%), six neutered and three intact, with an average age



**Figure 2. A.** Box plot of resistive index distribution in Control and Obese cats. **B.** Box plot of resistive index distribution in Control and Obese male (M) and female (F) cats.



**Figure 3.** Scatter plot and trend line with BMI versus RI, demonstrating a positive correlation between body mass index (BMI) and intrarenal resistive index (RI).

of  $4.5 \pm 2.3$  years. The Obese group ( $n = 15$ ) was composed of seven spayed females (46.7%) and eight neutered males (53.3%), with an average age of  $6.5 \pm 2.9$  years.

Body Weight, BCS, BMI, age, and SAP were statistically higher in the Obese group (Table I) compared to the Control Group. Based on the age of obese cats (adult: two to six years old; and senior: > seven years), there were no differences between adult ( $n = 8$ ) and senior ( $n = 7$ ) cats ( $p = 0.83$ ), which had intrarenal RI values of  $0.64 \pm 0.09$  and  $0.63 \pm 0.08$ , respectively. High

**Table I.** Demographic data for obese ( $n = 15$ ) and control cats ( $n = 15$ ).

Parameters	Groups		P
	Control	Obese	
Age (years)	4.5 ± 2.3	6.5 ± 2.9	0.04
Weight (Kg)	4.2 ± 0.7	6.2 ± 1.5	< 0.001
BCS	5.0 ± 0.0	8.4 ± 0.5	< 0.001
BMI	25.7 ± 5.4	38.9 ± 11.0	< 0.001
SAP (mmHg)	126.1 ± 19.7	151.2 ± 29.0	0.01
SDMA (µg/dL)	6.7 ± 1.5	8.8 ± 2.6	0.001
Urea (mg/dL)	53.9 ± 10.0	51.9 ± 8.2	0.57
Creatinine (mg/dL)	1.10 ± 0.2	1.02 ± 0.3	0.45

BCS = Body Condition Score; BMI = Body Mass Index;  
SAP = Systolic Arterial Pressure; SDMA = Symmetric dimethylarginine.

blood pressure or hypertension (SAP ≥ 150 mmHg) was observed in six cats (40%) of the Obese Group and two cats (13.3%) of the Control Group.

The intrarenal RI of the Obese group was higher than the Control group, although not statistically significant ( $p = 0.115$ ) (Figure 2A). The SDMA for the Obese group was higher than the Control group ( $p < 0.01$ ); however, all the values were within the normal range for cats. According to gender, RI ( $p = 0.026$ ) and SDMA ( $p = 0.007$ ) were significantly higher in females than males in the Obese group. Also, females in the Obese group presented a statistically significant increase in intrarenal RI compared to females in the Control group. For males, no differences were observed between the groups (Figure 2B). The Control group did not present differences between males and females. The general RI values for males and females of both groups are in Table II.

The intrarenal RI of at least one of the kidneys (right) presented a positive correlation with increased SDMA, body weight, and BMI (Table III). A weak positive correlation between RI and BMI ( $r = 0.42$ ) showed that increases in BMI are accompanied by a concurrent increase in the intrarenal RI (Figure 3). A weak positive RI correlation with age ( $r = 0.37$ ) was observed in the Obese but not in the Control group.

Based on the normality limits (RI < 0.70 for cats), six obese cats (40%) presented increased intrarenal RI in at least one kidney, while one animal (6.7%) in the Control group presented RI above the normal ranges. Considering the kidneys separately (right and left kidneys), eight kidneys of the Obese group (26.6%) presented increased RI, while one kidney (3.3%) from the Control group showed increased RI. A significant difference was observed when comparing the number of kidneys with increased intrarenal RIs in the Obese and Control groups using Fisher's test, and considering each kidney separately ( $p = 0.027$ ).

Despite the higher SAP values in Obese cats (Table I),

**Table II.** Intrarenal resistive index in male cats, female cats and both (general) from Control (normal-weight) ( $n = 15$ ) and Obese ( $n = 15$ ) groups.

Resistive Index	Groups		P-values
	Control (Mean ± Standard Deviation)	Obese (Mean ± Standard Deviation)	
General	0.60 ± 0.03	0.64 ± 0.08	0.12
Males	0.60 ± 0.05	0.60 ± 0.08	0.91
Females	0.60 ± 0.05	0.67 ± 0.06	0.008

**Table III.** Correlations between intrarenal resistive index (RI), body weight, body condition score (BCS), body mass index (BMI), systolic arterial pressure (SAP) and serum creatinine in Control (normal-weight) ( $n = 15$ ) and Obese ( $n = 15$ ) groups.

Correlated Measures	Correlation coefficient (r)	P-value
RI x SDMA	0.52	0.004*
RI x Body weight	0.38	0.04*
RI x BCS	0.27	0.14
RI x BMI	0.42	0.03*
RI x SAP	0.03	0.86
RI x Creatinine	0.04	0.82

\*Positive correlation in Pearson test.

a correlation between intrarenal RI and SAP was not observed. Six cats (30%) in the Obese group ( $n = 6$ ), and two (11.3%) in the Control group ( $n = 2$ ), presented high arterial pressure. Among these animals, two obese cats (33.3%) showed a concurrent increase in intrarenal RI. No correlation occurred between intrarenal RI and serum concentrations of urea and creatinine. Both groups had urea and creatinine levels within normal limits. On the other hand, a moderate correlation occurred between RI and serum SDMA (Table III).

## Discussion

The mean values of intrarenal RI in the Control group were  $0.60 \pm 0.03$ . The RI values and vessels evaluated to obtain RI in healthy non-sedated cats have shown variation among studies (Carvalho and Chammas 2011, Pollard *et al.* 1999, Novellas *et al.* 2007). In healthy Persian cats with a mean age of 30 months, the RI of the interlobar arteries was  $0.54 \pm 0.07$  (Carvalho and Chammas 2011). Neutered young adult domestic shorthair cats had renal RI values of  $0.58 \pm 0.06$  and  $0.55 \pm 0.03$  for right and left kidneys, respectively (Pollard *et al.* 1999). However, in healthy mixed-breed cats, mean age of 7.8 years, the RI measured from interlobar or arcuate arteries was  $0.62 \pm 0.04$  (Novellas *et al.* 2007), value relatively close to those obtained in the present study.

There was no significant difference between intrarenal RI of the Obese group and Control group, despite the mean RI value of  $0.64 \pm 0.08$  in the Obese Group. However, considering the upper limit of RI measured in interlobar renal arteries in non-sedated cats, such as 0.68 (Ostrowska *et al.* 2016) or 0.70 (Novellas *et al.* 2007), 40% of the obese animals ( $n = 6$ ) presented increased RI in at least one kidney. In HIV-1-infected patients with visceral obesity, it was observed higher intrarenal artery RI compared with those without visceral obesity, which was attributed to endothelial damage (Grima *et al.* 2010).

In addition, intrarenal RI in the Obese group was significantly higher in females than in males, and obese females presented a significant increase concerning control females, not observed among males. The influence of gender on intrarenal RI has shown conflicting results in human patients (Kaiser *et al.* 2007, Toledo *et al.* 2015). In intrarenal RI between healthy persons and those with fatty liver disease, it was not observed influence of gender, but age dependency was observed (Kaiser *et al.* 2007).

On the other hand, higher renal RI was reported in women afflicted by CKD28 associated with a possible hormonal influence, but the exact reason was not established (Toledo *et al.* 2015). The hormonal influence in the present study may not play a role since all female cats were spayed. Thus, the cause of higher RI in obese female cats needs further investigation.

In the present study, age was related to increased intrarenal RI in obese cats, and senior obese cats showed a tendency to a higher RI. However, the intrarenal RI between adult and aged cats (seven to 12 years old) did not show significant differences. In a previous study with dogs, the intrarenal RI was influenced by age, with higher values in young and senior dogs (Mamprim *et al.* 2018). However, none of the cats included in the present study was geriatric ( $> 12$  years).

A positive correlation occurred between intrarenal RI and BMI and body weight. A previous study with Korean domestic short-hair cats showed a high correlation between body weight and renal dimensions and a weak correlation with RI (Park *et al.* 2008). On the other hand, human patients with or without hypertension showed a correlation between intrarenal RI and BMI by univariate analysis, and RI was considered an indicator of vascular damage caused by atherosclerosis (Kawai *et al.*

2011). The association between increased BMI and risk factors for the end-stage of renal disease has already been shown in humans. Furthermore, the increased BMI and waist-hip ratio in obese persons have been considered independent conditions for the increased RI in human patients with high blood pressure (Trovato *et al.* 2012).

Although the present study did not find a correlation between SAP and RI, two of the six obese cats with high arterial pressure presented a concurrent increase in RI (33.3%). One study found no correlation between intrarenal RI and SAP in healthy dogs (Novellas *et al.* 2007). It is important to consider the stress effects of SAP in cats. A previous research evaluated physiologic parameters, such as blood pressure in cats in the home environment and the veterinary hospital, and a statistically significant increase in the veterinary hospital environment was reported (Quimby *et al.* 2011). Increases in blood pressure occur because of the environment measurement process, caused by autonomic nervous system alterations that arise from the effects of stress or anxiety, also called "white coat" hypertension in human patients (Acierno *et al.* 2018).

There were no differences between serum creatinine of the Obese and Control groups. However, there was a significant difference between SDMA of the Obese group and Control groups, despite the normal values in all the cats. Increased circulating methylarginines have linked to metabolic syndrome, and serum concentrations of SDMA is a more reliable and earlier marker for CKD compared with serum creatinine in human patients (Marliss *et al.* 2006). However, a study in normal-weight and overweight cats showed no differences in the concentrations of established markers of CKD, such as creatinine or SDMA (Pérez-López *et al.* 2020).

The main limitation of this study was a non-homogenous reproduction status between the groups, since three cats were not neutered in the control group. However, this difference did not alter the results, because it corresponded to only 10% of the animals.

In conclusion, the results obtained in this study suggest that the intrarenal RI may assist in monitoring renal function in obese cats. Increases in body weight, BMI, and age resulted in concurrent increases in RI, indicating that obesity status is associated with preclinical hemodynamic changes at the kidney level.

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