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Iron Status of Cats with Chronic Kidney Disease

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Background: Iron deficiency is a proposed mechanism for the anemia that occurs in cats with chronic kidney disease (CKD). Minimal research investigating the iron status of these cats has been performed.

Objective: To compare indicators of iron status in cats with CKD versus healthy cats and cats with nonrenal illness (NRI). To compare indicators of iron status in anemic versus nonanemic cats with CKD.

Animals: Thiry-nine client or employee owned healthy cats, 40 cats with CKD and 34 cats with NRI included.

Methods: Exclusion criteria included prior iron or erythropoiesis stimulating agent administration, blood transfusion, or concurrent CKD and NRI. Complete blood counts, serum chemistries, serum iron concentrations, total iron binding capacity (TIBC), and ferritin concentrations were measured and percent transferrin saturation (TSAT) calculated on all cats. Data were analyzed using nonparametric statistical testing.

Results: No statistically significant differences were detected among groups for iron concentration ($P = .50$), ferritin concentration ($P = .47$), or TSAT ($P = .19$). TIBC was significantly lower in CKD (median 262 μg/dL; IQR 233–302; range 165–488) versus healthy cats (median 316 μg/dL; IQR 272–345, range 196–464); ($P = .0030$). When comparing anemic (hemoglobin <9.5 g/dL) versus nonanemic cats with CKD, TSAT was significantly lower ($P = .033$) in anemic (median 20.2%; IQR 17.8–34.5; range 17.6–35.9) compared to nonanemic (median 29.0%; IQR 25.5–44.1; range 11.5–94.4). No statistically significant differences found for ferritin concentration ($P = .94$), iron concentration ($P = .21$) or TIBC ($P = .97$).

Conclusions and Clinical Importance: These results indicate that an iron deficient state exists in anemic cats with CKD and is more likely functional rather than absolute.

Key words: Anemia; Feline; Ferritin; Renal.

Anemia is a frequent complication in cats with chronic kidney disease (CKD). Anemia was present in 57% of cats with CKD in 1 study, with a median survival time of 100 days once anemia developed.[1] The etiology of anemia in cats with CKD is likely multifactorial although the main mechanism is inadequate erythropoietin production by diseased kidneys. Another potential contributor is an absolute iron deficiency, which occurs secondary to reduced oral iron intake, decreased gastrointestinal absorption, or loss through gastrointestinal bleeding.[2–4] Absolute iron deficiency is defined as a reduction in bone marrow reticuloendothelial iron and in human patients is suggested by a percent transferrin saturation (TSAT) <20% and a ferritin concentration <100 ng/mL.[2]

A functional iron deficiency, which occurs when there is an inability to utilize otherwise adequate body iron stores for erythropoiesis, is another potential contributor to anemia in cats with CKD.[2,4] This is generally manifested as low serum iron but increased available iron in the reticuloendothelial system and can occur because of the decreased erythropoietin production by diseased kidneys or secondary to inflammation.[4–6] In human patients, a functional iron deficiency is suspected when TSAT is <20% and ferritin levels are normal or >100 ng/mL.[2,7] Chronic inflammation has been shown to play a role in the pathogenesis of anemia primarily mediated by the acute phase protein hepcidin.[8,9] Hepcidin is upregulated in inflammatory states and leads to sequestration of iron within hepatocytes, enterocytes, and macrophages.[9,10] Erythropoiesis is also inhibited by proinflammatory cytokines such as IL-1, interferon-γ and TNF-α which appear to be upregulated in human patients with uremia compared to healthy controls.[4,7,11,12] These cytokines act via direct toxic effects on erythroid precursors, decreased expression of hematopoietic factors including erythropoietin and stem cell factor, and decreased expression of erythropoietin receptors.[10]

The first objective of this study was to compare indicators of iron status in cats with CKD versus healthy

Abbreviations:

CKD	chronic kidney disease
ESA	erythropoiesis stimulating agent
IL-1	interleukin 1
IL-6	interleukin 6
IQR	interquartile range
IRIS	International Renal Interest Society
KSVDL	Kansas State Veterinary Diagnostic Laboratory
MCV	mean corpuscular volume
MCHC	mean corpuscular hemoglobin concentration
NRI	nonrenal illness
TIBC	total iron binding capacity
TNF-α	tumor necrosis factor α
TSAT	percent transferrin saturation

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cats and cats with systemic nonrenal illness (NRI). The second objective was to compare indicators of iron status in anemic versus nonanemic cats with chronic kidney disease.

Materials and Methods

Case Selection

This was a cross sectional observational study including client and employee owned cats presenting to The Elmer & Mamdouha Bobst Hospital of The Animal Medical Center between January 2012 and November 2013. All subjects had a physical examination performed by a veterinarian. Venipuncture and collection of blood was performed with informed owner consent and study protocol was approved by the Institutional Animal Use and Care Committee of the Caspary Research Institute, The Animal Medical Center.

Employee and client owned cats were included in the healthy control group if they had an unremarkable physical examination excluding dental disease, no history of current disease and no clinical or biochemical abnormalities on a CBC and chemistry profile performed within the prior 30 days. These cats were not receiving any medications, with the exception of monthly heartworm and flea and tick prevention.

Cats with historical or newly diagnosed International Renal Interest Society (IRIS) Stage II CKD (plasma creatinine >1.6 mg/dL) or greater were eligible for inclusion in the chronic kidney disease group. Exclusion criteria included evidence of concurrent nonrenal disease based on any history, physical examination, laboratory or imaging abnormalities, evidence of acute or chronic kidney disease, patients with concurrent hyperthyroidism, bacteruria, prior iron supplementation, prior blood transfusion, or erythropoiesis stimulating agent (ESA) administration. Cats with a hemoglobin <5 g/dL were also excluded because of patient safety considerations.

Cats in the systemic nonrenal illness (NRI) group were included if they presented to the hospital for evaluation of any systemic nonrenal related illness. Exclusion criteria included evidence of concurrent acute or chronic kidney disease (based on any history, physical examination, and laboratory or imaging abnormalities). Additional exclusion criteria included diagnosis of hyperthyroidism, prior iron supplementation, prior blood transfusion, ESA administration, or a hemoglobin <5 g/dL.

Laboratory Testing

Blood samples for complete blood count and iron panel were collected simultaneously. Approximately 1 mm of blood for complete blood count was collected in a tube with EDTA and evaluated routinely by Animal Medical Center in-house ALX laboratory (January 2012–April 2013) or IDEXX laboratory (May 2013–November 2013) utilizing a Sysmex XT-2000i hematology analyzer, Sysmex America Inc, Mundelein, IL, USA.

Two milliliters of whole blood for measurement of iron indicators serum iron concentrations, total iron binding capacity (TIBC), and ferritin concentrations were collected in a serum separator tube and centrifuged immediately. The serum was separated, frozen and stored at −80°C and sent for evaluation at Kansas State Veterinary Diagnostic Laboratory (KSVDL, Manhattan, KS) in batches over 4 months. Spectrophotometric measurement of iron and TIBC was performed using a Ferrochem II-serum iron and TIBC analyzer, ESA Inc, Chemlsford, MA, USA. Percent transferrin saturation (TSAT) was calculated based on this data as [serum iron (mg/dL)/TIBC (mg/dL) × 100]. Ferritin concentrations were evaluated using a quantitative enzyme-linked immunosorbent assay using antiferritin monoclonal antibodies in a sandwich arrangement.

Serum chemistries were submitted to Animal Medical Center in-house laboratory using Olympus AU400 Chemistry Analyzer (January 2012–April 2013) or IDEXX laboratory using the Beckman Coulter AU680 Chemistry System, Olympus America Inc, Center Valley, PA, USA (May 2013–November 2013) and performed simultaneously or within no >30 days of collection of CBC and iron panel.

Statistical Analysis

Data were analyzed using a commercial statistical software program.[a] Unless specified otherwise, statistical significance was set at 0.05. Normality was assessed with a Shapiro-Wilk test. Because of the large number of variables with non-normal distribution, nonparametric data analysis was used for comparison of variables between groups. All data were described using median and range. A Kruskal-Wallis test was used to compare iron indicators, mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC) among the 3 groups (healthy, CKD, and NRI) of cats. A Wilcoxon rank sum test was used to determine which groups were different when inequality was detected. For Wilcoxon rank sum tests performed among the groups, a Bonferroni correction was used to adjust the level of statistical significance from 0.05 to 0.017. To compare iron indicators, MCV and MCHC between anemic and nonanemic cats, a Wilcoxon rank sum test was used.

Results

Subjects

Forty cats were initially enrolled in the healthy control group. One cat was excluded because of previously undiagnosed azotemia (n = 1). Thirty-nine cats were evaluated as healthy controls. The mean age was 7.5 years (range 0.9–15.0 years). This group included spayed females (n = 14), intact females (n = 2) and castrated males (n = 23). Represented breeds included domestic short hair (n = 34), Persians (n = 2), American curl (n = 1), Maine coon (n = 1), and Siamese (n = 1).

Forty-four cats were initially enrolled in the chronic kidney disease group; however, 4 were excluded because of a new diagnosis of neoplasia (n = 2), suspected acute or chronic kidney disease (n = 1) and a hemoglobin <5 g/dL (n = 1). Forty cats met the inclusion criteria for enrollment in the chronic kidney disease group. The mean age was 11.2 years (range 3.6–17.6 years). This population included spayed females (n = 16) and castrated males (n = 24). Represented breeds included primarily domestic short hair (n = 31), Persians (n = 4), Siamese (n = 2), Burmese (n = 1), Birman (n = 1), and Abyssinian (n = 1). IRIS Stage classification included stage II (n = 23), stage III (n = 12), and stage IV (n = 5). In addition, all cats had either minimally concentrated urine defined as a urine specific gravity <1.025, ultrasonographic renal changes consistent with chronic kidney disease, or both.

Thirty-eight cats were initially enrolled in the nonrenal illness group; however, 4 were excluded because of ultrasonographic renal changes (n = 2) or concurrent renal azotemia (n = 2). Thirty-four cats met the inclusion criteria for enrollment in the nonrenal illness group. The

mean age was 9.8 years (range 2.5–14.6 years). This population included spayed females (n = 11) and castrated males (n = 23), and breeds included domestic short hair (n = 28), Siamese (n = 2) and 1 each of Bengal, American curl, Ragdoll and Bombay. Disease categories included neoplasia (n = 8), endocrine (n = 5), cardiac disease (n = 4), dermatologic disease (n = 3), gastrointestinal disease (n = 3), respiratory (n = 3), hepatic (n = 2), infectious (n = 2), neurologic (n = 1), lower urinary tract (n = 1), pancreatitis (n = 1), and a hemoabdomen of unknown etiology (n = 1).

Iron Indicators

Total iron binding capacity was significantly lower in CKD cats compared to healthy cats ($P = .0030$). No significant differences were found for TIBC between CKD and NRI ($P = .34$) or between Healthy and NRI ($P = .087$). One cat did not have a TIBC measured because of lipemia-induced sample interference which also precluded calculation of TSAT.

No statistically significant difference was detected among any of the groups for serum iron concentrations ($P = .50$), TSAT ($P = .19$), or ferritin concentrations ($P = .47$).

Outliers for ferritin concentrations were noted in each group. One cat in the CKD group had an increased ferritin concentration of 1,280 ng/mL and 2 cats in the NRI group had increased ferritin concentrations of 4,296 and 2,106 ng/mL. One healthy cat had a ferritin concentration of 838 ng/mL.

Thirty-two cats with chronic kidney disease were classified as nonanemic and 8 as anemic using a definition of anemia as a hemoglobin <9.5 g/dL. These 8 anemic cats had reticulocyte counts range of 1,100–31,000/μL. The median TSAT for anemic cats with CKD (n = 7) was significantly lower at median 20.2% (IQR 17.8–34.5, range 17.6–35.9) compared to nonanemic cats with CKD (n = 32) median 29% (IQR 25.5–44.1, range 11.5–94.4) ($P = .033$). One cat did not have a TSAT measured. There were 4 outliers in the nonanemic group represented by TSAT's >70%. No significant difference was found for TIBC ($P = .97$), serum iron concentrations ($P = .21$), or ferritin concentrations ($P = .94$). Data are presented in Table 2.

All cats in the healthy group were nonanemic with a hemoglobin >9.5 g/dL. Four cats in the NRI group were classified as anemic.

MCV and MCHC Analysis

No statistically significant difference was detected between healthy, CKD, and nonrenal illness cats for MCV or MCHC (Table 1).

The median MCV for anemic cats with CKD (n = 8) was significantly lower at median 41 fL (IQR 40–43.5, range 38–49) versus nonanemic cats with CKD (n = 32) median 45 fL (IQR 43–47, range 35–55) ($P = .044$) (Table 2).

There was no difference between MCHC for anemic cats with CKD (n = 8) median 33.1 g/dL (IQR 31.2–33.7, range 30.7–34) versus nonanemic cats with CKD (n = 32) median 33.2 g/dL (IQR 31.7–34.8, range 29.2–40.6) ($P = .30$) (Table 2).

Table 1. Iron Variables for healthy cats, cats with CKD and cats with nonrenal illness.

	Healthy	CKD	Nonrenal Illness
Hemoglobin (g/dL)			
Median	12.9[a]	11.0	12.0
Interquartile range	12.1–14.0	9.6–12.9	10.1–13.5
Range	10.2–15.9	5.4–15.2	7.4–14.9
MCV (fL)			
Median	45.0	44.0	45.5
Interquartile range	42.0–49.3	41.3–46.8	41.5–50.0
Range	36.0–55.0	35.0–55.0	37.0–56.0
MCHC (g/dL)			
Median	33.0	33.2	33.2
Interquartile range	31.8–34.4	31.7–34.5	32.1–34.9
Range	27.9–37.8	29.2–40.6	29.2–41.9
Serum iron concentration (μg/dL)			
Median	92	88	97
Interquartile range	77–111.5	68–123	71–138.5
Range	31–171	29–208	32–219
TIBC (μg/dL)			
Median	316[b]	262[b]	296
Interquartile range	272–345	233–302	230–323
Range	196–464	165–488	114–469
Ferritin concentration (ng/mL)			
Median	238	257	259
Interquartile range	203–291.5	180.5–337	226.5–349
Range	138–838	71–1280	84–4296
TSAT (%)			
Median	30	28	37
Interquartile range	23–36	21–40	24–54
Range	12–68	12–94	12–84

ALX reference intervals: Hemoglobin 9.5–15 g/dL; MCV 39.6–51.6 fL; MCHC 29.0–37.5 g/dL.

IDEXX reference intervals: Hemoglobin 10.3–16.2 g/dL; MCV 39–56 fL; MCHC 28.5–37.8 g/dL.

KSVDL reference intervals: Serum iron concentration 33–157 μg/dL; TIBC 169–325 μg/dL.

Ferritin concentration 90–300 ng/mL. Median, IQR and range presented. Groups were compared with Kruskal-Wallis test.

[a]Hemoglobin available for 35 healthy cats.

[b]Statistically significant difference for TIBC of healthy cats compared to CKD ($P = .003$).

Discussion

Total iron binding capacity in these population of cats with chronic kidney disease was significantly lower than in these population of healthy cats. TIBC is decreased in inflammation thus our results support the presence of inflammation in this population of cats with CKD.[13–17] TSAT and MCV were significantly lower in anemic cats compared to nonanemic cats with chronic kidney disease. These findings are consistent with both an absolute and a functional iron deficiency.[3]

Total iron binding capacity is decreased in 31.6% of cats with inflammatory disease.[8] TIBC in these population of cats with chronic kidney disease was signifi-

Table 2. Hematologic and Iron Variables for anemic versus nonanemic cats with CKD (median, range).

	Anemic (n = 8)	Nonanemic (n = 32)	*P* value
Hemoglobin (g/dL)	7.7 (5.4–9.2)	11.3 (9.5–15.2)	<.001
Reticulocytes (/μL)	6,500 (1,100–31,000)	14,000[a] (1,300–40,000)	.086
MCV (fL)	41 (38–49)	45 (35–55)	.044
MCHC (g/dL)	33.1 (30.7–34.0)	33.2 (29.2–40.6)	.30
Serum iron concentration (μg/dL)	72.5 (19–183)	90 (41–208)	.21
TIBC (μg/dL)	258 (165–441)	272 (174–488)	.97
Ferritin concentration (ng/mL)	270 (167–349)	249.5 (71–1,280)	.94
TSAT (%)	20.2 (17.6–35.9)	29 (11.5–94.4)	.033

Median data presented. Statistically significant difference, $P < .05$.
[a]Reticulocyte count available for 22 nonanemic CKD cats.

cantly lower than these population of healthy cats supporting the presence of an inflammatory state in these animals. Both of these medians fall within the KSVDL reference interval of 169–325 μg/dL, however, and there is an overlap of the increased data points between groups indicating that this data should be interpreted with caution.

TSAT is a calculated value [serum iron/TIBC × 100] based on TIBC and provides an assessment of how much transferrin has bound iron.[13] TSAT is generally decreased in absolute iron deficiency anemia because of insufficient iron stores and is normal to decreased in anemia of inflammatory disease.[3] In these population of cats with chronic kidney disease the median TSAT was 20.2% for 7 anemic cats and 29% for 32 nonanemic cats. There is no reference range reported for cats; however, 25–45% is considered normal in human patients. These healthy cat population had a TSAT range of 12.5–67.8% and a large range of TSAT was noted in all of groups. There are 4 biological outliers in the nonanemic chronic kidney disease group represented by TSAT's >70%. This typically is indicative of iron overload, however, there was no evidence of iron or blood product administration in these cats and therefore the significance of these biological outliers is unknown.

Serum iron concentrations are decreased when demands for erythropoiesis exceed the iron flow from the diet and storage pool. Levels are thus considered fairly nonspecific and should not be used to estimate total body iron. In this study, we did not find a difference in iron concentrations between any of the population of cats which supports its inability to estimate total iron body iron stores.

Serum ferritin is involved in the storage of iron and is found primarily in the cytoplasm of hepatocytes.[3] Binding of iron to ferritin is thought to minimize the potential of iron to catalyze the formation of damaging free radicals.[7] Ferritin concentrations in human patients have good correlation with whole body iron storage and a decreased value is the single best parameter to diagnose iron deficiency without performing a bone marrow biopsy.[18–22] Ferritin concentrations correlate with tissue iron stores in dogs.[17] Serum ferritin levels, when evaluated in conjunction with serum iron levels, are the best indicator of total body iron supplies in cats.[15] There is no correlation between tissue iron stores and total iron binding capacity or serum iron concentration.[15]

Ferritin concentrations are primarily decreased in absolute iron deficiency anemia and increased in iron overload, hemochromatosis secondary to repeated blood transfusion and systemic inflammatory disease.[13,17,21] It is an acute phase protein and secretion is stimulated by proinflammatory cytokines including IL-1, IL-6, and TNF-α.[3,8,13,22,23] Inflammatory disease reportedly increases ferritin concentration in 63.2% of cats.[11] In this study, we did not find a difference among groups for serum ferritin. This finding warrants further investigation.

Two cats in the NRI group with exceedingly increased serum ferritin concentrations both had evidence of severe systemic inflammation. The first was a cat with a hemoabdomen of unknown etiology (ferritin concentration 4,296 ng/mL) and the second was a cat with a septic abdomen secondary to small intestinal necrosis (ferritin concentration 2,106 ng/mL). One cat in the CKD group had a severely increased ferritin concentration of 1,280 ng/mL. This cat was a 13 year old male castrated domestic short hair classified as IRIS Stage II. He had a normal leukogram, normal vitals and no evidence of a concurrent systemic inflammatory state on blood work or abdominal imaging; thus, the importance of this finding is unknown. One healthy cat had a ferritin concentration of 838 ng/mL. No historical evidence of systemic disease was described in this cat; however, abdominal imaging was not performed for further investigation.

Mean corpuscular volume and MCHC are relatively insensitive in identifying the presence of erythrocytes with abnormal volumes or hemoglobin concentrations.[13] Absolute iron deficiency results in deficient heme synthesis and eventual microcytic, hypochromic red blood cells, although acute iron deficiency anemia is generally normocytic and normochromic.[13] The MCV typically drops below the reference interval only after weeks to months of iron deficiency and a low MCHC is not commonly observed in cats.[24] In addition to absolute iron deficiency, functional iron deficiency secondary to anemia of inflammatory disease, copper deficiency, myelodysplastic disorders, drug or chemical toxicities, and possibly portosystemic shunts can result in micro-

cytic, hypochromic red blood cells.[13] Our findings are consistent with either an absolute or functional iron deficiency as these group of anemic cats with CKD had a lower median MCV compared to nonanemic cats with CKD. Four of 8 anemic cats with CKD were considered to have a microcytosis based on a reference interval of <40 fL compared to microcytosis in only 5 of 32 nonanemic cats with CKD.

Our study has several important limitations. The first is that there is no reported gold standard for noninvasive evaluation of iron status in cats for diagnosis of iron deficiency. In human patients, measurement of bone marrow reticuloendothelial iron is the gold standard for assessing iron stores[2,19]; however, healthy cats do not have visible iron stores in their bone marrow.[3,13] Iron stores have been evaluated in the feline liver and spleen and historically feline liver biopsies have been evaluated to assess tissue iron levels; however, this is not a commonly performed diagnostic test because of its invasive nature.[15] A second limitation to this study is that not all enrollees had urinalyses, thyroid levels or abdominal imaging performed and therefore we cannot definitively rule out early chronic kidney disease in these populations of healthy cats and cats with nonrenal illness, or additional nonrenal illness in cats with chronic kidney disease. A third limitation is that we had small, uneven populations with only 2 cases of IRIS stage IV CKD and only 8 anemic CKD cats. This small population of anemic cats is because of many potential enrollees with IRIS stage IV CKD having already been treated with iron or darbepoetin as well as our exclusion criteria of patients with a hemoglobin <5 g/dL because of safety concerns. The uneven distribution of patients across IRIS stages precluded direct comparisons among stages and could confound the results of this study. The diverse nature of the disease processes in the NRI group could also confound the interpretation of data within that group. Additionally, we did not age match these populations. Ferritin concentrations have been shown to increase with age and total iron binding capacity to decrease with age in human patients; however, this relationship has not been investigated in veterinary patients.[22,25,26] Lastly additional markers of inflammation such as hepcidin and C-reactive protein were not assessed which could provide additional information about whether an inflammatory state exists in veterinary patients with chronic kidney disease. C-reactive protein has been shown to increase progressively from CKD stages III to V in human patients.[19]

Conclusions

Total iron binding capacity was different between CKD and healthy cats; however, there was no difference between any of the groups for iron concentrations, ferritin concentrations or TSAT. Our results suggest that if an iron deficient state exists in cats with CKD, it is likely functional secondary to decreased erythropoiesis by diseased kidneys as well as anemia of inflammation.

Footnote

[a] Stata release 12, 1996–2013, StataCorp LP, College Station, TX.

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Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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