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Renal Lipidosis in Horses and Donkeys: 25 Cases (2008–2022)

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ABSTRACT

Background: Renal lipidosis is a well-documented histologic finding in humans and small animals with renal and metabolic disorders, but it is not well described in equids.

Objective: To describe the signalment, clinicopathologic indices, and postmortem findings of equids with a histologic diagnosis of both hepatic and renal lipidosis (HL + RL) and compare them to cases with hepatic lipidosis only (HL).

Animals: Equids with necropsy findings of renal or hepatic lipidosis (state diagnostic lab) between 2008 and 2022.

Methods: Retrospective case–control study. Signalment, history, necropsy diagnosis, and selected biochemical data at admission were extracted from medical records. Each case of HL + RL was assigned a matched case from group HL for comparison of clinical data.

Results: Renal lipidosis was diagnosed in 0.5% (25/4680) of equid necropsies. Donkeys (7/13) and pony/miniature horses (13/37) with hepatic lipidosis were more likely to also have renal lipidosis compared to horses (5/141; $p = 0.0006$, RR = 15.1and $p < 0.0001$, RR = 9.9, respectively). No cases of renal lipidosis were identified without concurrent hepatic lipidosis. The predominant presenting complaints involved gastrointestinal (16/25) and neurologic (12/25) systems. Compared to group HL, group HL + RL had significantly higher admission plasma lactate concentration (+6.2 mmol/L, 95% CI 0.04–13.1, $p = 0.04$) and GGT activity (+246 U/L, 95% CI −480.4–1870, $p = 0.02$). No significant differences were detected in creatinine or triglyceride concentrations.

Conclusions: Renal lipidosis is an occasional postmortem finding in equids with hepatic lipidosis and is more common in donkeys, ponies, and miniature horses compared to horses. The clinical implications of renal lipidosis remain unclear.

1 | Introduction

Hypertriglyceridemia is a common finding in equids in a negative energy balance state, especially ponies and donkeys [1, 2]. Conditions including inappetence, pregnancy, lactation, and systemic inflammation (e.g., colitis, pneumonia) might precipitate negative energy balances [1, 3, 4]. Obesity and metabolic disorders such as pituitary pars intermedia dysfunction (PPID) or equine metabolic syndrome (EMS) are associated with hyperinsulinemia and increased lipid mobilization in negative energy balance states [3]. Severe hypertriglyceridemia (serum triglyceride > 500 mg/dL without gross lipemia), hyperlipemia (serum triglyceride > 500 mg/dL with gross lipemia), hepatic lipidosis, and lipid deposition into other organs (e.g., kidneys) occur when

Abbreviations: ATP, adenosine triphosphate; BUN, blood urea nitrogen; CI, confidence interval; CKD, chronic kidney disease; EMS, equine metabolic syndrome; FFA, free fatty acid; GFR, glomerular Filtration Rate; GGT, gamma-glutamyl transpeptidase; H&E, hematoxylin and eosin; HL + RL, hepatic and renal lipidosis; HL, hepatic lipidosis; IRIS, International Renal Interest Society; PADLS, Pennsylvania Animal Diagnostic Laboratory System; PPID, pituitary pars intermedia dysfunction; RL, renal lipidosis; TCA, tricarboxylic acid cycle; VLDL, very low density lipoprotein.

the hepatic threshold for conversion of free fatty acids (FFAs) and triglyceride to plasma-soluble very low-density lipoprotein (VLDL) is exceeded [1–3, 5, 6]. Presenting clinical signs are often vague, including poor appetite and dull mentation, in addition to clinical signs associated with the primary disease process.

The pathophysiology of renal lipid accumulation is described in mouse models and various human disease processes. In health, serum lipoproteins are filtered in the glomerulus and then reabsorbed and metabolized in the renal proximal tubules [7, 8]. Markedly elevated serum lipoprotein concentration can lead to lipid accumulation within the renal tubular epithelium, podocytes, mesangial cells, and endothelial cells, resulting in the production of pro-inflammatory cytokines and reactive oxygen species, depletion of ATP, depolarization of mitochondrial membranes, and activation of pro-apoptotic pathways [5, 7, 8]. The proximal tubular epithelium appears to be the most sensitive to lipid toxicity compared to other renal cell types, likely due to the high metabolic demands of these cells, which rely upon mitochondrial fatty acid oxidation [5, 8, 9].

Renal lipid accumulation is a common histologic finding in cats with or without renal disease, and in humans with various chronic renal disorders, including nephrotic syndrome, diabetic kidney disease, focal segmental glomerulosclerosis, and chronic kidney disease (CKD) [8, 10–12]. Risk factors for CKD in humans include obesity, hypertriglyceridemia, and reduced high-density lipoprotein cholesterol [8, 13, 14]. Renal lipidosis is noted infrequently on renal biopsy and postmortem analysis in dogs [13, 15] and rarely in horses [2, 3]. In humans, renal lipidosis is often described as a secondary process associated with chronic renal inflammation [8, 10]. However, the lipid nephrotoxicity hypothesis posits that hyperlipidemia might also act as a primary disease process in the kidneys, leading to lipid droplet accumulation starting in the tubular interstitial cells and in severe cases progressing to glomerular lipid accumulation, glomerulosclerosis, and progressive renal dysfunction [8–10].

There have been few reports that mention renal lipid deposition in equids [1, 3, 16]. The prevalence and clinical implications of renal lipidosis have not been described in these species. The purpose of this study was to describe the clinicopathological findings in equids with renal lipidosis diagnosed at necropsy.

2 | Materials and Methods

2.1 | Data Collection

Electronic necropsy records from the Pennsylvania Animal Diagnostic Laboratory System (PADLS) were searched for equids diagnosed with either hepatic lipidosis, renal lipidosis, or both from January 1, 2008, to December 31, 2022. Fetal equids were excluded from analysis. Information was extracted from the necropsy reports and medical records from the New Bolton Center at the University of Pennsylvania. Information collected included signalment, reproductive status, presenting complaint, physical exam findings, treatment data (use of antibiotics, intravenous administration of dextrose, and insulin), clinicopathologic data at the time of admission and before euthanasia, clinical diagnosis, and postmortem findings for each equid. Definitive diagnoses of hepatic lipidosis and renal lipidosis were based on histopathologic findings of samples collected during necropsy. Cases with a histopathologic diagnosis of hepatic lipidosis without a finding of renal lipidosis were paired with each renal lipidosis case on the basis of age, sex, and breed. Selected clinicopathologic data (lactate, creatinine, triglycerides, blood urea nitrogen (BUN), and gamma-glutamyl transpeptidase (GGT)) were compared between these two groups.

2.2 | Histopathologic Grading Schemes

At necropsy, gross and microscopic examination of the liver and kidneys for each case was performed. Gross descriptions of the liver and kidneys were obtained from the necropsy reports. Histopathologic sections of the liver and kidney for each case were reviewed retrospectively and graded by one author (S. Bender) to standardize the severity grading descriptions. Hepatic lipidosis was classified as mild–moderate if hepatocellular lipid vacuoles had a multifocal or zonal distribution in the liver and severe if hepatocellular vacuolation was diffuse throughout the liver. Renal lipidosis was classified as mild if $< 50\%$ of the proximal tubular epithelium was affected with mostly small lipid vacuoles, moderate if $> 50\%$ of the proximal tubular epithelium was affected with a mixture of small and large lipid vacuoles, and severe if the proximal tubular epithelium was diffusely affected with mostly large lipid vacuoles (Figure 2).

2.3 | Statistical Analysis

Descriptive and inferential statistics were performed using GraphPad Prism (Prism 10 for macOS Version 10.0.2 (171)). Descriptive statistics were used to report clinical and clinicopathologic findings for cases of renal lipidosis. Numbers appear as frequency counts (percentage) for categorical variables and as medians (range) for continuous variables, unless otherwise specified. A Shapiro–Wilk test was used to assess for normality of selected clinicopathologic data, which were determined to be non-normal. Wilcoxon matched pairs signed-rank tests were performed for selected clinicopathologic data paired between breed, age, and sex-matched cases of hepatic lipidosis only and cases with both hepatic and renal lipidosis. Fisher's exact test was used to compare the proportion of equids with renal lipidosis between breeds. All analyses were conducted with two-sided tests of the hypothesis and a p-value of < 0.05 as criteria to define statistical significance.

3 | Results

A total of 5037 equid necropsies were performed in the 2008–2022 period, of which 4680 were non-fetuses. Postmortem records found a total of 210 horses and donkeys with a histopathologic diagnosis of hepatic lipidosis and 25 horses and donkeys with a histopathologic diagnosis of both hepatic lipidosis and renal lipidosis. No cases were identified with renal lipidosis in the absence of hepatic lipidosis. The prevalence of hepatic lipidosis and renal lipidosis was 4.4% (210/4680) and 0.5% (25/4680), respectively. Among equids with hepatic lipidosis, the prevalence of renal lipidosis was 11.9% (25/210).

The median age of affected animals was 9 years (range 3–21 years). Seven of the 25 animals were geldings or stallions, while 18 were mares. Breeds represented included miniature horse (9), miniature donkey (4), pony (4), standard donkey (3), thoroughbred (2), standardbred (1), warmblood (1), and Friesian (1). Two mares (1 pony, 1 miniature horse) were pregnant in late gestation, and five were lactating (1 horse, 1 pony, 2 miniature horse, 1 miniature donkey). Donkeys and pony/miniature horse breeds were significantly more likely to have both renal and hepatic lipidosis compared to horses (donkey 7/13, 54%; pony/miniature horse 13/37, 35%; horse 5/141, 4.2%; $p = 0.0006$, RR = 15.1 and $p < 0.0001$, RR = 9.9, respectively).

The most common presenting complaint for equids with renal lipidosis and hepatic lipidosis (group HL + RL) included signs of gastrointestinal (64%, 16/26) and neurologic disease (48%, 12). Less common presenting complaints included signs of reproductive tract disease (3), respiratory disease (2), and found dead (2). Some animals presented with clinical signs localizing to multiple body systems. Clinical diagnoses were highly variable, including infectious enterocolitis (5/20), hepatic lipidosis (4), acute kidney injury (4), hepatic encephalopathy (3), unknown hepatopathy (3), botulism (3), unknown neurologic disease (2), unknown cause of death (2), acute hepatitis (1), pneumonia (1), and *Streptococcus equi equi* guttural pouch empyema (1). Postmortem diagnoses in addition to hepatic and renal lipidosis included enterocolitis/typhlocolitis (7/25), metabolic encephalopathy (4), venous thromboses (3), suppurative bronchopneumonia (3), cerebral edema (2), gastric ulceration (2), gastrointestinal infarcts (1), toxic hepatopathy (1), gastric impaction (1), acute hepatitis (1), guttural pouch empyema (1), and unknown neurologic disease (1).

Fever (T > 101.5°F) was recorded in 8/17 cases for which admission rectal temperature was recorded. Rectal temperature was not recorded in 8 cases either due to incomplete medical records (2/8) or because the animal was presented for necropsy only (6/8). Admission blood lactate concentration was available for 10/12 cases with a median 7.3 mmol/L (range: 3.8–23.0), creatinine concentration was available in 12 cases with a median 2.7 mg/dL (range: 1.3–10.2), blood urea nitrogen (BUN) concentration was available in 6 cases with a median 11.5 mg/dL (range: 2.0–63.0), gamma-glutamyl transferase (GGT) activity was available for 11 cases with a median 212 U/L (range: 11–4880), and plasma triglyceride concentration was available in 8 cases with a median 433 mg/dL (range: 132–8855).

Serial plasma biochemistry values obtained during treatment were available for nine cases, though not all values were available for all cases. Looking at the last plasma biochemical analysis before euthanasia, a final blood lactate concentration was available in 7 cases with median of 4.7 mmol/L (range: 1.5–16.3). Final creatinine concentration was reported in 8 cases with median of 3.2 mg/dL (range: 1.7–8.1), final BUN concentration was reported in 4 cases with a median of 11.0 mg/dL (range: 4.0–50.0), final GGT activity was reported in 5 cases with a median 179 U/L (range: 15–607), and final triglyceride concentration was available in 6 cases with a median 414 mg/dL (range: 78–2819).

Admission plasma biochemistry variables were assessed in sex- and age-matched cases with a histologic diagnosis of hepatic lipidosis without renal lipidosis (group HL). Admission blood lactate concentration was available in 9/12 cases with a median 2.9 mmol/L (range: 0.8–12.0), admission creatinine concentration was available in 11/12 cases with a median 2.3 mg/dL (range: 0.9–14.3), admission BUN concentration was available in only 3 cases with a median 78.0 mg/dL (range: 66.0–105.0), admission GGT activity was available in 10 cases with a median 38 U/L (range: 15–226), and admission triglyceride concentration was available in 5 cases with a median 1131 mg/dL (range: 638–2425).

Compared to the HL group, the HL + RL group had significantly higher admission blood lactate concentration (+6.2 mmol/L, 95% CI 0.04–13.1, $p = 0.04$) and GGT activity (+246 U/L, 95% CI −480.4–1870, $p = 0.02$). Differences in admission values for creatinine and triglyceride concentrations were not significantly different (Figure 1). Not enough data points were available to determine the significance of BUN measurements.

At necropsy, gross yellow/tan discoloration of the kidneys was observed in 10/25 renal lipidosis cases (Figure 2a), and kidneys in four of these cases were reported to be soft or friable in addition to the discoloration. These gross findings were more commonly reported in renal lipidosis cases retrospectively classified as microscopically severe (6/8) than in mild or moderate cases (4/17). Microscopically, epithelial cells lining the proximal convoluted tubules and, in some cases, the proximal straight tubules had variably sized discrete clear vacuoles (lipid) in the cytoplasm, the larger of which displaced the

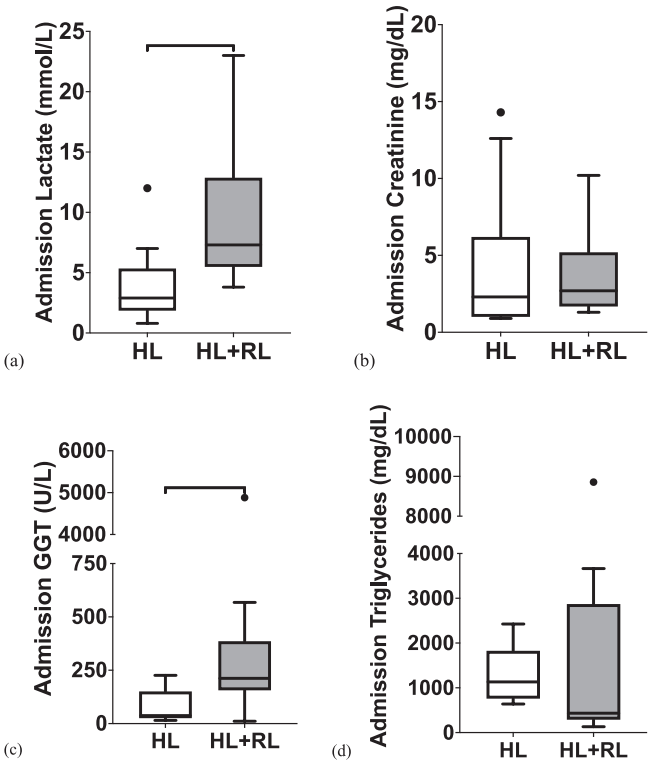

FIGURE 1 | (a) Initial blood lactate concentrations compared between cases of hepatic lipidosis (HL) and cases with both hepatic and renal lipidosis (HL + RL). (b) Initial serum creatinine concentrations of groups HL and HL + RL. (c) Initial serum GGT activity of groups HL and HL + RL. (d) Initial plasma triglyceride concentrations of groups HL and HL + RL.

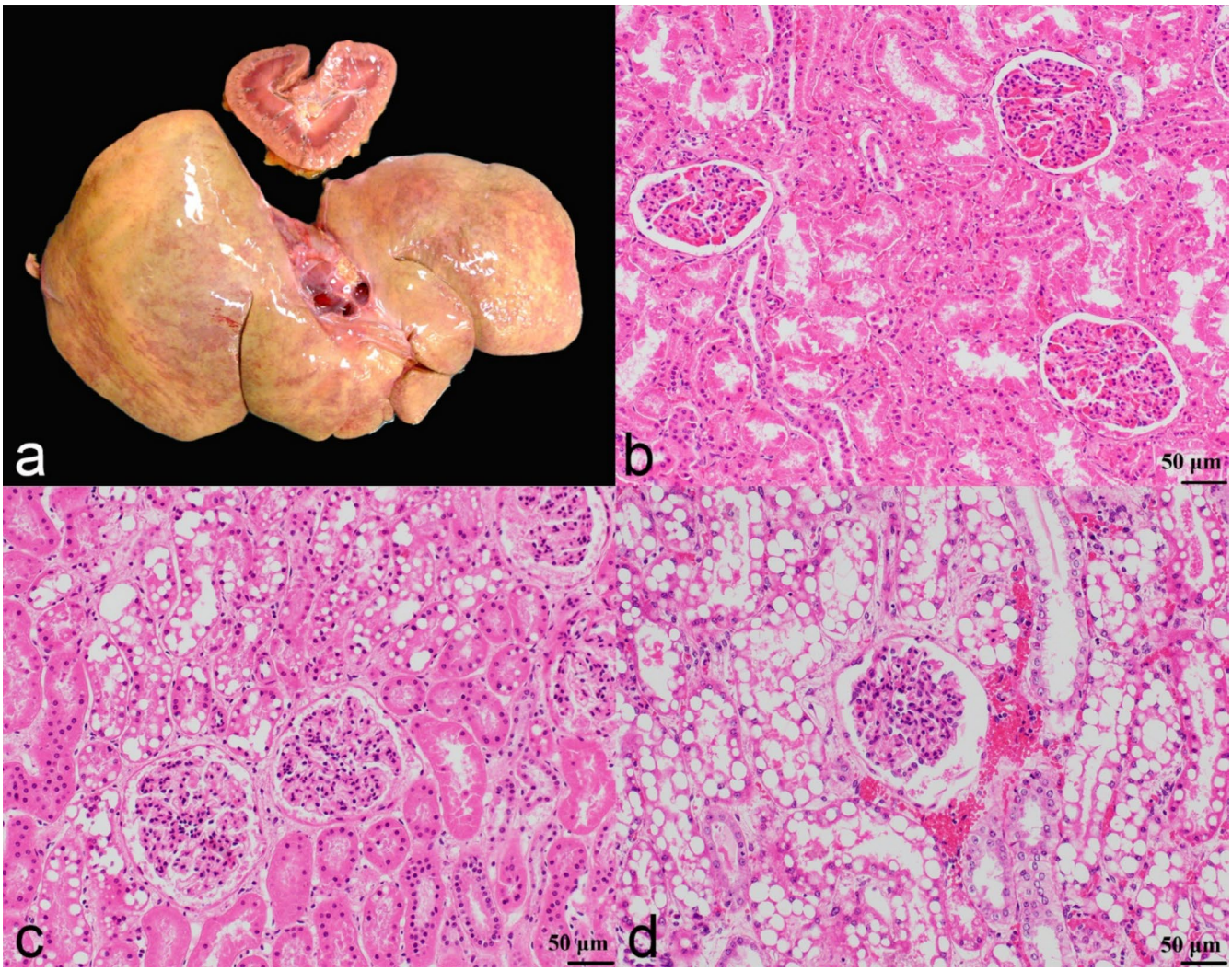

FIGURE 2 | (a) Photograph of kidney (top, longitudinally sectioned) and liver (bottom) from an equid with severe renal and hepatic lipidosis. The renal cortices are diffusely yellow-tan. The liver is diffusely enlarged and yellow-tan. Image courtesy of Dr. Perry Habecker. (b) Photomicrograph of kidney from an equid with mild renal lipidosis. Less than 50% of proximal tubular epithelial cells contain small clear vacuoles in the cytoplasm, with minimal distortion of the cell contours. H&E stain, 20X objective. (c) Photomicrograph of kidney from an equid with moderate renal lipidosis. Greater than 50% of proximal tubular epithelial cells contain clear vacuoles of varying size in the cytoplasm. Larger vacuoles displace the cell nucleus and distort the cell contour, while smaller vacuoles do not. H&E stain, 20X objective. (d) Photomicrograph of kidney from an equid with severe renal lipidosis. Proximal tubular epithelial cells diffusely contain discrete clear vacuoles in the cytoplasm that often displace the cell nucleus and distort the cell contour. H&E stain, 20X objective.

cell nucleus and distorted the outer contour of the cell. Of the 25 cases with identified renal lipidosis, 16% (4/25) were mild (Figure 2b), 52% (13/25) were moderate (Figure 2c), and 32% (8/25) were severe (Figure 2d). Additional renal lesions identified in a small subset of cases included acute tubular necrosis, intratubular protein or granular pigment (hemoglobin/myoglobin) casts, fibrin thrombi, and acute or chronic infarcts. Concurrent hepatic lipidosis was present in all cases of renal lipidosis and was classified as mild–moderate in 12% (3/25) and severe in 88% of cases (22/25). Cases of severe renal lipidosis were always associated with severe hepatic lipidosis (8/8).

4 | Discussion

This study found that renal lipidosis is a rare condition in equids, with an overall postmortem prevalence of only 0.53%, and 11.90% among necropsies of equids with hepatic lipidosis. A histopathologic diagnosis of renal lipidosis was only seen in conjunction with hepatic lipidosis, suggesting that renal lipidosis might be a progression of a primary disease process that also results in hepatic lipidosis. The most common presenting complaint for renal lipidosis cases in this study was signs of gastrointestinal disease, attributable to enterocolitis, gastric ulcers, and other gastrointestinal diseases. Gastrointestinal disease processes frequently lead to reduced feed intake, inducing a negative energy balance state that could favor conditions necessary for renal lipid accumulation.

Demographics of equids described as higher risk for the development of hypertriglyceridemia and hepatic lipidosis include ponies, donkeys, miniature horses, middle-aged horses, and mares [1, 2]. In hospitalized cases, the prevalence of hypertriglyceridemia in horses is low (0.5%) and much higher in ponies,

miniature horses, and donkeys (11%–18%), again suggesting a breed predilection toward this metabolic derangement during disease states [2]. Similarly, our study showed a breed predisposition for renal lipidosis which included donkeys, ponies, and miniature horses (20/25 HL + RL cases) as compared to full-size horses (5/25). The apparent observed breed difference is likely multifactorial, with influence from both genetic and environmental factors. Donkeys are predisposed to the development of obesity and insulin dysregulation due to an increased efficiency of conversion of caloric intake into energy as compared to horses [16–18]. Donkeys and miniature horses also demonstrate more efficient fat mobilization in response to increased energy demands, stress, and illness as compared to horses [16, 18]. Different management practices between donkeys, ponies, miniature horses, and horses, especially exercise and feeding practices, might also predispose donkeys, ponies, and miniature horses to the development of dyslipidemia. Alternatively, this might be due to the fact that in this study there was a larger proportion of donkeys presented for necropsy with severe hepatic lipidosis as compared to horses and ponies, the latter group with the majority mild–moderate hepatic lipidosis lesions.

Equids with renal lipidosis in this study frequently presented with multiple biochemical disturbances, including moderate hyperlactatemia, moderate azotemia, moderate to marked hypertriglyceridemia, and moderately to markedly increased GGT activity. However, only blood lactate concentration and plasma GGT activity were significantly higher in renal lipidosis cases compared to hepatic lipidosis cases.

The hyperlactatemia observed in renal lipidosis cases might be a Type A hyperlactatemia associated with reduced tissue oxygen delivery due to hypoperfusion from distributive shock. Severely ill equids, including those with endotoxemia such as from gastrointestinal disease, often develop shock and subsequent hyperlactatemia secondary to the primary disease process. In these cases, reduced renal perfusion could predispose them to functional ischemia and damage to the highly metabolically active proximal tubular cells, favoring renal tubular lipid deposition. This would suggest that more severely ill and systemically compromised equids would be at an increased risk of developing renal lipidosis.

Alternatively, hyperlactatemia in the renal lipidosis cases might be induced by a Type B hyperlactatemia wherein lactate is not appropriately cleared from the body. L-lactate clearance occurs predominantly in the liver and kidneys through one of two mechanisms: oxidation into pyruvate, a substrate of the tricarboxylic acid cycle (TCA), or entrance into gluconeogenesis pathways [19]. Excretion of lactate into the urine also occurs to a lesser extent [19]. Hepatocellular or renal dysfunction in these cases could result in reduced lactate clearance. In this case, hyperlactatemia would be a direct consequence of renal (and hepatic) lipidosis, indicating damage already present to these organs. Regardless of the cause of the hyperlactatemia, elevated blood lactate concentrations are associated with an increased risk of renal lipidosis. However, hyperlactatemia is a non-specific finding common to many disease processes, and as such, it is not a sensitive indicator of renal lipidosis risk.

Plasma GGT activity in the renal lipidosis cases was significantly higher than in the hepatic lipidosis cases. GGT is present in many tissues, including the biliary epithelium, renal tubular epithelium, and pancreatic ducts [20, 21]. Increased GGT activity is observed with cholestasis and non-specific hepatic dysfunction, including fatty liver syndrome, drug reactions, and alcoholism in humans [22]. In horses, GGT is considered a specific marker of biliary damage, as it is thought that other sources of GGT (kidneys, pancreas, lung) do not contribute appreciable amounts to serum GGT activity [23]. GGT produced in the renal proximal tubular epithelium is shed in the urine and is unlikely to cause serum GGT activity elevations [20, 21]. However, in humans, acute renal tubular injury induces considerable elevations in serum GGT activity [24].

Plasma creatinine concentrations were not significantly different between renal lipidosis cases and hepatic lipidosis cases. An association between dysregulated lipid metabolism and azotemia is documented in humans [25] and horses [26], although the underlying pathophysiology behind this relationship remains unclear. In humans, a frequent complication of nephrotic syndrome is hyperlipidemia and resultant lipid deposition in multiple organs including the kidneys [10, 27]. However, in these cases lipid accumulates in rafts within the renal podocytes and glomeruli, inducing a pro-inflammatory state and resulting in glomerulosclerosis and induction of significant proteinuria [10, 14, 27]. A similar condition is documented in cats, where as many as 85% of cats with CKD IRIS stage 2–4 have renal interstitial lipid on histopathology [11–13]. Glomerulosclerosis in these cases requires prior renal endothelial injury, such as with CKD or other nephropathies, as well as the presence of excess lipid in the blood [11, 15]. Glomerular lipid accumulation is thought to hasten the progression of CKD in humans and likely in cats as well [11, 14]. Glomerular lipid accumulation and resulting glomerulosclerosis are less frequently reported in dogs with kidney disease [15].

In contrast, equids with renal lipidosis in this study accumulated lipid exclusively in the proximal tubular epithelium. It is possible that the different lipid accumulation sites between equids and humans influence the degree of resulting azotemia; in humans, glomerular and podocyte injury results in a reduction in glomerular filtration rate (GFR) and the development of azotemia. In contrast, in equids the glomeruli appear to be spared from lipid accumulation, and therefore GFR might have been less severely impacted.

It is unclear whether equids that develop hepatic and renal lipidosis have a poorer prognosis compared to those with hepatic lipidosis alone. Identification of equids with renal lipidosis in the antemortem period has yet to be described, and therefore the case fatality rate associated with this disease process remains unknown. Antemortem identification of renal lipidosis in equids is critical in understanding its clinical importance. Risk factors identified in this study include hyperlactatemia and elevated serum GGT activity; however, these clinicopathologic changes are non-specific. Additional potential risk factors include sex (female) and reproductive state (pregnant or lactating). Monitoring for signs of acute tubular injury, including fractional electrolyte excretions and urinary GGT:creatinine ratios, might further aid in the identification of renal lipidosis cases. Renal ultrasonography to evaluate for altered cortical echogenicity or increased total renal size, although determined to be poorly sensitive and specific in the detection of renal cortical disease in

small animals [28], might be another avenue to pursue antemortem identification of renal lipidosis in equids.

In conclusion, renal lipidosis is a rare finding in equids and is identified exclusively in those equids with hepatic lipidosis. Donkeys, miniature horses, and ponies show a greater predisposition toward renal lipid accumulation, similar to the species and breed predilection seen for hepatic lipidosis.

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Disclosure

Authors declare no off-label use of antimicrobials.

Ethics Statement

Authors declare no Institutional Animal Care and Use Committee or other approval was needed. Authors declare human ethics approval was not needed.

Conflicts of Interest

The authors declare no conflicts of interest.

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