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Increased canine pancreatic lipase immunoreactivity (cPLI) and 1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6′-methylresorufin) ester (DGGR) lipase in dogs with evidence of portal hypertension and normal pancreatic histology: a pilot study

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Abstract. The clinical presentations of both liver disease and pancreatitis are nonspecific and overlapping, which may cause difficulty in diagnosis. In our retrospective pilot study, we assessed whether dogs with evidence of portal hypertension and absence of pancreatitis on pancreatic histology have increases in canine pancreatic lipase immunoreactivity (cPLI) and 1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6′-methylresorufin) ester (DGGR) lipase. We included dogs that had been presented between 2008 and 2019 if they had normal pancreatic histology, histologically confirmed hepatopathy, and if canine pancreas-specific lipase (Spec cPL; Idexx) or DGGR lipase had been measured. Only dogs with portal hypertension were included. Six dogs fulfilled the inclusion criteria. Four of 6 and 2 of 6 dogs had Spec cPL and DGGR lipase exceeding the upper reference limit, respectively. From the 4 dogs with increased Spec cPL, 2 had concentrations of 200–400 µg/L and 2 had concentrations ≥ 400 µg/L. Our results suggest that canine portal hypertension might lead to increased Spec cPL and DGGR lipase values in the absence of pancreatitis on histology. Until more evidence in a larger number of dogs with portal hypertension is available, both tests should be interpreted cautiously in the presence of portal hypertension.

Key words: cPLI (canine pancreatic lipase immunoreactivity); DGGR lipase (1,2-o-dilauryl-rac-glycero-3-glutaricacid-(6′-methylresorufin) ester); dogs; liver; MAPSS (multiple acquired portosystemic shunts); portal hypertension; Spec cPL (canine pancreas-specific lipase).

Introduction

Portal hypertension (PH) is defined as increased portal pressure caused by increased vascular resistance, increased portal venous blood flow, or a combination of both.[2] Several pathologic processes can cause PH, and these can be divided according to their anatomic location as prehepatic, hepatic, and posthepatic. Increased portal pressure may cause congestion of the visceral venous system and edema of the visceral organs, leading to organ dysfunction.[2] Clinical signs are nonspecific and include ascites and gastrointestinal signs, including vomiting, together with signs of any underlying liver disease such as cranial abdominal pain and jaundice.[2] The clinical presentations of both liver disease and pancreatitis are nonspecific and overlapping, which may cause difficulty in diagnosis.[34]

Pancreatitis occurs frequently in dogs, although the diagnosis can be challenging given that physical and clinicopathologic alterations are often nonspecific.[9,35] Pancreatic histology is still considered the "gold standard" for the diagnosis of pancreatitis, but its invasive nature, possibility of missing localized disease, and small size of samples obtained has prompted the development of noninvasive tests.[18,33] Canine pancreatic lipase immunoreactivity (cPLI) assays, including the canine pancreas-specific lipase assay (Spec cPL; Idexx), have been developed and are used widely and routinely in veterinary practice as detection tools for pancreatitis. Based on histopathologic criteria, specificities of 90–100% have been reported for Spec cPL; sensitivities vary depending on the severity of pancreatitis.[14,29]

However, the pancreas can be affected in other diseases, and there is some evidence that pancreatic hypoxia or edema,

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in the absence of pancreatitis, may elevate pancreatic enzymes. Congestive heart failure, hyperadrenocorticism, intervertebral disc disease, and immune-mediated hemolytic anemia can cause Spec cPL increases in the absence of clinical signs consistent with pancreatitis.[7,16,23,32] Also, Spec cPL may indicate a "false-positive" diagnosis of pancreatitis in up to 23% of dogs with acute abdominal signs in which another disease is diagnosed.[8] Increases in Spec cPL in the absence of clinical signs compatible with pancreatitis, or with a non-pancreatic disease explaining the clinical signs, might reflect subclinical pancreatic inflammation, edema, or hypoxia. Pancreatic histologic assessment could have been useful in confirming or refuting this theory, but none of the above-mentioned studies had pancreatic histologic assessment performed.[7,8,16,23,32] In another study, healthy dogs that received prednisolone had increases in cPLI in the absence of clinical signs compatible with pancreatitis, and pancreatic histologic assessment showed no evidence of pancreatitis.[19]

cPLI assays have been considered the preferred blood tests for use in the diagnosis of pancreatitis, although the 1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6′-methylresorufin) ester (DGGR) lipase assay has been shown to correlate well with Spec cPL.[4,12] DGGR lipase has the advantage of being more economical and is readily available in general biochemistry panels, unlike Spec cPL which must be shipped to external laboratories resulting in a greater length of time before results are available.

Hepatic congestion is associated with increased serum liver enzyme activities.[5] Similar effects are presumed to occur in the pancreas of dogs suffering from congestive heart failure, in which cPLI increases have been observed, although no clinical signs consistent with pancreatitis were present.[7] On abdominal ultrasonography, PH can cause pancreatic edema, which can sometimes be confused with pancreatitis, making misdiagnosis a possibility.[13] Furthermore, the combination of nonspecific clinical signs, such as lethargy, hyporexia/anorexia, vomiting, and abdominal pain seen with pancreatitis, can also be associated with hepatopathy. All of these factors could lead to a misdiagnosis of pancreatitis in a dog with liver disease and PH. Therefore, our objective in this pilot study was to characterize Spec cPL and DGGR lipase in dogs with PH and histologically normal pancreas.

Materials and methods

Animals

Dogs that died, were euthanized, or had simultaneous pancreatic and hepatic biopsies at the Small Animal Hospital, Ghent University (Merelbeke, Belgium), in 2016–2019, and Queen's Veterinary School Hospital, University of Cambridge (Cambridge, United Kingdom), in 2008–2018, were evaluated and selected retrospectively for inclusion in our study if they fulfilled the following criteria:

- PH was inferred based on clinical signs and ultrasound findings.
- Associated causative liver disease was confirmed on histopathology.
- At least one pancreatic biopsy was histologically normal.
- Spec cPL and DGGR lipase were measured, either at the time of diagnosis of PH or from frozen stored serum.

When available, reports of ultrasonographic findings and surgery reports of the dog's pancreas assessed by a board-certified radiologist (ECVDI) and by a board-certified surgeon (ECVS) were reviewed respectively. Dogs with documented, azotemia, immune-mediated hemolytic anemia, congestive heart failure, or hyperadrenocorticism/exogenous steroid administration were excluded, given that these factors can or might cause increases in lipases in the absence of clinical pancreatitis.[7,16,20,31,32]

Portal hypertension

PH was inferred based on the presence of abdominal effusion, either transudate or modified transudate, presence of multiple acquired portosystemic shunts (MAPSS), and serum albumin > 16 g/L in a dog with documented liver disease.

Determination of DGGR lipase and Spec cPL

All samples, when available, were stored at –80°C. The Spec cPL assay (Idexx) is a quantitative ELISA, and concentrations were measured on a microplate reader (Idexx Reference Laboratories, Germany, UK).[11] Dogs with Spec cPL values < 200 µg/L were considered to have values within the reference interval (RI). Based on the assumption that, in the absence of pancreatitis, assay values should be lower than the above-mentioned cutoff value, Spec cPL values > 200 µg/L were considered to be increased. In clinical settings and according to the manufacturer, Spec cPL concentrations of 201–400 µg/L are equivocal for the diagnosis of pancreatitis, and retesting is recommended in 2–3 wk. Spec cPL concentrations ≥ 400 µg/L are consistent with pancreatitis.

DGGR lipase activity was measured using a commercial assay (Lipase assay DGGR; Randox) at Central Diagnostic Services, University of Cambridge. The DGGR lipase assay had inter-assay CVs of 11% and 13% when control materials with mean lipase activities of 26 IU/L and 75 IU/L, respectively, were evaluated (n = 11, unpub. internal validation data). The RI for DGGR lipase (0–44 IU/L) was calculated by transference from the RI calculated for another previously validated lipase assay (Lipase DC FS; DiaSys),[4] which was correlated strongly with the Randox assay (R^2 = 0.983, n = 161; unpub. internal validation data).

Table 1. Signalment, clinical signs, and diagnosis of 6 dogs with evidence of portal hypertension (PH) and absence of pancreatitis on histologic assessment.

Case	Breed	Sex	Age	Clinical signs	Cause of PH
1	Giant Schnauzer	SF	1 y, 6 mo	Lethargy, anorexia	Systemic histiocytic sarcoma
2	Smooth Collie	F	4 mo	Lethargy, anorexia, abdominal distention	Arteriovenous malformation
3	Boxer cross	SF	1 y, 2 mo	Fever, icterus, vomiting, weight loss, hyporexia	Caroli syndrome
4	Pomeranian	M	6 y, 2 mo	Lethargy, anorexia, abdominal distention	Chronic hepatitis + unusual congenital hepatic malformation with 2 independent liver parts and 2 independent portal vessels
5	Maltese	SF	3 y, 6 mo	Lethargy, icterus, abdominal distention	Cirrhosis secondary to lobular dissecting hepatitis
6	Labradoodle	CM	4 y, 9 mo	Hyporexia, vomiting, abdominal distention	Chronic hepatitis

CM = castrated male; F = female; M = male; SF = spayed female.

Histology

All histologic samples were fixed in 10% neutral-buffered formalin at room temperature, processed routinely, and sections stained with hematoxylin and eosin. Histologic diagnoses of primary liver disease were based on the World Small Animal Veterinary Association criteria.[22] The pancreas was considered normal (absence of pancreatitis) when there was no evidence of pancreatic inflammation, necrosis, or fibrosis, according to criteria published previously.[18] Both hepatic and pancreatic samples obtained were examined by an ECVP diplomate.

Results

Animals

Six dogs fulfilled the inclusion criteria (Tables 1, 2). Five dogs (1–3, 5, 6) had pancreatic and liver tissue obtained immediately postmortem and placed in formalin < 30 min after death; dog 4 had biopsies obtained by celiotomy.

Spec cPL and DGGR lipase values

Serum samples were obtained a median of 3 d (range 1–10 d) before postmortem or pancreas biopsy, when abdominal effusion was already present (Table 2). Both Spec cPL and DGGR lipase were measured from the same serum sample in 5 dogs. In case 4, DGGR lipase was measured at diagnosis, and Spec cPL was measured 3 y later on the same sample; the sample had been frozen at –80°C for the 3 y. In case 3, Spec cPL and DGGR lipase were measured in different serum samples taken 1 d apart, and the serum sample from which DGGR lipase was measured had been frozen at –80°C for 10 mo. In all the other cases, Spec cPL and DGGR lipase were measured simultaneously after the serum samples were frozen for 1 mo (cases 1, 5, 6) and 6 mo (case 2). Four of 6 dogs had Spec cPL > 200 µg/L (2 dogs in the equivocal range, and 2 in the range suggestive of pancreatitis), and 2 of 6 dogs had DGGR lipase > 44 IU/L (Table 2).

Discussion

Our results suggest that dogs with PH can have increases in Spec cPL concentration and DGGR lipase activity in the presence of normal pancreatic histology. This is a relevant finding because liver disease and pancreatitis can have very similar clinical presentations, which could confuse clinical diagnosis.[34,35]

The cause of this elevation in lipase is not yet known, but it could be pancreatic edema or congestion caused by PH leading to extravasation of pancreatic lipase from acinar cells. On abdominal ultrasonography of some of these cases, hypoechoic and enlarged pancreases associated with hyperechoic peri-pancreatic fat, secondary to abdominal effusion, were noted. When combined with increases in serum lipases and clinical signs overlapping between pancreatitis and advanced chronic hepatitis, ultrasonography could lead to cases of PH being misdiagnosed as having pancreatitis, underlining the importance of undertaking our study.[3,13,30] The dogs in our study were not homogeneous, with different conditions causing PH. Not all dogs included had a clinical suspicion of pancreatitis; however, our objective was to describe the effect of PH on Spec cPL and DGGR lipase, which makes the dogs included appropriate.

It is important to mention that although 4 dogs had Spec cPL > 200 µg/L, 2 of these dogs had a Spec cPL concentration in the equivocal concentration range. Equivocal results reduce the chances of pancreatitis being over-diagnosed when compared to Spec cPL ≥ 400 µg/L, but might still lead to further investigations and treatment, adding time and costs to reaching the final diagnosis. The use of a DGGR lipase cutoff higher than the RI increases the specificity of the assay, but decreases the sensitivity, making false-positives more uncommon, but increasing false-negative results.[6] Therefore, a diagnosis of pancreatitis cannot be made solely based on increased Spec cPL and DGGR lipase; compatible clinical and imaging findings are also necessary.

Curiously, 2 cases in our study had increased Spec cPL values, but with DGGR lipase results remaining within RIs.

Table 2. Details regarding pancreas, cause of portal hypertension, time of blood sample relative to tissue sample, and Spec cPL and DGGR lipase results.

Case	No. of pancreatic sections examined	Macroscopic pancreatic appearance	Pancreas appearance on ultrasound	Time of blood sample relative to tissue sample (d)	Spec cPL (≤200 µg/L)	DGGR (≤44 IU/L)
1	4	Pale and unremarkable	Mildly hypoechoic	4	217†	20†
2	4	Normal	Mildly enlarged, diffusely mildly hypoechoic	3	95‡	10‡
3	4	Normal	No abnormalities	2 for cPLI, 3 for DGGR	1,330	13§
4	2	Cream and unremarkable	No abnormalities	3	230*	52
5	6	NA	Mildly to moderately enlarged, mildly hypoechoic	1	413†	107†
6	6	NA	No abnormalities	1	126†	43†

cPLI = canine pancreatic lipase immunoreactivity; DGGR = 1,2-o-dilauryl-rac-glycero-3-glutaricacid-(6′-methylresorufin) ester lipase; NA = not available; Spec cPL = specific canine pancreatic lipase. Number in parentheses is reference interval. Light gray boxes reflect equivocal Spec cPL, and dark gray boxes Spec cPL consistent with pancreatitis.
* Sample used to measure Spec cPLI was frozen at –80°C for 3 y.
† Samples were frozen at –80°C for 1 mo before lipases were measured.
‡ Sample was frozen at –80°C for 6 mo before lipases were measured.
§ Sample used to measure DGGR lipase was frozen at –80°C for 10 mo.

In one of the dogs (case 3), the sample used to measure Spec cPL was obtained 24 h before the sample used to measure DGGR lipase. The discrepancy between markedly increased Spec cPL and within-RI DGGR lipase could be explained by clearance of lipase from the circulation with time, although in an experimental model of canine pancreatitis, lipase took weeks to return to baseline.[28] Good overall correlation between DGGR lipase and Spec cPL has been reported in dogs for the diagnosis of pancreatitis, but discordant results are possible.[4,12] Moreover, DGGR is a catalytic assay that is not specific for pancreatic lipase and is reported to be within the RI in dogs suffering from exocrine pancreatic insufficiency, suggesting that DGGR is not exclusively hydrolyzed by pancreatic lipase; on the other hand, the antibody used in the Spec cPL test detects lipase in pancreatic acinar cells exclusively.[6,25,26] We can only speculate that factors intrinsic to the sample or methodology were responsible for this discrepancy between DGGR lipase and Spec cPL.

The main limitations of our study are the definition used for the diagnosis of PH, the absence of complete histologic examination of the pancreas, the fact that the serum samples were stored at variable times, and the small number of cases reported. Given the retrospective nature of our study and some of the cases included being obtained at autopsy, it was not possible to measure wedge hepatic vein pressure in any dog. In an experimental canine model of PH, MAPSS development took at least 4 wk to develop after administration of a hepatotoxic drug.[10] The presence of ascites and MAPSS in the absence of marked hypoalbuminemia strongly suggests the presence of PH; the PH cases that we included had advanced signs (e.g., ascites). The criteria used for including dogs with PH were likely highly specific but poorly sensitive given that PH might be present in the absence of obvious abdominal effusion.[1] Given the retrospective nature of our study and the difficulty in assessing PH in clinical practice, we opted to include dogs that had undoubtedly increased portal pressure, which decreased the number of dogs enrolled.

It would be interesting to observe if the Spec cPL and DGGR lipase results observed in our study are reproducible in cases in which ascites are not yet present even though portal pressure is already increased. Wedge hepatic vein pressure is invasive and involves anesthesia, which precludes its use in most veterinary cases. A less invasive method of assessing portal velocity by ultrasonography has been suggested in human medicine, but few papers have assessed its accuracy.[15] To our knowledge, no veterinary literature has assessed the accuracy of abdominal ultrasonography in the detection of PH in dogs.

Although multiple areas of the pancreas were evaluated in most of the dogs in our study, none of the dogs had the entirety of the pancreas evaluated. Given that pancreatitis can be focal, pancreatitis can be missed unless the entire pancreas is examined.[17] Pancreatic assessment during surgery is also a useful indicator of the presence or absence of underlying pancreatic disease, with a study reporting no histologic abnormalities in cases in which no macroscopic gross abnormalities were present.[21] In our study, all 5 dogs in which pancreas appearance had been recorded had a subjectively normal pancreas. This normal macroscopic pancreatic appearance and normal histology of the biopsies obtained strengthen the unlikelihood of the presence of pancreatitis, but focal disease cannot be excluded.

The short-term stability of cPLI has been assessed, and little variation in its value was reported after 21 d at temperatures of 24 to –80°C.[27] In a study evaluating the effects of induced chronic kidney disease on cPLI, samples stored for

> 20 y at –80°C were used. One of the samples had significantly increased cPLI.[24] However, studies assessing the long-term stability of cPLI are unavailable, making it possible to wonder if even higher values would be present if the samples were more recent. DGGR lipase has been shown to be stable for up to 12 mo when frozen at –80°C.[4] Some of our samples were stored for 3 y at –80°C, and in light of the available bibliography, it is not possible to know if storage affected Spec cPL and DGGR lipase values. It is also important to mention the small number of cases included. This is inevitable in a study requiring histologic confirmation of disease because of the difficulty in obtaining hepatic and pancreatic histology near the time of blood sampling. Pancreatic biopsies are rarely performed because they are not often justified clinically, and postmortem examination is rarely performed soon after blood sampling. The criteria for study inclusion were strict, making it difficult to increase the number of cases included. Nonetheless, because of the strict inclusion criteria, we think that ours is a valuable pilot study that should inform the design of a future prospective study with a higher number of cases included and the use of invasive portal pressure measurements and systematic pancreatic histologic assessment to provide a conclusive answer regarding the effects of PH on Spec cPL and DGGR lipase in histologically normal pancreas.

Declaration of conflicting interests

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