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Exocrine pancreatic insufficiency in canines: An update

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Abstract

Pancreatitis, or inflammation of the pancreas, is primary and principal disease seen in dogs and cats and presents a spectrum of disease severities from acute to chronic and mild to severe. It is usually sterile, but the etiology and pathogenesis remains poorly understood and is often misdiagnosed. During acute conditions, it possesses the potential for complete recovery but in chronic pancreatitis manifested by persistent pain, recovery is compromised and can lead to several dysfunctions within the body. Pancreas is among one of the organs within the body that possesses both exocrine and endocrine functions. Dogs with exocrine pancreatic insufficiency (EPI) secrete inadequate amount of essential digestive enzymes, which lead to malabsorption and maldigestion clinically manifested by anorexia, digestive disturbances, weight loss and loss of general body condition. Diagnosis of pancreatitis remains a challenge to veterinarians and most cases require a battery of tests including imaging, hematology and biochemical analysis. Various therapies are used for dog's suffering from EPI, but by far the most successful is pancreatic enzyme replacement therapy in association with dietary modification. This article reviews the outline of pancreas, prevalence, clinical signs, diagnosis, and treatment with special focus on exocrine pancreatic insufficiency in dogs.

Keywords: Dogs, exocrine pancreatic insufficiency, ultrasonography, trypsin like immunoreactivity

1. Introduction

The word pancreas literally means, "All flesh". The one who finally made the breakthrough was Claude Bernard, who published a book in 1856 entitled *Memoir on the Pancreas and on the Role of Pancreatic Juice in Digestive Processes Particularly in the Digestion of Neutral Fat*. Bernard made pancreatic fistulas in dogs, rabbits and cats and his experimental results confirmed that fats were emulsified and broken down into fatty acids and glycerol by pancreatic juice. Pancreas of dog is a V- shaped gland located in the cranial abdomen composed of an exocrine (acinar cells) and an endocrine portion (Islets of Langerhans). The exocrine pancreas secretes digestive enzymes, fluid and bicarbonate in response to food ingestion. More than 20 enzymes are secreted by exocrine pancreas.

In the absence of proper pancreatic secretion, maldigestion and malabsorption of nutrients may cause malnutrition and associated complications. Pancreatic exocrine insufficiency is a major result of pancreatic diseases (e.g. chronic pancreatitis, cystic fibrosis, severe acute necrotizing pancreatitis, pancreatic cancer) and gastrointestinal and pancreatic surgical resections. Chronic pancreatitis used to be considered uncommon in dogs, but recent pathological and clinical studies have confirmed that it is in fact a common and clinically significant disease [1]. In chronic pancreatitis there is permanent histological change and progressive loss of exocrine and endocrine function which may progress to exocrine pancreatic insufficiency (EPI) and/or diabetes mellitus (DM) if the dog lives long enough [2]. The pancreas has an enormous functional reserve capacity, so these diseases only develop if more than 80% to 90% of the functional mass is lost [1].

Pancreatitis is the most common disorder of the exocrine pancreas in dogs as reported by Anderson *et al.* [3]. The acute form of the disease is believed to be much more common in dogs, whereas chronic pancreatitis is thought to be the primary form in cats [4, 5]. Chronic pancreatitis has traditionally been thought to be much less common than acute pancreatitis in dogs as per report by Newman *et al.* [6]. Several complications and concurrent diseases can affect the outcome and long-term prognosis of patients with chronic pancreatitis [7]. Clinical diagnosis of chronic pancreatitis can be challenging because the disease is often subclinical or is associated with mild, nonspecific clinical signs and blood work abnormalities.

Consequently, most cases of canine and feline chronic pancreatitis likely remain undiagnosed [8-10]. Clinical signs of pancreatitis depend upon the severity of the condition, which can vary from sub-clinical to chronic and mild to severe. The clinical signs include vomiting, anorexia, depression, dehydration, fever and cranial abdominal pain depicted in the form of praying posture [11, 12]. Canine exocrine pancreatic insufficiency is an alimentary tract disorder characterized by inadequate production of digestive enzyme from pancreatic acinar cells leading to the characteristic clinical signs like polyphagia, weight loss, as well as increased fecal volume [13]. The pancreas has an enormous functional reserve capacity, so these diseases only develop if more than 80% to 90% of functional mass is lost. The pancreas is a dual organ with exocrine as well endocrine functions. The interrelationship of the endocrine- exocrine parts of the pancreas is a complex one, but recent clinical and experimental studies have expanded our knowledge. End stage of chronic pancreatitis is almost certainly a more important contributor to the etiology of diabetes mellitus. Hoeing [14] reported that 30% of cases of canine DM may be caused by end stage chronic pancreatitis.

2. Clinical Prevalence

2.1 Breed Association

Though all canine breeds are susceptible to EPI, but some breeds appear to be more predisposed than others. EPI is most commonly found in German Shepherds, followed by Rough-coated Collies, Chow Chows, and Cavalier King Charles Spaniels [15-18]. Miniature schnauzers and Yorkshire terriers may also be at increased risk for pancreatitis [19, 20]. Of all dogs diagnosed with EPI, approximately 50% to 70% were German Shepherds and in Finland, 20% of the cases are found in Rough-coated Collies [15, 17, 18]. In a study conducted by Batchelor *et al.* [18] German Shepherd represented 60% of all the cases of EPI.

2.2 Gender

Female dogs are more prone to EPI as compared to male dogs. However, studies conducted by Batchelor *et al.* [18] revealed that the relationship between genders was not clear for the Rough Coated Collies and no clear sex predisposition was identified but some reports depict the gender relationship in Rough coated collies.

2.3 Age

Age of dogs suffering from EPI vary from 3 months to 17 years and onset of EPI arises in young adult animals (median age 3 years). Dogs diagnosed with chronic pancreatitis are typically middle aged to older at diagnosis. Most dogs that present with pancreatitis are older than 5 years, obese and overweight [3, 4, 19, 21].

3. Diagnosis

3.1 Imaging

3.1.1 Radiography

Although conclusive diagnosis or exclusion of pancreatitis is not possible based on radiography alone, radiography still remains a logical initial approach to patients suspected of having pancreatitis because it is relatively inexpensive and is useful for the diagnosis or exclusion of other diseases that may cause similar signs. Abdominal radiography lacks specificity and sensitivity in identifying pancreatitis in dogs [4, 20, 22]. The sensitivity of abdominal radiography was very low (24%) in one study in dogs with fatal acute pancreatitis and

similar results would be expected for dogs with chronic disease [22].

3.1.2 Ultrasonography

The use of abdominal ultrasonography in dogs has been described only in patients with fatal acute pancreatitis, in which lesions are usually pronounced. The sensitivity of abdominal ultrasound for the diagnosis of chronic pancreatitis in dogs is unknown.

3.2 Fecal analysis

3.2.1 Canine fecal pancreatic elastase (cEI)

A new fecal test for diagnosing exocrine pancreatic dysfunction is the enzyme-linked immunosorbent assay determination of fecal pancreatic elastase. Canine fecal pancreatic elastase is a species- and pancreas- specific test with high sensitivity but relatively low specificity. A single fecal elastase concentration 20 µg/g can be used to exclude EPI in dogs with chronic diarrhea. A value of 20 µg/g fecal elastase in association with typical clinical signs of EPI is suggestive of severe pancreatic dysfunction [23, 24]. Spillman [23] reported the sensitivity of cEI for clinical exocrine pancreatic insufficiency from 95-96% whereas specificity varies from 85 to 92%. This test is not sufficiently sensitive to diagnose subclinical EPI and partial PAA [25].

3.3 Pancreatic enzymes

3.3.1 Serum Amylase and Lipase

Amylase and lipase activities have long been considered as the markers of pancreatic inflammation, however, these enzymes originate from many tissues and hence are non specific markers of pancreatic diseases, making their specificity for pancreatitis fairly low [26-10]. A significant amount of serum lipase and amylase activities are conserved in pancreatectomized dogs [8]. Moreover, dogs with EPI have serum lipase activity within the reference range that is not different from that of control dogs [28]. Serum amylase and/or lipase activities can even be elevated in non-pancreatic diseases like renal failure, hepatic diseases, intestinal diseases, and lymphoma [22, 29]. But in canine pancreatitis, measurement of amylase activity is not considered helpful as plasma amylase activity is not increased unless lipase is increased [27]. In a study conducted by Mansfield and Jones [30], reported that the sensitivity and specificity of amylase and lipase in the diagnostic of pancreatitis in dogs as 40% and 70%, and 66.7% and 60%, respectively. In histological confirmed chronic pancreatitis, the sensitivity of amylase and lipase (3 times above the upper limit of the reference range) were 14% and 28%, respectively [2]. These findings suggest that serum amylase is of little clinical use in the diagnosis of pancreatitis in dogs. Lipase might be considered useful as a screening test for pancreatitis in dogs, but it should not be used alone to make a definitive diagnosis of pancreatitis. Only elevations above 3 to 5 times the upper limit of the reference range of lipase might be considered suggestive of pancreatic damage [4, 10].

3.4 Pancreatic Lipase

Pancreatic lipase immunoreactivity (PLI) measurement has been made available after the isolation and purification of pancreas-specific lipase (PL) in dogs [9]. This enzyme is very specific to the pancreas in dogs. Several tests have been made available sequentially for the PLI measurement in dogs. Analytical validation of the Spec cPL test has shown good

precision and reproducibility and no interference of bilirubin, lipid, and hemoglobin on results [31]. The SNAP cPL has 96% to 100% agreement with the Spec cPL in samples with normal PLI and 88% to 92% agreement in samples with elevated PLI [32]. Several studies have shown that cPLI performs better than amylase activity, lipase activity and trypsin-like immunoreactivity assays [33, 34]. The reported sensitivities in these studies vary widely from 21% to 72%, while specificities vary from 78% to 100% [35, 26]. PL is stable for 21 days at temperatures ranging from -80°C to 24°C and is not affected by long-term prednisolone treatment in dogs as reported by Steiner *et al.* [36] or by the fat content of the diet [37]. However, there is a slight increase in canine PLI (cPLI) [37] after eating and therefore cPLI should be evaluated only in fasted animals. The effect of renal failure on cPL has been reported but the median cPLI in dogs with induced renal failure was not above the reference range [38]. Therefore, the effect of renal failure is still questionable and further studies on spontaneous cases are necessary. In a study conducted by Steiner *et al.* [36] among 22 dogs with macroscopic evidence of acute or chronic pancreatitis, serum PL measured by RIA or Spec cPL was above the cut-off values suggested for pancreatitis in 14/22 dogs and above the upper limit of the reference ranges in 17/22 and 16/22 dogs in RIA and Spec cPL, respectively. Amylase and lipase activities were above the reference range in 9/22 and 7/22 dogs, respectively, and 3 times above the upper limit of the reference range (suggested cutoff for pancreatitis) in 4/22 and 3/22 dogs, respectively. TLI was above the reference range in 8/22 dogs. The sensitivity of cPL is 93% and specificity of 78% of Spec cPL for the diagnosis of canine acute pancreatitis. cPL has been evaluated for the diagnosis of histologically confirmed canine chronic pancreatitis with a sensitivity of 26% or 58% depending on the cutoff [39]. This relatively modest sensitivity is probably explained by a combination of the rapid elimination of PL from the blood and the high intra-individual variability of serum PL measurement [40]. When using Spec PL for the diagnosis of pancreatitis, a cutoff has been fixed (400 g/L in dogs) and there is a gray zone between the cutoff and the upper limit of the reference range (200 g/L in dogs).

3.5 Trypsin Like Immunoreactivity (TLI)

The enzyme TLI is also specific to the pancreas. In dogs, sensitivities of canine TLI (cTLI) for the diagnosis of pancreatitis (acute or chronic) ranged from 38% to 45.5% [30, 36]. Two dogs with renal failure, among a control group of 28 dogs with nonpancreatic diseases, had increased cTLI (specificity of 92%) as reported by Mansfield *et al.* [41]. The sensitivity and specificity of serum canine TLI (cTLI) for the diagnosis of pancreatitis is less than optimal (sensitivity 36%) [41, 42]. Therefore, TLI is not sensitive but fairly specific (if renal failure is not present) for the diagnosis of pancreatitis in dogs. This lack of sensitivity is probably related to the very rapid elimination of trypsinogen from the blood (at least in dogs). However, it is unlikely that a dog with acute pancreatitis and increased cTLI will not have concurrently increased cPLI [36].

4. Treatment

4.1 Pancreatic Enzyme Replacement

Various therapies are used for dogs with EPI, but by far the most important is pancreatic enzyme replacement, although cases have reportedly been maintained for prolonged periods without supplementation [18, 43]. A range of products have been recommended including enteric-coated preparations

(including tablets, capsules, and granules), uncoated enzyme powder, and raw pancreas. There has been considerable debate about efficacy of such products, with earlier work suggesting that dogs given uncoated enzymes had a better response to therapy as reported by Hall *et al.* [45] but more recent work has not shown such a difference [18]. In an experiment conducted by Westermarck [43] to study the effect of different enzyme preparations (powder, granules, capsules, enteric coated tablets and finely chopped raw pig pancreas) in the treatment of dogs with EPI, the highest lipase activities in the jejunal samples were achieved with raw pig pancreas. Powder achieved the second highest activities, but the other commercial porcine enzyme preparations yielded activities that were only one tenth of those attained with the raw pancreas. As the raw chopped pancreas is not available in many countries, powder enzyme supplementation is the most common treatment regime for dogs with EPI. Widely accepted recommendations in the literature suggests that treatment in dogs with EPI can be initiated at a dose of 2 teaspoons of powdered pancreatic extract per 20 kg body weight at each meal [12]. Most dogs require at least 1 teaspoon of enzymes per meal. Aside from porcine pancreatic extracts, bacterial lipase has been reported to be effective in correcting steatorrhea in dogs with experimental EPI [45, 46].

4.2 Dietary Modification

Feeding a fat-supplemented diet, in combination with enzyme replacement therapy, optimizes fat absorption in an experimental model of canine EPI [46]. Feeding a 19% fat diet (on a dry matter basis) improves weight gain and fecal quality in dogs [47]. Although one short-term feeding study suggested that the clinical signs of some dogs with EPI improved best when feeding a high-fiber diet [48]. Dietary fiber can decrease nutrient assimilation in dogs, thereby adversely affecting digestibility of other macronutrients and this could be counterproductive for a cachectic EPI patient as reported by Burrows *et al.* [49].

4.3 Cobalamin Supplementation

Hypocobalaminemia is especially common in dogs with EPI and, in one recent study, was identified in > 80% of cases, with approximately one third having markedly reduced concentrations [18]. Therefore, parenteral supplementation should be considered in all cases presenting with hypocobalaminemia [50]. Cobalamin should be administered by subcutaneous injection and the dose currently recommended is 250 to 1000 μg depending on the size of the dog, weekly initially and then monthly as per a report by Ruaux [51].

4.4 Antibacterials

The use of antimicrobials is a common adjunctive strategy in dogs with EPI. Commonly used agents include oxytetracycline and metronidazole, with other agents such as amoxicillin-clavulanate, fluoroquinolones, trimethoprim / sulfonamide and tylosin being used occasionally. The main justification for their use is the fact that secondary small intestinal bacterial overgrowth is thought to be common in dogs with EPI, possibly resulting from loss of bacteriostatic factors normally present in pancreatic juice and a greater availability of undigested substrate for bacterial growth [52]. However, some studies have shown that the use of antibacterials may improve response [53]. Others suggest pancreatic enzyme replacement therapy alone can reduce

bacterial numbers in the small intestine^[52, 53]. Overall median survival time for treated dogs is approximately 5 years^[54].

5. Conclusion

In conclusion, pancreatitis due to its unspecific clinical symptoms is usually underestimated disease in canines resulting in severe morbidity or mortality in patients. For its effective diagnosis, combined interpretation of anamnesis, clinical observation, various biochemical, serological tests, and imaging techniques can be helpful for confirmation of the disease. Evaluation and assessment of general condition of dogs suffering from pancreatitis demands complete blood count, serum biochemistry and urinalysis. In addition, for the definitive diagnosis pancreatic lipase immunoreactivity (PLI) is currently the most reliable test in both canine due to its high sensitivity and specificity. Pancreatitis is a complex and unexplored condition and warrants further investigation so as to reach a definitive diagnosis in order to undertake a curative therapy.

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