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REVIEW

Diabetes mellitus and pancreatitis – cause or effect?

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Diabetes mellitus and pancreatitis are two distinct diseases encountered commonly in small animal practice. Whilst the clinical signs of diabetes mellitus are usually unmistakeable, a firm diagnosis of pancreatitis can prove more elusive, as clinical signs are often variable. Over the past 10 to 15 years, despite the fact that the clinical signs of diabetes mellitus are remarkably consistent, it has become more apparent that the underlying pathology of diabetes mellitus in dogs and cats is heterogeneous, with exocrine pancreatic inflammation accompanying diabetes mellitus in a number of cases. However, the question remains as to whether the diabetes mellitus causes the pancreatitis or whether, conversely, the pancreatitis leads to diabetes mellitus – as there is evidence to support both scenarios. The concurrence of diabetes mellitus and pancreatitis has clinical implications for case management as such cases may follow a more difficult clinical course, with their glycaemic control being "brittle" as a result of variation in the degree of pancreatic inflammation. Problems may also arise if abdominal pain or vomiting lead to anorexia. In addition, diabetic cases with pancreatitis are at risk of developing exocrine pancreatic insufficiency in the following months to years, which can complicate their management further.

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INTRODUCTION

Pancreatitis and diabetes mellitus (DM) have been reported to occur concurrently in many species – ranging from humans (Larsen 1993) to dogs and cats (Hess *et al*. 2000, Rand *et al*. 2004), to a cow (Doherty *et al*. 1998), a horse (Jeffrey 1968) and a sea lion (Meegan *et al*. 2008). It is more than 100 years since the relationship between DM and pancreatitis was first described in the scientific literature (Opie 1901), yet it is still not clear which disease occurs first, i.e. whether the DM is a cause or a consequence of the pancreatic inflammation (Cook *et al*. 1993, Zini *et al*. 2010b). The aim of this review is to examine current knowledge of the pathogenesis of both DM and pancreatitis in cats and dogs, and to examine the evidence for DM leading to pancreatitis or *vice versa*. There is of course a third option, where the two diseases are simply concurrent coincidentally, but the close anatomical relationship between the exocrine and endocrine tissues of the pancreas and the increased prevalence of pancreatitis in diabetic dogs (Hess *et al*. 2000) and cats (Goossens *et al*. 1998) compared to that in the non-diabetic canine and feline population would suggest that this is not the case.

Before attempting to evaluate causality in the relationship between DM and pancreatitis, it is first necessary to review what is known about the pathogenesis of the two conditions.

PATHOGENESIS OF CANINE DM

Canine DM is usually the result of insulin deficiency, and a classification scheme has been described and illustrated in Table 1 (Catchpole *et al*. 2005, Catchpole *et al*. 2008). There are several classification schemes for human DM, but in broad terms, type 1 and type 2 DM are the most commonly recognised conditions. Type 1 DM, accounting for approximately 10% of human diabetic patients, is characterised by pancreatic β-cell autoimmunity, insulin deficiency and disease onset in childhood. In contrast, type 2 disease is commonly associated with obesity and is characterised by insulin resistance and onset during adulthood. As it is a disease of insulin deficiency, canine DM historically has been regarded as most similar to human type 1 DM.

The prevalence of canine DM in the UK is estimated at 0·32% (Davison *et al*. 2005). In some cases, insulin deficiency may be preceded by a phase of insulin resistance, but by the time

Table 1. Classification of canine diabetes mellitus (Catchpole *et al.* 2005)

Insulin deficiency diabetes (IDD)
Primary IDD in dogs is characterised by a progressive loss of pancreatic β-cells. The aetiology of β-cell deficiency/destruction in diabetic dogs is currently unknown but a number of disease processes are thought to be involved: • Congenital β-cell hypoplasia/abiotrophy • β-Cell loss associated with exocrine pancreatic disease • Immune-mediated β-cell destruction • Idiopathic
Insulin resistance diabetes (IRD)
Primary IRD usually results from antagonism of insulin function by other hormones: • Dioestrous/gestational diabetes • Secondary to other endocrine disorders • Hyperadrenocorticism • Acromegaly • Iatrogenic • Synthetic glucocorticoids • Synthetic progestagens • Glucose intolerance associated with obesity might contribute to insulin resistance but is not a primary cause of diabetes in dogs

of diagnosis, most dogs are unable to synthesise and secrete adequate amounts of endogenous insulin from the pancreatic beta cells in response to hyperglycaemia (Hoenig 2002, Rand *et al.* 2004). Certain breeds, such as the Samoyed, Tibetan terrier and Cairn terrier, are predisposed to the disease, whereas others, such as the boxer, German shepherd dog and the golden retriever, have a reduced risk (Davison *et al.* 2005). Many genetic variants have been associated with risk of DM in the dog, mostly within genes involving innate and adaptive immune responses (Kennedy *et al.* 2006, Short *et al.* 2009, Catchpole *et al.* 2013). The fact that many reported diabetes-associated genetic variants are breed-specific highlights the possibility that the underlying mechanism(s) for the development of DM may differ between breeds.

A small number of cases of canine DM are diagnosed in young animals less than six months of age (Atkins *et al.* 1979), and these are considered to be congenital in origin. Usually these cases do not suffer exocrine pancreatic disease so the pathology is likely to be β-cell specific.

The insulin resistance that precedes diagnosis in an estimated 20 to 40% of adult canine DM cases may be caused by exogenous corticosteroid or progestagen treatment or endocrinopathies such as hyperadrenocorticism (Hess *et al.* 2000). In addition, by a physiological process unique to the canine species, insulin resistance severe enough to culminate in DM may arise in the progesterone-dominated phase of dioestrus in entire females, during which growth hormone production by the mammary glands also contributes to poor glucose tolerance and dioestrus DM (Selman *et al.* 1994, Poppl *et al.* 2013).

Chronic hyperglycaemia in dogs has been shown to result in permanent β-cell damage (Imamura *et al.* 1988), which is likely to contribute to the fact that almost without exception diabetic dogs are fully dependent on insulin from the time of diagnosis. Whilst some studies imply that obesity may also contribute to insulin resistance in dogs (Mattheeuws *et al.* 1984, Tvarijonaviciute *et al.* 2012), the evidence for obesity being a risk factor in the development of canine DM is limited (Klinkenberg *et al.* 2006). It is interesting to note, however, in the context of this review, that obesity is also a risk factor for pancreatitis in dogs, and that elevated postprandial triglyceride concentrations have been associated with increased markers of pancreatic inflammation in obese dogs (Verkest *et al.* 2012) and miniature schnauzers (Xenoulis *et al.* 2010).

However, not every dog that experiences insulin resistance develops hyperglycaemia. It is possible that breed-related differences in β-cell pancreatic reserve exist and it is also possible that hyperglycaemia may only develop in such circumstances in those dogs that have previously experienced a primary β-cell insult.

DM associated with pancreatitis may account for 28 to 40% of cases of canine DM (Alejandro *et al.* 1988, Hess *et al.* 2000). Clinical signs may not differ greatly from other forms of DM, although it is possible that classic signs of acute pancreatitis (AP) may be seen in addition to the characteristic diabetic signs of polyuria, polydipsia, glycosuria and weight loss. For example, some diabetic dogs with concurrent pancreatitis may present with abdominal pain, vomiting and anorexia – which is in particular contrast to the usually voracious appetite of diabetic cases. It is also of note that a recent study suggested that 41% of dogs with diabetic ketoacidosis (DKA) have biochemical and/or clinical evidence of AP (Hume *et al.* 2006), implying that one disease may contribute to the other. Although awareness of pancreatitis in canine DM is increasing, in some DM cases pancreatitis may still go unrecognised, especially those with concurrent DKA. This is because clinical signs of pancreatitis can be subtle and non-specific, especially in its chronic form and may be attributed by the clinician to the DKA itself.

The remaining cases of canine DM are suspected to be associated with β-cell autoimmunity, similar to type 1 DM in humans (Elie & Hoenig 1995). Serological evidence of reactivity to pancreatic autoantigens (Haines & Penhale 1985, Hoenig & Dawe 1992) such as GAD65, IA-2 (Davison *et al.* 2008b) and proinsulin (Davison *et al.* 2011) has been documented in a number of recently diagnosed canine diabetic cases, but more than 50% of diabetic dogs studied were negative for autoantibodies, reinforcing the heterogeneous nature of the underlying pathogenesis of canine DM. The "trigger" for autoimmunity in both humans and dogs is not clear, although many genetic and environmental factors are known to contribute to autoimmune disease. Although exocrine pancreatic inflammation is not a common feature or trigger of human type 1 disease, in dogs, it has been proposed that pancreatitis may lead to DM via "bystander" β-cell damage, resulting in the release of protein antigens usually "hidden" from the immune system and the initiation of β-cell autoreactivity (Hoenig 2002).

Autoimmune (type 1) DM in humans is characterised by lymphocytic infiltration of pancreatic islets (insulitis), which is not a common feature of canine DM, although insulitis was reported in pancreatic biopsies of 6 of 18 diabetic dogs in one study (Alejandro *et al.* 1988). It is unfortunate that large-scale pathological studies of canine pancreata at the time of diagnosis are lacking, as such data might help to answer the "cause or effect" question about DM. However, where data have been published, a mixed inflammatory picture in early disease is seen (Gepts & Toussaint 1967), followed by complete islet destruction as DM progresses. In the context of this review, it is interesting to note that in one study, 5 of the 18 diabetic dogs where the pancreas was examined were reported to have generalised pancreatic inflammation, affecting both endocrine and exocrine tissue (Alejandro *et al.* 1988).

PATHOGENESIS OF FELINE DM

Feline DM has an estimated UK prevalence of 1 in 230 cats (McCann *et al.* 2007) and in contrast to canine DM is usually characterised by insulin resistance rather than absolute insulin deficiency (Rand *et al.* 2004). The disease has a multifactorial aetiology which includes genetic factors and environmental influences such as obesity and physical inactivity (McCann *et al.* 2007, Slingerland *et al.* 2009, Backus *et al.* 2010), but the exact underlying cause is unclear as not all obese cats become diabetic. Feline DM appears to be more common with increasing age, and certain breeds such as the Burmese cat are predisposed, emphasising the genetic component to risk (McCann *et al.* 2007, Lederer *et al.* 2009). The recent increase in prevalence, however, is likely to be related to environmental factors (Prahl *et al.* 2007). Other diseases can lead to DM in non-obese cats either directly via β-cell damage such as pancreatic neoplasia (Linderman *et al.* 2013) and pancreatitis (Mansfield & Jones 2001b), or via insulin resistance, e.g. acromegaly (Niessen 2010) or hyperadrenocorticism (Neiger *et al.* 2004). In addition, overt DM may be triggered by drug therapy with pharmacological agents that antagonise insulin, e.g. corticosteroids or progestagens.

Overt DM in cats usually results from a combination of impaired insulin secretion from the pancreatic β-cells in addition to peripheral insulin resistance (Rand *et al.* 2004). Pancreatitis may contribute to both these aspects as the local environment may impact directly on β-cell function and in addition, inflammation is known to cause peripheral tissue insulin resistance (Shoelson *et al.* 2006). Most cats are thought to undergo a prediabetic glucose-intolerant phase before the islets are unable to keep up with the extra demand for insulin created by insulin resistance in the tissues (Osto *et al.* 2012).

Eighty to ninety-five percent of feline DM cases have been classified as similar to human type 2 DM (Rand 1999, O'Brien 2002) based on clinical and histological findings. The term "glucose toxicity" is used to describe the damage to pancreatic islets as the result of persistent hyperglycaemia (Rand 1999, Osto *et al.* 2012) – and although this may result in permanent damage or death of the cell, this typically does not lead to an inflammatory response because cell death occurs by apoptosis (programmed cell death) rather than necrosis (Majno & Joris 1995).

The phenomenon of a remission or "honeymoon" phase once a diabetic cat is treated with insulin occurs because, in contrast to dogs, who are unlikely to have any islets left at the time of diagnosis, feline diabetic cases usually have impaired islet function rather than absolute loss in β-cell numbers at diagnosis. Hence diabetic remission, where it occurs, is the result of β-cell recovery as the blood glucose is controlled by exogenous insulin (Rand & Marshall 2005). Recent studies suggest that this may be facilitated by a restricted carbohydrate diet (Kirk 2006, Coradini *et al.* 2011) and intensive insulin therapy to maintain blood glucose concentration within tight limits. Sustained experimental hyperglycaemia in cats (but not hyperlipidaemia) leads to early, severe β-cell dysfunction and β-cell loss via apoptosis (Zini *et al.* 2009). This means that if irreversible β-cell damage has occurred before or during the hyperglycaemic phase in a patient, apoptotic β-cell death will lead to failure of the patient to enter diabetic remission. It is not clear whether diabetic remission is less likely to be achieved in cats with concurrent pancreatitis (Zini *et al.* 2010a), but being aware of the presence of this additional complication will allow pain relief and other treatment to be provided as necessary which is likely to improve the welfare of the patient.

PATHOPHYSIOLOGY OF ACUTE AND CHRONIC PANCREATITIS IN DOGS

Pancreatitis specifically describes inflammation of the exocrine tissues of the pancreas, but in contrast to humans, no universally accepted classification system exists in veterinary medicine (Ruaux & Atwell 1998, Newman *et al.* 2006, Mansfield 2012a, Watson 2012). Clinically, the presentation may be acute, with some cases suffering from recurrent acute episodes, or chronic, potentially resulting in pancreatic fibrosis. It is therefore possible that AP might cause transient insulin deficiency, whereas chronic pancreatitis (CP) could lead to permanent loss of β-cells.

The exocrine tissue comprises 95% of the pancreas and surrounds the endocrine tissue, which is arranged in the islets of Langerhans, composed of insulin-secreting β-cells, glucagon-secreting α-cells and somatostatin-secreting δ-cells. Although pancreatitis is common, lesions in the exocrine pancreas evident at a histological level are much more frequent than gross lesions in dogs (Newman *et al.* 2006). It must also be remembered that much of the current knowledge of the pathophysiology of pancreatitis in dogs and cats is extrapolated from experimental studies, so a degree of caution is required in its interpretation.

Several "safeguards" are in place to ensure that the highly damaging pancreatic enzymes synthesised and secreted by the exocrine cells do not damage the delicate pancreatic tissues in humans and other species (Mansfield 2012b), such as the storage of enzymes as inactive zymogen precursors (Rinderknecht 1986), physical separation of the stored enzyme from the rest of the cell in granules, as well as pancreas-derived secretory trypsin inhibitors and circulating antiproteases in the blood to prevent the inappropriate conversion of trypsinogen to trypsin (Laskowski & Kato 1980).

These safeguards fail in pancreatitis, allowing activation of trypsin and other proteases within the pancreas itself. This is thought to be a key step in the initiation of the disease, leading to a cascade of local damage and inflammation (Mansfield 2012b).

As previously mentioned, when pancreatic cells die by apoptosis (programmed cell death), there is little inflammatory response

(Majno & Joris 1995). In contrast, however, where pancreatic necrosis occurs following protease exposure, a much more significant and damaging "cytokine storm" may follow (Makhija & Kingsnorth 2002). In AP, the cytokines interleukin (IL)-1, IL-6 and TNF-α all contribute to the inflammatory response, as well as encouraging recruitment of white blood cells such as monocytes to the area.

A single, isolated, acute pancreatic inflammatory event is not likely to cause DM (although this has occasionally been reported in humans (Raman *et al*. 2011)), but the endocrine tissue is more likely to become more seriously affected if inflammation and/or clinical signs persist as CP. The prevalence of CP in the UK canine population has been estimated at 34% (Watson *et al*. 2007), with a high proportion of cases with chronic pancreatic inflammation documented at necropsy showing no associated clinical signs in life. A recent study of 61 cases and 100 controls in the USA suggested that dogs with clinical CP have significantly higher histological scores for pancreatic necrosis and peri-pancreatic fat necrosis (usually more associated with acute disease) than dogs with incidental CP, implying that they may in fact have acute-on-chronic pancreatitis (Bostrom *et al*. 2013). This supports the necrosis-fibrosis theory of CP, which suggests that irreversible damage is caused by repeated acute insults to the pancreatic tissue.

Certain breeds appear to be predisposed to AP including spaniels, terriers, dachshunds and poodles. Recent work to examine the breed-related prevalence of CP in postmortem pancreata from first opinion practice in the UK suggested that histological evidence of CP in dogs is present in approximately 34% of cadavers, with Cavalier King Charles spaniels (CKCS), collies and boxers being over-represented (Watson *et al*. 2007). Intriguingly, boxers are under-represented in canine diabetic cohorts (Fall *et al*. 2007).

Definitive diagnosis and classification of pancreatitis has been discussed elsewhere (Cordner *et al*. 2010, Mansfield *et al*. 2012, Watson 2012). A presumptive non-invasive diagnosis is usually made using a combination of history, physical examination and clinical signs, in combination with measurement of canine pancreatic lipase immunoreactivity (cPLI) (Mansfield *et al*. 2012) and/or ultrasonographic examination of the pancreas.

PATHOPHYSIOLOGY OF ACUTE AND CHRONIC PANCREATITIS IN CATS

Similar to pancreatitis in dogs, the aetiology of pancreatitis in cats is also only partially understood (Xenoulis & Steiner 2008), but what is known of the pathophysiology has been well reviewed (Bazelle & Watson 2014). The basic protective mechanisms and anatomy of the pancreas are similar to those described in the dog (Mansfield & Jones 2001a). However, the diagnosis of feline pancreatitis can be even more challenging than in dogs because clinical signs may be very mild, non-specific and remain unnoticed by the owner (Xenoulis & Steiner 2008), such as partial anorexia or lethargy (Washabau 2001). This makes it difficult to assess its prevalence in the diabetic and non-diabetic population. Early studies suggested a prevalence of less than 3% (Steiner & Williams 1999), but more recent histopathological work implies that the prevalence of pancreatic inflammation in cats is much higher than this – 67% in animals with clinical signs and 45% in clinically healthy cats, with the majority of these cases having chronic rather than acute inflammatory infiltrates (De Cock *et al*. 2007). Within the diabetic cat population, the prevalence of pancreatic inflammation may be even higher still – with evidence of pancreatitis at postmortem examination being described in 19 of 27 diabetic cats examined (Goossens *et al*. 1998). The histopathological features of feline pancreatitis have been extensively reviewed (Mansfield & Jones 2001a) and vary in severity and chronicity. Pancreatitis in cats may also be associated with cholangiohepatitis and inflammatory bowel disease (Caney 2013).

As in dogs, the underlying cause of pancreatitis in cats is not clear, but genetics, infection (e.g. viral, parasitic), trauma and the presence of other common inflammatory conditions may all contribute to risk (Xenoulis & Steiner 2008). Diagnosis may be especially challenging in cats as already described, but a combination of history, clinical examination, diagnostic imaging and feline pancreas lipase immunoreactivity (fPLI) measurement is recommended (Forman *et al*. 2004, Xenoulis & Steiner 2008). As in dogs, CP in cats may eventually result in exocrine pancreatic insufficiency as the enzyme-producing cells are slowly replaced by fibrous tissue (Steiner & Williams 1999).

THE RELATIONSHIP BETWEEN EXOCRINE PANCREATIC INFLAMMATION AND DM IN HUMAN MEDICINE

As illustrated above, canine and feline DM have similar clinical signs but different underlying pathophysiology. It is therefore conceivable that the role of pancreatitis in each disease will be different. In dogs, the closest human parallel is type 1 DM and in cats the closest human parallel is type 2 DM, so the contribution of pancreatitis to both these diseases, and in contrast the potential contribution of both these diseases to pancreatitis, should be considered. However, there is very little published evidence of type 1 DM and acute (or chronic) pancreatitis coexisting in human medicine. This may be because type 1 DM usually occurs in young children (Hummel *et al*. 2012), and in this age group pancreatitis is usually confined to genetic or traumatic causes, meaning that the majority of human diabetes–pancreatitis studies relate to type 2 DM. There is clear evidence that patients with longstanding type 1 DM develop pancreatic atrophy (Williams *et al*. 2012), but to the author's knowledge, there are no clear human studies linking type 1 DM to risk of pancreatitis later in life.

Not surprisingly, human pancreatitis has many underlying causes, with acute disease commonly being associated with toxaemia, gallstones, trauma, medication or infection. One difference between humans and veterinary species is that bacterial translocation from the gut is a well-recognised and important source of infection in human AP, and may result in pancreatic abscessation (Schmid *et al*. 1999). In human AP, clinical signs include severe abdominal pain, fever, nausea, vomiting or dehydration and in those cases where pancreatic necrosis occurs, the disease may be fatal (Cruz-Santamaria *et al.* 2012).

The most common cause of CP in humans is chronic alcohol consumption but genetic predisposition, autoimmune disease or other diseases such as cystic fibrosis may also chronically impede exocrine pancreatic function and lead to pancreatic inflammation. CP shows similar clinical signs to acute disease but they are generally less severe and more prolonged. It is of particular note that in human type 2 DM, the risk of CP is two to three times higher than that in healthy subjects (Girman *et al.* 2010) and a recent meta-analysis indicated that type 2 diabetic patients are also at increased risk of AP (Yang *et al.* 2013).

This raises the question of why human type 2 DM patients are prone to pancreatitis – does the diabetic state itself contribute to the onset of pancreatic inflammation? This possibility is raised by a meta-analysis in which diabetic individuals had a 92% increased risk of development of CP, independent of other risk factors such as alcohol use, gallstones and hyperlipidaemia (Xue *et al.* 2012). Similarly in AP, a meta-analysis reported that insulin resistance and hyperglycaemia are important factors in the susceptibility of diabetic individuals to AP (Solanki *et al.* 2012). It is also of potential relevance that human patients with DM are at a greater risk of particularly severe AP, even if the DM was not originally associated with pancreatitis at diagnosis (Shen *et al.* 2012). Experimental rodent models of pancreatitis and DM suggest that the presence of hyperglycaemia can exacerbate AP and suppress regeneration of exocrine tissue (Zechner *et al.* 2012). This implies an important clinical point that poor glycaemic control may contribute to the severity of AP and aggravate the progression of the disease.

Although the studies mentioned above highlight the increased risk for pancreatitis in diabetic patients, the majority of the published evidence points to pancreatitis preceding the DM in humans, i.e. the DM is secondary to the pancreatitis rather than the DM causing pancreatic inflammation (Kazumi *et al.* 1983, Jap *et al.* 1992, Cavallini *et al.* 1993, Larsen 1993). A recent meta-analysis suggested that following an episode of AP, a patient has a twofold increased risk of developing DM within 5 years (Das *et al.* 2014). This type of DM is classified as neither type 1 nor type 2 DM, but a separate category of "other specific types of DM".

DM in human patients with CP is more likely to be found later in the course of the exocrine pancreatic disease (Singh *et al.* 2012), and similar to canine and feline cases, CP in humans may ultimately result in malabsorption due to exocrine pancreatic insufficiency. This timecourse is also similar to an obese rodent model of pancreatitis, in which DM develops later during the course of the disease. It is of particular interest in this model that the pancreatitis can be made less severe and the onset of DM delayed by dietary restriction (Akimoto *et al.* 2010).

As already discussed for dogs and cats, the exact mechanism by which CP results in DM is likely to be complex in humans. Studies of cytokine concentrations in pancreatic tissues from CP patients by flow cytometry demonstrate increased interferon-γ in both diabetic and non-diabetic patients, a cytokine which has been shown to impede β-cell function and therefore may play a role in DM associated with CP (Pavan Kumar *et al.* 2012). It is also apparent that patients with concurrent type 2 DM and CP have an increased risk of developing pancreatic cancer (Brodovicz *et al.* 2012), although no similar correlation has been reported in dogs or cats.

A more rare condition in humans, called autoimmune pancreatitis (AIP) is characterised radiologically by enlargement of the pancreas, narrowing of the pancreatic duct, lymphoplasmacytic pancreatic infiltrate and classically an elevation of serum IgG4 levels (Kamisawa *et al.* 2010). This disease is commonly associated with insulin-dependent DM in adults (Ito *et al.* 2011) and tends to be very responsive to steroid treatment. These patients rarely have the autoantibodies to islet antigens that characterise classical type 1 DM, although pancreatic histology suggests cellular islet infiltrates and reduced numbers of β-cells. The classic autoantigens in AIP are lactoferrins and carbonic anhydrase II (Hardt *et al.* 2008). The pathophysiology of the DM seen in AIP has not been fully elucidated but is not thought to be related to non-specific collateral damage from the pancreatic inflammatory process, but rather a specific immunological effect, thought to be triggered by the pancreatitis (Miyamoto *et al.* 2012). This would therefore again make the pancreatitis a cause rather than an effect of the DM and offers an alternative mechanism for immune-mediated islet destruction. At present, however, IgG4 measurement is not routinely performed in veterinary medicine, so a companion animal counterpart of AIP has not been identified, although studies are ongoing and it is possible that certain types of breed-related DM may share pathophysiological features with AIP.

THE RELATIONSHIP BETWEEN PANCREATITIS AND DM IN DOGS

In a study of 80 dogs with severe AP, 29 dogs had concurrent DM (Papa *et al.* 2011), making the prevalence of DM much higher in this population than in dogs without AP. In a recent UK retrospective study of DM in first opinion practice (Mattin *et al.* 2014), diabetic dogs diagnosed with pancreatitis also had a higher hazard of death. Having reviewed the underlying causes of both diseases and the relationship between these conditions in humans, the question remains: does canine pancreatitis cause DM or can canine DM result in pancreatitis? The intuitive answer is that pancreatitis is likely to occur first, with the β-cells succumbing to bystander damage, either by non-specific inflammation or the triggering of an autoimmune process and epitope spreading. However, the increased risk of pancreatitis in human diabetic patients also suggests that pancreatitis could theoretically be a *consequence* of DM, so it may be the case that both diseases may have a negative impact on each other.

It is possible too that a more broad, over-arching mechanism may be at work. In another recent study, canine CP cases were significantly more likely to have an endocrine disease than dogs without pancreatitis, specifically DM or hypothyroidism (Bostrom *et al.* 2013). It is therefore possible that the mechanisms for pancreatitis development in both hypothyroidism and DM are similar, implying that endocrine disease may be contributing to the initiation of the pancreatic inflammation. One such risk factor, shared between DM and hypothyroidism, may be the high cholesterol resulting from the endocrinopathy acting as a trigger for pancreatitis, as hyperlipidaemia has been shown to cause pancreatitis in humans (Tsuang *et al*. 2009) and dogs (Hess *et al*. 1999). However, it must also be remembered that in dogs, as in humans, there are shared genetic factors for DM and hypothyroidism so it is also possible that these may be shared with other genetic risk factors for pancreatitis. Sharing of genetic risk variants does not necessarily imply that one disease causes the other.

Is there any evidence at the cellular or molecular level that DM may trigger pancreatitis in dogs? Although the cytokine milieu in human and canine pancreatitis has been investigated to some extent (discussed earlier), very little is known about the local cytokine environment in the pancreatic islets in canine DM. However, despite the lack of local measurements, some circulating cytokine profiles have been reported in a study of healthy dogs, dogs with DM and dogs with DKA. The cytokines IL-18 and granulocyte-macrophage colony stimulating factor (GM-CSF) were elevated in DKA dogs before treatment compared to after successful treatment, and pro-inflammatory factors CXCL8 and monocyte chemoattractant protein 1 (MCP-1) were significantly higher in dogs with DM compared with controls (O'Neill *et al*. 2012). However, seven of the nine dogs with DKA in this study also had pancreatitis, and as IL-18 is a pro-inflammatory cytokine associated with pancreatitis in humans it is difficult to know if the presence of this cytokine is a cause or consequence of the pancreatitis. Nonetheless, CXCL8 and MCP-1 are both associated with inflammation, so have the potential to contribute to pancreatitis. A more recent study of alterations in innate immunity in dogs associated with DM also suggested that white blood cells from diabetic cases produce more pro-inflammatory cytokines in response to stimulation and hypothesised that this may predispose diabetic dogs to infectious and inflammatory complications (DeClue *et al*. 2012).

Another theoretical trigger for pancreatitis which may be associated with DM in dogs is the potential for the presence of circulating autoantibodies to pancreatic proteins or anti-insulin antibodies induced by treatment (Davison *et al*. 2003, Davison *et al*. 2008a) to form immune complexes in the pancreas. However, this is most likely an academic concern as it has not been proven in practice. Cats do not appear to suffer from autoimmune pancreatitis and nor do they commonly make antibodies to exogenous insulin so this mechanism appears even less likely to occur in this species (Hoenig *et al*. 2000).

Another particular challenge in establishing which disease occurs first relates to the fact that one condition may be clinically silent, e.g. CP. In a study of 14 confirmed canine cases of CP, the pancreas only appeared "abnormal" on 56% of ultrasound examinations and the sensitivity of cPLI when combined with amylase and lipase measurement was 44 to 67% when using a low cut-off value. (Watson *et al*. 2010). At present, it is not routine to test the glucose tolerance of all cases with AP or CP or to test pancreatic inflammatory markers in all newly diagnosed canine diabetic cases, nor, of course, are pancreatic biopsies routine in diabetic cases. However, some work has been undertaken to try to establish the prevalence of defective β-cell function amongst pancreatitis cases which gives some insight into the order in which the diseases may arise.

Watson & Herrtage (2004) used a glucagon stimulation test to evaluate endocrine pancreatic reserve in canine cases with clinical pancreatitis. By measuring the insulin and glucose response following an intravenous glucagon dose, a functional defect in endocrine pancreatic function was demonstrated in five of six dogs with pancreatitis, implying that inflammation can impair insulin secretion from β-cells without necessarily leading to overt DM. This suggests that in cases where the two diseases are concurrent, pancreatic inflammation may precede DM in dogs. A similar timeline was seen in a small case series of four dogs with EPI secondary to CP. Two of these dogs developed DM, and this happened after the diagnosis of CP but before the diagnosis of EPI (Watson 2003). This suggests an order of events beginning with pancreatitis, moving on to DM and culminating in pancreatic fibrosis and EPI, at least in some dogs. This mirrors the findings of recent human studies that suggest that in cases where DM develops secondary to CP, islet dysfunction occurs first due to the local inflammatory milieu but clinical DM does not manifest until later, when fibrosis causes islet destruction (Sasikala *et al*. 2012).

THE RELATIONSHIP BETWEEN PANCREATITIS AND DM IN CATS

One recent study reported that 26 of 40 cats with naturally occurring DM were found to have elevated lipase activity at the time of admission to a clinical facility (Zini *et al*. 2010b). Although elevation in serum lipase is not perfectly sensitive or specific for a diagnosis of pancreatitis, this study appears to concur with a 1998 study in which 19 of 37 diabetic cats were shown to have evidence of pancreatic inflammation on postmortem examination (Goossens *et al*. 1998). As the pathology of DM in cats relates to insulin resistance, which can be caused by a focus of inflammation within the body, it is not difficult to propose a causal role for pancreatitis in feline DM. If this is the case, similar mechanisms for islet cell damage to those discussed for canine pancreatitis may play a role.

However, to counter this argument, the biochemical states of hyperglycaemia and hyperlipidaemia, as seen in feline DM, have been shown to contribute to inflammatory responses in humans (Shoelson *et al*. 2007), implying that the metabolic changes in DM may contribute to pancreatitis developing subsequently. As feline DM is considered to be similar to human type 2 DM, it is possible that diabetic cats are subject to the same increased risk for pancreatitis as already described for humans with type 2 DM. One experimental study, designed to investigate the relationship between hyperglycaemia, hyperlipidaemia and pancreatitis in cats reported that 10 days of hyperglycaemia increased pancreatic neutrophils, but without causing pancreatic damage, a finding which was not seen in cats with experimentally induced hyperlipidaemia (Zini *et al*. 2010b). This suggests that hyperglycaemia may play a role in predisposing to feline pancreatitis but other factors are also involved in the early stages of pancreatic inflammation.

It is also helpful to recognise recent work in human type 2 DM and metabolic syndrome has demonstrated that obesity and inflammation are directly linked (Shoelson & Goldfine 2009). Adipose tissue can have a significant influence on metabolism and the immune system via synthesis and secretion of chemical mediators such as adipokines and adipocytokines (Whitehead *et al*. 2006). This pro-inflammatory environment can in turn lead to recruitment and activation of inflammatory cells and may also play a role in β-cell damage during hyperglycaemia via cytokines such as IL-6 and IL-1 β. If this type of inflammation occurs in obese cats, within the pancreas, then it is certainly possible that it may act as a trigger for pancreatitis.

A biochemical marker of AP, although not 100% sensitive, fPLI was found to be elevated in a different cohort of feline diabetic cases (Forcada *et al*. 2008), and correlated with serum fructosamine concentration, which may also reflect the relationship between inflammation and insulin resistance.

CLINICAL IMPLICATIONS OF THE RELATIONSHIP BETWEEN PANCREATITIS AND DM

Dogs: Based on the evidence presented here, the balance appears to be slightly in favour of pancreatitis preceding DM and hence in favour of the exocrine disease contributing to or triggering the endocrine disease. It is also clear, however, that there are multiple routes to lack of β-cell function in dogs and pancreatitis is only one potential causal factor. It is still theoretically possible that, at least in dogs, pancreatitis may develop in response to the hyperglycaemia or hyperlipidaemia associated with DM, a risk which may be even further exacerbated by the increased potential for bacterial infection (DeClue *et al*. 2012) and toxaemia in diabetic cases, but this is difficult to prove.

An important clinical observation is that where pancreatitis and DM do coexist, the practitioner may initially be blinded to the presence of one of these conditions. The prevalence of the two diseases concurrently in dogs is remarkably high, and it is important to recognise AP or CP as it increases insulin resistance as well as being significantly correlated with risk of DKA. In addition, there is the long-term risk of intermittent “flare-ups” of disease and the potential for glycaemic control to be complicated in future by the development of exocrine pancreatic insufficiency.

Although pancreatitis can be a difficult diagnosis to make clinically, for the reasons outlined above, serious consideration should be given to evaluating every diabetic dog, particularly those that are newly diagnosed or unstable, for exocrine pancreatic disease, for example, by measurement of cPLI. Whilst management of pancreatitis may appear fairly non-specific, being based on nutritional support, low fat food, intravenous fluid therapy and analgesia, the knowledge that a diabetic dog has accompanying exocrine pancreatic inflammation can make a further significant contribution to the clinical management and prognosis, allowing the owner and veterinary surgeon to make better informed decisions, improving the animal’s quality of life.

In contrast, however, there is insufficient evidence at present to recommend a glucagon stimulation test to evaluate endocrine function in every animal with pancreatitis, but it is still important that cases that are suspected to have pancreatitis should be regularly examined and owners warned of the potential risks of DM in the future.

Cats: The relationship between obesity/inactivity and DM in cats is undeniable, so regardless of coexisting pancreatitis, weight loss and increased activity, plus an appropriate diet are the most important factors in helping to prevent many cases of DM in cats. As discussed however, there is clearly also an important relationship between insulin resistance and pancreatitis in cats, in which the pancreatic exocrine tissue inflammation may even be initiated or exacerbated by hyperglycaemia in some cases. It is therefore important to consider the possibility of pancreatic inflammation in all diabetic cats, even if they have no history of AP, because hyperglycaemia resulting from obesity, acromegaly, inflammation or exogenous drug treatment has the potential to contribute to the development of exocrine pancreatic inflammation.

Where a diagnosis of pancreatitis predates documented hyperglycaemia, it appears likely that pancreatitis predisposes to the demise of β-cells and contributes to peripheral insulin resistance, precipitating DM in genetically susceptible or obese cats. The same principles discussed for dogs therefore also apply to cats, i.e. ideally the clinician should be consciously aware of both diseases, and should consider testing newly diagnosed diabetic cats for pancreatitis, especially because clinical signs may be so subtle and unregulated pancreatic inflammation may have a dramatic and negative impact on clinical outcome. This is especially true if an intensive protocol to achieve DM remission is being undertaken, as active pancreatic inflammation and its associated clinical signs, however subtle, may compromise the effectiveness of this approach.

Conclusions

Both DM and pancreatitis are complex diseases, showing many species-specific features in dogs, cats and humans. As the endocrine and exocrine tissues of the pancreas are so interlinked, it is not surprising that damage to one or the other has an impact on the surrounding tissues. The main conclusion that can be drawn is that whilst the most common direction of progression may be that DM occurs secondary to pancreatitis, the two diseases may still be seen in the “reverse order” in certain circumstances.

Additionally, DM and pancreatitis may arise by a number of mechanisms but there are particular environmental triggers and genetic predispositions which make this more likely. Figure 1 illustrates the “circular argument” of cause and effect, including putative (but not necessarily proven) factors from each of the two diseases which could increase the risk of the second disease developing. The most important message is that clinicians continue to remain aware of the potential for both diseases to coexist. The benefits to the diabetic patient when a serious complication is recognised and treated, despite it having potentially only subtle clinical signs, will be just as

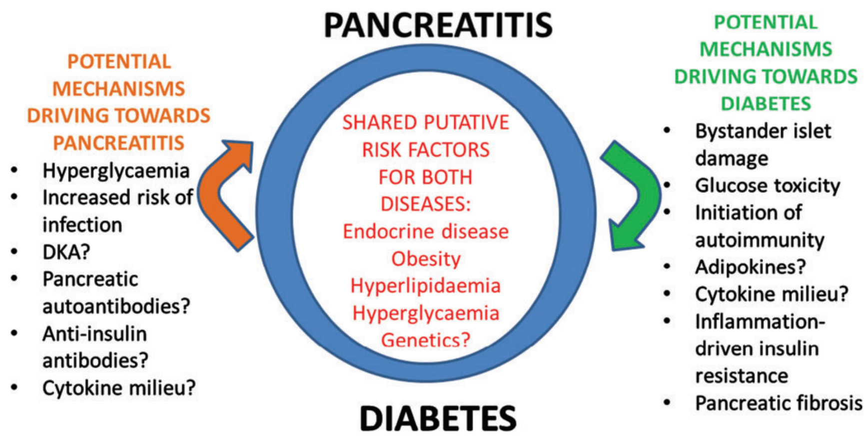

FIG 1. The putative influences of diabetes on pancreatitis and vice versa

-important whether or not the pancreatitis is present as a cause or consequence of the DM.

Conflict of interest

The author of this article has no financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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