1 **Diabetes mellitus and pancreatitis in dogs and cats – cause or effect?**

2

3 **SUMMARY**

4 Diabetes mellitus (DM) and pancreatitis are two distinct diseases encountered commonly in small

5 animal practice. Whilst the clinical signs of DM are usually unmistakeable, a firm diagnosis of

6 pancreatitis can prove more elusive, as clinical signs are often variable. Over the past 10-15 years,

7 despite the fact that the clinical signs of DM are remarkably consistent, it has become more

8 apparent that the underlying pathology of DM in dogs and cats is heterogeneous, with exocrine

9 pancreatic inflammation accompanying DM in a number of cases. However, the question remains as

10 to whether the DM causes the pancreatitis or whether, conversely, the pancreatitis leads to DM - as

11 there is evidence to support both scenarios. The concurrence of DM and pancreatitis has clinical

12 implications for case management as such cases may follow a more difficult clinical course, with

13 their glycaemic control being 'brittle' as a result of variation in the degree of pancreatic

14 inflammation. Problems may also arise if abdominal pain or vomiting lead to anorexia. In addition,

15 diabetic cases with pancreatitis are at risk of developing exocrine pancreatic insufficiency in the

16 following months to years, which can complicate their management further.

17

18

19 **INTRODUCTION**

20 Pancreatitis and diabetes mellitus (DM) have been reported to occur concurrently in many species –

21 ranging from humans (Larsen 1993), to dogs and cats (Hess and others 2000, Rand and others 2004),

22 to a cow (Doherty and others 1998), a horse (Jeffrey 1968) and a sea lion (Meegan and others 2008).

23 It is more than 100 years since the relationship between DM and pancreatitis was first described in

24 the scientific literature (Opie 1901), yet it is still not clear which disease occurs first i.e. whether the

25 DM is a *cause* or a *consequence* of the pancreatic inflammation (Cook and others 1993, Zini and

26 others 2010b). The aim of this review is to examine current knowledge of the pathogenesis of both

27 DM and pancreatitis in cats and dogs, and to examine the evidence for DM leading to pancreatitis or

28 *vice versa*. There is of course a third option, where the two diseases are simply concurrent co-

29 incidentally, but the close anatomical relationship between the exocrine and endocrine tissues of

30 the pancreas and the increased prevalence of pancreatitis in diabetic dogs (Hess and others 2000)

31 and cats (Goossens and others 1998) compared to that in the non-diabetic canine and feline

32 population would suggest that this is not the case.

33 Prior to attempting to evaluate causality in the relationship between DM and pancreatitis, it is first

34 necessary to review what is known about the pathogenesis of the two conditions.

Pathogenesis of Canine DM

36 Canine DM is usually the result of insulin deficiency and a classification scheme has been described,

37 illustrated in Table 1 (Catchpole and others 2005, Catchpole and others 2008). There are several

38 classification schemes for human DM, but in broad terms, type 1 and type 2 DM are the most

39 commonly recognised conditions. Type 1 DM, accounting for approximately 10% of human diabetic

40 patients, is characterised by pancreatic beta cell autoimmunity, insulin deficiency and disease onset

41 in childhood. In contrast, type 2 disease is commonly associated with obesity and is characterised by

42 insulin resistance and onset during adulthood. As it is a disease of insulin deficiency, canine DM

43 historically has been regarded as most similar to human type 1 DM.

44 The prevalence of canine DM in the UK is estimated at 0.32% (Davison and others 2005). In some

45 cases insulin deficiency may be preceded by a phase of insulin resistance, but by the time of

46 diagnosis, most dogs are unable to synthesise and secrete adequate amounts of endogenous insulin

47 from the pancreatic beta cells in response to hyperglycaemia (Hoenig 2002, Rand and others 2004).

48 Certain breeds are predisposed to the disease such as the Samoyed, Tibetan terrier and Cairn terrier

49   whereas others have a reduced risk such as the boxer, German shepherd dog and the golden

50   retriever (Davison and others 2005). Many genetic variants have been associated with risk of DM in

51   the dog, mostly within genes involving innate and adaptive immune responses (Kennedy and others

52   2006, Short and others 2009, Catchpole and others 2012). The fact that many reported diabetes-

53   associated genetic variants are breed-specific highlights the possibility that the underlying

54   mechanism(s) for the development of DM may differ between breeds.

55   A small number of cases of canine DM are diagnosed in young animals less than 6 months of age

56   (Atkins and others 1979), and these are considered to be congenital in origin. Usually these cases do

57   not suffer exocrine pancreatic disease so the pathology is likely to be beta-cell specific.

58   The insulin resistance that precedes diagnosis in an estimated 20-40% of adult canine DM cases may

59   be caused by exogenous corticosteroid or progestagen treatment or endocrinopathies such as

60   hyperadrenocorticism (Hess and others 2000). In addition, by a physiological process unique to the

61   canine species, insulin resistance severe enough to culminate in DM may arise in the progesterone-

62   dominated phase of dioestrus in entire females, during which growth hormone production by the

63   mammary glands also contributes to poor glucose tolerance and dioestrus DM (Selman and others

64   1994, Poppl and others 2012).

65   Chronic hyperglycaemia in dogs has been shown to result in permanent beta cell damage (Imamura

66   and others 1988), which is likely to contribute to the fact that almost without exception, diabetic

67   dogs are fully dependent on insulin from the time of diagnosis. Whilst some studies imply that

68   obesity may also contribute to insulin resistance in dogs (Mattheeuws and others 1984,

69   Tvarijonaviciute and others 2012), the evidence for obesity being a risk factor in the development of

70   canine DM is limited (Klinkenberg and others 2006). It is interesting to note, however, in the context

71   of this review, that obesity is also a risk factor for pancreatitis in dogs, and that elevated post

72   prandial triglyceride concentrations have been associated with increased markers of pancreatic

73 inflammation in obese dogs (Verkest and others 2012) and miniature schnauzers (Xenoulis and

74 others 2010) .

75 However, not every dog that experiences insulin resistance develops hyperglycaemia. It is possible

76 that breed-related differences in beta cell pancreatic reserve exist and it is also possible that

77 hyperglycaemia may only develop in such circumstances in those dogs who have previously

78 experienced a primary beta cell insult.

79 Diabetes mellitus associated with pancreatitis may account for 28-40% of cases of canine DM

80 (Alejandro and others 1988, Hess and others 2000). Clinical signs may not differ greatly from other

81 forms of DM, although it is possible that classic signs of acute pancreatitis (AP) may be seen in

82 addition to the characteristic polyuria, polydipsia, glycosuria and weight loss DM signs. For example

83 some diabetic dogs with concurrent pancreatitis may present with abdominal pain, vomiting and

84 anorexia – which is in particular contrast to the usually voracious appetite of diabetic cases. It is also

85 of note that a recent study suggested that 41% of canine cases with diabetic ketoacidosis (DKA) have

86 biochemical and / or clinical evidence of AP (Hume and others 2006), implying that one may

87 contribute to the other. Although awareness of pancreatitis in canine DM is increasing, in some DM

88 cases pancreatitis may still go unrecognised, especially those with concurrent DKA. This is because

89 clinical signs of pancreatitis can be subtle and non-specific, especially in its chronic form and may be

90 attributed by the clinician to the DKA itself.

91 The remaining cases of canine DM are suspected to be associated with beta cell autoimmunity,

92 similar to Type 1 DM in humans (Elie and Hoenig 1995). Serological evidence of reactivity to

93 pancreatic autoantigens (Haines and Penhale 1985, Hoenig and Dawe 1992) such as GAD65, IA-2

94 (Davison and others 2008b) and proinsulin (Davison and others 2011) has been documented in a

95 number of recently diagnosed canine diabetic cases, but more than 50% of diabetic dogs studied

96 were negative for autoantibodies, reinforcing the heterogeneous nature of the underlying

97 pathogenesis of canine DM. The 'trigger' for autoimmunity in both humans and dogs is not clear,

98   although many genetic and environmental factors are known to contribute to autoimmune disease.

99   Although exocrine pancreatic inflammation is not a common feature or trigger of human type 1

100   disease, in dogs it has been proposed that pancreatitis may lead to DM via 'bystander' beta cell

101   damage, resulting in the release of protein antigens usually 'hidden' from the immune system and

102   the initiation of beta cell autoreactivity (Hoenig 2002).

103   Autoimmune (Type 1) DM in humans is characterised by lymphocytic infiltration of pancreatic islets

104   (insulitis), which is not a common feature of canine DM, although insulitis was reported in pancreatic

105   biopsies of 6 of 18 diabetic dogs in one study (Alejandro and others 1988). It is unfortunate that

106   large scale pathological studies of canine pancreas at the time of diagnosis are lacking, as such data

107   might help to answer the 'cause or effect' question about DM. However, where data have been

108   published, a mixed inflammatory picture in early disease is seen (Gepts and Toussaint 1967),

109   followed by complete islet destruction as DM progresses. In the context of this review, it is

110   interesting to note that in one study, 5 of the 18 diabetic dogs where the pancreas was examined

111   were reported to have generalised pancreatic inflammation, affecting both endocrine and exocrine

112   tissue (Alejandro and others 1988).

113   **Pathogenesis of Feline DM**

114   Feline DM has an estimated UK prevalence of 1 in 230 cats (McCann and others 2007) and in

115   contrast to canine DM is usually characterised by insulin resistance rather than absolute insulin

116   deficiency (Rand and others 2004). The disease has a multifactorial aetiology which includes genetic

117   factors and environmental influences such as obesity and physical inactivity (McCann and others

118   2007, Slingerland and others 2009, Backus and others 2010), but the exact underlying cause is

119   unclear as not all obese cats become diabetic. Feline DM appears to be more common with

120   increasing age, and certain breeds such as the Burmese cat are predisposed, emphasising the

121   genetic component to risk (McCann and others 2007, Lederer and others 2009). The recent increase

122   in prevalence, however, is likely to be related to environmental factors (Prahl and others 2007).

123   Other diseases can lead to DM in non-obese cats either directly via beta cell damage such as

124   pancreatic neoplasia (Linderman and others 2012), and pancreatitis (Mansfield and Jones 2001b), or

125   via insulin resistance e.g. acromegaly (Niessen 2010) or hyperadrenocorticism (Neiger and others

126   2004). In addition, overt DM may be triggered by drug therapy with pharmacological agents which

127   antagonise insulin e.g. corticosteroids or progestagens.

128   Overt DM in cats usually results from a combination of impaired insulin secretion from the

129   pancreatic beta cells in addition to peripheral insulin resistance (Rand and others 2004). Pancreatitis

130   may contribute to both these aspects as the local environment may impact directly on beta cell

131   function and in addition, inflammation is known to cause peripheral tissue insulin resistance

132   (Shoelson and others 2006). Most cats are thought to undergo a pre-diabetic glucose-intolerant

133   phase before the islets are unable to keep up with the extra demand for insulin created by insulin

134   resistance in the tissues (Osto and others 2012).

135   Eighty to ninety five percent of feline DM cases have been classified as similar to human type 2 DM

136   (Rand 1999, O'Brien 2002) based on clinical and histological findings. The term 'glucose toxicity' is

137   used to describe the damage to pancreatic islets as the result of persistent hyperglycaemia (Rand

138   1999, Osto and others 2012) – and although this may result in permanent damage or death of the

139   cell, this typically does not lead to an inflammatory response because cell death occurs by apoptosis

140   (programmed cell death) rather than necrosis (Majno and Joris 1995).

141   The phenomenon of a remission or 'honeymoon' phase once a diabetic cat is treated with insulin

142   occurs because, in contrast to dogs, who are unlikely to have any islets left at the time of diagnosis,

143   feline diabetic cases usually have impaired islet function rather than absolute loss in beta cell

144   numbers at diagnosis. Hence diabetic remission, where it occurs, is the result of beta cell recovery as

145   the blood glucose is controlled by exogenous insulin (Rand and Marshall 2005). Recent studies

146   suggest that this may be facilitated by a restricted carbohydrate diet (Kirk 2006, Coradini and others

147   2011) and intensive insulin therapy to maintain blood glucose concentration within tight limits.

148 Sustained experimental hyperglycaemia in cats (but not hyperlipidaemia) leads to early, severe beta

149 cell dysfunction and beta cell loss via apoptosis (Zini and others 2009). This means that if irreversible

150 beta cell damage has occurred before or during the hyperglycaemic phase in a patient, apoptotic

151 beta cell death will lead to failure of the patient to enter diabetic remission. It is not clear whether

152 diabetic remission is less likely to be achieved in cats with concurrent pancreatitis (Zini and others

153 2010a), but being aware of the presence of this additional complication will allow pain relief and

154 other treatment to be provided as necessary which is likely to improve the welfare of the patient.

155 **Pathophysiology of acute and chronic pancreatitis in dogs**

156 Pancreatitis specifically describes inflammation of the exocrine tissues of the pancreas, but in

157 contrast to humans, no universally accepted classification system exists in veterinary medicine

158 (Ruaux and Atwell 1998, Newman and others 2006, Mansfield 2012a, Watson 2012). Clinically, the

159 presentation may be acute, with some cases suffering recurrent acute episodes, or chronic,

160 potentially resulting in pancreatic fibrosis. It is therefore possible that AP might cause transient

161 insulin deficiency, whereas chronic pancreatitis (CP) could lead to permanent loss of beta cells.

162 The exocrine tissue comprises 95% of the pancreas and surrounds the endocrine tissue, which is

163 arranged in the islets of Langerhans, composed of insulin-secreting beta cells, glucagon-secreting

164 alpha cells and somatostatin-secreting delta cells. Although pancreatitis is common, lesions in the

165 exocrine pancreas evident at a histological level are much more frequent than gross lesions in dogs

166 (Newman and others 2006). It must also be remembered that much of the current knowledge of the

167 pathophysiology of pancreatitis in dogs and cats is extrapolated from experimental studies, so a

168 degree of caution is required in its interpretation.

169 Several 'safeguards' are in place to ensure that the highly damaging pancreatic enzymes synthesised

170 and secreted by the exocrine cells do not damage the delicate pancreatic tissues in humans and

171 other species (Mansfield 2012b), such as the storage of enzymes as inactive zymogen precursors

172   (Rinderknecht 1986), physical separation of the stored enzyme from the rest of the cell in granules,

173   as well as pancreas-derived secretory trypsin inhibitors and circulating anti-proteases in the blood

174   to prevent the inappropriate conversion of trypsinogen to trypsin (Laskowski and Kato 1980).

175   These safeguards fail in pancreatitis, allowing activation of trypsin and other proteases within the

176   pancreas itself. This is thought to be a key step in the initiation of the disease, leading to a cascade of

177   local damage and inflammation (Mansfield 2012b).

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

179   little inflammatory response (Majno and Joris 1995). In contrast, however, where pancreatic necrosis

180   occurs following protease exposure, a much more significant and damaging 'cytokine storm' may

181   follow (Makhija and Kingsnorth 2002). In AP, the cytokines IL-1, IL-6 and TNF-alpha all contribute to

182   the inflammatory response, as well as encouraging recruitment of white blood cells such as

183   monocytes to the area.

184   A single, isolated, acute pancreatic inflammatory event is not likely to cause DM (although this has

185   occasionally been reported in humans (Raman and others 2011)), but the endocrine tissue is more

186   likely to become more seriously affected if inflammation and / or clinical signs persist as CP. The

187   prevalence of CP in the UK canine population has been estimated at 34% (Watson and others 2007),

188   with a high proportion of cases with chronic pancreatic inflammation documented at necropsy

189   showing no associated clinical signs in life. A recent study of 61 cases and 100 controls in the USA

190   suggested that dogs with clinical CP have significantly higher histological scores for pancreatic

191   necrosis and peri-pancreatic fat necrosis (usually more associated with acute disease) than dogs with

192   incidental CP, implying they may in fact have acute-on-chronic pancreatitis (Bostrom and others

193   2013). This supports the necrosis-fibrosis theory of CP which suggests that irreversible damage is

194   caused by repeated acute insults to the pancreatic tissue.

195   Certain breeds appear to be predisposed to AP including spaniels, terriers, dachshunds and poodles.

196   Recent work to examine the breed-related prevalence of CP in post mortem pancreata from first

197   opinion practice in the UK suggested that histological evidence of CP in dogs is present in

198   approximately 34% of cadavers, with Cavalier King Charles spaniels (CKCS), collies and boxers being

199   over represented (Watson and others 2007). Intriguingly, boxers are under-represented in canine

200   diabetic cohorts (Fall and others 2007).

201   Definitive diagnosis and classification of pancreatitis has been discussed elsewhere (Cordner and

202   others 2010), Mansfield and others 2012, (Watson 2012). A presumptive non-invasive diagnosis is

203   usually made using a combination of history, physical examination and clinical signs, in combination

204   with measurement of canine pancreatic lipase immunoreactivity (cPLI) (Mansfield and others 2012)

205   and / or ultrasonographic examination of the pancreas.

206   **Pathophysiology of acute and chronic pancreatitis in cats**

207   Similar to pancreatitis in dogs, the aetiology of pancreatitis in cats is also only partially understood

208   (Xenoulis and Steiner 2008), but what is known of the pathophysiology has been well reviewed

209   (Bazelle and Watson 2014). The basic protective mechanisms and anatomy of the pancreas are

210   similar to those described in the dog (Mansfield and Jones 2001a). However, the diagnosis of feline

211   pancreatitis can be even more challenging than in dogs because clinical signs may be very mild, non-

212   specific and remain unnoticed by the owner (Xenoulis and Steiner 2008), such as partial anorexia or

213   lethargy (Washabau 2001). This makes it difficult to assess its prevalence in the diabetic and non-

214   diabetic population. Early studies suggested a prevalence of less than 3% (Steiner and Williams 1999)

215   but more recent histopathological work implies that the prevalence of pancreatic inflammation in

216   cats is much higher than this – 67% in animals with clinical signs and 45% in clinically healthy cats,

217   with the majority of these cases having chronic rather than acute inflammatory infiltrates (De Cock

218   and others 2007). Within the diabetic cat population, the prevalence of pancreatic inflammation

219   may be even higher still – with evidence of pancreatitis at post mortem examination being described

220 in 19 out of 27 diabetic cats examined (Goossens and others 1998). The histopathological features

221 of feline pancreatitis have been extensively reviewed (Mansfield and Jones 2001a) and vary in

222 severity and chronicity. Pancreatitis in cats may also be associated with cholangiohepatitis and

223 inflammatory bowel disease (Caney 2013).

224 As in dogs, the underlying cause of pancreatitis in cats is not clear, but genetics, infection (e.g. viral,

225 parasitic), trauma and the presence of other common inflammatory conditions may all contribute to

226 risk (Xenoulis and Steiner 2008). Diagnosis may be especially challenging in cats as already described,

227 but a combination of history, clinical examination, diagnostic imaging and feline pancreas specific

228 lipase (fPLI) measurement is recommended (Forman and others 2004, Xenoulis and Steiner 2008). As

229 in dogs, CP in cats may eventually result in exocrine pancreatic insufficiency as the enzyme-

230 producing cells are slowly replaced by fibrous tissue (Steiner and Williams 1999).

231 **The relationship between exocrine pancreatic inflammation and DM in human medicine**

232 As illustrated above, canine and feline DM have similar clinical signs but different underlying

233 pathophysiology. It is therefore conceivable that the role of pancreatitis in each disease will be

234 different. In dogs, the closest human parallel is type 1 DM and in cats the closest human parallel is

235 type 2 DM, so the contribution of pancreatitis to both these diseases, and in contrast the potential

236 contribution of both these diseases to pancreatitis, should be considered. However, there is very

237 little published evidence of type 1 DM and acute (or chronic) pancreatitis co-existing in human

238 medicine. This may be because type 1 DM usually occurs in young children (Hummel and others

239 2012) and in this age group pancreatitis is usually confined to genetic or traumatic causes, meaning

240 that the majority of human diabetes – pancreatitis studies relate to type 2 DM. There is clear

241 evidence that patients with longstanding type 1 DM develop pancreatic atrophy (Williams and

242 others 2012), but to the author's knowledge, there are no clear human studies linking type 1 DM to

243 risk of pancreatitis later in life.

244 Not surprisingly, human pancreatitis has many underlying causes, with acute disease commonly

245 being associated with toxaemia, gallstones, trauma, medication or infection. One difference

246 between humans and veterinary species is that bacterial translocation from the gut is a well-

247 recognised and important source of infection in human AP, and may result in pancreatic

248 abscessation (Schmid and others 1999). In human AP, clinical signs include severe abdominal pain,

249 fever, nausea, vomiting or dehydration and in those cases where pancreatic necrosis occurs, the

250 disease may be fatal (Cruz-Santamaria and others 2012).

251 The most common cause of CP in humans is chronic alcohol consumption but genetic predisposition,

252 autoimmune disease, or other diseases such as cystic fibrosis may also chronically impede exocrine

253 pancreatic function and lead to pancreatic inflammation. Chronic pancreatitis shows similar clinical

254 signs to acute disease but they are generally less severe and more prolonged. It is of particular note

255 that in human type 2 DM, the risk of CP is two to three times higher than that in healthy subjects

256 (Girman and others 2010) and a recent meta-analysis indicated that type 2 diabetic patients are also

257 at increased risk of AP (Yang and others 2013).

258 This raises the question of why human type 2 DM patients are prone to pancreatitis – does the

259 diabetic state itself contribute to the onset of pancreatic inflammation? This possibility is raised by a

260 meta-analysis in which diabetic individuals had a 92% increased risk of development of CP,

261 independent of other risk factors such as alcohol use, gallstones and hyperlipidaemia (Xue and

262 others 2012). Similarly in AP, a meta-analysis reported that insulin resistance and hyperglycaemia

263 are important factors in the susceptibility of diabetic individuals to AP (Solanki and others 2012). It is

264 also of potential relevance that human patients with DM are at a greater risk of particularly severe

265 AP, even if the DM was not originally associated with pancreatitis at diagnosis (Shen and others

266 2012). Experimental rodent models of pancreatitis and DM suggest that the presence of

267 hyperglycaemia can exacerbate AP and suppress regeneration of exocrine tissue (Zechner and others

268   2012). This implies an important clinical point - that poor glycaemic control may contribute to the

269   severity of AP and aggravate the progression of the disease.

270   Although the studies mentioned above highlight the increased risk for pancreatitis in diabetic

271   patients, the majority of the published evidence points to pancreatitis preceding the DM in humans

272   i.e. the DM is secondary to the pancreatitis rather than the DM causing pancreatic inflammation

273   (Kazumi and others 1983, Jap and others 1992, Cavallini and others 1993, Larsen 1993). A recent

274   meta-analysis suggested that following an episode of AP, a patient has a two-fold increased risk of

275   developing DM within 5 years (Das and others 2014). This type of DM is classified as neither type 1

276   nor type 2 DM, but a separate category of "other specific types of DM".

277   Diabetes mellitus in human patients with CP is more likely to be found later in the course of the

278   exocrine pancreatic disease (Singh and others 2012), and similar to canine and feline cases, CP in

279   humans may ultimately result in malabsorption due to pancreatic insufficiency. This timecourse is

280   also similar to an obese rodent model of pancreatitis, in which DM develops later during the course

281   of the disease. It is of particular interest in this model that the pancreatitis can be made less severe

282   and the onset of DM delayed by dietary restriction (Akimoto and others 2010).

283   As already discussed for dogs and cats, the exact mechanism by which CP results in DM is likely to be

284   complex in humans. Studies of cytokine concentrations in pancreatic tissues from CP patients by

285   flow cytometry demonstrate increased interferon gamma in both diabetic and non-diabetic patients,

286   a cytokine which has been shown to impede beta cell function and therefore may play a role in DM

287   associated with CP (Pavan Kumar and others 2012). It is also apparent that patients with concurrent

288   type 2 DM and CP have an increased risk of developing pancreatic cancer (Brodovicz and others

289   2012), although no similar correlation has been reported in dogs or cats.

290   A more rare condition in humans, called Autoimmune Pancreatitis (AIP) is characterised

291   radiologically by enlargement of the pancreas, narrowing of the pancreatic duct, lymphoplasmacytic

292 pancreatic infiltrate and classically an elevation of serum IgG4 levels (Kamisawa and others 2010).

293 This disease is commonly associated with insulin-dependent DM in adults (Ito and others 2011) and

294 tends to be very responsive to steroid treatment. These patients rarely have the autoantibodies to

295 islet antigens that characterise classical type 1 DM, although pancreatic histology suggests cellular

296 islet infiltrates and reduced numbers of beta cells. The classic autoantigens in AIP are lactoferrins

297 and carbonic anhydrase II (Hardt and others 2008). The pathophysiology of the DM seen in AIP has

298 not been fully elucidated but is not thought to be related to non-specific collateral damage from the

299 pancreatic inflammatory process, but rather a specific immunological effect, thought to be triggered

300 by the pancreatitis (Miyamoto and others 2012). This would therefore again make the pancreatitis a

301 cause rather than an effect of the DM and offers an alternative mechanism for immune-mediated

302 islet destruction. At present, however, IgG4 measurement is not routinely performed in veterinary

303 medicine, so a companion animal counterpart of AIP has not been identified, although studies are

304 ongoing and it is possible that certain types of breed-related DM may share pathophysiological

305 features with AIP.

306

307 The relationship between pancreatitis and DM in dogs

308 In a study of 80 dogs with severe AP, 29 dogs had concurrent DM (Papa and others 2011), making

309 the prevalence of DM much higher in this population than in dogs without AP. In a recent UK

310 retrospective study of DM in first opinion practice (Mattin and others 2014), diabetic dogs diagnosed

311 with pancreatitis also had a higher hazard of death. Having reviewed the underlying causes of both

312 diseases, and the relationship between these conditions in humans, the question remains, does

313 canine pancreatitis cause DM or can canine DM result in pancreatitis? The intuitive answer is that

314 pancreatitis is likely to occur first, with the beta cells succumbing to bystander damage, either by

315 non-specific inflammation or the triggering of an autoimmune process and epitope spreading.

316 However, the increased risk of pancreatitis in human diabetic patients also suggests that pancreatitis

317   could theoretically be a *consequence* of DM, so it may be the case that both diseases may have a

318   negative impact on each other.

319   It is possible too that a more broad, over-arching mechanism may be at work. In another recent

320   study, canine CP cases were significantly more likely to have an endocrine disease than dogs without

321   pancreatitis, specifically DM or hypothyroidism (Bostrom and others 2013). It is therefore possible

322   that the mechanisms for pancreatitis development in both hypothyroidism and DM are similar,

323   implying that endocrine disease may be contributing to the initiation of the pancreatic inflammation.

324   One such risk factor, shared between DM and hypothyroidism, may be the high cholesterol resulting

325   from the endocrinopathy acting as a trigger for pancreatitis, as hyperlipidaemia has been shown to

326   cause pancreatitis in humans (Tsuang and others 2009) and dogs (Hess and others 1999). However,

327   it must also be remembered that in dogs, as in humans, there are shared genetic factors for DM and

328   hypothyroidism so it is also possible that these may be shared with other genetic risk factors for

329   pancreatitis. Sharing of genetic risk variants does not necessarily imply that one disease causes the

330   other.

331   Is there any evidence at the cellular or molecular level that DM may trigger pancreatitis in dogs?

332   Although the cytokine milieu in human and canine pancreatitis has been investigated (discussed

333   earlier), very little is known about the local cytokine environment in the pancreatic islets in canine

334   DM. However, despite the lack of local measurements, some circulating cytokine profiles have been

335   reported in a study of healthy dogs, dogs with DM and dogs with DKA. The cytokines IL-18 and GM-

336   CSF were elevated in DKA dogs before treatment compared to after successful treatment, and pro-

337   inflammatory factors CXCL8 and MCP-1 were significantly higher in dogs with DM compared to

338   controls (O'Neill and others 2012). However, 7 of the 9 dogs with DKA in this study also had

339   pancreatitis, and as IL-18 is a pro-inflammatory cytokine associated with pancreatitis in humans it is

340   difficult to know if the presence of this cytokine is a cause or consequence of the pancreatitis.

341   Nonetheless, CXCL8 and MCP-1 are both associated with inflammation, so have the potential to

342   contribute to pancreatitis. A more recent study of alterations in innate immunity in dogs associated

343   with DM also suggested that white blood cells from diabetic cases produce more pro-inflammatory

344   cytokines in response to stimulation and hypothesised that this may predispose diabetic dogs to

345   infectious and inflammatory complications (DeClue and others 2012).

346   Another theoretical trigger for pancreatitis which may be associated with DM in dogs is the potential

347   for the presence of circulating autoantibodies to pancreatic proteins or anti-insulin antibodies

348   induced by treatment (Davison and others 2003, Davison and others 2008a) to form immune

349   complexes in the pancreas. However, this is most likely an academic concern as it has not been

350   proven in practice. Cats do not appear to suffer from autoimmune pancreatitis and nor do they

351   commonly make antibodies to exogenous insulin so this mechanism appears even less likely to occur

352   in this species (Hoenig and others 2000).

353   Another particular challenge in establishing which disease occurs first relates to the fact that one

354   condition may be clinically silent e.g. CP. In a study of 14 confirmed canine cases of CP, the pancreas

355   only appeared 'abnormal' on 56% of ultrasound examinations and the sensitivity of cPLI when

356   combined with amylase and lipase measurement was 44 to 67% when using a low cut off value.

357   (Watson and others 2010). At present, it is not routine to test the glucose tolerance of all cases with

358   AP or CP or to test pancreatic inflammatory markers in all newly diagnosed canine diabetic cases.

359   Nor, of course are pancreatic biopsies routine in diabetic cases. However, some work has been

360   undertaken to try to establish the prevalence of defective beta cell function amongst pancreatitis

361   cases which gives some insight into the order in which the diseases may arise.

362   Watson and Herrtage (2004) used a glucagon stimulation test to evaluate endocrine pancreatic

363   reserve in canine cases with clinical pancreatitis. By measuring the insulin and glucose response

364   following an intravenous glucagon dose, a functional defect in endocrine pancreatic function was

365   demonstrated in 5 of 6 dogs with pancreatitis, implying that inflammation can impair insulin

366   secretion from beta cells. This suggests that in cases where the two diseases are concurrent,

367 pancreatic inflammation may precede DM in dogs. A similar timeline was seen in a small case series

368 of 4 dogs with EPI secondary to CP. Two of these dogs developed DM, and this happened after the

369 diagnosis of CP but before the diagnosis of EPI (Watson 2003). This suggests an order of events

370 beginning with pancreatitis, moving on to DM and culminating in pancreatic fibrosis and EPI, at least

371 in some dogs. This mirrors the findings of recent human studies which suggest that in cases where

372 DM develops secondary to CP, islet dysfunction occurs first due to the local inflammatory milieu but

373 clinical DM does not manifest until later, when fibrosis causes islet destruction (Sasikala and others

374 2012).

375 **The relationship between pancreatitis and DM in cats**

376 One recent study reported that 26 of 40 cats with naturally occurring DM were found to have

377 elevated lipase concentration at the time of admission to a clinical facility (Zini and others 2010b).

378 Although elevation in serum lipase is not perfectly sensitive or specific for a diagnosis of pancreatitis,

379 this study appears to concur with a 1998 study in which 19 of 37 diabetic cats were shown to have

380 evidence of pancreatic inflammation on post mortem examination (Goossens and others 1998). As

381 the pathology of DM in cats relates to insulin resistance, which can be caused by a focus of

382 inflammation within the body, it is not difficult to propose a causal role for pancreatitis in feline DM.

383 If this is the case, similar mechanisms for islet cell damage to those discussed for canine pancreatitis

384 may play a role.

385 However, to counter this argument, the biochemical states of hyperglycaemia and hyperlipidaemia,

386 as seen in feline DM, have been shown to contribute to inflammatory responses in humans

387 (Shoelson and others 2007) implying that the metabolic changes in DM may contribute to

388 pancreatitis developing subsequently. As feline DM is considered to be similar to human type 2 DM,

389 it is possible that diabetic cats are subject to the same increased risk for pancreatitis as already

390 described for humans with type 2 DM. One experimental study, designed to investigate the

391 relationship between hyperglycaemia, hyperlipidaemia and pancreatitis in cats reported that 10 days

392   of hyperglycaemia increased pancreatic neutrophils, but without causing pancreatic damage, a

393   finding which was not seen in cats with experimentally induced hyperlipidaemia (Zini and others

394   2010b). This suggests that hyperglycaemia may play a role in predisposing to feline pancreatitis but

395   other factors are also involved in the early stages of pancreatic inflammation.

396   It is also helpful to recognise recent work in human type 2 DM and metabolic syndrome has

397   demonstrated that obesity and inflammation are directly linked (Shoelson and Goldfine 2009).

398   Adipose tissue can have a significant influence on metabolism and the immune system via synthesis

399   and secretion of chemical mediators such as adipokines and adipocytokines (Whitehead and others

400   2006). This pro-inflammatory environment can in turn lead to recruitment and activation of

401   inflammatory cells and may also play a role in beta cell damage during hyperglycaemia via cytokines

402   such as IL-6 and IL-1 beta. If this type of inflammation occurs in obese cats, within the pancreas, then

403   it is certainly possible that it may act as a trigger for pancreatitis.

404   A biochemical marker of AP, although not 100% sensitive, feline pancreatic lipase immunoreactivity

405   was found to be elevated in a different cohort of feline diabetic cases (Forcada and others 2008),

406   and correlated with serum fructosamine concentration, which may also reflect the relationship

407   between inflammation and insulin resistance.

408   **Clinical implications of the relationship between pancreatitis and DM**

409   *Dogs:* Based on the evidence presented here, the balance appears to be slightly in favour of

410   pancreatitis preceding DM and hence in favour of the exocrine disease contributing to or triggering

411   the endocrine disease. It is also clear, however, that there are multiple routes to lack of beta cell

412   function in dogs and pancreatitis is only one potential causal factor. It is still theoretically possible

413   that, at least in dogs, pancreatitis may develop in response to the hyperglycaemia or

414   hyperlipidaemia associated with DM, a risk which may be even further exacerbated by the increased

415   potential for bacterial infection (DeClue and others 2012) and toxaemia in diabetic cases, but this is

416   difficult to prove.

417   An important clinical observation is that where pancreatitis and DM do co-exist, the practitioner may

418   be blinded to the presence of one of these conditions. The prevalence of the two diseases

419   concurrently in dogs is remarkably high, and it is important to recognise AP or CP as it increases

420   insulin resistance as well as being significantly correlated with risk of DKA. In addition there is the

421   long term risk of intermittent 'flare-ups' of disease and the potential for glycaemic control to be

422   complicated in future by the development of exocrine pancreatic insufficiency.

423   Although pancreatitis can be a difficult diagnosis to make clinically, for the reasons outlined above,

424   in the author's opinion, serious consideration should be given to evaluating every diabetic dog,

425   particularly those who are newly diagnosed or unstable, for exocrine pancreatic disease, for example

426   by measurement of cPLI. Whilst management of pancreatitis may appear fairly non-specific, - being

427   based on nutritional support, low fat food, intravenous fluid therapy and analgesia, the *knowledge*

428   that a diabetic dog has accompanying exocrine pancreatic inflammation can make a further

429   significant contribution to the clinical management and prognosis, allowing the owner and

430   veterinary surgeon to make better informed decisions, improving the animal's quality of life.

431   In contrast, however, there is insufficient evidence at present to recommend a glucagon stimulation

432   test to evaluate endocrine function in every animal with pancreatitis, but it is still important that

433   cases that are suspected to have pancreatitis should be regularly examined and owners warned of

434   the potential risks of DM in the future.

435   *Cats:* The relationship between obesity / inactivity and DM in cats is undeniable, so regardless of co-

436   existing pancreatitis, weight loss and increased activity, plus an appropriate diet are the most

437   important factors in helping to prevent many cases of DM in cats. As discussed however, there is

438   clearly also an important relationship between insulin resistance and pancreatitis in cats, in which

439   the pancreatic exocrine tissue inflammation may even be initiated or exacerbated by

440   hyperglycaemia in some cases. It is therefore important to consider the possibility of pancreatic

441   inflammation in all diabetic cats, even if they have no history of AP, because hyperglycaemia

442   resulting from obesity, acromegaly, inflammation or exogenous drug treatment has the potential to

443   contribute to the development of exocrine pancreatic inflammation.

444   Where a diagnosis of pancreatitis pre-dates documented hyperglycaemia, it appears likely that

445   pancreatitis predisposes to the demise of beta cells and contributes to peripheral insulin resistance,

446   precipitating DM in genetically susceptibly or obese cats. The same principles discussed for dogs

447   therefore also apply to cats, i.e. ideally the clinician should be consciously aware of *both* diseases,

448   and should consider testing newly diagnosed diabetic cats for pancreatitis, especially because clinical

449   signs may be so subtle and unregulated pancreatic inflammation may have a dramatic and negative

450   impact on clinical outcome. This is especially true if an intensive protocol to achieve DM remission is

451   being undertaken, as active pancreatic inflammation and its associated clinical signs, however

452   subtle, may compromise the effectiveness of this approach.

453   **CONCLUSIONS:**

454   Diabetes mellitus and pancreatitis are both complex diseases, showing many species-specific

455   features in dogs, cats and humans. As the endocrine and exocrine tissues of the pancreas are so

456   interlinked, it is not surprising that damage to one or the other has an impact on the surrounding

457   tissues. The main conclusion that can be drawn is that whilst the most common direction of

458   progression may be that DM occurs secondary to pancreatitis, the two disease may still be seen in

459   the 'reverse order' in certain circumstances.

460   Additionally, DM and pancreatitis may arise by a number of mechanisms but there are particular

461   environmental triggers and genetic pre-dispositions which make this more likely. Figure 1 illustrates

462   the 'circular argument' of cause and effect, including putative (but not necessarily proven) factors

463   from each of the two diseases which could increase the risk of the second disease developing. The

464   most important message is that clinicians continue to remain aware of the potential for both

465   diseases to co-exist. The benefits to the diabetic patient when a serious complication is recognised

466   and treated, despite it having potentially only subtle clinical signs, will be just as important whether

467   or not the pancreatitis has arisen as a cause or consequence of the DM.

468

469

References:

470 **References:**

472 T. Akimoto, M. Terada, A. Shimizu, N. Sawai & H. Ozawa (2010) The influence of dietary restriction
473 on the development of diabetes and pancreatitis in female WBN/Kob-fatty rats. *Exp Anim* **59**, 623-
474 630

475 R. Alejandro, E. C. Feldman, F. L. Shienvold & D. H. Mintz (1988) Advances in canine diabetes mellitus
476 research: etiopathology and results of islet transplantation. *J Am Vet Med Assoc* **193**, 1050-1055

477 C. E. Atkins, J. R. Hill & R. K. Johnson (1979) Diabetes mellitus in the juvenile dog: a report of four
478 cases. *J Am Vet Med Assoc* **175**, 362-368

479 R. C. Backus, N. J. Cave, V. K. Ganjam, J. B. Turner & V. C. Biourge (2010) Age and body weight effects
480 on glucose and insulin tolerance in colony cats maintained since weaning on high dietary
481 carbohydrate. *J Anim Physiol Anim Nutr (Berl)* **94**, e318-328

482 J. Bazelle & P. Watson (2014) Pancreatitis in cats: is it acute, is it chronic, is it significant? *J Feline*
483 *Med Surg* **16**, 395-406

484 B. M. Bostrom, P. G. Xenoulis, S. J. Newman, R. R. Pool, G. T. Fosgate & J. M. Steiner (2013) Chronic
485 pancreatitis in dogs: A retrospective study of clinical, clinicopathological, and histopathological
486 findings in 61 cases. *Vet J* **195**, 73-79

487 K. G. Brodovicz, T. D. Kou, C. M. Alexander, E. A. O'Neill, S. S. Engel, C. J. Girman & B. J. Goldstein
488 (2012) Impact of diabetes duration and chronic pancreatitis on the association between type 2
489 diabetes and pancreatic cancer risk. *Diabetes Obes Metab* **9999**

490 S. M. Caney (2013) Pancreatitis and diabetes in cats. *Vet Clin North Am Small Anim Pract* **43**, 303-317

491 B. Catchpole, J. P. Adams, A. L. Holder, A. D. Short, W. E. Ollier & L. J. Kennedy (2012) Genetics of
492 canine diabetes mellitus: Are the diabetes susceptibility genes identified in humans involved in
493 breed susceptibility to diabetes mellitus in dogs? *Vet J*

494 B. Catchpole, L. J. Kennedy, L. J. Davison & W. E. Ollier (2008) Canine diabetes mellitus: from
495 phenotype to genotype. *J Small Anim Pract* **49**, 4-10

496 B. Catchpole, J. M. Ristic, L. M. Fleeman & L. J. Davison (2005) Canine diabetes mellitus: can old dogs
497 teach us new tricks? *Diabetologia* **48**, 1948-1956

498 G. Cavallini, B. Vaona, P. Bovo, M. Cigolini, L. Rigo, F. Rossi, E. Tasini, M. P. Brunori, V. Di Francesco &
499 L. Frulloni (1993) Diabetes in chronic alcoholic pancreatitis. Role of residual beta cell function and
500 insulin resistance. *Dig Dis Sci* **38**, 497-501

501 A. K. Cook, E. B. Breitschwerdt, J. F. Levine, S. E. Bunch & L. O. Linn (1993) Risk factors associated
502 with acute pancreatitis in dogs: 101 cases (1985-1990). *J Am Vet Med Assoc* **203**, 673-679

503 M. Coradini, J. S. Rand, J. M. Morton & J. M. Rawlings (2011) Effects of two commercially available
504 feline diets on glucose and insulin concentrations, insulin sensitivity and energetic efficiency of
505 weight gain. *Br J Nutr* **106 Suppl 1**, S64-77

506 A. P. Cordner, P. J. Armstrong, S. J. Newman, R. Novo, L. C. Sharkey & C. Jessen Emeritus (2010)
507 Effect of pancreatic tissue sampling on serum pancreatic enzyme levels in clinically healthy dogs. *J*
508 *Vet Diagn Invest* **22**, 702-707

509 D. M. Cruz-Santamaria, C. Taxonera & M. Giner (2012) Update on pathogenesis and clinical
510 management of acute pancreatitis. *World J Gastrointest Pathophysiol* **3**, 60-70

511 S. L. Das, P. P. Singh, A. R. Phillips, R. Murphy, J. A. Windsor & M. S. Petrov (2014) Newly diagnosed
512 diabetes mellitus after acute pancreatitis: a systematic review and meta-analysis. *Gut* **63**, 818-831

513 L. J. Davison, M. E. Herrtage & B. Catchpole (2005) Study of 253 dogs in the United Kingdom with
514 diabetes mellitus. *Vet Rec* **156**, 467-471

515 L. J. Davison, M. E. Herrtage & B. Catchpole (2011) Autoantibodies to recombinant canine proinsulin
516 in canine diabetic patients. *Res Vet Sci* **91**, 58-63

517 L. J. Davison, J. M. Ristic, M. E. Herrtage, I. K. Ramsey & B. Catchpole (2003) Anti-insulin antibodies in
518 dogs with naturally occurring diabetes mellitus. *Vet Immunol Immunopathol* **91**, 53-60

519 L. J. Davison, B. Walding, M. E. Herrtage & B. Catchpole (2008a) Anti-insulin antibodies in diabetic
520 dogs before and after treatment with different insulin preparations. *J Vet Intern Med* **22**, 1317-1325

521 L. J. Davison, S. M. Weenink, M. R. Christie, M. E. Herrtage & B. Catchpole (2008b) Autoantibodies to
522 GAD65 and IA-2 in canine diabetes mellitus. *Vet Immunol Immunopathol* **126**, 83-90
523 H. E. De Cock, M. A. Forman, T. B. Farver & S. L. Marks (2007) Prevalence and histopathologic
524 characteristics of pancreatitis in cats. *Vet Pathol* **44**, 39-49
525 A. E. DeClue, J. Nickell, C. H. Chang & A. Honaker (2012) Upregulation of proinflammatory cytokine
526 production in response to bacterial pathogen-associated molecular patterns in dogs with diabetes
527 mellitus undergoing insulin therapy. *J Diabetes Sci Technol* **6**, 496-502
528 M. L. Doherty, A. M. Healy & W. J. Donnelly (1998) Diabetes mellitus associated with lymphocytic
529 pancreatitis in a cow. *Vet Rec* **142**, 493
530 M. Elie & M. Hoenig (1995) Canine immune-mediated diabetes mellitus: a case report. *J Am Anim*
531 *Hosp Assoc* **31**, 295-299
532 T. Fall, H. H. Hamlin, A. Hedhammar, O. Kampe & A. Egenvall (2007) Diabetes mellitus in a population
533 of 180,000 insured dogs: incidence, survival, and breed distribution. *J Vet Intern Med* **21**, 1209-1216
534 Y. Forcada, A. J. German, P. J. Noble, J. M. Steiner, J. S. Suchodolski, P. Graham & L. Blackwood
535 (2008) Determination of serum fPLI concentrations in cats with diabetes mellitus. *J Feline Med Surg*
536 **10**, 480-487
537 M. A. Forman, S. L. Marks, H. E. De Cock, E. J. Hergesell, E. R. Wisner, T. W. Baker, P. H. Kass, J. M.
538 Steiner & D. A. Williams (2004) Evaluation of serum feline pancreatic lipase immunoreactivity and
539 helical computed tomography versus conventional testing for the diagnosis of feline pancreatitis. *J*
540 *Vet Intern Med* **18**, 807-815
541 W. Gepts & D. Toussaint (1967) Spontaneous diabetes in dogs and cats. A pathological study.
542 *Diabetologia* **3**, 249-265
543 C. J. Girman, T. D. Kou, B. Cai, C. M. Alexander, E. A. O'Neill, D. E. Williams-Herman & L. Katz (2010)
544 Patients with type 2 diabetes mellitus have higher risk for acute pancreatitis compared with those
545 without diabetes. *Diabetes Obes Metab* **12**, 766-771
546 M. M. Goossens, R. W. Nelson, E. C. Feldman & S. M. Griffey (1998) Response to insulin treatment
547 and survival in 104 cats with diabetes mellitus (1985-1995). *J Vet Intern Med* **12**, 1-6
548 D. M. Haines & W. J. Penhale (1985) Autoantibodies to pancreatic islet cells in canine diabetes
549 mellitus. *Vet Immunol Immunopathol* **8**, 149-156
550 P. D. Hardt, N. Ewald, K. Brockling, S. Tanaka, T. Endo, H. U. Kloer, R. G. Bretzel, C. Jaeger, H. Shimura
551 & T. Kobayashi (2008) Distinct autoantibodies against exocrine pancreatic antigens in European
552 patients with type 1 diabetes mellitus and non-alcoholic chronic pancreatitis. *JOP* **9**, 683-689
553 R. S. Hess, P. H. Kass, F. S. Shofer, T. J. Van Winkle & R. J. Washabau (1999) Evaluation of risk factors
554 for fatal acute pancreatitis in dogs. *J Am Vet Med Assoc* **214**, 46-51
555 R. S. Hess, H. M. Saunders, T. J. Van Winkle & C. R. Ward (2000) Concurrent disorders in dogs with
556 diabetes mellitus: 221 cases (1993-1998). *J Am Vet Med Assoc* **217**, 1166-1173
557 M. Hoenig (2002) Comparative aspects of diabetes mellitus in dogs and cats. *Mol Cell Endocrinol* **197**,
558 221-229
559 M. Hoenig & D. L. Dawe (1992) A qualitative assay for beta cell antibodies. Preliminary results in
560 dogs with diabetes mellitus. *Vet Immunol Immunopathol* **32**, 195-203
561 M. Hoenig, C. Reusch & M. E. Peterson (2000) Beta cell and insulin antibodies in treated and
562 untreated diabetic cats. *Vet Immunol Immunopathol* **77**, 93-102
563 D. Z. Hume, K. J. Drobatz & R. S. Hess (2006) Outcome of dogs with diabetic ketoacidosis: 127 dogs
564 (1993-2003). *J Vet Intern Med* **20**, 547-555
565 K. Hummel, K. K. McFann, J. Realsen, L. H. Messer, G. J. Klingensmith & H. P. Chase (2012) The
566 increasing onset of type 1 diabetes in children. *J Pediatr* **161**, 652-657 e651
567 T. Imamura, M. Koffler, J. H. Helderman, D. Prince, R. Thirlby, L. Inman & R. H. Unger (1988) Severe
568 diabetes induced in subtotally depancreatized dogs by sustained hyperglycemia. *Diabetes* **37**, 600-
569 609

T. Ito, T. Nakamura, N. Fujimori, Y. Niina, H. Igarashi, T. Oono, M. Uchida, K. Kawabe, R. Takayanagi, I. Nishimori, M. Otsuki & T. Shimosegawa (2011) Characteristics of pancreatic diabetes in patients with autoimmune pancreatitis. *J Dig Dis* **12**, 210-216

T. S. Jap, C. F. Kwok & L. T. Ho (1992) Metabolic control and B cell function in patients with diabetes mellitus secondary to chronic pancreatitis. *Zhonghua Yi Xue Za Zhi (Taipei)* **49**, 141-146

J. R. Jeffrey (1968) Diabetes mellitus secondary to chronic pancreatitis in a pony. *J Am Vet Med Assoc* **153**, 1168-1175

T. Kamisawa, K. Takuma, N. Egawa, K. Tsuruta & T. Sasaki (2010) Autoimmune pancreatitis and IgG4-related sclerosing disease. *Nat Rev Gastroenterol Hepatol* **7**, 401-409

T. Kazumi, M. Ohya, I. Suehiro, N. Mizuno, S. Morita, M. Oimomi & S. Baba (1983) Diabetes mellitus secondary to idiopathic chronic calcifying pancreatitis in an adolescent woman. *Endocrinol Jpn* **30**, 261-266

L. J. Kennedy, L. J. Davison, A. Barnes, A. D. Short, N. Fretwell, C. A. Jones, A. C. Lee, W. E. Ollier & B. Catchpole (2006) Identification of susceptibility and protective major histocompatibility complex haplotypes in canine diabetes mellitus. *Tissue Antigens* **68**, 467-476

C. A. Kirk (2006) Feline diabetes mellitus: low carbohydrates versus high fiber? *Vet Clin North Am Small Anim Pract* **36**, 1297-1306, vii

H. Klinkenberg, M. H. Sallander & A. Hedhammar (2006) Feeding, exercise, and weight identified as risk factors in canine diabetes mellitus. *J Nutr* **136**, 1985S-1987S

S. Larsen (1993) Diabetes mellitus secondary to chronic pancreatitis. *Dan Med Bull* **40**, 153-162

M. Laskowski, Jr. & I. Kato (1980) Protein inhibitors of proteinases. *Annu Rev Biochem* **49**, 593-626

R. Lederer, J. S. Rand, N. N. Jonsson, I. P. Hughes & J. M. Morton (2009) Frequency of feline diabetes mellitus and breed predisposition in domestic cats in Australia. *Vet J* **179**, 254-258

M. J. Linderman, E. M. Brodsky, L. P. de Lorimier, C. A. Clifford & G. S. Post (2012) Feline exocrine pancreatic carcinoma: a retrospective study of 34 cases. *Vet Comp Oncol*

G. Majno & I. Joris (1995) Apoptosis, oncosis, and necrosis. An overview of cell death. *Am J Pathol* **146**, 3-15

R. Makhija & A. N. Kingsnorth (2002) Cytokine storm in acute pancreatitis. *J Hepatobiliary Pancreat Surg* **9**, 401-410

C. Mansfield (2012a) Acute pancreatitis in dogs: advances in understanding, diagnostics, and treatment. *Top Companion Anim Med* **27**, 123-132

C. Mansfield (2012b) Pathophysiology of acute pancreatitis: potential application from experimental models and human medicine to dogs. *J Vet Intern Med* **26**, 875-887

C. S. Mansfield, G. A. Anderson & A. J. O'Hara (2012) Association between canine pancreatic-specific lipase and histologic exocrine pancreatic inflammation in dogs: assessing specificity. *J Vet Diagn Invest* **24**, 312-318

C. S. Mansfield & B. R. Jones (2001a) Review of feline pancreatitis part one: the normal feline pancreas, the pathophysiology, classification, prevalence and aetiologies of pancreatitis. *J Feline Med Surg* **3**, 117-124

C. S. Mansfield & B. R. Jones (2001b) Review of feline pancreatitis part two: clinical signs, diagnosis and treatment. *J Feline Med Surg* **3**, 125-132

D. Mattheeuws, R. Rottiers, J. J. Kaneko & A. Vermeulen (1984) Diabetes mellitus in dogs: relationship of obesity to glucose tolerance and insulin response. *Am J Vet Res* **45**, 98-103

M. Mattin, D. O'Neill, D. Church, P. D. McGreevy, P. C. Thomson & D. Brodbelt (2014) An epidemiological study of diabetes mellitus in dogs attending first opinion practice in the UK. *Vet Rec* **174**, 349

T. M. McCann, K. E. Simpson, D. J. Shaw, J. A. Butt & D. A. Gunn-Moore (2007) Feline diabetes mellitus in the UK: the prevalence within an insured cat population and a questionnaire-based putative risk factor analysis. *J Feline Med Surg* **9**, 289-299

J. M. Meegan, I. F. Sidor, J. M. Steiner, D. Sarran & J. L. Dunn (2008) Chronic pancreatitis with secondary diabetes mellitus treated by use of insulin in an adult California sea lion. *J Am Vet Med Assoc* **232**, 1707-1712

Y. Miyamoto, T. Kamisawa, T. Tabata, S. Hara, S. Kuruma, K. Chiba, Y. Inaba, G. Kuwata, T. Fujiwara, H. Egashira, K. Koizumi, R. Sekiya, J. Fujiwara, T. Arakawa, K. Momma & T. Asano (2012) Short and long-term outcomes of diabetes mellitus in patients with autoimmune pancreatitis after steroid therapy. *Gut Liver* **6**, 501-504

R. Neiger, A. L. Witt, A. Noble & A. J. German (2004) Trilostane therapy for treatment of pituitary-dependent hyperadrenocorticism in 5 cats. *J Vet Intern Med* **18**, 160-164

S. J. Newman, J. M. Steiner, K. Woosley, D. A. Williams & L. Barton (2006) Histologic assessment and grading of the exocrine pancreas in the dog. *J Vet Diagn Invest* **18**, 115-118

S. J. Niessen (2010) Feline acromegaly: an essential differential diagnosis for the difficult diabetic. *J Feline Med Surg* **12**, 15-23

T. D. O'Brien (2002) Pathogenesis of feline diabetes mellitus. *Mol Cell Endocrinol* **197**, 213-219

S. O'Neill, K. Drobatz, E. Satyaraj & R. Hess (2012) Evaluation of cytokines and hormones in dogs before and after treatment of diabetic ketoacidosis and in uncomplicated diabetes mellitus. *Vet Immunol Immunopathol* **148**, 276-283

E. L. Opie (1901) On the Relation of Chronic Interstitial Pancreatitis to the Islands of Langerhans and to Diabetes Melutus. *J Exp Med* **5**, 397-428

M. Osto, E. Zini, C. E. Reusch & T. A. Lutz (2012) Diabetes from humans to cats. *Gen Comp Endocrinol* **182C**, 48-53

K. Papa, A. Mathe, Z. Abonyi-Toth, A. Sterczer, R. Psader, C. Hetyey, P. Vajdovich & K. Voros (2011) Occurrence, clinical features and outcome of canine pancreatitis (80 cases). *Acta Vet Hung* **59**, 37-52

P. Pavan Kumar, G. Radhika, G. V. Rao, R. Pradeep, C. Subramanyam, R. Talukdar, D. N. Reddy & M. Sasikala (2012) Interferon gamma and glycemic status in diabetes associated with chronic pancreatitis. *Pancreatology* **12**, 65-70

A. G. Poppl, T. S. Mottin & F. H. Gonzalez (2012) Diabetes mellitus remission after resolution of inflammatory and progesterone-related conditions in bitches. *Res Vet Sci*

A. Prahl, L. Guptill, N. W. Glickman, M. Tetrick & L. T. Glickman (2007) Time trends and risk factors for diabetes mellitus in cats presented to veterinary teaching hospitals. *J Feline Med Surg* **9**, 351-358

V. S. Raman, R. W. Loar, V. S. Renukuntla, K. V. Hassan, D. S. Fishman, M. A. Gilger & R. A. Heptulla (2011) Hyperglycemia and diabetes mellitus in children with pancreatitis. *J Pediatr* **158**, 612-616 e611

J. Rand (1999) Current understanding of feline diabetes: part 1, pathogenesis. *J Feline Med Surg* **1**, 143-153

J. S. Rand, L. M. Fleeman, H. A. Farrow, D. J. Appleton & R. Lederer (2004) Canine and feline diabetes mellitus: nature or nurture? *J Nutr* **134**, 2072S-2080S

J. S. Rand & R. D. Marshall (2005) Diabetes mellitus in cats. *Vet Clin North Am Small Anim Pract* **35**, 211-224

H. Rinderknecht (1986) Activation of pancreatic zymogens. Normal activation, premature intrapancreatic activation, protective mechanisms against inappropriate activation. *Dig Dis Sci* **31**, 314-321

C. G. Ruaux & R. B. Atwell (1998) A severity score for spontaneous canine acute pancreatitis. *Aust Vet J* **76**, 804-808

M. Sasikala, R. Talukdar, P. Pavan kumar, G. Radhika, G. V. Rao, R. Pradeep, C. Subramanyam & D. Nageshwar Reddy (2012) beta-Cell dysfunction in chronic pancreatitis. *Dig Dis Sci* **57**, 1764-1772

S. W. Schmid, W. Uhl, H. Friess, P. Malfertheiner & M. W. Buchler (1999) The role of infection in acute pancreatitis. *Gut* **45**, 311-316

P. J. Selman, J. A. Mol, G. R. Rutteman, E. van Garderen & A. Rijnberk (1994) Progestin-induced growth hormone excess in the dog originates in the mammary gland. *Endocrinology* **134**, 287-292

669   H. N. Shen, Y. H. Chang, H. F. Chen, C. L. Lu & C. Y. Li (2012) Increased risk of severe acute
670   pancreatitis in patients with diabetes. *Diabet Med* **29**, 1419-1424

671   S. E. Shoelson & A. B. Goldfine (2009) Getting away from glucose: fanning the flames of obesity-
672   induced inflammation. *Nat Med* **15**, 373-374

673   S. E. Shoelson, L. Herrero & A. Naaz (2007) Obesity, inflammation, and insulin resistance.
674   *Gastroenterology* **132**, 2169-2180

675   S. E. Shoelson, J. Lee & A. B. Goldfine (2006) Inflammation and insulin resistance. *J Clin Invest* **116**,
676   1793-1801

677   A. D. Short, B. Catchpole, L. J. Kennedy, A. Barnes, A. C. Lee, C. A. Jones, N. Fretwell & W. E. Ollier
678   (2009) T cell cytokine gene polymorphisms in canine diabetes mellitus. *Vet Immunol Immunopath*
679   **128**, 137-146

680   N. Singh, P. Bhardwaj, R. M. Pandey & A. Saraya (2012) Oxidative stress and antioxidant capacity in
681   patients with chronic pancreatitis with and without diabetes mellitus. *Indian J Gastroenterol* **31**, 226-
682   231

683   L. I. Slingerland, V. V. Fazilova, E. A. Plantinga, H. S. Kooistra & A. C. Beynen (2009) Indoor
684   confinement and physical inactivity rather than the proportion of dry food are risk factors in the
685   development of feline type 2 diabetes mellitus. *Vet J* **179**, 247-253

686   N. S. Solanki, S. G. Barreto & G. T. Saccone (2012) Acute pancreatitis due to diabetes: the role of
687   hyperglycaemia and insulin resistance. *Pancreatology* **12**, 234-239

688   J. M. Steiner & D. A. Williams (1999) Feline exocrine pancreatic disorders. *Vet Clin North Am Small*
689   *Anim Pract* **29**, 551-575

690   W. Tsuang, U. Navaneethan, L. Ruiz, J. B. Palascak & A. Gelrud (2009) Hypertriglyceridemic
691   pancreatitis: presentation and management. *Am J Gastroenterol* **104**, 984-991

692   A. Tvarijonaviciute, J. J. Ceron, S. L. Holden, D. J. Cuthbertson, V. Biourge, P. J. Morris & A. J. German
693   (2012) Obesity-related metabolic dysfunction in dogs: a comparison with human metabolic
694   syndrome. *BMC Vet Res* **8**, 147

695   K. R. Verkest, L. M. Fleeman, J. M. Morton, S. J. Groen, J. S. Suchodolski, J. M. Steiner & J. S. Rand
696   (2012) Association of postprandial serum triglyceride concentration and serum canine pancreatic
697   lipase immunoreactivity in overweight and obese dogs. *J Vet Intern Med* **26**, 46-53

698   R. J. Washabau (2001) Feline acute pancreatitis--important species differences. *J Feline Med Surg* **3**,
699   95-98

700   P. Watson (2012) Chronic pancreatitis in dogs. *Top Companion Anim Med* **27**, 133-139

701   P. J. Watson (2003) Exocrine pancreatic insufficiency as an end stage of pancreatitis in four dogs. *J*
702   *Small Anim Pract* **44**, 306-312

703   P. J. Watson, J. Archer, A. J. Roulois, T. J. Scase & M. E. Herrtage (2010) Observational study of 14
704   cases of chronic pancreatitis in dogs. *Vet Rec* **167**, 968-976

705   P. J. Watson, A. J. Roulois, T. Scase, P. E. Johnston, H. Thompson & M. E. Herrtage (2007) Prevalence
706   and breed distribution of chronic pancreatitis at post-mortem examination in first-opinion dogs. *J*
707   *Small Anim Pract* **48**, 609-618

708   J. P. Whitehead, A. A. Richards, I. J. Hickman, G. A. Macdonald & J. B. Prins (2006) Adiponectin--a key
709   adipokine in the metabolic syndrome. *Diabetes Obes Metab* **8**, 264-280

710   A. J. Williams, S. L. Thrower, I. M. Sequeiros, A. Ward, A. S. Bickerton, J. M. Triay, M. P. Callaway & C.
711   M. Dayan (2012) Pancreatic volume is reduced in adult patients with recently diagnosed type 1
712   diabetes. *J Clin Endocrinol Metab* **97**, E2109-2113

713   P. G. Xenoulis & J. M. Steiner (2008) Current concepts in feline pancreatitis. *Top Companion Anim*
714   *Med* **23**, 185-192

715   P. G. Xenoulis, J. S. Suchodolski, C. G. Ruaux & J. M. Steiner (2010) Association between serum
716   triglyceride and canine pancreatic lipase immunoreactivity concentrations in miniature schnauzers. *J*
717   *Am Anim Hosp Assoc* **46**, 229-234

718   Y. Xue, Y. Sheng, H. Dai, H. Cao, Z. Liu & Z. Li (2012) Risk of development of acute pancreatitis with
719   pre-existing diabetes: a meta-analysis. *Eur J Gastroenterol Hepatol* **24**, 1092-1098

720   L. Yang, Z. He, X. Tang & J. Liu (2013) Type 2 diabetes mellitus and the risk of acute pancreatitis: a
721   meta-analysis. *Eur J Gastroenterol Hepatol* **25**, 225-231
722   D. Zechner, M. Spitzner, A. Bobrowski, N. Knapp, A. Kuhla & B. Vollmar (2012) Diabetes aggravates
723   acute pancreatitis and inhibits pancreas regeneration in mice. *Diabetologia* **55**, 1526-1534
724   E. Zini, M. Hafner, M. Osto, M. Franchini, M. Ackermann, T. A. Lutz & C. E. Reusch (2010a) Predictors
725   of clinical remission in cats with diabetes mellitus. *J Vet Intern Med* **24**, 1314-1321
726   E. Zini, M. Osto, M. Franchini, F. Guscetti, M. Y. Donath, A. Perren, R. S. Heller, P. Linscheid, M.
727   Bouwman, M. Ackermann, T. A. Lutz & C. E. Reusch (2009) Hyperglycaemia but not hyperlipidaemia
728   causes beta cell dysfunction and beta cell loss in the domestic cat. *Diabetologia* **52**, 336-346
729   E. Zini, M. Osto, S. Moretti, M. Franchini, P. H. Kook, H. Lutz, F. Guscetti, A. Perren, L. E. Hoelzle, M.
730   Ackermann, T. A. Lutz & C. E. Reusch (2010b) Hyperglycaemia but not hyperlipidaemia decreases
731   serum amylase and increases neutrophils in the exocrine pancreas of cats. *Res Vet Sci* **89**, 20-26

732

733

734

735

736

737

738

739

740

741

742

743

744

745

746

747

748

749 **Table 1**

Classification of canine diabetes mellitus (Catchpole and others 2005)

Insulin deficiency diabetes (IDD)

Primary IDD in dogs is characterised by a progressive loss of pancreatic beta cells. The aetiology of beta cell deficiency/destruction in diabetic dogs is currently unknown but a number of diseases processes are thought to be involved:
• Congenital beta cell hypoplasia/abiotrophy
• Beta cell loss associated with exocrine pancreatic disease
• Immune-mediated beta 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

785

786

787

788

Figure 1 – The putative influences of diabetes on pancreatitis and vice versa

790

PANCREATITIS

POTENTIAL
MECHANISMS
DRIVING TOWARDS
PANCREATITIS

- Hyperglycaemia
- Increased risk of infection
- DKA?
- Pancreatic autoantibodies?
- Anti-insulin antibodies?
- Cytokine milieu?

SHARED PUTATIVE
RISK FACTORS
FOR BOTH
DISEASES:
Endocrine disease
Obesity
Hyperlipidaemia
Hyperglycaemia
Genetics?

POTENTIAL
MECHANISMS
DRIVING TOWARDS
DIABETES

- Bystander islet damage
- Glucose toxicity
- Initiation of autoimmunity
- Adipokines?
- Cytokine milieu?
- Inflammation-driven insulin resistance
- Pancreatic fibrosis

DIABETES

791
792
793
794
795
796