Diabetes mellitus remission after resolution of inflammatory and progesterone-related conditions in bitches

A.G. Pöppl, T.S. Mottin, F.H.D. González

One of the subtypes of canine diabetes mellitus (CDM) in bitches can be compared to gestational diabetes mellitus (GDM) in humans, characterizing a subtype of insulin-resistant diabetes mellitus (IRD) (Catchpole et al., 2005; Fall et al., 2007). Since the 1950s, development of diabetes shortly after estrus has been well recognized in bitches and ovariohysterectomy (OHE) has been recommended as radical treatment of CDM (Campbell, 1958; Wilkinson, 1960). In the 1960s, Krook et al. (1960) first correlated CDM with pyometra, another typical condition associated with diestrus (Noakes et al., 2001) characterized by purulent fluid collection within the uterus with variable amounts of inflammatory cells in the uterine wall, that may or may not be preceded by cystic endometrial hyperplasia (Feldman and Nelson, 2004). Although insulin resistance mediated by progesterone is well characterized (Scaramal et al., 1997; Connolly et al., 2004; Batista et al., 2005), there is a paucity of case reports correlating CDM with diestrus, and mainly on its remission after spaying (Fall et al., 2008, 2010).

Moreover, although Fall et al. (2010) described a diagnostic prevalence of 17% for pyometra in females with concomitant CDM during diestrus, to our knowledge, there is no case report on the remission of diabetes after the resolution of the cystic endometrial hyperplasia–pyometra (CEH–P) complex, a condition associated with more severe insulin resistance due to the hormonal profile during diestrus and also to the septic/inflammatory process (Pöppl et al., 2009). The aim of this study was to investigate CDM remission after the resolution of clinical conditions associated with ovarian luteal activity.

A retrospective study was carried out by analyzing medical records of patients treated at the Division of Veterinary Endocrinology between 2006 and 2011, searching for female dogs diagnosed with remission of CDM after resolution of clinical situations related to ovarian luteal activity. The criteria used to confirm the diagnosis of CDM were clinical signs, especially polyuria and polydipsia, as well as persistent glucosuria and hyperglycemia (>200 mg/dL). The criteria used to define the remission of CDM were maintenance of normal blood glucose levels after discontinuation of insulin therapy, often defined after recurrent hypoglycemia, even after successive reductions in insulin dose. This study was approved by the Ethics Committee on Animal Experimentation of our University (CEUA/18.336).

Out of 117 female dogs diagnosed with CDM (patients with concomitant hyperadrenocorticism or hypothyroidism were not included), 72 (62%) had not been spayed at diagnosis, and from those, 35 (30%) were diagnosed during the diestrus phase of the estrus cycle. From those 72 intact bitches, 57 (79%) were spayed after CDM diagnosis. Six patients, with mean age of 8.5 years (range of 6–12 years), met the criteria for remission of CDM, after...
variable periods on insulin therapy. Only one patient had sponta-
neous remission of the disease at the end of diestrus (11 days after
diagnosis and onset of insulin therapy), whereas the remaining five
patients (9%) showed remission, on average 13.6 days (range of 4–
39 days) after ovariectomy or OHE. Table 1 shows some clinical
and laboratory details of each case.

Progestosterone-related clinical conditions whose resolution was
associated with the remission of CDM in these patients were: diestrus,
gestation, ovarian remnant syndrome (n = 1 each) and CEH–P
(n = 3). Surprisingly, four of these patients were initially diagnosed
with severe diabetic ketoacidosis due to severe anapathy, anorexia, vomiting,
Kussmaul breathing, severe hyperglycemia (>500 mg/dL) and severe
ketonuria (>80 mg/dL). One patient with initial presentation in
ketosis, had already been spayed, but often showed signs of heat. The
Abdominal ultrasound evaluation suggested the presence of
ovarian remnant tissue, with quick remission of diabetes within
4 days after ovariectomy. CEH–P was observed and confirmed by
histopathology in two patients after uterine examination in the
postoperative period, and CEH–P was strongly suggested in an-
other patient by abdominal ultrasound before surgery. As to the
pregnant patient, the owner’s decision to terminate pregnancy was
only made after failure to control blood glucose levels 4 days
after stabilization of diabetic ketosis detected at initial diagnosis.

The patient with spontaneous remission of diabetes at the end of
diestrus had a relapse when the animal came into heat again
4 months after remission, but this time the condition was
permanent.

While dogs diagnosed with CDM are totally dependent upon
insulin therapy for control of their clinical signs (Catchpole et al.,
2005; Feldman and Nelson, 2004), case reports on remission of dia-
betes after control of situations which cause insulin resistance re-
veal that, in some cases, beta cells are not yet completely impaired
diagnosis and, therefore, they can maintain normal glucose lev-
els, provided that the cause of insulin resistance is identified and
eliminated. It has been demonstrated by Imamura et al. (1988) that
chronic exposure to hyperglycemia may induce severe insulin-
dependent diabetes in dogs (glucotoxicity).

Despite the fact that CDM is often associated with destruction
of beta cells secondary to pancreatitis, or secondary to an autoimmune
attack (Catchpole et al., 2005; Feldman and Nelson, 2004), whose
inheritance (Catchpole et al., 2008) is to be unraveled, Fall et al.
(2010), in a case series of diabetes secondary to diestrus or gestation
in the Norwegian Elkhound breed, showed that none of the patients
had GAD-65 autoantibodies, thus indicating a non-autoimmune eti-
ology. Moreover, some environmental factors such as overweight,
lack of physical activity and an unbalanced diet have been impli-
cated as risk factors for the development of CDM (Klingenberg
et al., 2006) and overweight was described as a risk factor for dia-
betes secondary to diestrus in Elkhounds (Weidmark et al., 2011).

Likewise, in humans, CDM is also associated with advanced age,
family history, ethnicity, and overweight (Phillips, 2006).

Nordic Spitz dogs are usually overrepresented in epidemiologi-
cal studies on diabetes (Guptill et al., 2003; Fall et al., 2007, 2008),
suggesting a probable genetic factor, whereas the Norwegian Elkh-

Please cite this article in press as: Popp, A.G., et al. Diabetes mellitus remission after resolution of inflammatory and progestosterone-related conditions in

Table 1

<table>
<thead>
<tr>
<th>Breed, age, BS (1–5) and BW (kg)</th>
<th>E–DM (weeks)</th>
<th>FGD (mg/dL)</th>
<th>DM–OHE (days)</th>
<th>OHE–NG (days)</th>
<th>FGR (mg/dL)</th>
<th>P4-related condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teckel, 12y, 2, 5, 2</td>
<td>4</td>
<td>493</td>
<td>46</td>
<td>39</td>
<td>78</td>
<td>CEH–P</td>
</tr>
<tr>
<td>Beagle, 8y, 3, 11, 17</td>
<td>5</td>
<td>513</td>
<td>37</td>
<td>20</td>
<td>109</td>
<td>CEH–P</td>
</tr>
<tr>
<td>Brittany, 6y, 3, 10</td>
<td>2</td>
<td>542</td>
<td>5</td>
<td>4</td>
<td>96</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Poodle, 8y, 2, 4</td>
<td>2</td>
<td>&gt;600</td>
<td>81</td>
<td>10</td>
<td>95</td>
<td>CEH–P</td>
</tr>
<tr>
<td>Mongrel, 7y, 2, 36</td>
<td>2</td>
<td>&gt;600</td>
<td>3</td>
<td>4</td>
<td>89</td>
<td>ORS</td>
</tr>
<tr>
<td>Mongrel, 10y, 2, 29, 8</td>
<td>3</td>
<td>305</td>
<td>–</td>
<td>–</td>
<td>76</td>
<td>Diabetes</td>
</tr>
</tbody>
</table>

BS, body score; BW, body weight; E–DM, interval between the end of estrus and diabetes diagnosis; FGD, fasting glucose at diagnosis; DM–OHE, interval between diabetes
diagnosis and gonadectomy; OHE–NG, interval between gonadectomy and normoglycemia; FGR, fasting glucose at diabetes remission; P4, progesterone; CEH–P, cystic
endometrial hyperplasia–pyometra; ORS, ovarian remnant syndrome.
gestational diabetes occurs at younger ages than diabetes secondary to diestrus (Fall et al., 2008).

While progesterone-induced GH secretion plays a major role in CDM development during diestrus, the magnitude of GH response to progesterone as well as tissue response to GH and the glycemic/insulinemic responses to this phenomenon is quite variable from dog to dog (Eingenmann et al., 1983; Selman et al., 1994), due to many unclear variables such as genetics, nutrition, and environment (Guptill et al., 2003; Klinkenberg et al., 2006; Wejdmark et al., 2011). In this scenario, the role played by inflammatory cytokines in inducing insulin resistance cannot be ruled out as in the case of CEH–P (Pöppl et al., 2009). The largest concentration of inflammatory cytokines (TNF-α, IL-1, IL-6) under sepsis, or chronic inflammation conditions, inhibits the intracellular signaling of insulin through different mechanisms (Tilg and Moschen, 2008), explaining the severe insulin resistance observed in bitches with pyometra (Pöppl et al., 2009). Nonetheless, studies that correlate insulin sensitivity with septic/infammatory processes in dogs are rare (Pöppl et al., 2009; Fall et al., 2010) and ever since Kbrook et al. (1960) correlated diabetes with pyometra, no other study linking these diseases frequently seen in routine practice has been published. The remission of CDM after resolution of CEH–P strengthens this association. Moreover, remission of progesterone-related diabetes in dogs is expected to occur only if progesterone withdrawal occurs few weeks after CDM diagnosis (Eingenmann et al., 1993; Fall et al., 2008, 2010). The unexpected long interval (37, 46 and 81 days) between diabetes diagnosis and OHE in three bitches reinforces this possible role of insulin resistance due to CEH–P when compared with the other bitches that were neutered quickly after CDM diagnosis.

Although there is agreement that the chance of remission is higher when OHE is performed as soon as possible after the development of diabetes mellitus (Feldman and Nelson, 2004), we conclude that remission is possible even after some weeks between diagnosis and therapeutic OHE in some specific cases, even when severe ketosis is observed at presentation. It is assumed that maintenance of insulin therapy played a crucial role for protection against severe glucotoxicity in this case series. Different aspects led to the remission of CDM in these cases, but OHE played a key role, being therefore recommended for bitches with DM, not only as a way to prevent treatment complications, but also as a way to induce remission of the disease by allowing a new hormonal balance after the removal of the progesterone source, or elimination of inflammatory cytokines in case of pyometra.

Conflict of interest

None of the authors of this paper has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

Acknowledgment

This study was supported by CNPq (Brazilian National Research Council).

References


