Feline diabetes mellitus
Assessment of risk factors and treatment protocols

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Licentiate thesis in veterinary medicine
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This licentiate thesis consists of a literature review and a retrospective study. Diabetes mellitus is a common endocrinopathy in cats. It mainly resembles type II diabetes mellitus of humans, where the dysfunction of pancreatic beta cells together with peripheral insulin resistance causes increased blood glucose concentrations. Along with other risk factors such as breed and neuter status, obesity is closely related to the development of feline diabetes mellitus.

The aim of the retrospective study was to assess risk factors and treatment protocols of diabetes mellitus. Factors influencing treatment outcome were also investigated. The results were compared with current scientific evidence. The hypotheses were that diabetic cats with an optimal body condition score (BCS) are more likely to achieve stable disease requiring administration of exogenous insulin and are more likely to achieve remission, where administration of exogenous insulin is no longer needed.

The veterinary patient database ProvetNet was used to search for cats with diabetes mellitus presented to the University of Helsinki, Small Animal Teaching Hospital and the Saari Small Animal Clinic between March 2006 and March 2016. Data such as breed, gender, BCS and concurrent diseases were recorded for 123 cats. Statistical analyses were performed using GraphPad Prism.

Neutered male cats had 2.8 times the risk of developing diabetes mellitus when compared to intact cats and neutered females. Domestic shorthair cats had 1.7 times the risk of developing diabetes mellitus when compared to other breeds. Remission rates were substantially lower than what has been reported in literature.

The results did not support the hypotheses. Cats with an optimal BCS were not more likely to achieve stable disease or remission. However, the small sample size should be taken into consideration when interpreting the results.

Investigating the relationship between BCS and diabetes mellitus was difficult due to incomplete documentation of BCS values and limitations of the veterinary patient database. Measures should be taken to develop the database so the evaluation and recording of BCS is a convenient routine. Further research into risk factors for both diabetes mellitus and obesity as well as treatment protocols resulting in remission is needed, so evidence-based data can be used for prevention and remission of the disease.
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Retrospektiivinen tutkimusosion tavoite oli selvittää sairauden syntyyn liittyviä riskitekijöitä ja hoito protokollia. Lisäksi tutkittiin hoitovasteeseen vaikuttavia tekijöitä. Tuloksia vertailtiin kirjallisuuskatsauksessa esiteltyyn tietoon. Tutkimushypotees oli, että ihanteellisen kuntoluokan omaavilla diabetessä sairastuneilla kissoilla on suurempi todennäköisyys saavuttaa vakaa hoitovaste, jossa ulkoisen insuliinin annostelu on välttämätöntä ja suurempi todennäköisyys saavuttaa remissio, jossa ulkoisen insuliinin annostelua ei tarvita.


Kuntoluokan vaikutuksen arvioiminen koisojen sairastuvuudessa diabetes mellitukseen on vaiinnaisa puuttuevien kirjaamiskäytäntöjen sekä potilaatietojärjestelmän asettamien rajoitteiden vuoksi. Potilaatietojärjestelmään tulisi kehitellä niin, että kuntoluokan arvioiminen ja kirjaaminen olisi tulevaisuudessa helppoja ja käytännöllisiä. Tutkimusta diabetes mellituselle ja lihavuudelle altistavista tekijöistä sekä remissioon johtavista hoitoprotokolleista on tarpeen, jotta sairautta voidaan tehokkaasti hoitaa ja ennaltaehkäistä käytännön potilaistyössä.

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diabetes mellitus, kissa, altistavat tekijät, lihavuus, kuntoluokka, remissio, retrospektiivinen tutkimus

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1 INTRODUCTION

Feline diabetes mellitus is a relatively common endocrinopathy in the modern day domestic cat. The prevalence of diabetes mellitus has been estimated to be around 0.5-1% (Prahl et al. 2007, McCann et al. 2007) and seems to have increased in the past few decades (Prahl et al. 2007). The etiology of the disease is multifactorial and multiple risk factors have been identified. These include obesity, increasing age, breed, male gender and physical inactivity (Panciera et al. 1990, McCann et al. 2007, Prahl et al. 2007, Lederer et al. 2009, Öhlund et al. 2015, O’Neill et al. 2016).

Feline diabetes mellitus mainly resembles type II diabetes mellitus of humans. It is characterized by the dysfunction of beta cells in the pancreas and concomitant insulin resistance, which causes an increase in the blood glucose concentration (O’Brien 2002, Reusch 2015). The resulting chronic hyperglycemia is toxic to beta cells, which results in further dysfunction of the cells (O’Brien 2002, Reusch 2015). Other pathophysiological mechanisms such as hypersomatotropism and hyperadrenocorticism have been described to induce feline diabetes mellitus (Gilor et al. 2016, Nelson and Reusch 2014).

The literature review set to outline the current knowledge of feline diabetes mellitus and its association with obesity. Risk factors for the development of diabetes mellitus, treatment options and factors influencing treatment are discussed. The potential for remission of diabetes mellitus and factors contributing to it are considered. Complications of feline diabetes mellitus are also briefly addressed.

The objective of the licentiate thesis is to assess risk factors associated with the development of diabetes mellitus, different treatment protocols and factors influencing the outcome of feline diabetes mellitus in a Finnish cat population and to compare the results with current scientific evidence. The prevalence of diabetes mellitus in the study population is assessed. The hypotheses tested are that cats with diabetes mellitus and an optimal body condition score (BCS) of 3 on the 5-point scale are more likely to achieve stable disease requiring administration of exogenous insulin and to achieve remission, where exogenous insulin is no longer needed. The study population consists of cats with diabetes mellitus presented to the
University of Helsinki Small Animal Teaching Hospital and the Saari Small Animal Clinic between March 2006 and March 2016.
2 LITERATURE REVIEW

2.1 Feline diabetes mellitus

Diabetes mellitus is a common endocrinopathy in cats. Various studies have investigated the prevalence of the disease, which seems to be increasing in the United States from 0.25% in 1990 (Panciera et al. 1990) to 1.24% in 1999 (Prahl et al. 2007). In the United Kingdom (UK), the prevalence was 0.5% in 2007 (McCann et al. 2007). In a Swedish population the incidence of diabetes mellitus did not increase between 2009 and 2013, with incidence rates of 11.6 cases per 10,000 cat-years at risk (Öhlund et al. 2015).

Feline diabetes mellitus usually resembles the type II diabetes mellitus of humans, which arises from the combination of insulin resistance and decreased function of pancreatic beta cells (O’Brien 2002, Reusch 2015). Insulin resistance is defined as the inability of insulin to increase glucose uptake at concentrations that are effective in normal individuals (Reusch 2015). At first, insulin resistance in peripheral tissues results in hyperinsulinemia as pancreatic beta cells increase insulin production to meet the increased demand (O’Brien 2002, Reusch 2015). Hypoinsulinemia develops when the insulin producing capacity of pancreatic beta cells runs out. It is suspected that amyloid deposition has a part in the destruction of beta cells (Reusch 2015). Islet amyloid polypeptide (IAPP), also known as amylin, is a hormone secreted by beta cells that is stored and secreted together with insulin. IAPP levels are increased in conditions associated with insulin resistance and IAPP-derived amyloid depositions have been found in the pancreata of diabetic cats (Herndon et al. 2014). Amyloid deposits have, however, also been found in healthy non-diabetic cats, suggesting that they may advance beta cell damage but are not the primary cause (Herndon et al. 2014, Reusch 2015).

Hyperglycemia occurs when glucose uptake into cells is reduced. Chronic hyperglycemia has a negative effect on beta cell function, a phenomenon known as glucotoxicity (Zini et al. 2009, Reusch 2015). Beta cell dysfunction and apoptosis has been shown to happen rapidly in ten days of sustained hyperglycemia in cats (Zini et al. 2009). Insulin gene expression is decreased with sustained hyperglycemia but not hyperlipidemia, suggesting that high levels of free fatty acids might not be as damaging to beta cells as glucose (Zini et al. 2009).
Antibodies against beta cells or insulin have not been documented, suggesting that the pathogenesis behind feline diabetes mellitus is not immune-mediated (Hoenig et al. 2000a).

Other pathophysiological mechanisms behind feline diabetes mellitus have also been described. Overproduction of insulin-antagonistic hormones, such as cortisol in hyperadrenocorticism and growth hormone in hypersomatotropism have been reported to occur together with diabetes mellitus (Niessen et al. 2007b, Niessen et al. 2013). Overproduction of growth hormone is caused by a somatotrophic adenoma or hyperplasia in the pars distalis of the anterior pituitary gland (Niessen et al. 2007a, Niessen et al. 2007b). The oversupply of growth hormone results in overproduction of insulin-like growth factor (IGF-1). The excess production of these hormones together results in the clinical syndrome of acromegaly (Niessen et al. 2013).

The prevalence of hypersomatotropism is unknown and only a few studies have been published to date. In a small pilot screening study, 59 out of 184 diabetic cats (32%) had increased serum insulin-like growth factor (IGF-1) levels (Niessen et al. 2007b). A later study showed that 26% of a total of 1,221 diabetic cats evaluated had elevated IGF-1 levels (Niessen et al. 2015). In this study, diabetic cats with high IGF-1 levels had significantly higher serum fructosamine concentrations and required higher daily insulin doses. A recent review suggests screening for hypersomatotropism if there is poor control of diabetes mellitus within two to four months after beginning of treatment or if required dosages of insulin are 1.5 IU/kg or more (Niessen et al. 2013). Interestingly, only 24% of the clinicians treating these acromegalic cats suspected hypersomatotropism (Niessen et al. 2015). Only 37% of the confirmed hypersomatotrophic cats in this study had broad facial features typically associated with hypersomatotropism. Injectable somatostatin analogue pasireotide has been used to treat cats with hypersomatotropism and resulting diabetes mellitus in an uncontrolled prospective study by Gostelow et al. (2017). Some cats went into diabetic remission after treatment with pasireotide. However, many severe adverse effects such as hypoglycemia and diarrhea were reported and further studies with larger sample sizes are warranted (Gostelow et al. 2017).

Excess production or administration of glucocorticoids can induce diabetes mellitus through various mechanisms. Glucocorticoids decrease sensitivity to insulin in tissues, increase hepatic gluconeogenesis, contravene with insulin’s inhibitory effect on appetite and inhibit insulin secretion by pancreatic beta cells (Davison 2017). In a UK study, 7.5% of diabetic cats had a history of glucocorticoid administration (McCann et al. 2007). Cats with diabetes mellitus
induced by treatment with glucocorticoids have an increased probability of remission of the disease when compared to cats with diabetes mellitus due to hypersomatotropism or pancreatic beta cell destruction (Roomp et al. 2009).

2.2 Risk factors

2.2.1 Breed

Some cat breeds are more likely to develop diabetes mellitus than others. In a UK population, Burmese cats were 3.7 times more likely to develop the disease compared to non-pedigree cats (McCann et al. 2007). The Burmese breed was overrepresented also in a study by O’Neill et al. (2016). Other breeds with an increased risk for the development of diabetes mellitus in this study were the Tonkinese and Norwegian Forest cat. Along with the Burmese and Norwegian Forest cat, the Russian Blue and Abyssinian have also been identified as high-risk breeds in a study by Öhlund et al. (2015). Domestic or crossbred cats have been reported to have a slightly greater risk of developing diabetes mellitus when compared to purebred cats (Öhlund et al. 2015).

The Bengal, Birman, Persian, Ragdoll and British Shorthair have been associated with a lower risk for diabetes mellitus (Öhlund et al. 2015). Purebred female cats were found to be at a lower risk when compared to crossbred cats (Prahl et al. 2007).

2.2.2 Gender

Male gender has been identified as a risk factor in multiple studies (Panciera et al. 1990, McCann et al. 2007, Prahl et al. 2007). In most studies there was no difference in the prevalence of diabetes mellitus between Burmese male and female cats (McCann et al. 2007, Öhlund et al. 2015), although in an Australian population, male Burmese cats were more likely to be affected (Lederer et al. 2009). Sex was not identified as a risk factor at all after other risk factors had been accounted for in a study by O’Neill et al. (2016).

Neutering has been reported as a potential risk factor in some studies (McCann et al. 2007) but was not associated with disease in others (Prahl et al. 2007). Neutering has been shown to increase the risk of obesity (Courcier et al. 2010, Bjornvad et al. 2014) and this could be a
contributing factor in the occurrence of diabetes mellitus in neutered cats. Cats are often neutered and the sample size of entire animals in these clinical trials was small.

### 2.2.3 Age

Increasing age has been identified as a risk factor in multiple studies (Prahlt et al. 2007, Öhlund et al. 2015, O’Neill et al. 2016). In one study the peak risk was at 13 years of age, after which the risk of developing diabetes mellitus decreased (Öhlund et al. 2015). Burmese cats had a significantly higher mean age at first diagnosis compared to other breeds in an Australian population (Lederer et al. 2009). As age increases, so does the incidence of other conditions and diseases that could contribute to insulin resistance, such as acromegaly (Niessen et al. 2007b).

### 2.2.4 Diet

Studies regarding the association of the type of food and diabetes mellitus are inconclusive. The proportion of dry food in the cat’s diet was not found to be a risk factor for diabetes mellitus (Slingerland et al. 2009). In another study, cats on a high carbohydrate diet had higher postprandial mean and peak glucose concentrations than cats on a high fat or high protein diet, even though the energy intake was lower in the high carbohydrate group (Farrow et al. 2013). Indoor confinement and low physical activity have been associated with the development of diabetes mellitus (Slingerland et al. 2009, Rowe et al. 2015).

### 2.2.5 Body condition and obesity

The risk for diabetes mellitus has been shown to increase with bodyweight (O’Neill et al. 2016). The frequency of occurrence was found to be significantly greater for cats weighing over 5 kg (McCann et al. 2007, O’Neill et al. 2016). Obesity, measured as increased body condition scores (BCS) of 7-8 on a scale of 1-9, has been associated with increased concentrations of insulin and IAPP in nondiabetic, euglycemic cats (Henson et al. 2011). Even mild obesity may predispose to the development of diabetes mellitus (Henson et al. 2011). However, not all obese cats develop diabetes mellitus. Distinguishing between healthy cats predisposed by their high BCS to diabetes mellitus and cats with an optimal BCS was not possible based on hematologic testing in a study by Hoenig et al. (2013).
Obesity is the accumulation of excessive amounts of adipose tissue in the body. A subjective 5-point or 9-point BCS system is widely used to assess obesity and has been shown to correlate with body fat mass (LaFlamme 1997, Bjornvad et al. 2011). Each unit increase in the 9-point system is associated with an increase of about 5% body fat (LaFlamme 1997). Physically inactive cats have a higher body fat content and less muscle mass compared to physically active cats with the same BCS (Bjornvad et al. 2011).

A BCS between 2.5 and 3.5 in the 5-point system, corresponding to a BCS between 4 and 6 in the 9-point system, is considered optimal (Toll et al. 2010). In addition to the BCS system, a further subdivision of obese cats with a BCS of 5 on the 5-point scale to obese (5a), very obese (5b) and morbidly obese (5c) has been proposed (Toll et al. 2010). If optimal weight is known for a certain breed, cats between 10 to 20% above optimal weight can be classified as overweight and those over 20% above optimal as obese (Toll et al. 2010).

Obesity is closely entwined with a decreased life span and metabolic and hormonal changes (Kil et al. 2010, Zoran 2010). A BCS of over 6 on the 9-point scale has been recently associated with multiple health conditions listed in table 1 (Teng et al. 2018). In this study, cats with a BCS of 3 or 4 of 9 had fewest associations with said health conditions. The risk of diabetes mellitus was significantly higher for cats with a BCS of 8 or 9 compared to a BCS of 5 on the 9-point scale (Teng et al. 2018).

Although the prevalence of obesity is thought to be increasing there have also been epidemiological studies showing otherwise (Cave et al. 2012). Owners’ underestimation of their obese cat’s BCS is common and may lead to overfeeding, which should be taken into account in weight loss and diet plans (Courcier et al. 2010, Cave et al. 2012).
Table 1. Health conditions associated with obesity (Teng et al. 2018).

- Dermatological conditions such as atopic dermatitis
- Musculoskeletal conditions such as arthritis
- Hypertension
- Respiratory conditions such as asthma
- Oral conditions
- Diarrhea
- General and lower urinary tract conditions
- Ophthalmic conditions
- Diabetes mellitus
- Allergic conditions

2.2.5.1 Risk factors and genetics of obesity

Several risk factors have been associated with the development of obesity. These often differ depending on local management habits of the study populations. Increasing age, male gender and neutering have been identified as common risk factors in most studies (Cave et al. 2012, Courcier et al. 2012, Bjornvad et al. 2014). Indoor confinement around the age of one year has been suggested to double the risk of obesity (Rowe et al. 2015). In a study by Courcier et al. (2010) access to the outdoors was not associated with an increased risk for the development of obesity.

Feeding mainly dry food has been associated with obesity (Rowe et al. 2015). Canned moist and semi-moist foods have higher proportions of water and lower caloric density than dry food, meaning the cat can eat a higher volume of food and get the same amount of energy as from a smaller portion of dry food (Behrend et al. 2018). Portion control might be easier to achieve with prepacked canned foods. Portion control instead of ad libitum feeding after neutering has been suggested to avoid obesity (Alexander et al. 2011).

Neutering increases food intake for both male and female cats, possibly due to the loss of estrogen hormones (Cave et al. 2007a). Food intake has been shown to decrease following
supplementation by exogenous estrogen (Cave et al. 2007b). Neutering created a period of increased food intake in kittens resulting in a higher BCS when compared to entire littermates (Alexander et al. 2011). Age at neutering was not associated with the prevalence of obesity in a study by Spain et al. (2004).

Polymorphisms in the melanocortin 4 receptor gene (MC4R) have been associated with diabetes mellitus in obese cats (Foracada et al. 2014). MC4R has an important role in appetite regulation and is associated with obesity and type II diabetes mellitus in humans (Xi et al. 2012).

Obesity has not been associated with low-grade inflammation in cats, despite the association between impaired immunity and obesity (Jaso-Friedmann et al. 2008, Tvarijonaviciute et al. 2012). An increased adipocyte cell size is seen in feline obesity (Van de Velde et al. 2013).

2.2.5.2 Adipokines and insulin resistance

Insulin resistance induced by obesity is partly communicated by adipokines, which are a group of hormones produced by adipose tissue (Antuna-Puente et al. 2008, Bjornvad et al. 2014). Adipokines have effects on various processes including inflammation, immune response, insulin secretion, insulin sensitivity, and glucose metabolism.

The adipokine leptin has been widely studied in humans. It decreases food intake and acts as an antiobesity hormone (Friedman et al. 1998). The plasma concentrations of leptin increase with obesity and have been found to promote insulin resistance also in cats (Appleton et al. 2002, Bjornvad et al. 2014). Cats with impaired insulin sensitivity had higher leptin concentrations than cats without insulin resistance regardless of their body condition score in a study by Appleton et al. (2001). Lean cats with initially low insulin sensitivity have been found to be more at risk for developing diabetes mellitus (Appleton et al. 2001). Insulin sensitivity is decreased by over 50% in obese cats (Appleton et al. 2001).

The most abundant adipokine is adiponectin which decreases insulin resistance (Kadowaki et al. 2006). Neutered male cats had significantly lower adiponectin concentrations when compared to neutered female cats (Bjornvad et al. 2014). Obese cats had lower plasma concentrations of the active adiponectin multimer and decreased glucose tolerance (Bjornvad
et al. 2014). Adiponectin levels of previously obese cats increased after weight loss, suggesting better insulin sensitivity (Tvarijonaviciute et al. 2012). Altered adipokine gene expression leading to an increase in the number of T-lymphocytes has been seen in feline obesity (Van de Velde et al. 2013).

2.3 Treatment
2.3.1 Treatment goals

The goals of treating feline diabetes mellitus depend on how much time has passed after initial diagnosis of the disease. Clinical remission, while avoiding complications such as hypoglycemia, is the treatment goal for cats with recently diagnosed diabetes mellitus (Behrend et al. 2018). This often requires a tight glycemic control protocol that aims for euglycemia, with blood glucose values measured with a device calibrated for cats kept between 4.4 and 7.2 mmol/l (Roomp and Rand 2009, Behrend et al. 2018).

Treatment goals for cats that have been diagnosed over six months ago are eliminating clinical signs such as polydipsia and polyuria by keeping blood glucose concentration below the renal threshold level and avoiding complications of the disease such as diabetic ketoacidosis and hypoglycemia (Sparkes et al. 2015, Behrend et al. 2018). The renal threshold level is the blood glucose concentration at which glucose is not reabsorbed by the proximal convoluted tubules back into the bloodstream (Sjaastad et al. 2016, Rand and Gottlieb 2017). This results in glycosuria, the presence of glucose in urine, and creates osmotic diuresis leading to polyuria and thus polydipsia (Rand and Gottlieb 2017). The renal threshold level for cats is considered to be around 14 mmol/l (Sparkes et al. 2015, Behrend et al. 2018).

2.3.2 Insulin types

The recommended starting dose for intermediate or longer-acting insulin preparations in a non-ketotic cat is 0.25 IU/kg if blood glucose concentration is <20 mmol/l (Sparkes et al. 2015, Rand and Gottlieb 2017, Behrend et al. 2018). If blood glucose concentration is >20 mmol/l, the recommended starting dose is 0.5 IU/kg (Sparkes et al. 2015, Rand and Gottlieb 2017, Behrend et al. 2018). Ideal body weight is used to determine insulin dosage. Insulin is administered subcutaneously twice daily with an insulin pen.
2.3.2.1 Glargine

Glargine insulin (Lantus, Sanofi-Aventis) is the current recommendation for treatment of feline diabetes mellitus (Sparkes et al. 2015, Behrend et al. 2018). Glargine is a long-acting human analogue insulin that has a rapid onset (Bloom et al. 2014). In most healthy cats, glargine suppresses blood glucose levels for at least 24 hours, but administering glargine twice daily is recommended to reduce the periods of hyperglycemia in cats with diabetes mellitus (Marshall et al. 2008a). Fluctuations in blood glucose concentrations are common in the first weeks after beginning treatment with glargine (Roomp and Rand 2009). Glargine is better at controlling blood glucose levels and has been associated with a higher probability of remission when compared to lente and protamine zinc insulin (Marshall et al. 2009).

Good glycemic control in diabetic cats was achieved with twice daily glargine with or without a low carbohydrate high protein diet (Hall et al. 2009). In the study, cats fed a low carbohydrate and high protein diet had lower serum fructosamine concentrations, suggesting that combining insulin with dietary modification may have additional benefits.

2.3.2.2 Detemir

Detemir insulin (Levemir, Novo Nordisk) is another long-acting human insulin analogue. Detemir insulin seems to be as effective as glargine in providing glycemic control (Roomp and Rand 2012). Control of clinical signs are expected within the first 3 months of treatment (Hoelmkjaer et al. 2015). Overall remission rates of around 67% were similar to glargine, with higher remission rates of 81% reported in cats that began treatment within the first 6 months after diagnosis (Roomp and Rand 2012). Much lower remission rates of 21% have been reported with a less intensive blood glucose monitoring protocol (Hoelmkjaer et al. 2015). It should be noted that these studies reporting remission rates have very small sample sizes, with 18 cats in the former and 14 in the latter study. Lower median maximal doses are required with detemir when compared to glargine (Roomp and Rand 2012).

2.3.2.3 Protamine zinc

Protamine zinc (ProZinc, Boehringer Ingelheim Vetmedica) is a long-acting human recombinant insulin. In a study by Nelson et al. (2009) the control of clinical signs happened within 45 days of treatment with protamine zinc. Biochemical hypoglycemia during treatment
was common in this study but clinical hypoglycemia was rare. Mean time for lowest blood glucose concentration was between five and seven hours and blood glucose levels increased in most cats nine hours after administering protamine zinc (Nelson et al. 2009). This suggests that treatment twice daily could be more effective than once daily.

2.3.2.4 Porcine lente

Porcine lente insulin (Caninsulin, MSD Animal Health) is an intermediate-acting mixture of short-acting and long-acting insulin. Lente has a shorter duration of action and results in higher mean daily glucose values in healthy cats compared to treatment with glargine or protamine zinc (Marshall et al. 2008a). Around 60% of diabetic cats treated with lente insulin were clinically stable after three months of treatment (Michiels et al. 2008). However, average serum fructosamine concentrations remained high in this study, suggesting that glycemic control was not very effective (Michiels et al. 2008). A recent study showed that transitioning from porcine lente to protamine zinc insulin reduced clinical signs, improved fructosamine levels and quality of life of both diabetic cats and their owners (Gustelow et al. 2018). Several cats also went into remission after transitioning from lente to protamine zinc insulin (Gustelow et al. 2018).

2.3.3. Oral hypoglycemics and incretins

Oral hypoglycemics are often ineffective and recommended only if owners refuse insulin therapy (Sparkes et al. 2015, Rand and Gottlieb 2017, Behrend et al. 2018). Oral hypoglycemics work by stimulating beta cell insulin secretion, increasing tissue insulin sensitivity or slowing down intestinal glucose absorption (Nelson 2000).

Oral glipizide is a sulfonylurea which stimulates insulin secretion. It has been used for treatment of diabetes mellitus in the past but has been associated with severe adverse effects such as vomiting, hypoglycemia and cholestasis (Nelson et al. 1993, Ford 1995, Feldman et al. 1997). Reported remission rates using glipizide are as low as 12% (Feldman et al. 1997). The majority of cats in this study failed to respond adequately to glipizide and required injectable insulin. Transdermal administration of glipizide has been studied but absorption was not consistent (Bennett et al. 2005). Oral glipizide administration has been associated with pancreatic islet amyloid deposits in cats with experimentally induced diabetes mellitus, suggesting the drug may advance pancreatic beta cell damage (Hoenig et al. 2000b). It should be noted that most of the studies done on glipizide are over 20 years old.
Thiazolidinediones such as pioglitazone increase insulin sensitivity in tissues. Pioglitazone has been shown to be rapidly absorbed when administered orally (Clark et al. 2012) and to increase insulin sensitivity in obese cats (Clark et al. 2014). However, it should be noted that insulin needs to be present for pioglitazone to be effective, which might make it ineffective in diabetic cats (Clark et al. 2014).

Incretin hormones are secreted from the gastrointestinal tract after consuming food and increase insulin secretion, thus causing a decrease in blood glucose levels (Reusch and Padrutt 2013). One example of an incretin is glucagon-like polypeptide-1 (GLP-1). Treatment with subcutaneous injections of GLP-1 agonists is associated with lower blood glucose levels in healthy cats (Gilor et al. 2011, Padrutt et al. 2015, Rudinsky et al. 2015). Liraglutide, a GLP-1 analog, has been associated with a decreased appetite and weight loss, suggesting it might have use as a weight loss drug in obese cats (Hall et al. 2015). The main disadvantage of GLP-1 analogues is that they must be administered subcutaneously (Gilor et al. 2011, Hall et al. 2015). An orally given alternative is sitagliptin which inhibits GLP-1 degradation. Sitagliptin has been shown to enhance insulin secretion in healthy cats (Furrer et al. 2010, Padrutt et al. 2015).

2.4. Factors influencing treatment and treatment outcome

2.4.1. Monitoring

Monitoring blood glucose values is essential in the treatment of diabetes mellitus. Traditionally, portable blood glucose meters are used to evaluate treatment response (Roomp et al. 2013). The use of a continuous glucose monitoring system similar to those used by human diabetics has been evaluated in cats (Dietiker-Moretti et al. 2011). The blood glucose profiles created by both devices were similar and resulted in similar insulin dose adjustments, but the continuous glucose monitoring system was better at detecting lowest blood glucose concentrations (Dietiker-Moretti et al. 2011).

Home monitoring is an important part of the treatment of diabetes mellitus, especially if aiming for remission (Roomp and Rand 2009, Nack and DeClue 2014). A tight glycemic control protocol requires the owner to measure the cat’s blood glucose levels with a portable glucose meter 3-7 times a day (Roomp and Rand 2009). This aims at euglycemia, defined as keeping blood glucose between 4.4 and 7.2 mmol/l measured with a device calibrated for felines (Roomp and Rand 2009). Biochemical hypoglycemia has been shown to be quite common but
clinical hypoglycemic episodes very rare with this protocol (Roomp and Rand 2009). Owners that did home blood glucose monitoring were less worried about the disease and the complications associated with it in a recent study by Hazuchova et al. (2018). Most owners found blood glucose monitoring to be fairly straightforward to perform at home, although technical difficulties and finding the time to perform the blood glucose monitoring were reported issues (Hazuchova et al. 2018).

Daily subcutaneous injections of insulin seem to be as effective in controlling blood glucose levels as intensive intravenous infusion of insulin (Roomp et al. 2009, Roomp et al. 2012, Hafner et al. 2014). Intravenous infusion treatment is expensive and requires hospitalization for some time (Hafner et al. 2014), which can be considered more inconvenient than daily injections administered by the owner. Intravenous infusion of insulin is, however, necessary in the treatment of diabetic ketoacidosis (O’Brien 2017).

Use of an implantable insulin pump has been studied by Zini et al. (2017). Technical problems regarding the device were frequent in this study. Glargine insulin, which is the insulin most often used in the treatment of cats with diabetes mellitus, might not be applicable with the device. It seemed to be rapidly inactivated in the pump and plasma levels of glargine insulin were not increased by successive boluses delivered by the device (Zini et al. 2017).

Rebound hyperglycemia, also known as Somogyi effect, is defined as hyperglycemia due to a surge of counter regulatory hormones such as glucagon, cortisol and adrenaline after a hypoglycemic episode induced by insulin (Roomp et al. 2016). It was believed to be common in both humans and cats but data in humans has largely rejected this phenomenon (Høi-Hansen et al. 2005, Cloudhary et al. 2013). Rebound hyperglycemia was rare in cats treated with glargine on tight glycemic control protocol (Roomp et al. 2016). This suggests that the insulin dose should not be reduced without evidence of biochemical or clinical hypoglycemia, especially in the first weeks or months after starting treatment with glargine (Roomp et al. 2016).

Insulin doses should not be increased more often than every five to seven (Reusch 2015, Sparkes et al. 2015) or even 7-14 days (Behrend et al. 2018). Adequate control of blood glucose levels often takes one to three months (Reusch 2015) and blood glucose fluctuations are expected in the first few days to weeks after changing glargine insulin doses (Roomp and Rand
After glucotoxicity has been reversed with exogenous insulin administration, the recovered pancreatic beta cells could be able to produce some amount of insulin again (Zini et al. 2009, Reusch 2015, Rand and Gottlieb 2017). This depends on the degree of pancreatic beta cell destruction that is not assessable prior to the beginning of treatment. If glycemic control is not achieved with moderate amounts of insulin, further diagnostics are required. Doses of >5 IU/cat (Behrend et al. 2018) or >1.5 IU/kg (Niessen et al. 2013) warrant re-evaluation of the owner’s capability administering and handling insulin, the cat’s diet as well as concurrent medications and diseases that might cause insulin resistance (Reusch 2015, Rand and Gottlieb 2017, Behrend et al. 2018).

2.4.2 Diet

A low carbohydrate and high protein diet may be beneficial in the treatment of diabetes mellitus (Hall et al. 2009). A low carbohydrate and high protein diet decreased serum fructosamine concentrations of both healthy non-diabetic cats and cats with diabetes mellitus (Webb et al. 2009). Both the International Society of Feline Medicine (ISFM) Consensus Guidelines and the American Animal Hospital Association (AAHA) Guidelines for treating diabetes mellitus in dogs and cats suggest low carbohydrate and high protein diets for diabetic cats (Sparkes et al. 2015, Behrend et al. 2018). Dividing the daily food intake into multiple rations is recommended (Behrend et al. 2018), although ad libitum feeding is also acceptable (Zoran et al. 2013). Feeding canned food instead of dry food is recommended because of the lower caloric density and ease of portion control (Behrend et al. 2018).

2.4.3 Quality of life

Feline diabetes mellitus can be successfully managed and cats may even achieve remission, but the impact of the daily treatment regimen on the quality of life of both the owner and the cat is an issue to be acknowledged. This has been evaluated by Niessen et al. (2010) in a questionnaire study of 221 diabetic cat owners. Factors which owners identified as affecting the quality of life most negatively are presented in table 2 (Niessen et al. 2010). Over 94% of owners evaluated their cat’s quality of life to be at least “as good as it could possibly be”, but 69% felt the disease had a negative impact on the overall quality of the cat’s life.
Table 2. Factors affecting quality of life of diabetic cats and their owners (Niessen et al. 2010).

- Boarding difficulties
- The owner wanting more control over diabetes mellitus
- Difficulties leaving cat with friends/family
- Worry about the disease
- Worry about hypoglycemia
- Adapting social life around regular treatment
- Costs relating to the disease
- Adapting work life around regular treatment

2.4.4 Prognosis

Cats with newly diagnosed diabetes mellitus have been found to have a fair to good prognosis in a retrospective case series (Callegari et al. 2013). The median survival time of diabetic cats varied in different studies from 13 months (Little et al. 2008) to 18 months (Callegari et al. 2013) and 25 months (Goossens et al. 1998). It should be noted that these retrospective studies often had missing data, such as the type of insulin used, that could affect the survival times. Some owners opted for euthanasia at diagnosis which might have skewed the results of retrospective studies.

High serum creatinine levels have been associated with a poor outcome of treatment, leading to death by natural means or euthanasia (Callagari et al. 2013). Sex, breed, body weight or type of insulin used were not associated with a poor outcome in this study. Diabetic cats were found to be more likely to have some form of cardiac disease in a study by Little et al. (2008). Even though the sample size of 19 cats was small, the findings of the study suggest that diabetes mellitus on its own does not cause cardiac disease but may promote or aggravate an existing heart condition.
2.5 Remission

Diabetic remission is defined as persistent euglycemia together with the disappearance of clinical signs of diabetes mellitus for over four weeks without exogenous insulin therapy (Zini et al. 2010, Tschuor et al. 2011, Gottlieb et al. 2014). Remission is thought to occur when glucotoxicity has been reversed with exogenous insulin and pancreatic beta cells have recovered enough to secrete adequate amounts of insulin (Sieber-Ruckstuhl et al. 2008, Zini et al. 2009, Rand and Gottlieb 2017).

Remission rates of 35% (Nack and DeClue 2014), 39.5% (Callagari et al. 2013), 50% (Zini et al. 2010) and 84% (Roomp and Rand 2009) have been reported. The median duration of insulin treatment prior to remission in studies ranged from 84 days (Nack and DeClue 2014) to 114 days (Callagari et al. 2013). Remission has been reported even after years of treatment with another type of insulin when switched to glargine insulin (Roomp and Rand 2009). It should be noted that multiple protocols can lead to remission and not one factor can be singled out to predict remission (Gostelow et al. 2014).

Fast glycemic control following diagnosis has been associated with a higher probability of diabetic remission (Marshall et al. 2009, Roomp and Rand 2009). Regardless of insulin type, low average glucose concentrations soon after beginning treatment might be a good prognostic sign for remission (Marshall et al. 2009, Zini et al. 2010, Tschuor et al. 2011). Using a tight glycemic control protocol aiming at euglycemia has been shown to increase remission rates without an observable increase in episodes of hypoglycemia (Roomp and Rand 2009, Roomp and Rand 2012, Nack and DeClue 2014, Hoelmkjaer et al. 2015). Cats on a tight glycemic control protocol were five times as likely to go into remission when compared to cats on less intense monitoring of blood glucose levels (Nack and DeClue 2014).

Cats with diabetes mellitus induced by treatment with glucocorticoids were more likely to achieve remission after stopping steroid treatment than cats with diabetes mellitus of other pathophysiological backgrounds (Roomp and Rand 2009). Remission is possible also for cats presenting with diabetic ketoacidosis (Sieber-Ruckstuhl et al. 2008). It should be noted that almost half of the cats with diabetic ketoacidosis that achieved remission in this study had had diabetes mellitus induced by glucocorticoid treatment and remission occurred after steroid treatment was withdrawn.
Increasing age has been associated with achieving remission (Zini et al. 2010). 70% of cats over the age of 12 achieved remission in this study, whereas the percentage for cats under the age of nine was only 35%. However, age was not associated with the probability of remission in another study by Nack and DeClue (2014).

Plantigrade stance or other signs of peripheral neuropathy at diagnosis have been associated with a less likely chance of remission (Roomp and Rand 2009). Obesity at diagnosis was not a negative prognostic factor for remission (Roomp and Rand 2009, Zini et al. 2010). Increased levels of cholesterol have been associated with a decreased chance of remission (Zini et al. 2010).

Blood glucose concentrations of previously diabetic cats in remission should be monitored regularly (Gottlieb et al. 2015), as an estimated 30-40% relapse and require further insulin therapy later on (Roomp and Rand 2009, Zini et al. 2010, Gottlieb et al. 2015). The duration of remission has varied from months to years (Zini et al. 2010). The period of remission has been reported to be longer with higher body weights and shorter with higher blood glucose concentrations (Zini et al. 2010). Monitoring blood glucose levels 1-2 months after going into remission and annually from then onwards is recommended (Gottlieb et al. 2015). Cats with fasting glucose concentrations of >7.5 mmol/l have been associated with significantly higher chances of relapsing when compared to cats with lower fasting glucose concentrations (Gottlieb et al. 2015).

2.6 Complications

Complications related to feline diabetes mellitus arise from the blood glucose concentration being too low (hypoglycemia) or too high (hyperglycemia). Issues with hypoglycemia happen much faster than those with hyperglycemia (Rand and Gottlieb 2017). Hypoglycemia occurs due to an overdose of insulin. This may happen when too much insulin is administered accidentally or if exogenous insulin is administered during remission, when the pancreatic beta cells have already recovered enough to start secreting endogenous insulin (Rand and Gottlieb 2017). Hyperglycemia occurs when there is a problem with the injection of insulin, the insulin does not function properly, the insulin dosage is not sufficient or something interferes with insulin function in the body (O’Brien 2017).
2.6.1 Hypoglycemia

Hypoglycemia can be biochemical and asymptomatic or clinical (Rand and Gottlieb 2017). Biochemical asymptomatic hypoglycemia has been more common than clinical hypoglycemia in studies (Nelson et al. 2009, Roomp and Rand 2009). A cut-off value of 2.8-3.0 mmol/l has been used to indicate biochemical hypoglycemia, measured with a blood glucose meter for humans (Sparkes et al. 2015, Rand and Gottlieb 2017). Portable blood glucose meters calibrated for humans often show lower blood glucose values for cats than glucose values obtained by hexokinase or glucose oxidation methods. Use of veterinary portable blood glucose meters is recommended (Mori et al. 2017). Healthy cats fasted overnight have had blood glucose concentrations of around 2.8 mmol/l measured with a blood glucose meter for felines (Gottlieb et al. 2015).

The brain cannot store or synthesize glucose and relies on a continuous supply of glucose transported by blood (Loose et al. 2008). Clinical signs of hypoglycemia are variable and include lethargy, ataxia, vomiting and tremors (Sparkes et al. 2015, Rand and Gottlieb 2017). As plasma glucose levels decrease, seizure activity, brain damage, coma and eventually death can occur (Loose et al. 2008, Rand and Gottlieb 2017).

Rapid treatment of hypoglycemia is required. If clinical signs are mild, feeding a meal high in carbohydrates is suggested. Insulin therapy should be stopped and reinstated when hyperglycemia happens (Rand and Gottlieb 2017). Subsequent insulin doses should be decreased (Behrend et al. 2018). In more severe cases, honey or glucose syrup can be applied to mucous membranes before transport to the veterinarian (Sparkes et al. 2015). Care should be taken to avoid aspiration. Severe hypoglycemia requires treatment in-hospital with parenteral glucose (Rand and Gottlieb 2017).

2.6.2 Diabetic ketoacidosis

Diabetic ketoacidosis is characterized by hyperglycemia, glycosuria, ketonemia or ketonuria with high anion gap metabolic acidosis (O’Brien 2017). Ketonemia develops when, despite high blood glucose concentrations, glucose cannot enter cells because of the lack of insulin (O’Brien 2017). In turn, cells start using free fatty acids for energy (O’Brien 2017). Free fatty acids are converted by hepatocytes into triglycerides and ketones (O’Brien 2017).
Presence of concurrent diseases is thought to contribute to the development of diabetic ketoacidosis through increased levels of cortisol and adrenaline (Cooper et al. 2015, O’Brien 2017). These counter regulatory hormones promote lipolysis and ketone formation (O’Brien 2017). Acute pancreatitis (Sieber-Ruckstuhl et al. 2008, Cooper et al. 2015), chronic manifestations of pancreatic disease (Sieber-Ruckstuhl et al. 2008), and young age (Cooper et al. 2015) have been associated with diabetic ketoacidosis. The Siamese breed has been associated with a higher risk for the development of diabetic ketoacidosis (Cooper et al. 2015).

Prognosis for diabetic ketoacidosis is considered poor. However, once recovered from diabetic ketoacidosis, the condition was not associated with a decreased survival time in one study, where 32% of cats that recovered from diabetic ketoacidosis survived for over three years (Callagari et al. 2013). Survival rates for diabetic ketoacidosis range around 60-70% with in-hospital treatment (Cooper et al. 2015, Gallagher et al. 2015). It should be noted that some owners opted for euthanasia instead of treatment at diagnosis which may have skewed the results. Remission from diabetes mellitus is possible for cats that have been treated for diabetic ketoacidosis (Sieber-Ruckstuhl et al. 2008). Poor outcome for diabetic ketoacidosis has been associated with increased serum creatinine, total magnesium and blood urea nitrogen concentrations in a study by Cooper et al. (2015), suggesting that concomitant renal dysfunction is a negative prognostic factor. High total bilirubin concentration was also associated with death (Cooper et al. 2015).

Treatment of diabetic ketoacidosis aims at restoring intravascular blood volume and correcting dehydration, electrolyte and acid-base imbalances, decreasing blood glucose levels, eliminating ketones, and treating underlying illnesses (O’Brien 2010, O’Brien 2017). Treatment protocol often consists of fluid therapy for four to eight hours to correct hypovolemia before instituting short-acting insulin therapy (O’Brien 2017). A constant rate infusion of regular insulin is the current recommendation for insulin treatment (O’Brien 2017). Potassium, phosphate, magnesium and sometimes sodium bicarbonate are used to correct electrolyte and acid-base imbalances (O’Brien 2017).

It is suspected that the severe dehydration associated with diabetic ketoacidosis leads to decreased insulin absorption if administered subcutaneously, although the pharmacodynamics or pharmacokinetics of this administration route have not been studied in cats (Marshall et al. 2013). Intramuscular and subcutaneous administration of glargine insulin in the treatment of
diabetic ketoacidosis has been studied (Marshall et al. 2013, Gallagher et al. 2015). In a retrospective case series by Marshall et al. (2013), diabetic ketoacidosis of all 15 cats in the study resolved with intramuscular glargine alone or combined with subcutaneous glargine treatment. Of these cats 33% achieved remission, but it should be noted that two out of the five cats achieving remission had diabetes mellitus induced by glucocorticoid treatment and remission occurred after steroid treatment was withdrawn (Marshall et al. 2013). Cats on a protocol of subcutaneous glargine combined with intramuscular regular insulin had shorter hospitalization periods than cats on a low-dose regular insulin protocol (Gallagher et al. 2015). Survival rate did not differ between the two groups, but the sample size in this study was small, comprising of eight animals in each group.

2.6.3. Neurological and ophthalmic complications

Chronic hyperglycemia may lead to other complications besides diabetic ketoacidosis. Hyperglycemia causes changes in nerve function and structure, resulting in neurological signs ranging from difficulties in jumping to a plantigrade stance, which is often the most notable neurological deficit (Mizisin et al. 2002). Irritability when touching the feet, muscle atrophy in hind limbs and a base-narrow gait were often observed (Mizisin et al. 2002, Mizisin et al. 2007). Pelvic limbs are most commonly affected, but neurological signs can progress to thoracic limbs (Mizisin et al. 2002). Conduction velocity in motor nerves and peripheral sensory nerves was decreased in diabetic cats compared to nondiabetic cats (Mizisin et al. 2002). Histologically, Schwann cell injury leading to demyelination has been detected (Mizisin et al. 2002, Mizisin et al. 2007). Axonal injury has also been described (Mizisin et al. 2007). Electrophysiologic abnormalities and severity of neurological deficits were related to high blood glucose levels (Mizisin et al. 2002). The pathogenesis behind diabetic neuropathy is not fully understood and is likely to be multifactorial (Reusch 2015). Good glycemic control may alleviate signs in some cats (Reusch 2015).

Cataract development is an ophthalmic complication of diabetes mellitus, which is most likely related to an increased activity of the enzyme aldose reductase in the lens when hyperglycemia is present (Richter et al. 2002). This leads to sorbitol accumulation and swelling of the lens fibers. Diabetic cats had significantly more cataracts than healthy cats in a study by Williams and Heath (2006). Some degree of lens opacification was observed in 96% of the diabetic cats in this study, although none of the cats were fully blind (Williams and Heath 2006). This is in
contrast to diabetic cataracts in the dog, where lens opacification is more severe and of higher clinical relevance. Interestingly, aldose reductase activity has been shown to be significantly lower in lenses of older cats, which might prevent cataract formation in diabetic cats (Richter et al. 2002).
3 MATERIALS AND METHODS

3.1 Case selection

Medical records of all diabetic cats presented to the University of Helsinki Small Animal Teaching Hospital and the Saari Small Animal Clinic between March 2006 and March 2016 were reviewed. The university’s veterinary patient database (ProvetNet, Finnish Net Solutions) was used to find cats with a mention of diabetes mellitus in the diagnosis or summary part.

Cats were included in the study if they had at least one visit at either of the clinics related to the diagnosis and treatment of diabetes mellitus. Hyperglycemia, glycosuria and typical clinical signs were required for diagnosis of diabetes mellitus. Patients referred to the University Small Animal Teaching Hospital that already had a confirmed diagnosis of diabetes mellitus were also included in the dataset. Data was gathered for both cats that were alive and deceased at the time of the data collection. Cats were excluded from the study if the owner had chosen euthanasia over treatment at diagnosis or diabetes mellitus was not confirmed with blood and urine testing. Remission, the length of remission and possible relapse were based on the assessment of the treating veterinarian.

3.2 Medical records review

Data gathered for cats meeting the inclusion criteria are listed in table 3. All data was gathered in a spreadsheet application (Microsoft Excel, Microsoft Corporation).
Table 3. Data recorded for cats with diabetes mellitus presented to the Small Animal Teaching Hospital and the Saari Small Animal Clinic, University of Helsinki, between March 2006 and March 2016.

- Age, gender, neuter status, breed, weight and body condition score on a 5-point scale, where a BCS of 2.5 to 3.5 is considered optimal
- Treatment with glucocorticoids prior to diagnosis
- Insulin type and possible changes in doses and type of insulin used
- Blood glucose levels and fructosamine concentrations
- Remission including length and possible relapse
- Concurrent diseases such as pancreatitis and chronic kidney disease
- Complications relating to diabetes mellitus, such as diabetic ketoacidosis, clinical hypoglycemic episodes requiring hospitalization and diabetic neuropathies
  Different incidents of the same complication were listed only once for each cat
- Date of death and reason for euthanasia

### 3.3 Statistical analysis

Statistical analyses were performed using GraphPad Prism version 8.00 for Mac OS X (GraphPad Software, La Jolla California, USA). The Shapiro-Wilk test was used to determine whether the results were normally distributed. Fisher's exact test was used to assess for independence between body condition score and stable disease requiring exogenous insulin as well as body condition score and remission of diabetes mellitus. Odds ratio (OR), risk ratio (RR) and 95% confidence interval (CI) levels were calculated for different genders and breeds. These were calculated only for breeds with over four individuals to reduce the effect of coincidence. The significance threshold was set at p < 0.05.
4 RESULTS

4.1 Descriptive data

4.1.1 Prevalence

Between March 2006 and March 2016, 18,292 cats were presented to the University of Helsinki Small Animal Teaching Hospital and the Saari Small Animal Clinic. A mention of diabetes mellitus in the diagnosis or summary was recorded in the data of 154 cats. After exclusion, a total of 123 cats were included in the retrospective study. The prevalence for diabetes mellitus in this feline population was 0.7%.

4.1.2 Age

Age was not recorded for nine cats. Age of cats with diabetes mellitus in this study ranged from 4 to 19 years. Age was not normally distributed. Age at diagnosis was not recorded for an additional 13 cats that were diagnosed elsewhere. The median age at diagnosis for the 101 cats with a full dataset was 11 years. Age at diagnosis of diabetes mellitus ranged from 4 to 19 years.

4.1.3 Concurrent diseases

Concurrent diseases occurred in 58/123 cats (47.2%) and are listed in table 4. In addition, there was one strong suspicion of hypersomatotropism in one other cat, but this was not confirmed.
Table 4. Concurrent diseases reported in cats with diabetes mellitus presented to the Small Animal Teaching Hospital and the Saari Small Animal Clinic, University of Helsinki, between March 2006 and March 2016.

<table>
<thead>
<tr>
<th>Concurrent disease</th>
<th>n</th>
<th>% of all 123 diabetic cats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis</td>
<td>17</td>
<td>13.8</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>12</td>
<td>9.8</td>
</tr>
<tr>
<td>Cholangiohepatitis</td>
<td>5</td>
<td>4.1</td>
</tr>
<tr>
<td>Tumor</td>
<td>5</td>
<td>4.1</td>
</tr>
<tr>
<td>Hepatic lipidosis</td>
<td>4</td>
<td>3.0</td>
</tr>
<tr>
<td>Asthma</td>
<td>3</td>
<td>2.4</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>3</td>
<td>2.4</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>2</td>
<td>1.6</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Allergic dermatitis</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Eosinophilic syndrome</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Hyperadrenocorticism</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Keratoconjunctivitis sicca</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Primary bone marrow change</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Pyometra</td>
<td>1</td>
<td>0.8</td>
</tr>
</tbody>
</table>

4.2 Risk factors for development of diabetes mellitus
4.2.1 Gender

Gender was not recorded for one cat (0.8%). Gender analysis of all diabetic cats revealed that 86/123 cats (69.9%) were male with 84/86 cats (97.7%) neutered and 2/86 cats (2.3%) intact. Of all diabetic cats 36/123 animals (29.2%) were female, with 34/36 cats (94.5%) neutered and 2/36 cats (5.6%) intact. Altogether for cats with recorded gender status, 118/122 cats (96.7%) were neutered and 4/122 (3.3%) intact. In contrast, of all cats presented to the hospital during the study period 9,868/18,292 animals (53.9%) were male with 7,968/9,868 cats (80.8%) neutered and 1,900/9,868 cats (19.3%) intact. Of all cats 8,424/18,292 animals (46.1%) were female with 5,945/8,424 cats (70.6%) neutered and 2,479/8,424 cats (29.4%) intact.

Statistical analysis for neutered males and females is presented in table 5. Statistical analysis includes data for all cats presented to the Small Animal Teaching Hospital during this time period. In summary, the gender analysis revealed that neutered male cats had 2.8 times the risk
of developing diabetes mellitus when compared to intact males and females and neutered females (RR 2.79 [CI 95% RR 1.91-4.08]; p <0.001).

Table 5. Gender distribution of cats with diabetes mellitus and the prevalence of the disease in the stated gender displayed in percentages of all cats and of all cats of the same gender presented to the Small Animal Teaching Hospital and the Saari Small Animal Clinic, University of Helsinki, between March 2006 and March 2016, odds ratio and relative risk for development of diabetes mellitus including confidence intervals

<table>
<thead>
<tr>
<th>Gender of diabetic cats</th>
<th>n</th>
<th>% of all cats</th>
<th>% of intact/neutered cats</th>
<th>OR</th>
<th>OR 95% confidence interval</th>
<th>p value</th>
<th>RR</th>
<th>RR 95% confidence interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>2</td>
<td>0.01</td>
<td>0.11</td>
<td>0.14</td>
<td>0.04-0.57</td>
<td>0.006</td>
<td>0.14</td>
<td>0.04-0.58</td>
<td>0.006</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>0.01</td>
<td>0.08</td>
<td>0.10</td>
<td>0.03-0.42</td>
<td>0.002</td>
<td>0.11</td>
<td>0.03-0.43</td>
<td>0.002</td>
</tr>
<tr>
<td>Male</td>
<td>84</td>
<td>0.46</td>
<td>1.05</td>
<td>2.81</td>
<td>1.92-4.11</td>
<td>&lt;0.001</td>
<td>2.79</td>
<td>1.91-4.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>34</td>
<td>0.19</td>
<td>0.57</td>
<td>0.79</td>
<td>0.53-1.18</td>
<td>0.25</td>
<td>0.79</td>
<td>0.54-1.18</td>
<td>0.25</td>
</tr>
</tbody>
</table>

4.2.2 Breed

Several different breeds are represented in the study population. Of the study population, 108/123 cats (87.8%) were crossbred domestic shorthairs and 15/123 cats (12.2%) were purebred. Of the 15 purebred cats four (3.3%) were Norwegian forest cats and one (0.8%) of each of the following breeds: Burmese, Devon Rex, European, Maine Coon, Ocicat, Oriental shorthair, Ragdoll, Sacred Birma and Siamese. For all cats presented to the hospital during this time period breed was recorded for 16,530 cats, of which 13,322/16,530 cats (80.6%) were domestic shorthairs and 329/16,530 cats (1.9%) were Norwegian forest cats.

Statistical analysis for different breeds is presented in table 6. Statistical analysis includes data for all cats presented to the Small Animal Teaching Hospital during this time period. In summary, the breed analysis revealed that crossbred domestic shorthair cats had a slightly higher risk of developing diabetes mellitus compared to other breeds (RR 1.73 [CI 95% RR 1.01-2.97]; P 0.05).
Table 6. Breed distribution of cats with diabetes mellitus and the prevalence of the disease in the stated breed displayed in percentages of all cats and of all cats of the same breed presented to the Small Animal Teaching Hospital and the Saari Small Animal Clinic, University of Helsinki, between March 2006 and March 2016, odds ratio and relative risk for development of diabetes mellitus including confidence intervals.

<table>
<thead>
<tr>
<th>Breed</th>
<th>n</th>
<th>% of all cats</th>
<th>% of cats of same breed</th>
<th>OR 95% confidence interval</th>
<th>p value</th>
<th>RR 95% confidence interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domestic shorthair</td>
<td>108</td>
<td>0.66</td>
<td>0.82</td>
<td>1.74</td>
<td>1.01-2.99</td>
<td>0.05</td>
<td>1.73</td>
</tr>
<tr>
<td>Norwegian Forest Cat</td>
<td>4</td>
<td>0.02</td>
<td>1.22</td>
<td>1.66</td>
<td>0.61-4.53</td>
<td>0.32</td>
<td>1.66</td>
</tr>
</tbody>
</table>

### 4.3 Outcome

Of the cats in this study population, 59/123 (48.0%) were alive and 64/123 (52.0%) dead at the end of the study period. It should be noted that for some cats, monitoring and follow-up of the disease was done elsewhere and thus data on the survival or death of these individuals was not accessible through the veterinary patient database (ProvetNet) of the University Small Animal Teaching Hospital. Remission for a variable period of time was achieved in 11/123 (8.9%) cats. Of these cats four (36.4%) had stable remission without further relapse and seven (63.6%) relapsed, requiring treatment with exogenous insulin. Of the cats that relapsed, five were euthanized later on. Altogether stable disease with a need for exogenous insulin treatment occurred in 55/123 cats (44.7%) in this study population.

### 4.4 Factors possibly influencing treatment outcome

#### 4.4.1 Body condition

BCS was recorded for 53/123 cats with diabetes mellitus (43.0%) in this study. Data was not normally distributed. Median BCS was 4 on the 5-point scale. Based on BCS, 15/53 cats (28.3%) were underweight and 10/53 cats (18.9%) were of optimal weight. Over half (52.8%) were considered overweight or obese. An optimal BCS was not significantly associated with either stable disease requiring exogenous insulin (p = 0.63) or diabetic remission (p = 0.31).
BCS was recorded in the epicrisis of 310/18,292 (1.7%) of all cats presented to the Small Animal Teaching Hospital and Saari clinic during this time period. Median BCS for these cats was 3 on the 5-point scale. Based on BCS of all cats presented to the university during this time, 152/310 cats (49.0%) were underweight, 51/310 cats (16.5%) optimal weight and 107/310 cats (34.5%) overweight or obese. Body condition scores of all cats and cats with diabetes mellitus are presented in figure 1.

Figure 1. Body condition scores of all cats and of cats with diabetes mellitus presented to the Small Animal Teaching Hospital and the Saari Small Animal Clinic, University of Helsinki, between March 2006 and March 2016.
4.4.2 Treatment protocols

Glargine insulin treatment was performed in 67 / 123 cats (54.5%) in this study of which 9 / 67 cats (13.4%) achieved remission. Two of these nine cats (22.2%) relapsed. Lente insulin was initially used for 11 / 123 cats (8.9%), of which one cat (9.0%) achieved remission. NPH insulin was initially used for 14 / 123 cats (11.4%), of which one cat first achieved remission and then relapsed.

Glargine was the most used insulin. Five cats initially treated with lente insulin and four initially treated with NPH insulin were switched to glargine insulin. Altogether 78 / 123 cats (63.4%) were treated with glargine insulin at some point. No treatment for diabetes mellitus was instituted for 16 / 123 cats (13.0%). Treatment type was not specified for 2 / 123 cats (1.6%).

Oral hypoglycemic drugs glyburide and glipizide were used for 3 / 123 cats (2.4%). Response to treatment was poor. Two cats were switched to glargine insulin and one was euthanized because of the owner’s reluctance to injecting insulin.

4.4.3 Glucocorticoid treatment prior to diagnosis of diabetes mellitus

Glucocorticoid treatment prior to the diagnosis of diabetes mellitus was given to 13 / 123 cats (10.6%) in this study population. Eight cats with prior glucocorticoid treatment had at least three visits to the hospital. Of these eight cats four (50.0%) achieved remission after insulin treatment was instituted and steroid treatment stopped. One cat that required continuous inhalant cortisone treatment for asthma relapsed and the other cats did not.

4.4.4 Complications of diabetes mellitus

Complications of diabetes mellitus occurred in 85 / 123 cats (69.1%). Of all diabetic cats, 8 / 123 (6.5%) had diabetic neuropathy and 3 / 123 (2.4%) had diabetic cataracts. Diabetic ketoacidosis occurred at least once in 40 / 123 cats (35.5%) and hypoglycemic episodes requiring hospitalization in 22 / 123 cats (17.9%). Diabetic ketoacidosis led to death by either euthanasia or natural means in 21 / 40 of the cases (52.5%) and hypoglycemia in 7 / 21 of the cases (33.3%).
5 DISCUSSION

5.1 Descriptive data

5.1.1 Prevalence

The prevalence of diabetes mellitus in this feline population of a Finnish referral hospital was 0.7%. This is in line with results from previous studies, where prevalence ranged from 0.25% to 1.24% (McCann et al. 2007, Prahl et al. 2007). The sample size in this study was small with 123 cats and thus the result is not directly comparable to the prevalence of feline diabetes mellitus in the aforementioned studies, where large national veterinary medical databases of first-opinion clinics provided sample sizes of 14,030 and 618,814 cats, respectively.

5.1.2 Age

The median age at diagnosis in this study was 11 years and the range 4-19 years. This is similar to previously reported peak median ages at diagnosis of 11-13 years (Öhlund et al. 2015, O’Neill et al. 2016). Association between age and diabetes mellitus could not be measured by calculating OR and RR, because comparisons between the ages of cats with diabetes mellitus and all 18,292 cats presented to the University of Helsinki Small Animal Teaching Hospital and the Saari Small Animal Clinic could not be made. The age of a given cat is shown at the time of viewing the data, not at time of diagnosis in the veterinary patient database (ProvetNet).

5.1.3 Concurrent diseases

The Small Animal Teaching Hospital’s status as a referral hospital is likely to increase the number of patients with multiple chronic illnesses. Evaluation of concurrent diseases should take into account the fact that many of the diseases were anecdotal evidence from the referring vet and information on for example feline pancreatic lipase values was often not available in the database. Interestingly 2.4% of cats in this study had hypertrophic cardiomyopathy which has been found to be common in diabetic cats (Little et al. 2008). Information on the prevalence of hypertrophic cardiomyopathy in the whole cat population presented to the Small Animal Teaching Hospital during this time period is not available. Asthma, eosinophilic syndrome and allergic dermatitis were seen in cats treated with glucocorticoids prior to development of diabetes mellitus.
The prevalence of hypersomatotropism in this study was 0.8%. This is considerably less than in studies where hypersomatotropism was screened for, with reported prevalences of 26% (Niessen et al. 2015) to 32% (Niessen et al. 2007b). Screening for hypersomatotropism when response to treatment was poor or the insulin dosages high was not routinely performed in this study population. The prevalence of hypersomatotropism and other complicating factors relating to diabetes mellitus might be greater in this study population because of the Small Animal Teaching Hospital’s status as a referral clinic. This might result in the referral of cats with very poor glycemic control and not reflect the prevalence of the more classic type II diabetes mellitus resulting from pancreatic beta cell destruction. Differentiating between hypersomatotropic and true type II diabetic cats is crucial when analyzing the response to treatment and probability of remission. This should be taken into account in the inclusion criteria of diabetic cats in prospective studies as well.

5.2 Risk factors for development of diabetes mellitus

5.2.1 Gender

In this population neutered male cats had 2.8 times the risk of developing diabetes mellitus when compared to neutered females and intact males and females. Neutered males have been reported to be more at risk for diabetes mellitus than other genders (McCann et al. 2007), although in some studies neither neutering nor gender has been significantly associated with disease (Prahl et al. 2007, O’Neill et al. 2016). The 95% confidence interval for neutered females included the null value and the results were not significant.

Neutering has been shown to increase food intake in both male and female cats (Cave et al. 2007a, Cave et al. 2007b) which results in a higher BCS (Alexander et al. 2011). Insulin sensitivity in cats with a high BCS has been shown to be much lower than in lean cats (Appleton et al. 2001), which predisposes these cats to developing diabetes mellitus. It should be noted that the vast majority of both cats with and without diabetes mellitus in this study population were neutered and thus the sample size of intact animals was very small, with just two intact males and females with diabetes mellitus. This affects study power and could lead to failure in detecting significant differences between the groups.
5.2.2 Breed

Domestic shorthair cats had 1.7 times the risk of developing diabetes mellitus when compared to other breeds in this population. Domestic shorthair cats have been reported to have a higher risk of developing diabetes mellitus when compared to purebred cats (Öhlund et al. 2015). The Norwegian Forest Cat has previously been identified as a high-risk breed for developing diabetes mellitus (Öhlund et al. 2015). In our small sample size of four Norwegian Forest Cats the 95% confidence interval included the null value and the results were not significant. Although the study population included cats of multiple breeds, the number of cats in all breeds apart from domestic shorthairs and Norwegian Forest cats was very low with only one cat per breed, which could skew the results. A larger sample size with more individuals per breed could yield different results.

5.3 Outcome

Comparisons between the prognosis of cats with diabetes mellitus in this study population and reported values in literature cannot be made, as median survival times were not determined in this study population. Survival times could be reliably determined retrospectively only for the cats that were monitored after diagnosis or treatment at the Small Animal Teaching Hospital or the Saari Clinic. Datasets for the cats included in this study population were too fragmented for reliable data analysis.

5.4 Factors possibly influencing treatment outcome

5.4.1 Body condition

No association between an optimal BCS and stable disease requiring administration of exogenous insulin was seen in this study population (p = 0.63). There is no objective definition of what amount of body fat is considered excessive in cats, which makes the analysis of results and drawing conclusions from literature difficult. The optimal BCS is considered to be between 2.5 and 3.5 on the 5-point scale, which corresponds to a BCS between 4 and 6 on the 9-point scale (Toll et al. 2010). The 5-point system is currently used at the Small Animal Teaching Hospital. Excess weight, defined as a BCS of over 6 on the 9-point scale, corresponding to over 3.5 on the 5-point scale, has been associated with multiple different health conditions (Teng et al. 2018). These health conditions in turn may contribute to the development of diabetic ketoacidosis in cats with diabetes mellitus (Cooper et al. 2015, O’Brien 2017). Diabetic
ketoacidosis has a relatively poor prognosis, with survival rates around 60-70% with intensive treatment (Cooper et al. 2015, Gallagher et al. 2015).

BCS was not associated with diabetic remission in this population of cats with diabetes mellitus (p = 0.31), which is in line with results from studies by Roomp and Rand (2009) and Zini et al. (2010).

Fisher’s exact test was chosen to test statistical significance because of the small sample size of 53 cats with recorded body condition scores. A statistically significant difference between BCS and stable disease or BCS and diabetic remission could perhaps be seen with a larger sample size. Formatting the study design and hypothesis differently could have been more informative. Investigation of the association between a high BCS of over 3 on the 5-point scale with a poor outcome might have yielded different results.

Body condition scores of the diabetic cat population are not directly comparable with the body condition scores of all cats presented to the University during the study period. Association between BCS and diabetes mellitus could not be measured by calculating OR and RR because of the incomplete recording of BCS in both the study population and all cats presented to the Small Animal Teaching Hospital during the study period. The BCS can be recorded in multiple different locations of the veterinary patient database (ProvetNet), which might lead to an incomplete data set when all BCS quotes are not found during data review. Reliable results for BCS of all cats presented to the University were obtained in this study only by searching for the mention of the BCS in the epicrisis of the patient. It is possible that BCS is mentioned here more often when it is far from optimal. This is likely to account for the apparent lack of cats with optimal body condition scores in the whole population.

5.4.2 Treatment protocols

Insulin treatments protocols used at the Small Animal Teaching Hospital are in line with the current ISFM and AAHA recommendations (Sparkes et al. 2015, Behrend et al. 2018). In this study population glargine was most used and oral hypoglycemics were rarely administered.

Remission rate for cats treated with glargine insulin in this study population was 13.4%, which is much lower than reported remission rates of 35% (Nack and DeClue 2014) to 84% (Roomp
and Rand 2009). This might be due to different glycemic control protocols. In most cases in this study population there was no mention of how the diabetic cat was monitored at home. Home monitoring of blood glucose levels has significant effect on whether the cat has a chance of going into remission and this should be taken into account when evaluating the probability of remission with different insulin types.

The Small Animal Teaching Hospital is a referral hospital and the prevalence of complicating factors relating to diabetes mellitus might be greater in this study population than in a first-opinion practice. This could have an effect on the remission rates as well. The amount of time passed since the initial diagnosis of diabetes mellitus also has an effect on whether remission is even considered a treatment goal (Behrend et al. 2018). This should also be taken into account when interpreting results regarding remission.

5.4.3 Glucocorticoid treatment prior to diagnosis of diabetes mellitus

In this population, 10.6% of cats had a history of glucocorticoid treatment prior to the development of diabetes mellitus, which corresponds to a reported value of 7.5% in a UK population (McCann et al. 2007). 50.0% cats treated with glucocorticoids prior to diagnosis of diabetes mellitus in this study population achieved remission after insulin treatment was started and glucocorticoid treatment stopped. It should be noted that that the number of cats with prior glucocorticoid treatment in this study was only 13, so no significant conclusions can be drawn from these results. This is however in line with previous evidence that cats with diabetes mellitus induced by treatment with glucocorticoids were more likely to achieve remission after stopping steroid treatment than cats with diabetes mellitus of other pathophysiological backgrounds (Roomp and Rand 2009).

Glucocorticoids stimulate gluconeogenesis, promote lipolysis and stimulate amino acid mobilization from tissues (Davison 2017). The reversal of the resulting rise in blood glucose concentrations requires pancreatic beta cells to secrete more insulin, which is not possible in pre-diabetic or diabetic cats (Davison 2017). The amount of insulin secreted may be enough to maintain euglycemia when glucocorticoid treatment is stopped and administration of exogenous insulin reverses the effects of glucotoxicity.
5.4.4 Complications of diabetes mellitus

The vast majority, over two thirds (69.1%), of cats in this study population had at least one complication arising from diabetes mellitus. This may be seen as a depiction of difficulty managing the disease or failure to properly monitor glycemic control at home. Diabetic ketoacidosis was common in our study population, with 35.5% of cats suffering from it at one time or another. The Small Animal Teaching Hospital receives many referral patients in need of intensive care from all around the country. This is likely to have an effect on the prevalence of both diabetic ketoacidosis and hypoglycemia that require hospitalization. Reported survival rates for diabetic ketoacidosis of 60-70% (Cooper et al. 2015, Gallagher et al. 2015) are somewhat higher than in this population, where the survival rate was 47.5%. It should be noted that this is confounded by the fact that some cats had multiple episodes of diabetic ketoacidosis of which only the final one resulted in death.

5.5 Limitations of the study

There are multiple limitations in this retrospective study. The patient records have been documented by several people and include incomplete and inconsistent records. The relatively small sample size of 123 animals should be taken into consideration when interpreting the results.

The lack of recording body condition scores made assessing the relationship between obesity and outcome of diabetes mellitus difficult. BCS was recorded for only 43.0% of diabetic cats in this study. Optimal weights for different cat breeds and individuals vary, which makes the use of BCS necessary for individual monitoring purposes as well as retrospective studies. A qualitative description of obesity is much more subjective and not nearly as useful in monitoring the cat’s weight long-term. The World Small Animal Veterinary Association (WSAVA) nutritional assessment guidelines list nutritional assessment as the fifth vital sign of the standard physical examination (Freeman et al. 2011). Measures should be taken to make sure that the evaluation and recording of BCS during physical examination is a convenient routine. Currently the veterinary patient database (ProvetNet) in use has a distinct place for the recording of BCS, but this is located inconveniently apart from the other vital signs in the status page and is often forgotten to be filled. A separate place for the recording of BCS next to the animal’s weight on the front page of the database could be useful.
Recording BCS is a great aid in monitoring the patient and should be done at every visit. This is especially true for cats with diseases such as diabetes mellitus that require constant monitoring and where fluctuation in BCS may be directly related to the control (or lack thereof) of the disease. Keeping in mind that owners often underestimate the obesity of their cat (Courcier et al. 2012), teaching the owner to properly evaluate the body condition score at home in addition to weighing the cat might be very beneficial in regard to monitoring the disease.

A 5-point system is used at the University of Helsinki Small Animal Teaching Hospital to assess BCS. Half points are not recommended to be used and thus the number is rounded up or down if necessary, meaning that only a BCS of 3 out of 5 is considered optimal (Toll et al. 2010). A 9-point system might be more descriptive, as a BCS between 4 and 6 is considered optimal (Toll et al. 2010). Including the classification of obese cats into subdivisions as suggested by Toll et al. (2010) could be advantageous in monitoring an obese cat’s weight fluctuations.

Classifying domestic shorthair cats into overweight and underweight individuals by dividing the study population into genders and then subdividing these into quartiles as described by Rolph et al. (2014) was attempted. The top quartile and much of the third quartile could be considered overweight or obese and 5-10% of the lightest cats in both groups underweight (Rolph et al. 2014). However, this did not yield satisfactory results in our study because the amount of ketoacidotic and thus underweight cats was greater than 5-10%. This quartile method could work with a larger population of otherwise healthy animals to give an idea of the optimal weight for a Finnish domestic shorthair cat. This estimate of optimal weight could then be utilized in situations where the body condition scores of the patients are missing.

In some cases, the owner chose euthanasia instead of continuing or possibly changing treatment protocol. The latter might have had significantly different results regarding for example remission. This creates a bias with respect to outcome of treatment.

5.6 Areas for further research

Further research into remission of feline diabetes mellitus is needed as this excludes the need for insulin or oral hypoglycemic therapy. This eliminates issues such as worry about hypoglycemia and difficulties adapting life around treatment that are of concern to the owner, thus improving the quality of life for both the cat and the owner (Niessen et al. 2010).
It would be interesting to find out how often and with which treatment protocols remission is achieved in a prospective study with a larger population of client-owned cats in Finland. Motivating owners of cats with recently diagnosed diabetes mellitus to commit to treatment and intensive monitoring would perhaps be easier with more evidence-based data on the possibility of remission.

The number of humans with type II diabetes mellitus requiring insulin treatment is expected to rise substantially and with just three manufacturers producing most of the drug, the sufficiency of insulin in the future is uncertain (Basu et al. 2019). More research into the use of alternative treatment options such as incretins in the treatment of feline diabetes mellitus is warranted to ensure that there are adequate amounts of insulin to treat humans. Furthermore, the importance of preventing and managing feline obesity cannot be emphasized enough when communicating with cat owners.
REFERENCES


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Appendix 1. Positive and negative prognostic factors in cats with diabetes mellitus for stable disease requiring insulin and for remission of diabetes mellitus, where exogenous insulin is not required.

<table>
<thead>
<tr>
<th>Positive prognostic factors</th>
<th>Negative prognostic factors</th>
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<tbody>
<tr>
<td><strong>Stable diabetes mellitus</strong></td>
<td><strong>Remission of diabetes mellitus</strong></td>
</tr>
<tr>
<td>- Insulin type: glargine (Roomp and Rand 2009), detemir (Roomp and Rand 2012), protamine zinc (Gustelow et al. 2018)</td>
<td>- Use of oral hypoglycemics (Sparkes et al. 2015, Rand and Gottlieb 2017, Behrend et al. 2018)</td>
</tr>
<tr>
<td>- Glargine insulin twice daily (Marshall et al. 2008a, Hall et al. 2009)</td>
<td>- High serum creatinine concentrations (Callegari et al. 2013)</td>
</tr>
<tr>
<td>- Low carbohydrate high protein diet (Hall et al. 2009)</td>
<td>- Hypersomatropism (Niessen et al. 2007b)</td>
</tr>
<tr>
<td>- Daily food intake in multiple ratios (Behrend et al. 2018)</td>
<td>- Hypercholesterolemia (Zini et al. 2010)</td>
</tr>
<tr>
<td>- Canned food (Behrend et al. 2018)</td>
<td>- Peripheral neuropathy (Roomp and Rand 2009)</td>
</tr>
<tr>
<td>- Starting treatment within 6 months of diagnosis (Roomp and Rand 2009, Roomp and Rand 2012)</td>
<td>- Hypersomatropism (Niessen et al. 2007b)</td>
</tr>
<tr>
<td>- Tight glycemic control protocol aiming for euglycemia (Roomp and Rand 2009, Roomp and Rand 2012, Nack and DeClue 2014, Hoelmkjaer et al. 2015)</td>
<td>- Fasting blood glucose concentration of &gt;7.5 mmol/l after achieving remission (Gottlieb et al. 2015)</td>
</tr>
<tr>
<td>- Increasing age (Zini et al. 2010)</td>
<td>- Higher bodyweight (Zini et al. 2010)</td>
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