### Update on insulin treatment of dogs and cats with non-complicated diabetes mellitus

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# Update on insulin treatment of dogs and cats with non-complicated diabetes mellitus

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# Σύγχρονες απόψεις για τη θεραπεία με ινσουλίνη σε σκύλους και γάτες με απλό σακχαρώδη διαβήτη

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**ABSTRACT.** Diabetes mellitus is a common endocrine disease of dogs and cats. Treatment is mainly based on insulin administration and dietary modifications. The aim of this review is to provide updated information on insulin treatment of dogs and cats with non-complicated diabetes mellitus. During the last years, there has been significant progress in the management of this disease, thanks to the use of long-acting insulin preparations that do not cause pronounced fluctuations of blood glucose concentrations (insulin glargin and detemir) and because of the widespread use of home glucose monitoring by the owners of diabetic pets. Home glucose monitoring is based on capillary blood sampling from the ear pinnae or the foot pad and measurement of blood glucose concentration with a portable blood glucose meter. This can be done periodically (e.g. every week) to replace the traditional in-clinic blood glucose curve; in this case, blood glucose concentration is measured just before the morning insulin administration and then every 1-2 hours until the next dose (usually for 12 hours). Furthermore, especially for the cat, home glucose monitoring can be performed 3-5 times per day, on a daily basis, in order to safely adjust insulin dose and achieve tight control of hyperglycemia (i.e. blood glucose concentration between 50 and 200 mg dl$^{-1}$ throughout the day). The combination of dietary management, of insulin glargine or detemir administration and of the tight control of hyperglycemia has substantially increased the proportion of cats that enter into temporal or permanent diabetic remission and can be further managed without insulin. Another important achievement is the use of continuous glucose monitoring systems to monitor interstitial fluid glucose concentrations. These devices can be used in the clinic and at home and they can measure glucose concentration every 5 minutes for up to 72 consecutive hours, thus facilitating optimal adjustment of insulin treatment.

*Keywords:* cat; detemir; diabetes mellitus; diabetic remission; dog; glargin; insulin

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**ΠΕΡΙΛΗΨΗ.** Ο σακχαρώδης διαβήτης είναι μια συχνή ενδοκρινοπάθεια στους σκύλους και τις γάτες και η θεραπευτική του αντιμετώπιση στηρίζεται κυρίως στη χορήγηση ινσουλίνης και τα διαιτητικά μέτρα. Σκοπός της ανασκόπησης αυτής είναι η ενημέρωση του κλινικού Κτηνιάτρου για τα σύγχρονα δεδομένα της θεραπείας με ινσουλίνη σε σκύλους και γάτες με απλό σακχαρώδη διαβήτη. Τα τελευταία χρόνια έχει αλλάξει σημαντικά η θεραπευτική προσέγγιση του νοσήματος, χάρη στη χρησιμοποίηση ινσουλινών με μεγάλη και σταθερή διάρκεια δράσης που δεν προκαλούν έντονη αυξομείωση της συγκέντρωσης της γλυκόζης στο αίμα (ινσουλίνη glargine και detemir) και στην ευρεία εφαρμογή της μέτρησης της συγκέντρωσης της γλυκόζης στο αίμα από τον ιδιοκτήτη του ζώου, στο σπίτι. Η τελευταία γίνεται με τη βοήθεια γλυκοζόμετρου, ύστερα από λήψη τριχοειδικού αίματος από το πτερύγιο του αυτιού ή το πελματικό φύμα. Οι μετρήσεις στο σπίτι πραγματοποιούνται περιοδικά (π.χ. σε εβδομαδιαία βάση), κάθε 1-2 ώρες για το μεσοδιάστημα μεταξύ δυο διαδοχικών χορηγήσεων ινσουλίνης (συνήθως 12 ώρες), αντικαθιστώντας έτσι την καμπύλη γλυκόζης που γινόταν στην κλινική. Επιπλέον, στις γάτες έχει προταθεί να γίνονται 3-5 φορές ημερησίως, σε καθημερινή βάση, προκειμένου να επιτευχθεί με ασφάλεια ο στενός έλεγχος της υπεργλυκαιμίας (μεταξύ 50 και 200 mg dl⁻¹ καθ' όλη τη διάρκεια της ημέρας) με συνεχείς τροποποιήσεις της δόσης της ινσουλίνης. Μάλιστα, με το συνδυασμό των διαιτητικών μέτρων, της χορήγησης ινσουλίνης glargine ή detemir και του στενού ελέγχου της υπεργλυκαιμίας έχει αυξηθεί σημαντικά ο αριθμός των γατών εκείνων όπου επιτυγχάνεται προσωρινή ή μόνιμη ύφεση του σακχαρώδη διαβήτη, γεγονός που επιτρέπει τη διακοπή της χορήγησης ινσουλίνης (παροδικός σακχαρώδης διαβήτης). Μια ακόμα ελπιδοφόρα εξέλιξη είναι η ολοένα και συχνότερη χρησιμοποίηση των συσκευών συνεχούς μέτρησης της συγκέντρωσης της γλυκόζης στον υποδόριο ιστό. Χάρη στις συσκευές αυτές, που μπορούν να χρησιμοποιηθούν τόσο στην κλινική όσο και στο σπίτι, υπάρχει η δυνατότητα να μετράται η συγκέντρωση της γλυκόζης κάθε 5 λεπτά για χρονικό διάστημα μέχρι και 72 συνεχόμενων ωρών, γεγονός που επιτρέπει την καλύτερη ρύθμιση της θεραπείας με ινσουλίνη.

*Λέξεις ευρετηρίασης:* γάτα, ινσουλίνη detemir, ινσουλίνη glargine, παροδικός σακχαρώδης διαβήτης, σκύλος

## INTRODUCTION

Diabetes mellitus (DM) is one of the most common endocrine diseases of dogs and cats. Canine DM is typically the result of decreased insulin secretion by pancreatic b-cells (type I DM) whereas feline DM is usually attributed to decreased insulin sensitivity (type II DM). Despite the different pathogenesis, initial treatment of both dogs and cats with non-complicated DM is mainly based on insulin administration along with dietary modification. The aims of the treatment are to: a) control the clinical manifestations of the disease, b) avoid complications of DM such as diabetic ketosis and acidosis, cataract formation (especially in dogs) and polyneuropathy (especially in cats), c) control blood glucose concentrations throughout the day, ideally below the renal threshold for glycosuria (i.e. 175-220 mg dl⁻¹ for dogs and 210-290 mg dl⁻¹ for cats), d) avoid treatment complications, especially hypoglycemia, e) improve the quality of life of the diabetic dog or cat and the owner, and f) achieve diabetic remission in cats (Martin and Rand, 2007a; Zerrenner et al., 2007; Marshall et al., 2009; Niessen et al., 2010, 2012; Smith et al., 2012; Caney, 2013).

The aim of this article is to review recent developments in insulin treatment of dogs and cats with non-complicated DM, including the use of new types of insulin (glargin and detemir), techniques to accurately administer low doses of undiluted insulin, schedules of blood glucose monitoring by the owner at home setting, continuous glucose monitoring systems and, finally, protocols to tightly control blood glucose concentrations with the aim of diabetic remission in cats.

## TYPES OF INSULIN FOR DOGS AND CATS WITH NON-COMPLICATED DIABETES MELLITUS

Insulin is a 51 amino acid protein with two chains: the A chain consists of 21 amino acids (A1 to A21) and the B chain of 30 amino acids (B1 to B30) (Zerrenner et

al., 2007). Differences in the biological effects among insulin preparations depend on the origin of insulin (recombinant human, porcine or bovine), addition of zinc or protamine [lente, neutral protamine Hagedorn (NPH) or isophane, protamine zinc insulin (PZI)] and changes of insulin's molecular structure (glargine, detemir) (Zerrenner et al., 2007; Mori et al., 2008; Fleeman et al., 2009; Clark et al., 2012).

Various types of **recombinant human insulin** are widely available and they differ from canine and from feline insulin by one and four amino acids, respectively (Zerrenner et al., 2007; Rios and Ward, 2008). **Porcine insulin** has exactly the same amino acid sequence with canine insulin but differs from feline insulin by three amino acids (Rios and Ward, 2008; Fleeman et al., 2009). The closest available insulin to that of cats is **bovine insulin** because it differs by only one amino acid; also bovine insulin has quite similar molecular structure with that of canine insulin with differences in two amino acids (Davison et al., 2008; Rios and Ward, 2008) (Table 1). Recombinant human, porcine and bovine insulins are effective in lowering blood glucose concentrations of diabetic dogs and cats. Therefore, the importance of insulin origin is related to the potential of anti-insulin antibodies production due to administration of a heterologous protein (Fleeman et al., 2009). A mixed bovine-porcine PZI and a bovine lente insulin may induce anti-insulin antibodies in dogs (Cook, 2007; Zerrenner et al., 2007; Davison et al., 2008) and such antibodies were detected more frequently in diabetic dogs treated with bovine PZI (85%) or bovine lente (56%) insulin compared to those treated with a porcine lente insulin (12%), whereas there was no difference between the latter and the control group that included both healthy dogs and non-diabetic sick dogs (Davison et al., 2008). On the other hand, a negative impact of anti-insulin antibodies on the glycemic control of dogs and cats with DM has not been proven so far (Davison et al., 2008). Therefore, the origin of insulin is not cur-

rently considered a decisive factor for selecting insulin for a diabetic pet.

**Insulin lente** contains zinc and consists of amorphous (30%) and of crystalline insulin (70%); currently there are is only one commercially available veterinary preparation (Caninsulin®, MSD) of porcine origin at a strength of 40 U ml$^{-1}$ (Davison et al., 2008; Caney, 2013). Another veterinary preparation of bovine origin (Insuvet® Lente, 100 U ml$^{-1}$, originally distributed by Schering-Plough and later by Pfizer Animal Health) is not available anymore and the same applies to most recombinant human insulin lente preparations (Zerrenner et al., 2007; Davison et al., 2008). At least in theory, two peaks in the action and thus in the glucose lowering effect are to be expected, one occurring soon after subcutaneous (SC) administration and attributed to the amorphous insulin part and the second occurring later due to the crystalline insulin part of insulin lente (Cook, 2007; Zerrenner et al., 2007; Fleeman et al., 2009). However, the pharmacokinetics and pharmacodynamics exhibit considerable between-patient as well as day-to-day variation (Fleeman et al., 2009). For example, in a group of eight dogs with stable DM, onset of action occurred 1.5-6h (average: 3h) after SC administration, time to nadir (lowest blood glucose concentration) ranged from 4 to 22h (average: 8h) and the time period that blood glucose concentrations were bellow renal threshold varied from 10h to more than 24h (average: 14h) (Fleeman et al., 2009). In normal cats, onset of action occurs after approximately 1h, time to nadir is 3-6h (average: 4.7h) and the duration of action is usually 8-10h (Marshall et al., 2008; Caney, 2013). The most important drawbacks of insulin lente in diabetic cats is the fast rate of decrease in blood glucose concentrations, which may trigger counter regulatory mechanisms, along with the 2-6h time period of high blood glucose concentration that occurs between two consecutive administration at 12h intervals (Marshall et al., 2008).

**Table 1**. Number of amino acids that differ between the insulin of dogs or cats and the commercially available insulin preparations of different origin

| | Origin of commercially available insulin preparations | | |
| --- | --- | --- | --- |
| | Human | Porcine | Bovine |
| Dog | 1 | 0 | 2 |
| Cat | 4 | 3 | 1 |

Insulin lente has been used for many years in the management of dogs and cats with non-complicated DM (Aptekmann and Schwartz, 2011). Contrary to the manufacturer's recommendations proposing a starting dose of 0.75-1 U kg$^{-1}$ once daily (SID) and despite the fact that most clinicians start at 0.25 U kg$^{-1}$ every 12h (BID), based on the available pharmacokinetic and pharmadynamic information Caninsulin® treatment of diabetic dogs should start at 0.5 U kg$^{-1}$ BID and subsequently gradually increased, each time by 10-15%, in case of persistent hyperglycemia (blood glucose concentrations >250 mg dl$^{-1}$) or decreased by 25% in case of tendency for hypoglycemia (blood glucose concentration <70 mg dl$^{-1}$) or relatively low (<180 mg dl$^{-1}$) blood glucose concentration immediately before insulin administration (Cook, 2007; Zerrenner et al., 2007; Fleeman et al., 2009). For cats, current recommendations on the initial dose vary from 1-2 U per cat BID to 0.25 to 0.5 U kg$^{-1}$ of ideal body weight BID with a maximum of 3 U per cat (the higher end of the dose range is preferable for cats with a blood glucose concentration >340-360 mg dl$^{-1}$) (Martin and Rand, 2007b; Michiels et al., 2008; Marshall et al., 2009; Tschuor et al., 2011; Caney, 2013). Subsequent dose modifications are typically based on blood glucose curves that should be performed every 1-2 weeks: depending on the therapeutic protocol (i.e. aiming at diabetic remission or not) dose will be increased by 0.5-1 U per cat when blood glucose concentrations are higher than a predetermined value (i.e. 160 mg dl$^{-1}$ with protocols to achieve disease remission) and it will be decreased by 0.5 to more than 1 U per cat or by 50-75% in case of biochemical (<50 mg dl$^{-1}$) or clinical hypoglycemia with or without skipping the next dose (Martin and Rand, 2007b; Michiels et al., 2008; Tschuor et al., 2011; Caney, 2013). An alternative way to rapidly adjust the initial dose of diabetic cats is to hospitalize them and perform daily 12h glucose curves for the first three days of treatment: the dose will be decreased by 50%, by 1 U per cat or by 0.5 U per cat if the nadir is <50 mg dl$^{-1}$, 50-90 mg dl$^{-1}$ and 90-120 mg dl$^{-1}$, respectively (Marshall et al., 2009).

Depending on the protocol and study population, insulin lente is generally effective in controlling blood glucose concentrations and clinical signs of dogs and cats with non-complicated DM but it is not very likely to induce diabetic remission (see later), even in newly diagnosed diabetic cats (Martin and Rand, 2007b; Michiels et al., 2008). As expected, the major side effect is hypoglycemia that may (clinical hypoglycemia) or may not (biochemical hypoglycemia) be accompanied by clinical signs and occurs more frequently at higher doses (Michiels et al., 2008).

**Insulin NPH** contains zinc and protamine (a strongly basic protein extracted from salmon testes) that both prolong the duration of action and result in a solution of free and protamine-bound insulin (Zerrenner et al., 2007; Mori et al., 2008). Currently, only recombinant human insulin NPH is available since porcine and bovine-origin preparations have been withdrawn from the market (Zerrenner et al., 2007; Palm et al., 2009). Similarly to insulin lente, pharmacokinetics and pharmacodynamics exhibit considerable dog to dog variation, the peak activity occurs at 5h (1-10h in individual dogs) and the duration of action ranges from 4-24h (average 5.5h) (Mori et al., 2008; Palm et al., 2009; Clark et al., 2012). In cats, due to its short duration of action, insulin NPH results in poor glycemic control when administered BID (Zerrenner et al., 2007). Insulin NPH is commonly used for the treatment of canine DM, especially overseas (Aptekmann and Schwartz, 2011), and less frequently for feline DM, at an initial dose of 0.25-0.5 U kg$^{-1}$ BID that can be subsequently increased by 10-15% or decreased by 25% in case of persistent hyperglycemia (>250 mg dl$^{-1}$) or hypoglycemia (<70 mg dl$^{-1}$), respectively (Cook, 2007; Zerrenner et al., 2007; Sako et al., 2011).

**Insulin PZI** contains zinc and protamine (at a higher quantity compared to insulin NPH) that form complexes with the insulin molecule; these complexes precipitate at the neutral pH of the SC tissue, slowly dissociate by the action of proteolytic enzymes and the released insulin is subsequently absorbed (Zerrenner et al., 2007; Rios and Ward, 2008; Clark et al., 2012; Scott-Moncrieff et al., 2012). Bovine (Insuvet® PZI, 100 U ml$^{-1}$, originally distributed by Schering-Plough and later by Pfizer Animal Health) and 90% bovine-10% porcine (PZI Vet®, 40 U ml$^{-1}$, Idexx Laboratories) preparations are no longer available, but there is a human recombinant insulin PZI veterinary preparation (ProZinc™, 100 U ml$^{-1}$ Boehringer Ingelheim) that has been registered for treatment of feline DM (Davison et al., 2008; Nelson et al., 2009; Clark et al., 2012; Scott-Moncrieff et al., 2012; Smith et al., 2012; Caney, 2013; Roomp and Rand, 2013). Once again, pharmacokinetics and pharmacodynamics are highly variable: onset of action occurs between 0.5h and 14h

post-administration in dogs, peak action may be witnessed between 5h to more than 24h (average: 13-16h) in dogs and between 1h and 12h (average: 3.74.6h) in cats and the duration of action, which is usually longer than for insulin NPH, may range from 16h to more than 24h in dogs and from 8h to 24h in cats (Zerrenner et al., 2007; Marshall et al., 2008; Rios and Ward, 2008; Nelson et al., 2009; Clark et al., 2012). Besides its common use, especially in U.S.A. (Smith et al., 2012), insulin PZI is not typically recommended for dogs because of the highly unpredictable onset and duration of action and the lack of a benefit compared to other available preparations; however, it may be tried in selected cases experiencing difficulties in the management of DM due to the shorter duration of action of insulin Lente and NPH (Cook, 2007; Zerrenner et al., 2007; Maggiore et al., 2012). In cats it is used much more commonly, despite the possible appearance of a biphasic blood glucose curve, that may reflect activation of counter regulatory mechanisms secondarily to a fast decline of blood glucose concentration(Marshall et al., 2008).

When used to treat diabetic dogs, the usual starting dose is 0.5 U kg$^{-1}$ BID and the adjusted dose that was needed to control the clinical signs ranged from 0.4 to 1.5 U kg$^{-1}$ (Maggiore et al., 2012). However, some dogs may need SID administration; when nadir occurs at the beginning or the end of the 12h blood glucose curve or when Somogyi response is suspected, there is a clear indication to switch from BID to SID treatment (Maggiore et al., 2012). For diabetic cats, initial dose recommendations vary: 0.25-0.5 U kg$^{-1}$ BID with the higher end of the dose range used in cats with blood glucose concentrations >360 mg dl$^{-1}$ or 0.22-0.66 mg kg$^{-1}$ BID with the lower dose selected in newly diagnosed cases or 1-3 U per cat BID have all been suggested (Cook, 2007; Zerrenner et al., 2007; Marshall et al., 2009; Nelson et al., 2009). Similarly to insulin lente, rapid adjustment of the initial dose can be achieved if the cats are hospitalized for three days and daily 12h glucose curves are performed: the dose is decreased by 50%, by 1 U per cat or by 0.5 U per cat if the nadir is <50 mg dl$^{-1}$, 50-90 mg dl$^{-1}$ and 90-120 mg dl$^{-1}$, respectively and it is decreased to 1 U per cat SID for those cats that are treated with 1 U per cat BID and blood glucose concentrations before insulin administration are <210 mg dl$^{-1}$ (Marshall et al., 2009). In general, like in dogs, insulin PZI treated cats may be controlled with SID administration, especially when nadir occurs 10h after injection

or later and when Somogyi response is witnessed (Cook, 2007; Zerrenner et al., 2007; Nelson et al., 2009). The efficacy of insulin PZI for the control of hyperglycemia and of clinical signs of DM seems to be comparable to those of insulin lente and NPH: in two recent studies 82% of diabetic dog owners considered that their pet's condition had improved after 2 months, whereas good diabetic control was achieved in 85% of the cats in a 45 day period (Nelson et al., 2009; Maggiore et al., 2012). The incidence of hypoglycemia clearly depends on the dose and was recorded in 12-18% of the dogs and in up to 64% of the cats in the same studies (Nelson et al., 2009; Maggiore et al., 2012).

**Insulin glargine** (Lantus®, 100 U ml$^{-1}$, Sanofi-Aventis) is a recombinant human insulin analogue: asparagine has been replaced by glycine at the 23$^{rd}$ amino acid position of the A chain and two arginine amino acids have been added at the C-terminus of the B chain (Zerrenner et al., 2007; Gilor et al., 2010; Roomp and Rand, 2013). In the acidic (pH: 4) commercially available solution, insulin glargine is water soluble but after its injection into SC tissues, where pH is neutral, insulin crystals precipitate thus delaying absorption that remains steady over time (Mori et al., 2008; Gilor et al., 2010; Roomp and Rand, 2013). The pH-dependency is the reason why dilution or mixing with other insulin preparations is not allowed and also explains why insulin glargine acts like short-acting regular insulin if administered intravenously or intramuscularly (Zerrenner et al., 2007; Marshall et al., 2008; Roomp and Rand, 2013). The unopened vial can be stored at the refrigerator for up to 6 months but once open, it is stored at room temperature for one month (Zerrenner et al., 2007; Roomp and Rand, 2013). In humans, insulin glargine is marketed as "basal" insulin without significant peaks and troughs that mimics normal pancreatic insulin secretion between meals but it is not clear if the same applies to both diabetic dogs and cats. In dogs with DM, lack of significant differences among blood glucose concentrations at 2h, 4h, 6h and 8h after administration indicate a relative lack of peaks in insulin's action (Hess and Drobatz, 2013) but in other studies peaks have been witnessed, usually 6-10h post-injection (Mori et al., 2008; Fracassi et al., 2012); also

the duration of action was found to be 24h in normal dogs and the blood glucose lowering-effect is similar or slightly lower compared to insulin NPH (Mori et al., 2008; Sako et al., 2011). In cats pharmacokinetics and pharmacodynamics vary between patients so that a clear nadir of blood glucose concentration may or may not be seen; onset of action occurs after approximately 1-2h, glucose nadir may be seen any time between 2.5 and 16h, sometimes a biphasic action with an early and a late nadir is noticed and the duration of action varies between 7h and 24h but in most cats it exceeds 12h (Marshall et al., 2008; Rios and Ward, 2008; Roomp and Rand, 2009; Gilor et al., 2010; Smith et al., 2012). Also, potency (blood glucose lowering effect) of insulin glargin is generally similar but is some cats it may be lower than that of insulin lente, NPH and PZI (Marshall et al., 2008; Roomp and Rand, 2009; Ford and Lynch, 2013; Roomp and Rand, 2013).

Initial dose range for diabetic dogs is 0.25-0.5 U kg$^{-1}$ BID (Fracassi et al., 2012) but the results of a recent study indicate that 0.3 U kg$^{-1}$ BID is probably a safe starting point, taking into consideration the high incidence of hypoglycemia at higher doses (Hess and Drobatz, 2013). At subsequent examinations the initial dose may have to be increased or decreased by 5-20% or by 0.001-0.2 U kg$^{-1}$, each time depending on the amelioration of clinical signs (if not, dose is increased) and the results of blood glucose curves (if constantly >200 mg dl$^{-1}$ the dose is increased, whereas even a single value <80 mg dl$^{-1}$ is a clear indication for dose decrement) (Fracassi et al., 2012; Hess and Drobatz, 2013). Based on a limited body of information the final optimal dose of the control of canine DM ranges between 0.1 and 1.1 U kg$^{-1}$ but it is typically around 0.5-0.6 U kg$^{-1}$ (Fracassi et al., 2012; Hess and Drobatz, 2013). For cats with DM insulin glargine treatment is started at 0.25-0.5 U kg$^{-1}$ BID (the upper end of the dosing regimen is used when blood glucose concentration exceeds 360 mg dl$^{-1}$) or at 1-2 U per cat BID depending on the ideal body weight (1 U if ≤4 kg and 1.5-2 U if >4 kg) (Cook, 2007; Rios and Ward, 2008; Hall et al., 2009; Marshall et al., 2009; Tschuor et al., 2011). Some investigators advocate to adjust the initial dose by hospitalizing cats and performing serial blood glucose curves for the first one to three days of treatment, using one of the following three protocols: Protocol 1: the dose is decreased by 50%, or by 1 U per cat or by 0.5 U per cat if the nadir is <50 mg dl$^{-1}$, 50-90 mg dl$^{-1}$ and 90-120 mg dl$^{-1}$, respectively; also the dose remains the same but the frequency of administration is decreased to SID for those cats that are treated with 1 U per cat BID if blood glucose concentrations before insulin administration are <210 mg dl$^{-1}$ (Marshall et al., 2009). Protocol 2: the dose is decreased or increased by 0.5-1 U per cat if the nadir is <90 mg dl$^{-1}$ or >160 mg dl$^{-1}$, respectively (Tschuor et al., 2011). Protocol 3: the dose is decreased by 1 U per cat if the nadir is <70 mg dl$^{-1}$ (Cook, 2007). Like every insulin preparation the typical side effect is hypoglycemia, which is more frequently biochemical rather than clinical and can be witnessed in up to 70% of treated animals (Marshall et al., 2009; Fracassi et al., 2012; Hess and Drobatz, 2013).

Most dogs with DM can be controlled with insulin glargine but due to the limited scientific information it is unclear whether this treatment is superior to that with insulin lente or NPH (Fracassi et al., 2012; Hess and Drobatz, 2013). On the contrary, in diabetic cats insulin glargine treatment is clearly superior and carries an increased potential for diabetic remission (see later) compared to insulin lente and PZI (Marshall et al., 2009; Roomp and Rand, 2009) which explains why, despite its recent introduction into the market and lack of a veterinary formulation, it is the preferred insulin for treatment of feline DM for more than 25% of the veterinarians in the U.S.A. (Smith et al., 2012). However, a recent analysis did not demonstrate a benefit of insulin glargine over insulin lente of porcine origin in terms of the duration of survival of diabetic cats (Callegari et al., 2013)

**Insulin detemir** (Levemir®, 100 U ml$^{-1}$, Novo Nordisk) is also a recombinant human insulin analogue where threonine has been removed from the C-terminal of B chain and myristic acid has been bound to the lysine which is 29th amino acid of the same chain (Gilor et al., 2010; Sako et al., 2011; Roomp and Rand, 2012; Roomp and Rand, 2013). These molecular changes result in a slowly absorbed and highly albumin-bound molecule with long duration of action and increased

liver penetration (Gilor et al., 2010; Sako et al., 2011; Roomp and Rand, 2012; Roomp and Rand, 2013) which is also very stable and can be used for up to 6 weeks after opening if kept at room temperature and up to 6 months if refrigerated (Roomp and Rand, 2013). In normal dogs peak activity is witnessed at 8-10h and the duration of action is more than 24h (Sako et al., 2011), whereas the respective figures in cats are 5-9h (average: 7h) and 9-14h (average: 12h) (Gilor et al., 2010). In general the pharmacokinetics vary among cats, the time-action profile can either be long-acting without peaks or shorter-acting with a demonstrable nadir of blood glucose concentration and the duration of action is shorter compared to humans (Gilor et al., 2010). From the pharmacodynamic point of view, insulin detemir is probably of lower potency compared to insulin NPH and glargine in dogs, and in cats it is of lower potency compared to insulin lente, NPH and PZI but of similar potency to insulin glargine (Gilor et al., 2010; Sako et al., 2011; Roomp and Rand, 2012; Roomp and Rand, 2013).

The recommended starting dose for both diabetic dogs and cats is 0.25-0.5 U kg$^{-1}$ BID although the optimal dose can be substantially lower (Sako et al., 2011). The efficacy of insulin detemir for the management of canine DM seems to be adequate and it may prove to be superior to other insulin types, although the risk of hypoglycemia may be increased (Sako et al., 2011; Maggiore et al., 2012), whereas in cats it appears to be comparable to insulin glargine when intensive protocols aiming to diabetic remission are employed (see later). An additional indication to use insulin detemir may be the prevention of DM in non-diabetic dogs with pituitary-dependent hyperadrenocorticism and mild hyperglycemia (>100 mf dl$^{-1}$) but additional studies are needed to confirm the safety and efficacy of such as approach (Miceli et al., 2012).

## TECHNIQUES TO ACCURATELY ADMINISTER LOW DOSES OF UNDILUTED INSULIN

Insulin is usually administered with specific syringes and although BID SC injections are typically needed for life, most dogs tolerate the injections very well and owners can give them without the need for an assistant (Aptekmann and Schwartz, 2011). However, accurate measurement of undiluted insulin dose can be problematic in small dogs and in cats, especially with the current protocols for tight control of hyperglycemia (see later). In such cases, use of small volume U-100 insulin syringes, counting the number of drops corresponding to 2 insulin units, use of insulin pens or insulin rulers and dilution of insulin (if possible) may help the owner to administer the intended insulin dose.

**Insulin syringes** are available at two forms: U-40 and U-100. The former have a volume capacity of 1ml, they are marketed only for 40 U ml$^{-1}$ insulin preparations, like Caninsulin® and each line corresponds to 0.025ml that equals to 1 U of insulin. Therefore, when using such syringes the lowest possible increment or decrement of the dose is 1 U (Caney, 2013). On the contrary, U-100 syringes are available at a volume capacity of 0.3ml, 0.5ml and 1ml and each line corresponds to 0.01ml and thus to 1 U of a 100 U ml$^{-1}$ insulin or to 0.4 U of a 40 U ml$^{-1}$ insulin preparation. This offers a clear advantage for small dogs and cats treated with a 40 U ml$^{-1}$ insulin preparation (permits 0.4 U dose changes) whereas small volume syringes (i.e. 0.3ml) are preferable when the same patients are treated with 100 U ml$^{-1}$ insulin because they may enable the owner to implement 0.5 U dose changes (Cook, 2007; Smith et al., 2012). However, even with the 0.3ml U-100 syringes there is considerable variability in the administered dose that is typically higher than the intended one (Smith et al., 2012), partially because the printed scale on the syringe is not always accurate (Roomp and Rand, 2013).

Another technique that has been proposed to accurately administer small insulin doses is based on **counting the number of drops that correspond to 2 insulin units**. In this technique a specific brand and volume capacity U-100 insulin syringe is selected and constantly used. The owner is trained to drawn 2 U into the syringe (e.g. to fill the first 2 lines of the syringe with an 100 U ml$^{-1}$ insulin preparation), to hold the syringe vertically with the needle pointing downwards and to apply constant pressure on the plunger while counting the number of drops until the syringe is empty (Roomp and Rand, 2013). This is repeated numerous times until the same number of drops is counted repeatedly (Figure 1). For example, if 2 U correspond to eight drops, each drop contains 0.25 U and this facilitates administration of a dose as low as 0.25 U as well as
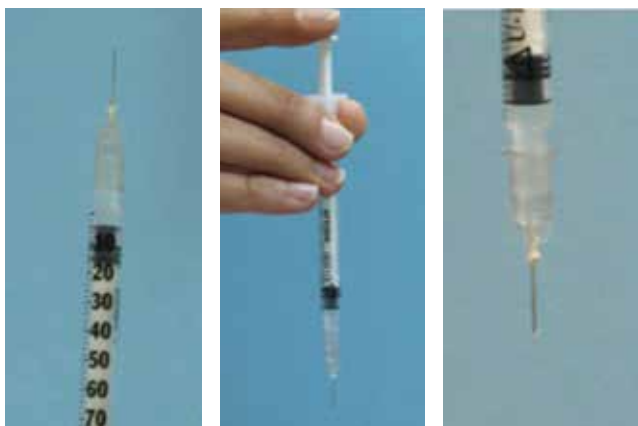
**Figure 1:** Administration of low insulin doses after counting the number of drops that correspond to 2 insulin units. Figure 1a: 2 units from a 100 U ml-1 insulin preparation are drawn into a U-100 insulin syringe. Figure 1b: syringe is held vertically and constant pressure is applied to the plunger. Figure 1c: counting the number of drops until the syringe becomes empty

0.25 U dose changes. In the above example, if 0.5 U insulin must be administered to a diabetic cat, 2 U are drawn into the syringe, six drops are discarded and the insulin that remains into the syringe corresponds to two drops and thus to 0.5 U. In the same cat the dose can be decreased to 0.25 U or increased to 0.75 U by discarding seven or five drops, respectively.

Both human and veterinary-purpose **insulin pens** are available (Caney, 2013). For veterinary-purpose pens caution is advised on the strength of the insulin preparation for which each pen has been designed, because if a U-40 pen is used for a 100 U ml$^{-1}$ insulin preparation the administered dose will be 2.5 higher. Human-purpose pens are U-100, the pediatric ones permit 0.5 U dose changes and they are considered more accurate than 0.3ml U-100 insulin syringes (Smith et al., 2012; Roomp and Rand, 2013).

**Insulin ruler** can be freely downloaded at www. diabetes-katzen.net/insulinruler.pdf. This ruler enables administration of very low doses (up to 0.1 U) of 100 U ml$^{-1}$ insulin preparations (Roomp and Rand, 2013). For accurate dosing, it has been recommended to use a sticker in order to attach the insulin vial on a vertical surface, to use one hand to hold the syringe and draw insulin and the other hand to keep the printed ruler next to the syringe (Roomp and Rand, 2013). Caution

is advised since this ruler must be printed in its original size and is applicable only for 100 U ml$^{-1}$ insulin preparations and a specific insulin syringe [Becton Dickinson U-100 syringes with the BD Ultra-Fine™ Needle 0.3 ml 31Gx5/16" (8mm) with 1/2 unit markings].

When none of the above is feasible, **dilution of insulin** just before use is the only alternative. Dilution with a specific diluent provided by the manufacturer or with normal saline or water for injection has been practiced for years for insulin lente, NPH and PZI 100 U ml$^{-1}$ preparations and it is also acceptable for insulin detemir (Roomp and Rand, 2013). Based on manufacturer's instructions and its pH dependency, insulin glargine should not be diluted, although some specialists report that it may be diluted with normal saline immediately before administration (Roomp and Rand, 2013). When insulin dilution is going to be practiced by the owner careful education and repeated training is necessary to avoid dose miscalculations. According to the author's experience, mistakes are common and may explain some cases of poor DM control and hypoglycemia.

## HOME MONITORING OF BLOOD GLUCOSE CONCENTRATIONS BY THE OWNER

For many years treatment monitoring of diabetic dogs and cats has been based on frequent evaluation of the history (control of the cardinal clinical signs of DM, such as polyuria, polydipsia and polyphagia), body weight, physical examination findings, urinalysis, measurement of surrogate markers of blood glucose concentration over time (glycosylated hemoglobin, fructosamine) and serial blood glucose curves performed at the hospital. In recent years there is a tendency to, at least partially, substitute the latter by owner-performed home monitoring of blood glucose concentrations. Thanks to the advancements of portable blood glucose meters (PBGMs) and the refinement of the techniques for blood sampling by the owner, such monitoring is feasible for many dogs and also for cats with DM (Niessen et al., 2010; Ford and Lynch, 2013). The use of PBGMs, their indications, the factors influencing their results and the techniques for blood sampling have been recently

reviewed (Athanasiou et al., 2014), and the interested reader is referred to that article.

Home monitoring of blood glucose concentration by the owner can be used to create a typical 12h blood glucose curve if measurements are made at 2h intervals. The theoretical advantages over performing the same procedure at the hospital include increased reliability of the results since there is no significant change of daily routine (feeding, exercise) or interference by the stress of hospitalization, and the reduced cost (Alt et al., 2007; Roomp and Rand, 2009; Ford and Lynch, 2013). Serial blood glucose curves at the hospital suffer from day to day variation in both diabetic dogs and cats; their repeatability, even when performed on consecutive days, is that low that may result in opposite recommendations for adjustment of insulin dose (Alt et al., 2007; Roomp and Rand, 2009; Ford and Lynch, 2013). However, even at the home environment day to day variation is also expected, although it is less problematic in well regulated diabetic animals (Alt et al., 2007).

Daily measurement of blood glucose concentrations is also an essential part of the intensive protocols aiming at diabetic remission in cats (see later). Also, the ability of the owner to measure blood glucose concentrations at home may be extremely helpful to confirm suspect episodes of hypoglycemia in insulin-treated dogs and cats (Roomp and Rand, 2009) and also enables the use of portable blood ketone monitors that can show increased concentrations of b-hydroxyburate days before urine dip sticks become positive for ketone bodies (Roomp and Rand, 2013).

It is emphasized that the results of home monitoring of blood glucose concentration can be used to modify insulin treatment only after consultation with the attending clinician or following a predetermined dose adjustment protocol (see later).

**CONTINUOUS GLUCOSE MONITORING SYSTEMS**

A recent addition to our armamentarium for care of diabetic pets is the use of continuous glucose monitoring systems (CGMSs) that may become standard of care in the near future (Rios and Ward, 2008). These systems use a small, flexible and disposable sensor that is inserted into SC tissue to constantly measure glucose concentration in the interstitial fluid with the glucose oxidase reaction; since blood and interstitial fluid glucose concentrations equilibrate relatively fast (5-12 min) and CGMSs are calibrated based on the former, they have the ability to accurately measure glucose concentration every 1-10sec, average and display the results every 3-5min and work constantly for up to 48-144h (Wiedmeyer and DeClue, 2008; Affenzeller et al., 2010; Moretti et al., 2010; Affenzeller et al., 2011; Dietiker-Moretti et al., 2011; Fleeman, 2011; Hoenig et al., 2012; Hafner et al., 2013; Mori et al., 2013; Surman and Fleeman, 2013).

There are commercially available CGMSs that differ in their SC tissue glucose concentration working range (20-600 mg dl$^{-1}$, depending on the device), duration of the initialization period between insertion of the sensor and the first display (0.5-2h), timing of the initial and subsequent calibrations, cable or wireless connection between the sensor and the monitor, and their ability for real-time display of the recordings or not (Rios and Ward, 2008; Wiedmeyer and DeClue, 2008; Affenzeller et al., 2010; Moretti et al., 2010; Dietiker-Moretti et al., 2011; Fleeman, 2011; Hafner et al., 2013; Surman and Fleeman, 2013). Continuous research efforts aim to optimize the site of the body where the sensor is inserted into the SC tissue and to validate different CGMSs for dogs and cats (Rios and Ward, 2008; Affenzeller et al., 2010; Moretti et al., 2010; Dietiker-Moretti et al., 2011; Hoenig et al., 2012; Hafner et al., 2013; Mori et al., 2013; Surman and Fleeman, 2013).

When CGMSs are used, instead of periodic blood sampling, they offer distinct advantages, including convenience, safety and, most importantly, increased accuracy for detection of Somogyi response, true nadir and brief periods of hypoglycemia that can be easily missed during a typical 12h serial blood glucose curve performed during the day if they occur between two sequential blood samplings or at night (Martin and Rand, 2007b; Rios and Ward, 2008; Wiedmeyer and DeClue, 2008; Affenzeller et al., 2010; Moretti et al.,

2010; Affenzeller et al., 2011; Dietiker-Moretti et al., 2011; Fleeman, 2011; Hoenig et al., 2012; Hafner et al., 2013; Mori et al., 2013; Surman and Fleeman, 2013). Besides the cost of the device, disadvantages of CGMs include the possibility of sensor disconnection or fouling, their dependence on accurate calibration based on blood glucose concentrations, the possible delay of measurement because, depending on the device, calibration is impossible when blood glucose concentration is very low (<20-40 mg dl$^{-1}$) or high (>400-600 mg dl$^{-1}$) and the inaccuracy of the results when used in animals with dehydration or under general anesthesia (Rios and Ward, 2008; Wiedmeyer and DeClue, 2008; Affenzeller et al., 2010; Moretti et al., 2010; Affenzeller et al., 2011; Dietiker-Moretti et al., 2011; Hoenig et al., 2012; Surman and Fleeman, 2013).

## PROTOCOLS TO TIGHTLY CONTROL BLOOD GLUCOSE CONCENTRATIONS WITH THE AIM OF DIABETIC REMISSION IN CATS

Until some years ago, efforts to tightly control blood glucose concentrations in cats with DM were discouraged due to the fear of hypoglycemia and lack of information on potential benefits. In recent years, protocols including administration of long-acting insulin (usually glargine and less commonly detemir or PZI), feeding a very low carbohydrate diet (≤10%), regular measurement of blood glucose concentrations with PBGM at home by the owner and changing insulin dose to tightly control blood glucose concentrations have been developed, offering distinct advantages: safety, better quality of life and an impressively high rate of diabetic remission (Martin and Rand, 2007a; Marshall et al., 2009; Roomp and Rand, 2009, 2012; Ford and Lynch, 2013; Roomp and Rand, 2013). It is emphasized that the recommended monitoring of cats treated with these protocols must be followed very closely in order to avoid hypoglycemia which is the most disastrous complication. If this is not feasible, it is better to be on the safe side and treat diabetic cats with a non-intense protocol, starting with the lowest recommended insulin dose.

The most aggressive published protocol requires: a) BID administration of insulin glargine or lente, b)

daily measurement of blood glucose concentrations at home, with a PBGM, at least three (i.e. before each insulin injection and then every 3-6h) and usually 4-5 times per day (i.e. in the morning before meal and insulin, one or twice in the middle of the day, in the evening before meal and insulin, and at bed time), c) checking for ketonuria at home, with urine dip sticks, twice daily for the first 3 days and then less frequently, and d) re-examinations at the hospital, initially every week and then every 2-4 weeks (Roomp and Rand, 2009, 2012; Ford and Lynch, 2013; Roomp and Rand, 2013). This protocol includes five phases: the initial phase (first 3 days), the second phase where insulin dose is gradually increased, the third phase where the dose that keeps blood glucose concentrations between 50 and 200 mg dl$^{-1}$ throughout the day is administered, the fourth phase where the dose is gradually reduced and the final phase of diabetic remission (Table 2). The only side effect of this protocol is hypoglycemia: biochemical hypoglycemia is quite frequent (10-12% of the serial blood glucose curves and at least once in up to 93% of the cats) but clinical hypoglycemia is seemingly rare (2-6% of the cats) and does not occur at a higher frequency compared to the traditional non-intensive treatment protocols (Roomp and Rand, 2009, 2012; Roomp and Rand, 2013; Surman and Fleeman, 2013). Also, Somoygi phenomenon is rare although an increase in glucose concentrations after each increment of insulin dose is expected in one fourth of the cats, most probably due to a mild counter-regulatory response (Roomp and Rand, 2009; Roomp and Rand, 2013). The major advantage of the protocol is that it offers the highest chances for diabetic remission and a good regulation of DM when remission cannot be achieved (Roomp and Rand, 2009, 2012; Roomp and Rand, 2013).

A second, less intense protocol is based on the same requirements as the previous one except that blood glucose concentrations are measured at home every 3-4h for 12h only once per week (less ideally every 2 weeks) instead of daily measurements (Roomp and Rand, 2013). Insulin glargine or detemir is administered initially at 0.25 or 0.5 U kg$^{-1}$ BID if blood glucose concentration is <360 mg dl$^{-1}$ or >360

**Table 2.** Intense protocol of insulin glargin or detemir administration and daily monitoring of blood glucose concentrations[1] aiming to diabetic remission in cats with non-complicated diabetes mellitus (adapted from: Roomp and Rand, 2009; Ford and Lynch, 2013; Roomp and Rand, 2013)

**Phase 1: initial treatment (duration: 3 days)**

Initial insulin dose: 0.25 U kg$^{-1}$ every 12h; if the cat had been previously treated with another insulin information from the history may be used to increase or decrease the initial dose; if there is a history of ketosis the initial dose is increased by 0.5 U per cat

| *Blood glucose* | *Insulin dose change* |
|---|---|
| >300 mg dl$^{-1}$ after 24-48h | Increase by 0.5 U per cat |
| <50-60 mg dl$^{-1}$ at any time | Decrease by 0.25-1 U per cat[2] |

**Phase 2: gradually increase insulin dose**

| *Blood glucose* | *Insulin dose change* |
|---|---|
| Nadir >300 mg dl$^{-1}$ | Increase by 0.5-1 U per cat every 3 days |
| Nadir: 200-300 mg dl$^{-1}$ | Increase by 0.25-0.5 U per cat every 3 days |
| Nadir <200 mg dl$^{-1}$ and zenith >200 mg dl$^{-1}$ | Increase by 0.25-1 U per cat every 5-7 days |
| <50-60 mg dl$^{-1}$ at any time | Decrease by 0.25-1 U per cat |
| <100 mg dl$^{-1}$ just before insulin | Decrease by 0.25-0.5 U per cat, give food **or** |
| | Give food and wait 1-2h[3] **or** |
| | Give food and 2/3 of insulin and wait 1-2h[4] |

**Phase 3: keep blood glucose concentrations 50-200 mg dl$^{-1}$ throughout the day**

| *Blood glucose* | *Insulin dose change* |
|---|---|
| <50-60 mg dl$^{-1}$ at any time | Decrease by 0.25-1 U per cat |
| >200 mg dl$^{-1}$ at any time | Increase by 0.25-1 U per cat |

**Phase 4: gradually decrease insulin dose**

| *Blood glucose* | *Insulin dose change* |
|---|---|
| Nadir <40 mg dl$^{-1}$ at any time | Decrease by 0.25-1 U per cat or by 50% |
| Nadir: 40-50 mg dl$^{-1}$ on 3 separate days | Decrease by 0.25-1 U per cat |
| Nadir: 50-100 mg dl$^{-1}$ every day x 7 days | Decrease by 0.25-0.5 U per cat |
| >200 mg dl$^{-1}$ at any time | Increase to the previously effective dose |

**Phase 5: achievement of diabetic remission**

After gradual dose reductions insulin had been discontinued (e.g. at a dose of 0.25 U per cat nadir was 40-50 mg dl$^{-1}$ on 3 separate days) and blood glucose concentrations are measured every week, 1h after feeding

| *Blood glucose* | *Insulin dose change* |
|---|---|
| >150 mg dl$^{-1}$ at any measurement | Restart at the last effective insulin dose |

[1]Blood glucose concentrations are measured by a portable blood glucose meter (PBGM) intended for use in human whole blood. If a veterinary-purpose PBGM or human plasma PBGM is used all reported blood glucose concentrations should be increased by 20 mg dl$^{-1}$

[2]Throughout this protocol, when a dose change (increment of decrement) of 0.25-1 U per cat is needed, a 0.25 U per cat dose change is recommended when the previous dose is low (<3 U per cat) whereas a 0.5-1 U per cat dose change is recommended when the previous dose is high (≥3 u per cat)

[3]If 1-2 after the meal blood glucose concentration is >100 mg dl$^{-1}$ the full insulin dose is administered but if it is <100 mg dl$^{-1}$ the dose is decreased by 0.25-0.5 U per cat

[4]If 1-2h after insulin administration blood glucose concentration is >100 mg dl$^{-1}$ the remaining 1/3 of the dose is administered but if it is <100 mg dl$^{-1}$ the remaining 1/3 of the dose is skipped

mg dl$^{-1}$, respectively, or at 1 U per cat BID when glucose monitoring during the next 3 days is not feasible. During the first week of the treatment the dose remains constant except if there is no appreciable reduction of blood glucose concentrations (dose increment) or hypoglycemia (dose decrement). Subsequent dose adjustments are based on nadir and glucose concentrations before the next insulin injection, observed on weekly measurements (Table 3). Also, if clinical hypoglycemia is witnessed, insulin dose should be reduced by 50% regardless of nadir and pre-insulin concentrations (Roomp and Rand, 2013).

When blood glucose concentrations cannot be measured by the owner, protocols using insulin glargine (Table 4), PZI (Table 5) or lente (Table 6) are available (Marshall et al., 2009; Roomp and Rand, 2013). However, it is important to note that besides reduced efficacy these protocols may be associated with an increased incidence of clinical hypoglycemia compared to the intense protocols with home monitoring of blood glucose concentration (Roomp and Rand, 2013).

Diabetic remission is rare in dogs, with the notable exception of a few cases with transient DM occurring during pregnancy or diestrus (Cook, 2007) or after

treatment of concurrent hyperadrenocorticism. On the contrary, it is currently considered a realistic goal in diabetic cats, especially those that are newly diagnosed. Diabetic remission is defined as maintenance of clinical remission and normal blood glucose concentrations (<216 mg dl$^{-1}$) without insulin injections for at least 2-4 weeks and is attributed to the reversal of the toxic effect of hyperglycemia on pancreatic b cells (Marshall et al., 2009; Zini et al., 2010; Smith et al., 2012; Callegari et al., 2013; Gottlieb and Rand, 2013). The importance of diabetic remission relates to the improved quality of life for the diabetic cat and the owner, the avoidance of hypoglycemia due to insulin administration and the dramatic prolongation of life expectancy (Callegari et al., 2013). There are numerous patient and treatment-related factors that have been associated with increased or decreased chances for diabetic remission, including the age of the cat, duration of DM, previous glucocorticoid administration, clinical and laboratory findings on admission and during treatment, treatment protocol and monitoring and the diet, since all studies on diabetic remission included cats fed on a very low carbohydrate diet (Gottlieb and Rand, 2013). More specifically, in some (Zini et al., 2010) but not all (Tschuor et al., 2011) studies, remission was witnessed more frequently in

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**Table 3.** Moderately intense protocol of insulin glargin or detemir administration and weekly (or biweekly) monitoring of blood glucose concentrations[1] aiming to diabetic remission in cats with non-complicated diabetes mellitus (adapted and modified from Roomp and Rand, 2013)

| **Nadir** | **Insulin dose change** |
|---|---|
| >180 mg dl$^{-1}$ | Increase by 0.25-1 U per cat |
| 90-180 mg dl$^{-1}$ | Same dose |
| 54-90 mg dl$^{-1}$ | Same dose or decrease by 0.25-0.5 U per cat[2] |
| <54 mg dl$^{-1}$ | Decrease by 0.5-1 U per cat[3] |
| **Pre-insulin blood glucose concentration** | **Insulin dose change** |
| >216 mg dl$^{-1}$ (and nadir >54 mg dl$^{-1}$) | Increase by 0.25-1 U per cat |
| 180-216 mg dl$^{-1}$ | Same dose or decrease by 0.25-0.5 U per cat[2] |
| <180 mg dl$^{-1}$ | Decrease by 0.5-1 U per cat[3] |

[1]Blood glucose concentrations are measured by a portable blood glucose meter (PBGM) intended for use in human whole blood. If a veterinary-purpose PBGM or human plasma PBGM is used all reported blood glucose concentrations should be increased by 20 mg dl$^{-1}$

[2]The decision to reduce the dose or not should be based on both the nadir and the pre-insulin blood glucose concentrations, the concentration before the next scheduled insulin administration, water consumption and urine glucose concentrations

[3]If the insulin dose is 0.5-1 U per cat, treatment is discontinued and the cat is monitored for sustained diabetic remission or not

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older cats. Glucocorticoid administration during the last 6 months and concurrent diagnosis of pancreatic disease have been associated with higher chances for remission, even in cats with diabetic ketoacidosis (Sieber-Ruckstuhl et al., 2008; Marshall et al., 2009; Roomp and Rand, 2009; Gottlieb and Rand, 2013), whereas peripheral neuropathy, high blood cholesterol and perhaps very high blood glucose concentrations on admission have been linked to a lower incidence of remission (Roomp and Rand, 2009; Zini et al., 2010; Tschuor et al., 2011; Gottlieb and Rand, 2013). Also, the likelihood of remission was higher for cats with

**Table 4.** Protocol of insulin glargin and in-clinic serial blood glucose curves[1] in cats with non-complicated diabetes mellitus (adapted and slightly modified from Marshall et al., 2009)

**Requirements**

Serial blood glucose curves on days 10, 17, 28 and then every 2 weeks

| Nadir | Insulin dose change |
|---|---|
| 126-162 mg dl^{-1} | Same dose |
| 90-126 mg dl^{-1} | Reduce by 0.5 U per cat |
| <90 mg dl^{-1} | Reduce by 1 U per cat |
| **Pre-insulin blood glucose concentration** | **Insulin dose change** |
| >252 md dl^{-1} | Increase by 0.5 U per cat |
| 216-252 mg dl^{-1} | Reduce by 0.5 U per cat |
| <216 mg dl^{-1} | Discontinue and check for remission |
| **Clinical signs** | **Insulin dose change** |
| Hypoglycemia | Reduce by 50% |

[1]Blood glucose concentrations are measured by a portable blood glucose meter (PBGM) intended for use in human whole blood. If a veterinary-purpose PBGM or human plasma PBGM is used all reported blood glucose concentrations should be increased by 20 mg dl^{-1}

**Table 5.** Protocol of insulin PZI and in-clinic serial blood glucose curves[1] in cats with non-complicated diabetes mellitus (adapted and modified from Marshall et al., 2009; Roomp and Rand, 2013)

**Requirements**

Serial blood glucose curves on days 10, 17, 28 and then every 2 weeks

| Nadir | Insulin dose change |
|---|---|
| >150 mg dl^{-1} | Increase by 25-100% |
| 80-150 mg dl^{-1} | Same dose |
| <80 mg dl^{-1} | Reduce by 25-100% or by 1 U per cat |
| **Pre-insulin blood glucose concentration** | **Insulin dose change** |
| >252 md dl^{-1} | Increase by 0.5 U per cat |
| 216-252 mg dl^{-1} | Reduce by 0.5 U per cat |
| <216 mg dl^{-1} | Discontinue and check for remission |
| **Clinical signs** | **Insulin dose change** |
| Hypoglycemia | Reduce by 50% |

[1]Blood glucose concentrations are measured by a portable blood glucose meter (PBGM) intended for use in human whole blood. If a veterinary-purpose PBGM or human plasma PBGM is used all reported blood glucose concentrations should be increased by 20 mg dl^{-1}

**Table 6.** Protocol of insulin lente and in-clinic serial blood glucose curves[1] in cats with non-complicated diabetes mellitus (adapted and modified from Marshall et al., 2009)

**Requirements**

Serial blood glucose curves on days 10, 17, 28 and then every 2 weeks

| Nadir | Insulin dose change |
|---|---|
| >216 mg dl$^{-1}$ | Increase by 1 U per cat |
| 180-216 mg dl$^{-1}$ | Increase by 0.5 U per cat |
| 126-180 mg dl$^{-1}$ | Same dose |
| 90-126 mg dl$^{-1}$ | Reduce by 0.5 U per cat |
| 54-90 mg dl$^{-1}$ | Reduce by 1 U per cat |
| <54 mg dl$^{-1}$ | Reduce by 50% |
| **Pre-insulin blood glucose concentration** | **Insulin dose change** |
| <216 mg dl$^{-1}$ | Discontinue and check for remission |
| **Clinical signs** | **Insulin dose change** |
| Hypoglycemia | Reduce by 50% |

[1]Blood glucose concentrations are measured by a portable blood glucose meter (PBGM) intended for use in human whole blood. If a veterinary-purpose PBGM or human plasma PBGM is used all reported blood glucose concentrations should be increased by 20 mg dl$^{-1}$

lower mean blood glucose concentration during a 12h serial blood glucose curve after 17 days of treatment with insulin glargine, PZI or lente (Marshall et al., 2009) as well as for cats with lower nadir, mean and maximal blood glucose concentrations after 12-16 weeks of treatment with insulin lente (Michiels et al., 2008). Intense protocols with regular monitoring of blood glucose concentrations and insulin dose adjustments increase the chances for remission (Hall et al., 2009; Zini et al., 2010; Gottlieb and Rand, 2013), especially when they start in the first 6 months after the appearance of clinical signs (Roomp and Rand, 2009, 2012; Gottlieb and Rand, 2013; Roomp and Rand, 2013). Finally, in most studies insulin glargine (17-100%) and detemir (42-81%) have been linked to increased probability of remission compared to insulin PZI (38-68%) or lente (17-63%), while insulin glargine can induce remission even in cats unsuccessfully treated with another insulin (Martin and Rand, 2007b; Michiels et al., 2008; Rios and Ward, 2008; Sieber-Ruckstuhl et al., 2008; Hall et al., 2009; Marshall et al., 2009; Roomp and Rand, 2009; Zini et al., 2010; Tschuor et al., 2011; Roomp and Rand, 2012; Caney, 2013; Gottlieb and Rand, 2013; Roomp and Rand, 2013).

The time frame that diabetic remission occurs after treatment initiation is quite variable, ranging from less than one month up to more than 1 year, but in most cases it is expected during the first 3-4 months (Martin and Rand, 2007b; Michiels et al., 2008; Sieber-Ruckstuhl et al., 2008; Dunning et al., 2009; Hall et al., 2009; Roomp and Rand, 2009; Zini et al., 2010; Tschuor et al., 2011; Roomp and Rand, 2012; Caney, 2013). It is important to remember that some cats may present overt clinical signs of DM and severe hyperglycemia even 1-2 weeks before remission (Martin and Rand, 2007b). Diabetic remission may be permanent or not, since DM will relapse in 0-57% of these cats (Martin and Rand, 2007b; Sieber-Ruckstuhl et al., 2008; Dunning et al., 2009; Roomp and Rand, 2009; Zini et al., 2010; Roomp and Rand, 2012; Caney, 2013; Gottlieb and Rand, 2013; Roomp and Rand, 2013) and the duration of the remission period has been found to be longer in heavier cats as well as in cats with lower blood glucose concentrations on diagnosis (Zini et al., 2010). In some cases administration of glucocorticoids and development of pancreatitis or hyperthyroidism may precipitate a relapse whereas in others reappearance of DM is attributed to the reduced b-cell mass and

function (Gottlieb and Rand, 2013; Roomp and Rand, 2013). A second remission is not very likely but may be achieved if treatment is instituted early, which underlines the importance of weekly measurements of blood glucose concentration 1h post-meal in all diabetic cats under remission and immediate implementation of insulin treatment if it exceeds 120-150 mg dl$^{-1}$ (Roomp and Rand, 2009; Zini et al., 2010; Roomp and Rand, 2012; Ford and Lynch, 2013; Gottlieb and Rand, 2013; Roomp and Rand, 2013).

## AUTHORS' NOTE

Not all insulin preparations and equipment mentioned in this article are currently commercially available in Greece. However, commercial availability changes over time and practitioners may purchase them from internet stores.

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