Continuous Glucose Monitoring in Small Animals

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KEYWORDS

- Diabetes mellitus • Continuous glucose monitoring systems
- Self-monitoring of blood glucose • Interstitial fluid • Subcutaneous • Cat • Dog

KEY POINTS

- Continuous glucose monitoring systems have proved to be accurate in small animal patients for monitoring sick/hospitalized and long-term stable diabetic patients.
- The most important advantage of continuous glucose monitoring over intermittent blood glucose measurements is that it facilitates detection of brief periods of hypoglycemia and provides information overnight. A greater number of data points are obtained over a longer time frame allowing for identification of asymptomatic hypoglycemia and Somogyi phenomena that may be missed with traditional monitoring. Monitoring overnight aids in the identification of nocturnal hypoglycemia.
- Other advantages include that it is less time consuming for staff compared with traditional monitoring; reduces patient stress and stress-related hyperglycemia; reduces the frequency of venipuncture and duration of indwelling catheterization; and affords the ability to make adjustments to treatment plans that may not be indicated based on traditional glucose monitoring methods.
- Disadvantages include the initial cost associated with purchasing a system; limited recording range of 40 to 400 mg/dL (2.2–22.2 mmol/L) for the MiniMed Gold, Guardian Real-Time, i-Pro, Seven Plus, and FreeStyle Navigator, and 20 to 600 mg/dL (1.1–33.3 mmol/L) for the GlucoDay; difficulty initializing and calibrating when glucose values are outside the recording range; limited wireless range for the Guardian Real-Time of only 1.5 m; lack of accuracy in dehydrated, hypovolemic, or shock patients; and lag time that may be seen between changes in plasma and interstitial glucose.

INTRODUCTION

Continuous glucose monitoring systems were initially developed for human use as an alternative to traditional blood glucose monitoring methods. Their primary use has been in the monitoring of hospitalized patients, both diabetic and nondiabetic, and

in self-monitoring of blood glucose. The goals of their use in hospitalized patients are to identify and promptly resolve hyperglycemia and hypoglycemia, which could affect morbidity and mortality, and reduce the need for frequent blood sampling. The goals of their use in self-monitoring of blood glucose are to improve glycemic control, prevent hyperglycemia and hypoglycemia, and thus delay the onset of diabetic complications and improve quality of life. Similar benefits can be achieved in veterinary patients. The use of continuous glucose monitoring systems in veterinary medicine is fairly new, but its use has increased over the past 10 years, with improved technology and veterinarian experience.

Several systems are available for human diabetic patients and some have been used in veterinary patients. These monitors differ in the method used to measure glucose and in various other features that are reviewed later in this article.

PATIENT GROUPS THAT BENEFIT FROM CONTINUOUS GLUCOSE MONITORING
Critical Care (Sick/Hospitalized Diabetic and Nondiabetic Patients): Usefulness

Diabetic cats and dogs are often hospitalized for treatment of illness both unrelated to, and as a complication of, their diabetes. Although the incidence of diabetic ketoacidosis in veterinary patients is unknown, it is recognized as a common life-threatening endocrine disorder in both cats and dogs[1–4]; 1 study found that 62% of cats with ketoacidosis were newly diagnosed diabetics.[1] Any concurrent illness in diabetic patients that causes inappetence, anorexia, or vomiting is rapidly complicated by dehydration, depression, and ketosis. Most diabetic cats that present with diabetic ketoacidosis have at least 1 concurrent disease; liver disease and pancreatitis are the most common.[1] In cats, diabetes mellitus is more commonly a sequela of pancreatitis rather than a risk factor for its development. An evaluation of pancreatitis in cats revealed that only 3% of cats with acute pancreatitis and 15% of cats with chronic pancreatitis had concurrent diabetes mellitus.[5] This is in contrast to dogs in which diabetes is usually classified as a preexisting condition.[3,6–8] Studies report concurrent pancreatitis in 13% to 36% of diabetic dogs[6–8] and in up to 52% of dogs with diabetic ketoacidosis.[3]

Hospitalized diabetics, regardless of the reason for hospitalization, still require insulin therapy. These patients are ideally treated with either a constant rate infusion[9–11] or intermittent intramuscular injections of short-acting insulin.[12] These intensive insulin treatments require close monitoring to ensure appropriate control of hyperglycemia and ketosis, while preventing complications caused by overly rapid correction of hyperglycemia, such as cerebral edema[2,13,14] or insulin-induced hypoglycemia. Such is also the case for nondiabetic patients at risk for altered glucose homeostasis, which includes critical care patients with a variety of conditions[15] including trauma, sepsis, the systemic inflammatory response syndrome,[16–18] portosystemic shunt,[19,20] insulinoma,[21] and liver failure,[22] as well as pediatric patients.

In human intensive care units, hyperglycemia occurs in up to 90% of all critically ill patients and is associated with increased morbidity and mortality.[23–26] The prevalence of hyperglycemia in critically ill nondiabetic cats has not been reported, although in dogs it is less frequent than reported for humans; in 1 study, only 16% of 245 nondiabetic dogs were hyperglycemic.[27] Whether the development of hyperglycemia in critically ill nondiabetic cats and dogs affects survival has yet to be determined. A retrospective evaluation of cats and dogs with head trauma failed to show any correlation between severity of hyperglycemia and survival,[28] although a more recent prospective study on dogs with a variety of critical illnesses did identify a significant association between the severity of hyperglycemia and length of hospital stay and survival.[27]

Continuous glucose monitoring and intensive glycemic control in critically ill human patients

Resulting from the high incidence of hyperglycemia and its association with increased morbidity and mortality, intensive protocols to maintain euglycemia have been investigated. The target and optimal method for achieving glucose control in the critical care setting are highly debated. In critically ill humans, one of the earliest studies to evaluate intensive insulin therapy with a goal of maintaining euglycemia (mean blood glucose level between 80 and 110 mg/dL; 4.4 and 6.1 mmol/L), showed a reduction in morbidity and mortality. The overall mortality rate dropped by 42%, with a decrease during hospitalization from 8.0% in the control group to 4.6% in the intensive insulin therapy group.[29] In addition, rates of infection, acute renal failure, transfusions, polyneuropathy, and mechanical ventilation were reduced.[29] Along with attaining euglycemia, reducing fluctuations and variability in glucose levels is significantly associated with decreased morbidity and mortality in humans.[30–32] Findings in subsequent studies on humans have been variable, with many showing a similar reduction in morbidity and mortality.[23,25,26,33]

Complicating the widespread acceptance of intensive insulin therapy in humans, several large prospective studies show either no benefit or even an increase in mortality for some patient groups. The largest such clinical trial, NICE-SUGAR, evaluated intensive insulin therapy in 6104 critically ill patients, and identified an increased mortality rate when the target blood glucose level was maintained between 81 and 108 mg/dL (4.5–6.0 mmol/L) compared with a less intensive protocol with a target blood glucose level of less than 180 mg/dL (10 mmol/L).[34] A follow-up meta-analysis concluded that intensive insulin protocols confer no benefit on mortality rates, but may still be useful in certain patient subsets, and may reduce the risk of end organ damage.[35] The most serious concern with intensive insulin therapy has been an increased risk of severe hypoglycemia.[25,33,35] In support of these findings, 2 large European clinical trials required early termination because of increased rates of severe hypoglycemia.[36,37] Hypoglycemia seems to be an important contributing factor in the increased mortality rates seen in intensive care patients, primarily those treated with intensive insulin therapy.[38,39] Despite these concerns, both the American Diabetes Association and the American Association of Clinical Endocrinologists recommend the use of intensive insulin protocols in the critical care setting, although with a more conservative target of 140 to 180 mg/dL (7.8–10 mmol/L).[40,41]

Conventional glucose monitoring requires the use of a point-of-care glucose meter and either frequent repeated venipuncture, capillary blood sampling, or placement of indwelling intravenous sampling catheters.[14] An important limitation of this technique is that it only allows for spot glucose determinations at a set interval, for example, every 2 to 4 hours, which limits the amount of information available on which to base treatment decisions and increases the workload on nursing staff and clinicians. It may also be a contributing factor to the frequency of severe hypoglycemia seen in patients treated with intensive insulin therapy, and directly affect morbidity and mortality rates.

The lack of improvement in morbidity and mortality seen with intensive insulin protocols may be partially due to the use of conventional glucose monitoring, as euglycemia may not actually be achieved. Using continuous glucose monitoring, investigators found that patients treated with intensive insulin therapy based on intermittent glucose monitoring achieved target blood glucose concentrations only 22% of the time.[42]

The use of a continuous glucose monitoring system would theoretically be a valuable tool in intensive insulin treatment of diabetic and nondiabetic feline patients in a critical care setting. Numerous studies on human patients have evaluated the ability of

continuous glucose monitoring systems to maintain euglycemia, limit glucose variability, and reduce the risk of severe hypoglycemia. For the most part, these studies have failed to show an improvement in glycemic control in the human intensive care setting.[26,43,44] However, the investigators of one particular study do note that treatment decisions were based on the actual blood glucose value rather than the trends; the ability to follow trends is a major advantage of continuous glucose monitoring.[44]

Despite inconsistency in reducing mortality rates, continuous glucose monitoring has proved useful in reducing the risk of severe hypoglycemia in critical care patients. Use of the Guardian Real-Time (Medtronic, Northridge, CA) continuous monitoring system with intensive insulin protocols has been shown to reduce the rate and absolute risk of severe hypoglycemia in human patients.[26,43] The MiniMed Gold (Medtronic, Northridge CA) has also proved beneficial in monitoring human patients with insulinoma, documenting frequent severe hypoglycemia, of which patients were often unaware, and documenting response to treatment with diazoxide and cure following surgical excision.[45]

Continuous glucose monitoring and intensive glycemic control in feline patients

Additional large prospective studies on feline patients are necessary to first determine whether hyperglycemia affects clinical outcome in critically ill patients, and second whether intensive insulin therapy to maintain euglycemia is beneficial. Lacking this information, intensive insulin therapy is not a consensus recommendation in critically ill cats, with the exception of diabetic ketoacidosis where maintaining euglycemia is necessary for resolution of the ketoacidotic state.

Similar to the theoretic and documented benefits in critically ill humans, continuous glucose monitoring systems are likely to have similar usefulness for sick diabetic and nondiabetic cats. Their use offers several advantages over conventional blood glucose monitoring. First, the frequency of venipuncture and associated patient stress, which can have negative consequences on glycemic status, is reduced.[46,47] The need for blood collection is not eliminated completely, as the monitoring system must be calibrated 2 to 3 times per day; however, this allows for substantially fewer blood samples than the 10 to 12 required with conventional blood glucose monitoring. In addition, blood for calibration can be collected from the ear or paw pad, eliminating the need for venipuncture.[48] A practical approach is to calibrate at the same time as other scheduled blood testing such as monitoring of serum electrolyte concentrations. Second, the need for indwelling catheters or the duration of time that they are left in place may be reduced, which in turn may reduce the risk of phlebitis/catheter site infection.[49–51] Third, glucose levels can be monitored continuously during treatment with insulin, leading to more targeted titration of insulin therapy, more rapid resolution of ketosis and clinical signs, shorter hospital stays, and a reduced risk of hypoglycemia.

To date, only the MiniMed Gold has been evaluated in sick diabetic veterinary patients. This system provides clinically accurate glucose concentrations in ketoacidotic dogs, buts its use is limited as glucose measurements are only available retrospectively.[52] In the critical care setting, a system with a real-time display is required as frequent adjustments to the insulin dose, fluid therapy, and glucose therapy are necessary. Although not clinically evaluated, in the authors' experience the Guardian Real-Time continuous glucose monitoring system is useful in sick diabetic cats (**Fig. 1**). Glucose measurements are available in real time allowing clinicians to continuously monitor glucose fluctuations in their patients at the cage side. As the device samples interstitial fluid, it is possible that it might not function as well in severely dehydrated patients. Therefore, this system should not be relied on until after initial fluid resuscitation. A practical approach is to attach the system after initial rehydration of the animal at the same time that short-acting insulin therapy is started.

Fig. 1. The Guardian Real-Time continuous glucose monitoring system used in a sick diabetic cat (diabetic ketoacidosis). Note the monitoring device attached to the cage receiving data wirelessly from a transmitter attached to the cat's back. This reduces the amount of material that must be directly connected to the cat, which would theoretically increase patient tolerance.

The usefulness of these systems for monitoring blood glucose concentration in critically ill nondiabetic veterinary patients has not yet been evaluated. Further study is required to determine whether the use of continuous glucose monitoring systems improves glycemic control and whether the benefits observed in human critical care can be realized in critically ill veterinary patients.

Critical Care (Sick/Hospitalized Diabetic and Nondiabetic Feline Patients): Accuracy

Accuracy is critical if these systems are to replace traditional assessment methods. Accuracy has been evaluated only once in veterinary patients. The MiniMed Gold was shown to have acceptable accuracy in feline and canine patients with diabetic ketoacidosis.[52] Correlation and agreement between values obtained from the continuous glucose monitoring system and those obtained using a portable glucose meter calibrated for human use were adequate (r = 0.86); the frequency of calibration had no effect on accuracy.[52] Consensus error grid analysis revealed that greater than 98% of the paired data points were in either zone A (no effect on the clinical decision made), or zone B (altered clinical decision unlikely to affect outcome). Less than 2% of the measurements were in zone C (altered clinical decision likely to affect outcome), and there were none in zone D or E (altered clinical decision posing a significant medical risk or having dangerous consequences).[52] The median average percent difference revealed good accuracy in both dogs (9%) and cats (10%); the median percentage difference never exceeded 22.6%.[52] Glucose estimates obtained at calibration times were included in this analysis, and calibration directly influences the glucose estimate by increasing the accuracy at those times. However, the results are clinically relevant as the standard calibration protocol for the device was followed. There was no difference in average percent difference when calibrated every 8 hours versus 12 hours.[52] Significant variability between patients was noted; estimates provided by continuous glucose monitoring systems were more accurate in some patients than others. No cause for this variation was identified, because there was no association with severity of ketosis, lactate, or rectal temperature, and only a weak association with hydration status.[52]

Long-Term Monitoring in Stable Feline Diabetic Patients: Usefulness

Diabetic feline patients are not likely to wear a continuous monitor long term on a day-to-day basis; however, these systems are useful for monitoring glucose in hospitalized

cats and dogs,[53–57] and may also replace repeated blood glucose concentration testing when used intermittently in the home setting.[58–60] They can be used during the initial adjustment phase of treatment to achieve stable control, and periodically thereafter to monitor that control, or to assess patients who have become uncontrolled. They are particularly useful to identify inadequate duration of insulin action, and preceding hypoglycemia as a cause for hyperglycemia.

Glycemic control is critical to abate clinical signs, maintain quality of life, and prevent complications. Effective management can decrease the amount of time patients spend with unregulated diabetes, resulting in improved health and quality of life, and reduced long-term costs. In addition, several studies have identified that improved and earlier glycemic control leads to higher rates of diabetic remission in cats.[61,62] This has been achieved with dietary therapy (low carbohydrate/high protein diet) and treatment with longer-acting insulin analogues such as protamine zinc insulin, glargine, or detemir.[61–64] Intensive protocols with either 3 consecutive days of blood glucose concentration monitoring in hospital, followed by weekly blood glucose curves in hospital or at home,[64] or daily home monitoring of blood glucose concentration have also been advocated.[61,62] These protocols have been evaluated in cats, and aim to ensure an appropriate starting dose and early glycemic control. Thus, higher rates of diabetic remission may be achieved compared with standard protocols; remission has been achieved in some cats previously treated for more than 6 months, albeit at lower rates than cats intensively treated earlier on.[61,62,64] When blood glucose concentration is closely monitored, it is expected that episodes of insulin-induced hypoglycemia can be identified earlier before clinical signs ensue, and the insulin dose adjusted appropriately.

Although intensive adjustment of insulin dose may be beneficial in achieving tight glycemic control and increasing the probability of diabetic remission in cats, it also can increase the risk of hypoglycemia, which can lead to irreversible brain damage, coma, and even death. Humans with both type 1 and 2 diabetes undergoing intensive at-home insulin therapy have a higher incidence of severe hypoglycemia compared with patients treated conventionally.[65] The prevalence of insulin-treated human patients experiencing a severe hypoglycemic event ranges from 1.5% to 7.3% annually; higher rates were seen in patients treated with intensive insulin therapy, 7.3% and 2.1%, versus 1.5% in patients with standard monitoring.[66,67] The incidence of mild asymptomatic hypoglycemia is even higher; 24% to 60% in 1 study. Some estimates indicate that many diabetics have mild hypoglycemia (<50–60 mg/dL; <2.7–3.3 mmol/L) up to 10% of the time.[68,69]

Asymptomatic nocturnal hypoglycemia is particularly common, especially in those human patients with overall good glycemic control.[70–72] A similar situation is seen in diabetic cats. In a study evaluating home monitoring of blood glucose in diabetic cats, 1/26 cats died of severe hypoglycemia.[48] Using the intensive protocols with either detemir or glargine insulin, asymptomatic hypoglycemia was common; nearly 12% and 10%, respectively, of all blood glucose concentration curves obtained had nadir values of less than 50 mg/dL (2.8 mmol/L).[61,62] Despite the high incidence of biochemical hypoglycemia, clinical hypoglycemia was seen only once for each insulin type, although episodes may have been under-reported. Both episodes were classified as mild with only restlessness and trembling seen.[61,62] Identifying hypoglycemia in insulin-treated diabetics, even when asymptomatic, is important for informing dose adjustments. If not addressed with appropriate dose adjustments, hypoglycemia may effect patient quality of life and if left untreated, could progress to fatal clinical hypoglycemia.

Insulin-induced hypoglycemic episodes can be short in duration, and easily missed with traditional in-hospital or home monitoring of serial blood glucose concentrations.

This is especially true for nocturnal hypoglycemia, as most hospitals do not have the facilities or staffing to perform overnight glucose monitoring, and most owners are unlikely to perform this task at home. In addition, hypoglycemia and the resultant Somogyi phenomenon can lead to persistent hyperglycemia during the subsequent 2 to 3 days due to counter-regulatory hormone production (**Figs. 2** and **3**).[70]

The most important advantage of continuous monitoring over intermittent blood glucose measurements is that it facilitates detection of brief periods of hypoglycemia and provides information overnight. Data can be recorded for multiple days, either in a clinic or at home. When used to monitor glycemia for a longer period, including overnight, there is evidence that a greater number of hypoglycemic events are detected.[60] When the GlucoDay (Menarini Diagnostics, Berkshire, United Kingdom) system was evaluated in the home environment in 10 diabetic dogs, investigators identified the Somogyi phenomenon, nocturnal hypoglycemia, and a brief episode of hypoglycemia in 3 of the 10 dogs.[60] In each instance, it is unlikely that traditional daytime blood glucose monitoring would have identified them, and erroneous treatment recommendations could have resulted.

The same situation occurred in diabetic cats when standard blood glucose concentration curves in the clinic were compared with curves obtained with continuous monitoring.[57] The investigators were blinded and made insulin dose recommendations based on these paired curves; this led to different dose recommendations between the 2 methodologies 30% of the time (19/63 treatment recommendations). The nadir obtained with continuous glucose monitoring was lower than that obtained with the standard curve 81% of the time. Based on these findings, the investigators concluded that the benefit was primarily in their ability to provide a more complete glucose profile and the detection of nadirs not identified with standard curves.[57]

Therefore, continuous glucose monitoring is valuable for determining the cause of hyperglycemia, and whether the most appropriate response is to increase or decrease the insulin dose or change to a longer-acting insulin.

To date, systems with or without a real-time data display have been evaluated primarily in the hospital setting to replace standard blood glucose concentration curves.[53–55,58] The readings are typically reviewed at the end of the sampling period and clinical recommendations made. Both wireless[55] and wired recording
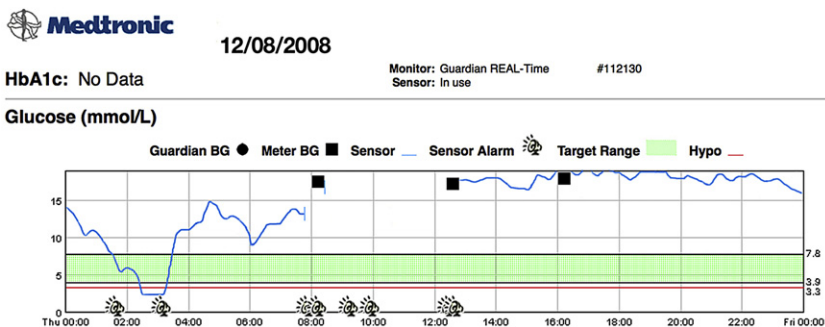
Fig. 2. Twenty-four hour continuous glucose concentration curve obtained using the Guardian Real-Time monitoring system in a diabetic dog. In this instance, use of continuous glucose monitoring identified the Somogyi phenomenon, with a blood glucose concentration less than the lower detection limit of the monitor (<40 mg/dL; 2.2 mmol/L) at 03:00 AM as shown by the flat line. This is an example of nocturnal hypoglycemia with a subsequent rapid increase in blood glucose within minutes that is sustained for the remainder of the tracing (minimum 20 hours).
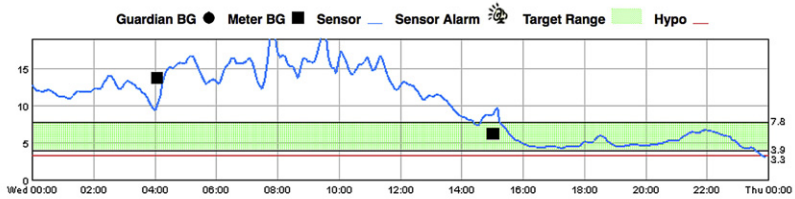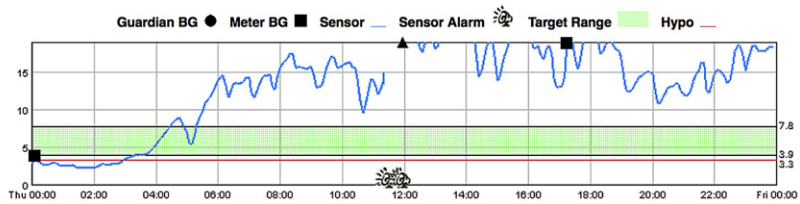
Fig. 3. Consecutive 24-hour tracings obtained using the Guardian Real-Time monitoring system in a diabetic cat. In this instance, use of continuous monitoring allowed for detection of nocturnal hypoglycemia, blood glucose <60 mg/dL (3.3 mmol/L) at around 00:00 AM and continuing until 03:00 AM.

devices[53,54,58] are reliable, but the wireless devices tend to be more convenient in the hospital setting as the monitor can be positioned outside the kennel (**Fig. 4**). In the home setting, even if a wireless device is used, it still requires attachment to the patient, because there is a maximum transmitting distance from the sensor to the monitor. The device can be attached using bandaging or garments with secured pockets, similar to those used with cardiac monitoring (Holter and event monitoring).
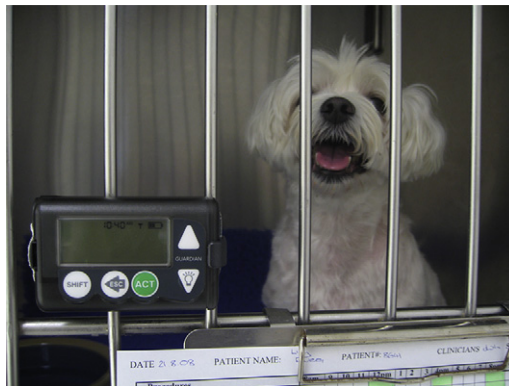
Fig. 4. Example of the Guardian Real-Time continuous glucose monitoring system monitor placed outside the patient's cage for real-time monitoring of blood glucose concentrations.

These garments are commonly used in large breed dogs for cardiovascular monitoring, and recent studies show they are well tolerated in cats.[73–75] Devices designed to record data, such as the i-Pro (Medtronic, Northridge CA), rather than transmit in real-time to a monitor would be ideal in a home setting because they are smaller and the need for extensive bandaging or garments is reduced.

Although glucose monitoring systems are a reliable alternative to conventional daytime serial blood glucose concentration monitoring[57] and are well tolerated by patients, the question arises as to whether they provide benefits over conventional monitoring that would justify the additional cost. In human diabetics receiving at home intensive insulin therapy, the introduction of long-term continuous glucose monitoring has reduced the incidence of hyperglycemia without increasing the risk of hypoglycemia,[76,77] and diabetic cats may get the same benefit.

Long-Term Monitoring in Stable Diabetic Patients: Accuracy

Continuous glucose monitoring systems rely on interstitial fluid glucose concentrations, therefore their ability to accurately predict blood glucose concentrations is critical; this was first evaluated using the MiniMed Gold on diabetic dogs with poor glycemic control.[53] Ten dogs were hospitalized for a minimum of 30 hours and received food and insulin treatment according to their usual routine. Standard blood glucose curves using a portable glucose meter calibrated for human use with samples collected every 1 to 3 hours were compared with the results of continuous monitoring, resulting in 428 hours of data and 183 paired glucose measurements. Data were similar with good correlation ($r = 0.81$); however, the blood glucose concentrations obtained with continuous glucose monitoring were statistically lower, an effect that was most pronounced during periods of hyperglycemia and 1 to 2 hours postprandially.[53] Because portable glucose meters calibrated for human use tend to give lower results than those calibrated for veterinary use or laboratory methods, it is likely that the discrepancy is greater than was reported.

For optimal accuracy, it is recommended that the correlation coefficient for compared measurements be a minimum of 0.79.[78] Subsequent studies on the accuracy of the MiniMed Gold have achieved better correlations than earlier studies, more consistent with those seen in humans using the same system.[79,80] Assessment in a population of diabetic and healthy animals gave correlations of $r = 0.997$ (dogs; $n = 7$) and 0.974 (cats; $n = 5$),[58] and evaluation in 16 diabetic cats identified similarly high correlation ($r = 0.932$) between blood and interstitial fluid measurements.[54] Excluding the blood glucose measurements used to calibrate the sensor, which are expected to be more accurate as a result of a direct effect on sensor readings, correlation was still adequate at $r = 0.862$.[54]

The MiniMed Gold has a working range of only 40 to 400 mg/dL (2.2–22.2 mmol/L). When evaluated in 14 cats, 16 blood glucose traces were obtained, with 7/16 affected by the limited recording range. Prolonged hypoglycemia and hyperglycemia were seen in 2/16 and 3/16 traces, respectively, and both hypoglycemia and hyperglycemia in 1/16, during which actual glucose concentrations were not measured. In addition, 1 cat initially had a blood glucose concentration of 282 mg/dL (15.7 mmol/L), but this increased and remained greater than 400 mg/dL (22.2 mmol/L) with the result that the device could not be calibrated and no trace was generated.[54]

Diabetic Patients Undergoing Surgery or Anesthesia: Usefulness

Anesthetized patients at risk for hypoglycemia or hyperglycemia are generally monitored using point-of-care glucose meters. As in other clinical settings, use of intermittent readings may result in failure to detect clinically significant changes in glycemic status.

Although 1 study has shown that the Guardian Real-Time provides inaccurately low glucose readings in anesthetized veterinary patients,[81] other devices may still prove useful in this situation. Even the Guardian Real-Time may be useful for monitoring impending hypoglycemia. This device tends to underestimate the blood glucose concentration, so values that are within the normal range would not require verification, reducing the frequency of venipuncture. Values in the hypoglycemic range would need to be confirmed by measuring the blood glucose concentration, but being more conservative, may provide an earlier warning of impending hypoglycemia than conventional monitoring.

Diabetic Patients Undergoing Surgery/Anesthesia: Accuracy

The accuracy of the Guardian Real-Time in anesthetized human pediatric patients is acceptable. This was shown in children undergoing cardiac surgery with 99.6% of paired values falling within zones A or B in the consensus error grid analysis, indicating no alteration in clinical action, and a mean difference of only 17.6%.[82] In addition, no negative effect was seen with hypothermia, inotrope use, or subcutaneous edema.[82] Similar results were seen in a second study on humans, with a mean difference of 13% and all paired values falling within zones A or B.[83]

To date, only 1 veterinary study has evaluated the accuracy of continuous glucose monitoring in anesthetized patients, comparing the Guardian Real-Time with the ISTAT portable chemistry analyzer (Abbott Laboratories, Abbott Park, IL).[81] In contrast to the confirmed accuracy in human patients under anesthesia, the same result was not obtained in dogs. Of 126 paired data points from 10 nondiabetic dogs under general anesthesia for routine abdominal surgery, acceptable agreement (<21% difference) was seen in only 57% of samples.[81] The Guardian Real-Time consistently recorded values lower than the blood glucose concentration for all discordant data points. In addition, hypoglycemia, blood glucose level less than 60 mg/dL (3.3 mmol/L), was recorded in 25/126 paired samples, whereas the portable chemistry analyzer recorded hypoglycemia in only 1 of these.[81]

GLUCOSE METER TECHNOLOGY
Laboratory Glucose Monitoring

Traditionally, glucose is measured as part of the routine biochemistry panel, using either in-house or reference laboratory analyzers. In the management of diabetics, serial measurements of blood glucose concentration using laboratory reference systems is impractical.

Glucose can be measured on either whole blood or on plasma/serum. Whole blood generally gives a lower glucose concentration than plasma/serum as a result of the higher water content of plasma (93% water) compared with erythrocytes (73% water). When glucose is reported based on whole blood, a multiplier of 1.1 is recommended to convert to the plasma/serum glucose concentration.[84,85]

The glucose molecule cannot be measured directly, and as a result 3 main methods have been developed to determine the concentration of glucose in a sample: reducing methods, condensation methods, and enzymatic methods. Because of problems with reducing and condensation methods, nearly all modern glucose measurements use indirect enzymatic methods.

Most reference laboratories use the enzyme hexokinase in assessing glucose concentrations. Hexokinase catalyzes the reaction between glucose and adenosine triphosphate, thereby phosphorylating glucose into glucose 6-phosphate. Subsequently, the enzyme glucose-6-phosphate dehydrogenase, in the presence of nicotinamide adenine

dinucleotide (NAD), oxidizes glucose 6-phosphate to reduced NAD (NADH) and 6-phosphogluconate. NADH can then be measured spectrophotometrically.[86]

Point-of-Care Glucose Monitoring

Blood glucose concentration testing using point-of-care glucose meters is the mainstay of monitoring for human diabetics, and is becoming increasingly popular amongst the owners of diabetic dogs and cats. The greatest advance came in the late 1980s with the development of portable glucose meters that use either photometric or electrochemical methods. These meters use enzyme systems specific for glucose, called oxidoreductases, the most common being glucose oxidase and glucose dehydrogenase. In addition, they also contain coenzymes, mediator systems, and indicators. The specific oxidoreductase, mediator, coenzymes, and indicators used vary with the individual glucose meter. To quantify the concentration of glucose in the sample, 2 main technologies are used: either a photometric or an electrochemical technique. In general, oxidation of glucose via a specific oxidoreductase, in the presence of coenzymes, generates electrons that are transferred to a mediator molecule, an organic or inorganic chemical that can alternate between an oxidized and reduced state (accept or donate electrons). These mediator molecules are then capable of donating electrons to either an electrode (electrochemical method) or an indicator molecule, which forms a color (photometric method).[87] Electrochemical methods contain either glucose oxidase or glucose dehydrogenase, and most commonly rely on hexacyanoferrate III/hexacyanoferrate II as the mediator system, generating an electric current that is calibrated to measure the concentration of glucose in the specimen. Most photometric methods use glucose oxidase and rely on the generation of hydrogen peroxide (mediator), similar to the technique used in colorimetric test strips. In contrast, the light reflected off the test strip is not measured by a reflectance meter, but rather generates an electric current after contact with a photodetector.[88]

Until recently, most portable glucose meters available for use on veterinary patients were intended for human use and so their validation was based on human blood. They assume a constant and unchanging relationship between plasma and whole blood, with erythrocytes and plasma each containing 50% of glucose. This distribution is not uniform across all species. Dogs have 12.5% and 87.5% of glucose in erythrocytes and plasma, respectively, and the disparity is even greater in cats (7% and 93%, respectively).[89] Because portable glucose meters typically evaluate plasma glucose after separation of erythrocytes from plasma, use of a human glucose meter on canine or feline blood often underestimates the true glucose concentration. Veterinary-use glucose meters have now been developed that provide more accurate results for cat and dog blood. Veterinary glucose meters available at the time of writing include the AlphaTRAK meter (Abbott Laboratories, Abbot Park, IL), the g-Pet meter (Woodley Equipment Company Ltd., Horwich United Kingdom), and the i-Pet meter (UltiCare Inc., St. Paul, MN). The AlphaTRAK meter has been evaluated in dogs, cats, and horses and the results have been published.[90–92] The manufacturers of the g-Pet and i-Pet meters provide comparable results for their products, although these have not been published in the peer-reviewed literature.[93,94] In all species, there is high correlation, accuracy, and precision between the AlphaTRAK meter and the reference method. In comparison, human glucose meters typically give significantly lower results compared with the AlphaTRAK and reference method in cats and dogs.[90–92]

The AlphaTRAK meter offers several advantages over the other veterinary glucometers, most notably the small sample size required to obtain a glucose measurement. The AlphaTRAK meter requires only 0.3 μL of blood,[90–92] whereas the g-Pet and i-Pet each require 1.5 μL.[93,94] The smaller sample size means that an adequate sample

volume is more reliably obtained from capillary sampling in veterinary patients, reducing or eliminating the need for venipuncture. This is especially important in individuals at risk for anemia from frequent venipuncture including feline patients in intensive care and pediatric patients. Capillary sampling is also essential for at-home continuous glucose monitoring, as owners must obtain blood samples to calibrate the system.

Interstitial and Plasma Glucose Relationships

An understanding of the relationship between interstitial and plasma glucose is essential to understanding the accuracy and limitations of devices. However, this topic is still under debate. The most commonly recognized model to explain interstitial-plasma glucose relationships is a 2-compartment model in which the capillary wall separating the plasma from the interstitial fluid acts as a barrier to the diffusion of glucose.[95,96] The interstitial glucose concentration in this model depends on the rate of diffusion across the capillary membrane, and the rate of glucose clearance from the interstitium. Glucose clearance from the interstitial space depends on insulin-mediated uptake by the surrounding cells, with a clearance rate proportional to the concentration of glucose in the interstitium and the rate of uptake by cells. If the rate of glucose uptake by surrounding cells is negligible and the diffusion rate between the plasma and interstitium is constant, a steady-state relationship will exist between interstitial and plasma glucose concentrations. Whether glucose uptake by the surrounding tissues is truly negligible is an area of debate, but, in general, there is a consensus that it is a steady-state relationship between plasma and interstitial glucose.[95,96]

Despite this steady-state relationship, diffusion of glucose from the plasma into the interstitial space is not immediate, and a corresponding lag phase exists between rapid changes in blood and interstitial glucose. Rapid changes in blood glucose concentration lead to corresponding changes in interstitial glucose, but with a delay of between 5 and 12 minutes in dogs.[79,96] Similar results have been identified in cats, with a lag time of approximately 11 minutes after an intravenous bolus of glucose.[55] Diffusion of glucose from the interstitium into the sensor may also affect the lag phase; however, available continuous glucose monitoring systems have digital filters designed to compensate for this delay.

Continuous Glucose Monitoring System Technology

Available systems use similar technology to portable blood glucose monitoring devices; glucose in the subcutaneous tissue is oxidized to gluconic acid and hydrogen peroxide. The latter is oxidized and donates electrons to the working electrode, which generates an electrochemical signal proportional to the concentration of glucose in the interstitial fluid.[55,59] Most current systems use electrochemical sensors implanted in the subcutaneous space and, to date, this remains the primary technology in the MiniMed Gold and Guardian Real-Time systems, as well as the i-Pro, Seven Plus (Dexcom, San Diego, CA), and FreeStyle Navigator (Abbott Diabetes Care, Alameda CA), all of which have been approved by the US Food and Drug Administration (FDA). More recently, a microdialysis system, GlucoDay, has been evaluated and approved for use in Europe, but is not yet FDA approved. Only the MiniMed Gold, Guardian Real-Time, and GlucoDay systems have been evaluated in veterinary patients.[52–56,58,60,81,97]

All sensor-based systems have multiple components: a glucose monitor that records data, a sterile single-use sensor, and a communication device for data download. In addition, wireless devices utilize a transmitter to distribute information from the sensor to the monitor. Each sensor is embedded in a split needle system to allow introduction into the subcutaneous space, and once in place, the needle is withdrawn;

the gauge of the needle varies with the individual system (**Table 1**). The sensor consists of an electroenzymatic 3-electrode cell that maintains a constant potential of 0.6 V between the working and reference electrodes. The sensor is enclosed in flexible tubing and contains a side window that exposes the working electrode to the subcutaneous space. A polyurethane membrane that is glucose diffusion limited, maintains a linear relationship between glucose concentration and sensor current, and covers the working electrode in the side window.[55,59] All reactions take place within the sensor and occur within the body.

In contrast, microdialysis-based systems use an implantable microdialysis fiber facilitating diffusion of interstitial fluid into the fiber, which is then carried to a central processing unit/monitoring device. The reaction that provides an estimate of blood glucose concentration is the same, but all reactions take place outside the body.[56]

SPECIFIC CONTINUOUS GLUCOSE MONITORING SYSTEMS

See **Table 1** for specific information regarding the available continuous glucose monitoring systems.

What is Available?

Currently, many systems have been approved for use throughout the world; however, only 3 systems have been clinically evaluated in dogs and cats: the MiniMed Gold; the Guardian Real-Time; and the GlucoDay. The Guardian Real-Time has effectively replaced the MiniMed Gold; however, this system is still in use and will likely continue to be in the near future. It consists of an electrochemical sensor that is inserted subcutaneously, to which a transmitting device is attached. This delivers data wirelessly to the monitor for review and storage (**Fig. 5**). Data can then be downloaded off the monitor.[55] In addition, the FDA has recently approved the i-Pro for use. The i-Pro and Guardian Real-Time use the same electrochemical sensor; however, the wireless transmitter used with the Guardian Real-Time is replaced with a recording device for data storage with the i-Pro.[98] There is no real-time display with the i-Pro, but it does allow for retrospective analysis. The Seven Plus and FreeStyle Navigator may also be applicable; however, they are yet to be evaluated in veterinary patients. These systems have similarities but there are also important differences that may affect the purchasing decision. Ultimately decisions should be based on individual needs.

Display/Recording

Continuous glucose monitoring systems can be divided based on their technology as previously discussed but also based on the display and recording type.

The MiniMed Gold and GlucoDay are wired systems, meaning the sensor or microdialysis fiber is directly connected to the recording device or processing unit.[52–54,56,58,60,81,97] The GlucoDay system is technically wireless as it can transmit wirelessly to a computer; however, the dialysis fiber is directly attached to the processing unit and thus animals must wear this even when in a hospital cage. The Guardian Real-Time, Seven Plus, and FreeStyle Navigator all function wirelessly, transmitting data to a monitor for storage and download.[55,99,100] A wireless device such as the Guardian Real-Time is more practical for hospitalized cats and dogs as the monitor can be placed outside the cage without the inconvenience of a connecting cable. In the home setting, even a wireless system requires attachment to the patient as the maximum transmitting distances are relatively short.

Table 1
Specifications of available continuous glucose monitoring systems

	MiniMed Gold[a]	Guardian Real-Time[b]	i-Pro[c]	GlucoDay[d]	FreeStyle Navigator[e]	Seven Plus[f]
Company	Medtronic	Medtronic	Medtronic	Menarini Diagnostics	Abbott	Dexcom
Availability	FDA approved, no longer manufactured	FDA approved	FDA approved	EU approved, not FDA approved	FDA approved	FDA approved
Evaluated in veterinary patients	Yes	Yes	No	Yes	No	No
Technology	Amperometric electrochemical sensor; glucose oxidase	Amperometric electrochemical sensor; glucose oxidase	Amperometric electrochemical sensor; glucose oxidase	Amperometric microdialysis fiber; glucose oxidase	Amperometric electrochemical sensor; glucose oxidase	Amperometric electrochemical sensor; glucose oxidase
Senor/transmitter weight	N/A	79 g (2.8 oz)	79 g (2.8 oz)	N/A	13.61 g (0.48 oz)	6.7 g (0.24 oz)
Transmitter/sensor size (L × W × H)	N/A	4.2 × 3.6 × 0.9 cm (1.64 × 1.4 × 0.37 in)	4.2 × 3.6 × 0.9 cm (1.64 × 1.4 × 0.37 in)	N/A	5.2 × 3.1 × 1.1 cm (2.5 × 1.23 × 0.43 in)	3.8 × 2.3 × 1.0 cm (1.5 × 0.9 × 0.4 in)
Monitor weight	113 g (4 oz)	114 g (4 oz)	N/A	245 g (8.6 oz)	100 g (3.5 oz)	100 g (3.5 oz)
Monitor size (L × W × H)	9.1 × 2.3 × 7.1 cm (3.6 × 0.9 × 2.8 in)	8.1 × 2.0 × 5.1 cm (3.2 × 0.8 × 2 in)	N/A	11 × 2.5 × 7.5 cm (4.3 × 1 × 3 in)	8.1 × 2.0 × 5.1 cm (2.5 × 3.2 × 0.9 in)	11.4 × 5.8 × 2.2 cm (4.5 × 2.3 × 0.85 in)
Recording range	40–400 mg/dL (2.2–22.2 mmol/L)	40–400 mg/dL (2.2–22.2 mmol/L)	40–400 mg/dL (2.2–22.2 mmol/L)	20–600 mg/dL (1.1–33.3 mmol/L)	40–400 mg/dL (2.2–22.2 mmol/L)	40–400 mg/dL (2.2–22.2 mmol/L)
Real-time display	No	Yes	No	Yes	Yes	Yes
Retrospective analysis	Yes	Yes	Yes	Yes	Yes	Yes

|						
Wireless transmission	No	Yes	No	Yes	Yes	Yes[a]
Wireless transmission range	N/A	23 m (10 feet)	N/A	N/A	3 m (10 feet)	1.5 m (5 feet)
Sensor needle insertion size	24 gauge	22 gauge (Sof-sensor) 27 gauge (Enlite sensor)	24 gauge	18 gauge	21 gauge	26 gauge
Sensor life	72 h	72 h (Sof-sensor) 144 h (Enlite sensor)	72 h (Sof-sensor) 144 h (Enlite sensor)	48 h	120 h	168 h
Sensor initialization period	1 h	2 h	1 h	1 h	2 h	2 h
Calibration	2–3 times per 24 h	2 h after insertion, within the next 6 h, then every 12 h	1 and 3 h after insertion, then minimum of once every 12 h	Minimum of 1 time point per 48 h, 2 if used in real time	10 h after insertion, within the next 2–4 h, then every 12 h	2 calibrations, 2 h after insertion, then every 12 h
Recording frequency	Data collected every 10 s, mean value reported every 5 min	Data collected every 10 s, mean value reported every 5 min	Data collected every 10 s, mean value reported every 5 min	Data collected every 1 s, mean value reported every 3 min	Data collected every 10 s, mean value reported every 5 min	Data collected every 10 s, mean value reported every 5 min

[a] Product specifications.[108]
[b] Product specifications.[55,109]
[c] Product specifications.[98]
[d] Product specifications.[56]
[e] Product specifications.[110]
[f] Product specifications.[111]
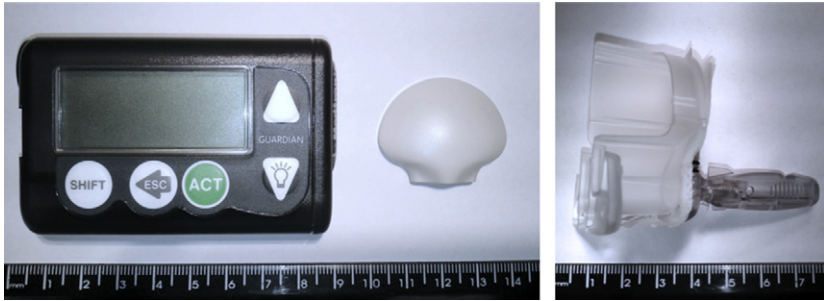
Fig. 5. The Guardian Real-Time continuous glucose monitoring system. From left to right: monitor, wireless transmitter, and electrochemical sensor.

The MiniMed Gold and i-Pro systems function retrospectively, meaning they store data that must be downloaded to a computer for analysis.[52–54,58,81,97,98] Clinical recommendations must therefore be delayed until the data can be retrospectively evaluated. Retrospective evaluation is advantageous in the home setting as owners are unable to visualize blood glucose results, reducing the likelihood they will alter treatment without consulting a veterinarian. These devices are not suitable for anesthetized or sick patients, as there is no real-time display to guide treatment. The Guardian Real-Time, Seven Plus, FreeStyle Navigator, and GlucoDay also record data but use a real-time display for immediate analysis of blood glucose data.[55,78]

Summary

- To replace or augment routine home or hospital blood glucose concentration monitoring, a continuous glucose monitoring system, with or without a real-time display, is appropriate, because the insulin dose can then be adjusted based on multiple readings.
- In anesthetized or sick patients, a real-time display is required; therefore the Guardian Real-Time or GlucoDay are the only systems applicable that have been evaluated in veterinary patients (others are available but have not been evaluated in veterinary patients).
- Wireless or wired devices are both practical options, although the wireless device is preferred in hospitalized cats and dogs.

PLACEMENT STRATEGIES AND PATIENT TOLERANCE

Placement and attachment of the various continuous glucose monitoring systems require that a site is chosen, clipped, and prepped for insertion of the sensor or dialysis fiber. Application of a small quantity of adhesive glue or suture can aid attachment of the sensor and reduce or eliminate the requirement for bandaging. Theoretically, implantation can be performed in any region that has sufficient subcutaneous space. The most commonly used sites are the flank, lateral thorax, and intrascapular region.[53,55,58,101] The most reliable site for placement of the Medtronic Guardian Real-Time sensor has been shown to be dorsal neck in cats, and the same is likely true for dogs.[102] For the GlucoDay system, a higher rate of microdialysis fiber collapse was reported in the intrascapular region than the lateral thoracic region.[56] However, collapse was attributed to the bandage technique; the use of only a protective coating rather than a firm bandage eliminated fiber collapse.[56]

The MiniMed Gold and Guardian Real-Time devices have been evaluated for in-hospital and at-home use in multiple studies, with few instances of adverse reaction.

Early studies evaluated animals in both the home and hospital setting, using the wired system. Placement of the sensor resulted in minimal discomfort, no irritation or inflammation at the site of attachment, and no abnormal behaviors, such as chewing, rolling, or biting, as reported by owners and clinical staff.[58,59] Some mild discomfort during removal of the sensor and associated redness was reported, likely related to the adhesive that was applied to attach the sensor to the skin.[58,59] A second study evaluating 16 diabetic cats in the hospital environment revealed similar results with no evidence of irritation at the site of sensor placement in any cat on any occasion. However, 1/16 patients removed the sensor after 12 hours, and 2/16 cats kinked the sensor during recording, requiring placement of a second sensor.[54]

More recently, the wireless Guardian Real-Time system has been evaluated; the patients were required to wear the sensor and a small transmitter, but not the monitor.[55] This was also the largest sample size evaluated, with 39 diseased cats and 5 healthy cats. These cats showed no signs of irritation or abnormal behavior, and no signs of skin irritation or reaction.[55] This system may be preferable as the monitor is the largest piece of equipment, and not wearing the monitor means that less material is required to secure the system, improving tolerance and compliance. This advantage only applies in the hospital setting, because the transmitting distance is only 3 m. Use of this system in the home environment would require patients to wear the monitor, as with wired systems.

The i-Pro system eliminates the need for patients to wear the monitor, because there is no wireless transmitter; the data are stored directly on the recording device. This dramatically reduces the size of the system that must be attached to the patient, even when used in the home environment.[98] This could facilitate a more simplified process for attaching the system to the patient, and improve patient tolerance. There are as yet no reports of the use of this system in veterinary medicine, but it would be ideal for at-home use.

As with standard in-hospital and at-home monitoring, critically ill patients tolerate the continuous glucose monitoring systems well.[52] The only adverse event seen was mild bleeding at the time of sensor insertion, which stopped with the application of direct pressure. No systems had to be removed because of irritation, pain, bleeding, or infection.[52] Although uncommonly reported in the literature, in our experience some cats succeed in removing the sensor despite bandaging. With small systems such as the Guardian Real-Time or i-Pro, the sensor can be taped in place to prevent removal (**Fig. 6**).

Fig. 6. Adhesive bandage tape used to secure the Guardian Real-Time sensor/transmitting device in a cat that repeatedly attempted to remove it despite standard bandaging.

Microdialysis-based systems such as the GlucoDay are also well tolerated, with limited adverse reactions. In the 2 veterinary studies evaluating this, 4/6 healthy and 3/10 diabetic dogs showed mild agitation/shaking after placement. In addition, 0/6 healthy and 4/10 diabetic dogs showed mild erythema after removal of the fiber, which soon resolved.[56,60] This system is yet to be clinically evaluated in cats, but the large processing unit may limit its use.

Summary

- The most suitable location for placement of the Medtronic Guardian Real-Time sensor is the dorsal neck, whereas the lateral thorax is preferred for the GlucoDay system.
- All systems are generally well tolerated, with no differences reported.
- Newer more compact systems like the i-Pro are likely to improve patient tolerance and minimize adverse reactions, because they require less bandaging, leading to greater patient comfort. This has not yet been clinically evaluated in veterinary patients.

SENSOR LIFESPAN/STABILITY

All systems use the same enzymatic reaction to estimate the blood glucose concentration based on interstitial glucose concentration. The MiniMed Gold, Guardian Real-Time, i-Pro, Seven Plus, and FreeStyle Navigator are sensor based, whereas the GlucoDay is microdialysis based. Although both technologies are sufficiently accurate for clinical use, some advocate the use of microdialysis fibers to harvest interstitial fluid over the use of implantable sensors.[56,60] The rationale is based on separation of the dialysis fiber from the biosensor so that all reactive substances and waste products such as hydrogen peroxide remain external to the body. As a result, they cannot diffuse into the surrounding tissues, eliminating contact with inflammatory cells and serum proteins, which can cause degradation/biofouling of the implanted material. In theory, this can interfere with the performance of the sensor.[103] Others argue that the short insertion time of only 48 to 72 hours for sensors currently available negates the effect of biofouling.[104,105]

Each sensor/dialysis fiber has a lifespan, after which time it must be replaced. The time varies with the individual sensor. The dialysis fiber used in the GlucoDay system has a lifespan of approximately 48 hours.[56] With regard to the Guardian Real-Time and i-Pro, sensor technology has recently changed. The original Sof-sensor (Medtronic, Northridge, CA) had a lifespan of 72 hours, whereas the new Enlite sensor (Medtronic, Northridge, CA) has a lifespan of 144 hours.[55,106,107] At the end of the initial 72 hour monitoring period using the Guardian Real-Time system, the monitor will prompt the user to change the sensor. Rather than placing a new sensor, the transmitter can be reattached to the original sensor, and the system restarted to allow a further 72 hours of monitoring, although sensor accuracy subjectively may decrease after 48 hours. This would theoretically provide more data and contribute more information to help better guide treatment decisions.

Summary

- Microdialysis technology may prove advantageous in that performance may be less affected by inflammation/tissue reaction; however, head-to-head comparisons have not been performed in veterinary medicine to determine clinically relevant superiority in short-term use.

- With the development of the Enlite sensor, the Guardian Real-Time and i-Pro now provide the option of continuous monitoring for 144 hours.

INITIALIZATION/CALIBRATION

Despite the continuous measurement of interstitial glucose, all monitors must be calibrated daily to ensure accurate results. Calibration can be performed with venous blood obtained via venipuncture or via a capillary prick. Because of the species differences in glucose homeostasis/concentrations, a veterinary glucose meter should be used for calibration if possible. There is a lag of approximately 10 to 15 minutes between blood and interstitial glucose concentrations, therefore it is important to avoid calibration whenever the glucose concentration is changing rapidly, such as during excitement or struggling. If calibration is necessary when the blood glucose concentration is changing rapidly, it is recommended that calibration be repeated once the blood glucose concentration has stabilized.

With real-time continuous glucose monitors, human patients are encouraged to calibrate before meals, at bedtime, and not within the first few hours after insulin administration to avoid periods of rapidly changing glucose concentrations. Real-time systems incorporate directional arrows on the monitor advising the user as to the direction and rate of change of the blood glucose concentration. The manufacturers advise not to calibrate if indicator arrows are showing on their device. For the Guardian Real-time, 1 arrow indicates a change of 18–36 mg/dL (1 to 2 mmol/L) in the last 20 minutes, and 2 arrows represent > 36mg/dL (2 or more mmol/L) in the last 20 minutes. With units that do not provide real-time display, such as the i-Pro, because the calibration glucose measurements are inputted into the program after the data is downloaded, having the blood glucose stable at the time of testing is not as important, because a different algorithm is used for calibration of the i-Pro compared with the real-time continuous glucose monitors.

In cats, consumption of a low carbohydrate diet is unlikely to cause rapid changes in glucose concentration. Glucose concentrations can change rapidly in some cats after insulin administration, depending on the insulin used and the individual cat, and after hypoglycemia during a Somogyi event. In most diabetic cats, the blood glucose concentration is likely to be most stable just before each insulin injection and feeding. Because the pre-insulin blood glucose concentration is also used for adjustment of dose for long-acting insulin, it would be of most benefit to measure blood glucose at this time, and use the value for calibration. For real-time units, this would provide quality control for the glucose concentrations that are important for dosing decisions; and for retrospective units being using for at-home blood glucose monitoring, it would help to prevent an inappropriately high dose of insulin being administered when the blood glucose concentration is within or less than the normal range.

For the MiniMed Gold and Guardian Real-Time systems, calibration must be performed once within the first 2 hours, with further calibration varying according to the manufacturer's recommendations.[59,97,101] For the MiniMed Gold, 3 calibrations per 24-hour period are recommended, although there are no significant differences in glucose estimates when calibrated 2 versus 3 times daily in veterinary patients. As a result, the MiniMed Gold could be used with only twice daily calibration, rather than according to the manufacturer's recommendations.[52] The manufacturer of the Guardian Real-Time recommends recalibration after 6 hours, and then 2 calibrations per 24-hour period.[55]

Manufacturer recommendations for the GlucoDay system recommend 1 or 2 calibrations per 48-hour period with the first performed 1 to 2 hours after placement. A

study of varying calibration schemes in healthy dogs found that 2 calibrations, once at the beginning and again at the end of the observation period, provided the most accurate results.[56] There was no advantage to more frequent calibration.[56,60]

All these calibrations are performed prospectively during the recording period. The i-Pro manufacturer recommends calibration at 1 and 3 hours after insertion, then 2 times per 12 hours. In contrast to other available systems, the blood glucose concentration and time it was measured are entered retrospectively at the end of the recording period, which may prove advantageous, because it would simplify the process when calibration is performed by nursing staff or owners.[98,100]

As with all continuous glucose monitoring systems, more frequent calibration often provides superior accuracy. It is possible that fewer calibrations per day may be adequate for various systems, but with the exception of the MiniMed Gold and Gluco-Day systems, this has not yet been tested in veterinary patients.

In addition to the frequency of calibration needed to obtain accurate results, the ability to perform the initial calibration can sometimes be an issue. The MiniMed Gold, Guardian Real-Time, and i-Pro systems have a range of 40 to 400 mg/dL (2.2–22.2 mmol/L)[55,59,97,98,101]; values outside this range are not reported. The Gluco-Day has a wider range of 20 to 600 mg/dL (1.1–33.3 mmol/L).[56] When the initial blood glucose concentrations are outside this range, the manufacturers recommend delaying sensor insertion until the blood glucose is within range. In our experience, the Guardian Real-Time sensor can still be inserted and the system initialized even when the blood glucose concentration is outside this range. In hyperglycemic patients with blood glucose concentrations greater than 400 mg/dL (>22.2 mmol/L), calibration with a value of 400 mg/dL (22.2 mmol/L) allows for operation of the device. The specific readings will not be accurate, but trends can still be observed. For example, a patient with an initial blood glucose concentration of 580 mg/dL (32.2 mmol/L), which is outside the range for the MiniMed Gold and Guardian Real-Time systems, could be calibrated using 400 mg/dL (22.2 mmol/L) as the initial value. The system can then be used to ensure therapy is having the desired effect as represented by a gradual decrease in the glucose readings. Visualizing this decrease would eliminate the need to perform frequent blood sampling, as the trend is reliable. Because of the fairly linear relationship between plasma and interstitial glucose levels, once the display reads 184 mg/dL (10.2 mmol/L), the blood glucose concentration can be assumed to have decreased to approximately 400 mg/dL (22.2 mmol/L), and can be verified using a portable glucose meter. Once the blood glucose concentration is within range, the system can be recalibrated and subsequent values deemed accurate.

The working range of these systems is not a practical limitation in the clinical setting. For treatment decisions, it is usually sufficient to know that an animal's glucose concentration is less than 40 mg/dL (<2.2 mmol/L) or greater than 400 mg/dL (>22.2 mmol/L). Direct blood glucose measurements can be performed if a more accurate result is required.

Summary

- Calibration should be avoided when a rapid change in blood glucose concentration is anticipated, or when directional arrows are showing on the monitor.
- The GlucoDay system has a wider working range than the MiniMed Gold and Guardian Real-Time systems and so can be accurately calibrated in hyperglycemic animals (up to 600 mg/dL, 33.3 mmol/L).
- The reduced frequency of calibration (2 calibrations/48 hours), while maintaining accuracy, is a substantial advantage of the GlucoDay system compared with the

MiniMed Gold and Guardian Real-Time systems (2–3 calibrations/24 hours), primarily when calibration is inconvenient, for example at night and in the home setting.

SUMMARY

More information is needed regarding the accuracy and usefulness of continuous glucose monitoring systems for anesthetized patients; as yet, their use in monitoring nondiabetic patients with altered glucose homeostasis has not been evaluated. The Guardian Real-Time system is a versatile monitoring system because its real-time display means that it can be used in all settings. It is likely to be better tolerated due to its small size and wireless nature. The same may apply to the GlucoDay system; however, it may be less ideal for small patients or in-hospital use because patients must wear the dialysis fiber and processing unit. The i-Pro has yet to be investigated in veterinary patients, but may be the most advantageous system for at-home monitoring because of its small size, lack of a monitor, and retrospective analysis.

REFERENCES

1. Bruskiewicz KA, Nelson RW, Feldman EC, et al. Diabetic ketosis and ketoacidosis in cats: 42 cases (1980-1995). J Am Vet Med Assoc 1997;211(2):188–92.
2. Feldman E, Nelson R. Diabetic ketoacidosis. In: Feldman E, Nelson R, editors. Canine and feline endocrinology and reproduction. 3rd edition. St Louis (MO): Elsevier; 2004. p. 580–615.
3. Hume DZ, Drobatz KJ, Hess RS. Outcome of dogs with diabetic ketoacidosis: 127 dogs (1993-2003). J Vet Intern Med 2006;20(3):547–55.
4. Greco DS. Complicated diabetes mellitus. In: Bonagura JD, Twedt DC, editors. Current veterinary therapy XIV. St Louis (MO): Elsevier; 2009. p. 214–8.
5. Ferreri JA, Hardam E, Kimmel SE, et al. Clinical differentiation of acute necrotizing from chronic nonsuppurative pancreatitis in cats: 63 cases (1996-2001). J Am Vet Med Assoc 2003;223(4):469–74.
6. Cook AK, Breitschwerdt EB, Levine JF, et al. Risk factors associated with acute pancreatitis in dogs: 101 cases (1985-1990). J Am Vet Med Assoc 1993;203(5):673–9.
7. Hess RS, Kass PH, Shofer FS, et al. Evaluation of risk factors for fatal acute pancreatitis in dogs. J Am Vet Med Assoc 1999;214(1):46–51.
8. Papa K, Mathe A, Abonyi-Toth Z, et al. Occurrence, clinical features and outcome of canine pancreatitis (80 cases). Acta Vet Hung 2011;59(1):37–52.
9. Macintire DK. Treatment of diabetic ketoacidosis in dogs by continuous low-dose intravenous infusion of insulin. J Am Vet Med Assoc 1993;202(8):1266–72.
10. Claus MA, Silverstein DC, Shofer FS, et al. Comparison of regular insulin infusion doses in critically ill diabetic cats: 29 cases (1999-2007). J Vet Emerg Crit Care (San Antonio) 2010;20(5):509–17.
11. Sears KW, Drobatz KJ, Hess RS. Use of lispro insulin for treatment of diabetic ketoacidosis in dogs. J Vet Emerg Crit Care (San Antonio) 2012;22(2):211–8.
12. Chastain CB, Nichols CE. Low-dose intramuscular insulin therapy for diabetic ketoacidosis in dogs. J Am Vet Med Assoc 1981;178(6):561–4.
13. Hoorn EJ, Carlotti AP, Costa LA, et al. Preventing a drop in effective plasma osmolality to minimize the likelihood of cerebral edema during treatment of children with diabetic ketoacidosis. J Pediatr 2007;150(5):467–73.
14. O'Brien MA. Diabetic emergencies in small animals. Vet Clin North Am Small Anim Pract 2010;40(2):317–33.

15. Knieriem M, Otto CM, Macintire D. Hyperglycemia in critically ill patients. Compendium 2007;29(6):360–2, 364–72; [quiz: 372].
16. Hardie EM, Rawlings CA, George JW. Plasma-glucose concentrations in dogs and cats before and after surgery: comparison of healthy animals and animals with sepsis. Am J Vet Res 1985;46(8):1700–4.
17. Bonczynski JJ, Ludwig LL, Barton LJ, et al. Comparison of peritoneal fluid and peripheral blood pH, bicarbonate, glucose, and lactate concentration as a diagnostic tool for septic peritonitis in dogs and cats. Vet Surg 2003;32(2):161–6.
18. DeClue AE, Williams KJ, Sharp C, et al. Systemic response to low-dose endotoxin infusion in cats. Vet Immunol Immunopathol 2009;132(2–4):167–74.
19. Center SA, Magne ML. Historical, physical examination, and clinicopathologic features of portosystemic vascular anomalies in the dog and cat. Semin Vet Med Surg (Small Anim) 1990;5(2):83–93.
20. Bostwick DR, Twedt DC. Intrahepatic and extrahepatic portal venous anomalies in dogs: 52 cases (1982-1992). J Am Vet Med Assoc 1995;206(8):1181–5.
21. Greene SN, Bright RM. Insulinoma in a cat. J Small Anim Pract 2008;49(1):38–40.
22. Sherding RG. Acute hepatic failure. Vet Clin North Am Small Anim Pract 1985; 15(1):119–33.
23. Finney SJ, Zekveld C, Elia A, et al. Glucose control and mortality in critically ill patients. JAMA 2003;290(15):2041–7.
24. Krinsley JS. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. Mayo Clin Proc 2003;78(12):1471–8.
25. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin Proc 2004;79(8):992–1000.
26. Holzinger U, Warszawska J, Kitzberger R, et al. Real-time continuous glucose monitoring in critically ill patients: a prospective randomized trial. Diabetes Care 2010;33(3):467–72.
27. Torre DM, deLaforcade AM, Chan DL. Incidence and clinical relevance of hyperglycemia in critically ill dogs. J Vet Intern Med 2007;21(5):971–5.
28. Syring RS, Otto CM, Drobatz KJ. Hyperglycemia in dogs and cats with head trauma: 122 cases (1997-1999). J Am Vet Med Assoc 2001;218(7):1124–9.
29. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359–67.
30. Egi M, Bellomo R, Stachowski E, et al. Variability of blood glucose concentration and short-term mortality in critically ill patients. Anesthesiology 2006;105(2): 244–52.
31. Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. Crit Care Med 2008;36(11):3008–13.
32. Krinsley JS, Meyfroidt G, van den Berghe G, et al. The impact of premorbid diabetic status on the relationship between the three domains of glycemic control and mortality in critically ill patients. Curr Opin Clin Nutr Metab Care 2012;15(2): 151–60.
33. Reed CC, Stewart RM, Sherman M, et al. Intensive insulin protocol improves glucose control and is associated with a reduction in intensive care unit mortality. J Am Coll Surg 2007;204(5):1048–54 [discussion: 1054–5].
34. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360(13):1283–97.
35. Griesdale DE, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ 2009;180(8):821–7.

36. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008;358(2):125–39.
37. Devos P, Presier J, Melot C. Impact of tight glucose control by intensive insulin therapy on ICU mortality and the rate of hypoglycemia: final results of the glucose control study. Intensive Care Med 2007;33:S189.
38. Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. Crit Care Med 2007;35(10):2262–7.
39. Krinsley J, Schultz MJ, Spronk PE, et al. Mild hypoglycemia is strongly associated with increased intensive care unit length of stay. Ann Intensive Care 2011; 1:49.
40. American Diabetes Association. Standards of medical care in diabetes–2012. Diabetes Care 2012;35(Suppl 1):S11–63.
41. Moghissi ES, Korytkowski MT, DiNardo M, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Endocr Pract 2009;15(4):353–69.
42. De Block C, Manuel YK, Van Gaal L, et al. Intensive insulin therapy in the intensive care unit: assessment by continuous glucose monitoring. Diabetes Care 2006;29(8):1750–6.
43. Steil GM, Langer M, Jaeger K, et al. Value of continuous glucose monitoring for minimizing severe hypoglycemia during tight glycemic control. Pediatr Crit Care Med 2011;12(6):643–8.
44. Brunner R, Adelsmayr G, Herkner H, et al. Glycemic variability and glucose complexity in critically ill patients: a retrospective analysis of continuous glucose monitoring data. Crit Care 2012;16(5):R175.
45. Munir A, Choudhary P, Harrison B, et al. Continuous glucose monitoring in patients with insulinoma. Clin Endocrinol 2008;68(6):912–8.
46. Nelson R. Stress hyperglycemia and diabetes mellitus in cats. J Vet Intern Med 2002;16(2):121–2.
47. Rand JS, Kinnaird E, Baglioni A, et al. Acute stress hyperglycemia in cats is associated with struggling and increased concentrations of lactate and norepinephrine. J Vet Intern Med 2002;16(2):123–32.
48. Kley S, Casella M, Reusch CE. Evaluation of long-term home monitoring of blood glucose concentrations in cats with diabetes mellitus: 26 cases (1999-2002). J Am Vet Med Assoc 2004;225(2):261–6.
49. Blaiset MA, Couto CG, Evans KL, et al. Complications of indwelling, silastic central venous access catheters in dogs and cats. J Am Anim Hosp Assoc 1995;31(5):379–84.
50. Mathews KA, Brooks MJ, Valliant AE. A prospective study of intravenous catheter contamination. J Vet Emerg Crit Care (San Antonio) 1996;6(1):33–43.
51. Seguela J, Pages JP. Bacterial and fungal colonisation of peripheral intravenous catheters in dogs and cats. J Small Anim Pract 2011;52(10):531–5.
52. Reineke EL, Fletcher DJ, King LG, et al. Accuracy of a continuous glucose monitoring system in dogs and cats with diabetic ketoacidosis. J Vet Emerg Crit Care (San Antonio) 2010;20(3):303–12.
53. Davison LJ, Slater LA, Herrtage ME, et al. Evaluation of a continuous glucose monitoring system in diabetic dogs. J Small Anim Pract 2003;44(10):435–42.
54. Ristic JM, Herrtage ME, Walti-Lauger SM, et al. Evaluation of a continuous glucose monitoring system in cats with diabetes mellitus. J Feline Med Surg 2005;7(3):153–62.
55. Moretti S, Tschuor F, Osto M, et al. Evaluation of a novel real-time continuous glucose-monitoring system for use in cats. J Vet Intern Med 2010;24(1):120–6.

56. Affenzeller N, Benesch T, Thalhammer JG, et al. A pilot study to evaluate a novel subcutaneous continuous glucose monitoring system in healthy Beagle dogs. Vet J 2010;184(1):105–10.

57. Dietiker-Moretti S, Muller C, Sieber-Ruckstuhl N, et al. Comparison of a continuous glucose monitoring system with a portable blood glucose meter to determine insulin dose in cats with diabetes mellitus. J Vet Intern Med 2011;25(5):1084–8.

58. Wiedmeyer CE, Johnson PJ, Cohn LA, et al. Evaluation of a continuous glucose monitoring system for use in dogs, cats, and horses. J Am Vet Med Assoc 2003;223(7):987–92.

59. Wiedmeyer CE, Johnson PJ, Cohn LA, et al. Evaluation of a continuous glucose monitoring system for use in veterinary medicine. Diabetes Technol Ther 2005;7(6):885–95.

60. Affenzeller N, Thalhammer JG, Willmann M. Home-based subcutaneous continuous glucose monitoring in 10 diabetic dogs. Vet Rec 2011;169(8):206.

61. Roomp K, Rand J. Intensive blood glucose control is safe and effective in diabetic cats using home monitoring and treatment with glargine. J Feline Med Surg 2009;11(8):668–82.

62. Roomp K, Rand J. Evaluation of detemir in diabetic cats managed with a protocol for intensive blood glucose control. J Feline Med Surg 2012;14(8):566–72.

63. Marshall RD, Rand JS, Morton JM. Glargine and protamine zinc insulin have a longer duration of action and result in lower mean daily glucose concentrations than lente insulin in healthy cats. J Vet Pharmacol Ther 2008;31(3):205–12.

64. Marshall RD, Rand JS, Morton JM. Treatment of newly diagnosed diabetic cats with glargine insulin improves glycaemic control and results in higher probability of remission than protamine zinc and lente insulins. J Feline Med Surg 2009;11(8):683–91.

65. Unger J. Uncovering undetected hypoglycemic events. Diabetes Metab Syndr Obes 2012;5:57–74.

66. Leese GP, Wang J, Broomhall J, et al. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. Diabetes Care 2003;26(4):1176–80.

67. Zoungas S, Patel A, Chalmers J, et al. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010;363(15):1410–8.

68. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. Diabetes Care 2003;26(6):1902–12.

69. Brod M, Christensen T, Thomsen TL, et al. The impact of non-severe hypoglycemic events on work productivity and diabetes management. Value Health 2011;14(5):665–71.

70. Stephenson JM, Schernthaner G. Dawn phenomenon and Somogyi effect in IDDM. Diabetes Care 1989;12(4):245–51.

71. Wentholt IM, Maran A, Masurel N, et al. Nocturnal hypoglycaemia in Type 1 diabetic patients, assessed with continuous glucose monitoring: frequency, duration and associations. Diabet Med 2007;24(5):527–32.

72. Woodward A, Weston P, Casson IF, et al. Nocturnal hypoglycaemia in type 1 diabetes–frequency and predictive factors. QJM 2009;102(9):603–7.

73. Petrie JP. Practical application of holter monitoring in dogs and cats. Clin Tech Small Anim Pract 2005;20(3):173–81.

74. Hanas S, Tidholm A, Egenvall A, et al. Twenty-four hour Holter monitoring of unsedated healthy cats in the home environment. J Vet Cardiol 2009;11(1):17–22.

75. Rasmussen CE, Vesterholm S, Ludvigsen TP, et al. Holter monitoring in clinically healthy Cavalier King Charles Spaniels, Wire-haired Dachshunds, and Cairn Terriers. J Vet Intern Med 2011;25(3):460–8.

76. Kovatchev B, Clarke W. Continuous glucose monitoring (CGM) reduces risks for hypo- and hyperglycaemia and glucose variability in diabetes. Diabetes 2007; 56(Suppl 1). pA23.

77. Garg S, Zisser H, Schwartz S, et al. Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: a randomized controlled trial. Diabetes Care 2006;29(1):44–50.

78. Mastrototaro J. The MiniMed Continuous Glucose Monitoring System (CGMS). J Pediatr Endocrinol Metab 1999;12(Suppl 3):751–8.

79. Rebrin K, Steil GM, van Antwerp WP, et al. Subcutaneous glucose predicts plasma glucose independent of insulin: implications for continuous monitoring. Am J Phys 1999;277(3 Pt 1):E561–71.

80. Bode BW, Gross TM, Thornton KR, et al. Continuous glucose monitoring used to adjust diabetes therapy improves glycosylated hemoglobin: a pilot study. Diabetes Res Clin Pract 1999;46(3):183–90.

81. Bilicki KL, Schermerhorn T, Klocke EE, et al. Evaluation of a real-time, continuous monitor of glucose concentration in healthy dogs during anesthesia. Am J Vet Res 2010;71(1):11–6.

82. Piper HG, Alexander JL, Shukla A, et al. Real-time continuous glucose monitoring in pediatric patients during and after cardiac surgery. Pediatrics 2006; 118(3):1176–84.

83. Vriesendorp TM, DeVries JH, Holleman F, et al. The use of two continuous glucose sensors during and after surgery. Diabetes Technol Ther 2005;7(2):315–22.

84. Holtkamp HC, Verhoef NJ, Leijnse B. The difference between the glucose concentrations in plasma and whole blood. Clin Chim Acta 1975;59(1):41–9.

85. McMillin J. Blood glucose. Boston: Butterworths; 1990.

86. Henry JB. Clinical diagnosis and management by laboratory methods. Philadelphia: WB Saunders; 1979.

87. Hones J, Muller P, Surridge N. The technology behind glucose meters: test strips. Diabetes Technol Ther 2008;10(Suppl 1):s10–26.

88. Montagnana M, Caputo M, Giavarina D, et al. Overview on self-monitoring of blood glucose. Clin Chim Acta 2009;402(1–2):7–13.

89. Coldman MF, Good W. The distribution of sodium, potassium and glucose in the blood of some mammals. Comp Biochem Physiol 1967;21(1):201–6.

90. Zini E, Moretti S, Tschuor F, et al. Evaluation of a new portable glucose meter designed for the use in cats. Schweiz Arch Tierheilkd 2009;151(9):448–51.

91. Hackett ES, McCue PM. Evaluation of a veterinary glucometer for use in horses. J Vet Intern Med 2010;24(3):617–21.

92. Paul AE, Shiel RE, Juvet F, et al. Effect of hematocrit on accuracy of two point-of-care glucometers for use in dogs. Am J Vet Res 2011;72(9):1204–8.

93. Laboratory, diagnostic and critical care products direct to worldwide vet distributors. g-Pet glucose veterinary monitoring system. 2012. Available at: http://www.woodleyequipment.com/veterinary-diagnostics.html?&flag=y. Accessed November 29, 2012.

94. Ulti-Care iPet glucose monitoring system. 2012. Available at: http://www.ulti-care.com/ipet-blood-glucose-monitoring.html. Accessed November 29, 2012.

95. Sternberg F, Meyerhoff C, Mennel FJ, et al. Subcutaneous glucose concentration in humans. Real estimation and continuous monitoring. Diabetes Care 1995;18(9):1266–9.

96. Rebrin K, Steil GM. Can interstitial glucose assessment replace blood glucose measurements? Diabetes Technol Ther 2000;2(3):461–72.

97. DeClue AE, Cohn LA, Kerl ME, et al. Use of continuous blood glucose monitoring for animals with diabetes mellitus. J Am Anim Hosp Assoc 2004;40(3): 171–3.

98. i-Pro 2 Progessional continuous glucose monitoring system user guide. 2012. Available at: http://www.professional.medtronicdiabetes.com/hcp-products/ipro2. Accessed November 29, 2012.

99. Battelino T, Bolinder J. Clinical use of real-time continuous glucose monitoring. Curr Diabetes Rev 2008;4(3):218–22.

100. Hrabchak R, Taylor J. A new glucose monitoring option. J Fam Pract 2010;59(2): 81–8.

101. Wiedmeyer CE, DeClue AE. Continuous glucose monitoring in dogs and cats. J Vet Intern Med 2008;22(1):2–8.

102. Hafner M, Lutz TA, Reusch CE, et al. Evaluation of sensor sites for continuous glucose monitoring in cats with diabetes mellitus. Journal of feline medicine and surgery 2013;15(2):117–23.

103. Gerritsen M, Jansen JA, Kros A, et al. Influence of inflammatory cells and serum on the performance of implantable glucose sensors. J Biomed Mater Res 2001; 54(1):69–75.

104. Kvist PH, Iburg T, Bielecki M, et al. Biocompatibility of electrochemical glucose sensors implanted in the subcutis of pigs. Diabetes Technol Ther 2006;8(4): 463–75.

105. Kvist PH, Iburg T, Aalbaek B, et al. Biocompatibility of an enzyme-based, electrochemical glucose sensor for short-term implantation in the subcutis. Diabetes Technol Ther 2006;8(5):546–59.

106. Keenan DB, Mastrototaro JJ, Zisser H, et al. Accuracy of the Enlite 6-day glucose sensor with guardian and Veo calibration algorithms. Diabetes Technol Ther 2012;14(3):225–31.

107. Adolfsson P, Ornhagen H, Eriksson BM, et al. Continuous glucose monitoring– a study of the Enlite sensor during hypo- and hyperbaric conditions. Diabetes Technol Ther 2012;14(6):527–32.

108. Mastrototaro JJ. The MiniMed continuous glucose monitoring system. Diabetes Technol Ther 2000;2(Suppl 1):S13–8.

109. Introducing the Guardian REAL-Time continuous glucose monitoring system. 2010. Available at: http://www.medtronic-diabetes-me.com/Guardian-REAL-Time.html. Accessed November 18, 2012.

110. FreeStyle Navigator continuous glucose monitoring system. 2008. Available at: https://www.healthyoutcomes.com/pdf/freestylenavigatoruserguide.pdf. Accessed November 18, 2012.

111. Dexcom Seven continuous glucose monitoring system user's guide 2010. Available at: http://www.dexcom.com/sites/dexcom.com/files/seven/docs/SEVEN_System_Users_Guide.pdf. Accessed November 18, 2012.