



The Secrets to Managing Problem Diabetics Mini Series

Session One: A Rational Approach to the Unstable Diabetic

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The Secrets to Managing Problem Diabetics

Study notes Session 1 - Rational approach to the unstable diabetic

Introduction

Some diabetic cases go like a dream but many are a real headache require considerable input of time and energy with many being a marathon rather than a sprint. This 3 part webinar mini-series aims to look at the potential causes, how they can be recognised and solutions that might be available. In the speaker's experience more problems are related to insulin dose, especially over-swing and fewer to intercurrent disease than previously suggested.

This first session is focused on obtaining and interpreting glucose curves, investigation of causes of instability and improving understanding of the different types of insulin that are now advocated for use in diabetic cats and dogs.

It is critical when approaching difficult diabetic cases to remember that some diabetics ARE unstable and that their instability is driven by factors that you cannot change or are outside your control. Despite all the billions of pounds spent on diabetic research and the sophisticated insulin monitoring systems that are available for use in humans, some human diabetics are 'brittle' and the same is true of our cats and dogs.

Outline

- What constitutes an unstable diabetic?
- Investigation of the unstable or poorly responsive diabetic.
- Interpreting glucose curves in unstable or poorly responsive diabetes – the advantages and disadvantages of spot testing, home monitoring, mini-curves, 24 hour curves and continuous monitoring.
- Changing insulin therapy in unstable or poorly responsive diabetics – when to change the dose and when to change the insulin.
- Managing the unstable diabetic on a tight budget.
- Achieving diabetic remission in cats.

What constitutes and unstable diabetic?

There is no formal definition of what constitutes poor diabetic stability. Unstable diabetes is a term used to describe hard-to-control cases in which blood glucose levels swing unpredictably. With periods, often prolonged, of hyperglycaemia and then apparent sudden response to insulin. Poor diabetic control tends to refer to patients whose blood glucose seems consistently high. An important part of managing diabetic cases is to agree at the outset with the owners what treatment is being expected to achieve. This may vary a lot between owners but may be controlling PU/PD to the point the patient no longer urinates in the house or it may be to stabilise body weight or increase exercise tolerance back to pre-diabetic levels. The degree of glycaemic control will therefore vary with the criteria used to deem that the treatment is being successful.

There seems to be less value in cats and dogs in tight diabetic control probably reflecting the fact that our patients are not diabetic for tens of years making clinically significant diabetic nephropathy, vascular and cardiovascular disease uncommon. Tight diabetic control is a great aim but the tighter the control the greater the risk of hypoglycaemia. As such, it is also difficult to achieve unless the patient is monitored at home and insulin dose adjusted according to the glucose level with short acting insulin.

Investigation of the unstable or poorly responsive diabetic

A logic approach to the poorly responsive diabetic is essential otherwise potentially simple but critical factors can be missed; it is very easy for a veterinary professional with experience of diabetic patients to assume that owners of diabetic patients have a much greater degree of knowledge and understanding than in fact they do. An apocryphal (possibly true) story is told of a poorly responsive diabetic dog that seemed always to respond well to insulin when brought into the surgery for treatment but not at home. Eventually the owner was asked to come into the practice to show exactly how the insulin was administered. The correct amount of insulin was duly drawn up and then from her pocket the owner drew an orange and injected the insulin into the orange and then fed the orange to the dog! This may seem slightly farcical as WE know that insulin is not absorbed orally but the owner was not aware of this. An orange had been used as a way of teaching the injection technique and for some reason this had failed to transfer to the dog. On this basis trying to give written instructions to the owner so that they can refer back to those instructions may be helpful. Such instruction could also respond to some FAQ and make sure advice across the practice is consistent. In the authors experience the most stable diabetics are usually those who have the most consistent regime day → day. If this is not the case it is better to try and either accept some instability e.g. at weekend, or modify the management to accommodate the owner's lifestyle rather than be too rigid leading to poor owner compliance.

For those cases that are unstable, the broad areas to investigate include

Owner & injection factors

- Insulin is being stored correctly (†2-8°C; out of sunlight)
- Dilution of insulin should be avoided
- Gentle agitation of the some types of insulin is required to form a homogeneous suspension e.g. Caninsulin; repeated shaking should be avoided as this can denature the insulin. Some types of insulin e.g. glargine should not be agitated
- Correct syringes and dose being given
- Injection is being given subcutaneously
- It is often worthwhile for someone to take time with the owners going through their regime step by step as it can be the minute that significantly affect the outcome – for example a client who was reusing her syringes but concerned about sterility was rinsing them out with surgical spirit which inactivated the insulin when the syringe was next used.

Incorrect insulin dosage

Under dose

- Most patients will stabilise at dose rates of 0.5-1 iU/kg/dose; if the dose is significantly less than this, under-dosing may be occurring.
 - 100iU/ml (orange top) being used for Caninsulin will only deliver 40% of the expected dose.

Overdose

- Overswing effects are probably one of the more common causes of diabetic instability (see interpreting glucose curves)
 - Using 40iU/ml (red top) syringes for 100iU/ml insulin can lead to serious 2.5X overdose and potentially fatal hypoglycaemia
 - Owner routine – multiple doses of insulin given by mistake
 - Patients that are unreliable eaters, vomit or are fed very variable amounts/types of calories day→day

Inappropriate duration of action

Rate of metabolism of insulin is very variable between individuals (Table 1)

Table 1. Onset, peak and duration of action of various insulin types

Type	Route	Onset (min/hr)	Peak effect dogs (hrs)	Peak effect cats (hrs)	Duration of action dogs (hrs)	Duration of action cats (hrs)
Soluble (neutral)	IV	0	0.5-2	0.5-2	1-4	1-4
	IM	10-30	1-4	1-5	3-8	3-8
	SC	10-30	1-5	1-5	4-8	4-8
Isophane	SC	0.5-3	2-10	2-8	6-24	4-12
Lente	SC	30-60	2-10	2-8	8-24	6-14
Ultralente	SC	2-8	4-16	4-16	8-28	8-24
PZI	SC	1-4	4-14	3-12	6-28	6-24
Glargine	SC	1-4	NA	NA	Unknown	12-24
Detemir	SC	1.8 ± 0.8	8-10	6.9 ± 3.1	<24	13.5 ± 3.5

IZS – insulin zinc suspension Lente = mixed or biphasic IZS, Isophane = neutral protamine Hagedorn (NPH), ultralente = crystalline IZS, PZI – protamine zinc insulin

Short duration

Common with twice daily NPH insulin in dogs and rarely Lente insulin

Common with twice daily Lente insulin in cats

Prolonged duration

If metabolism of insulin is slow, 'piggy-backing' of doses can occur – i.e. the previous dose is still having an effect when the next dose is administered. This effect can be cumulative over several days. Can be a particular issue with biphasic insulin such as Caninsulin in some dogs if the late effect of the insulin coincides with the rapid onset phase of the next dose. PZI in dogs and rarely in cats and glargine in cats can have duration of action > 24 hours if given twice daily.

REMEMBER THAT increasing insulin dose lowers the nadir AND extends the duration of action

Inappropriate coincidence of peak activity with peak glucose

In many dogs, the peak activity of Caninsulin if insulin is given after feeding will occur after the main phase of post-prandial hyperglycaemia which can contribute to diabetic instability in these patients and in some cases contribute to over-swing. The current recommendation in dogs that eat reliably is to give Caninsulin 45-60 minutes before feeding to try and improve the coincidence of peak activity with post-prandial rise. Ideally the timing of feeding in relationship to insulin should be refined based on glucose curve results. If blood glucose dips significantly after feeding and then rises sharply this suggests that peak activity precedes the post-prandial glucose peak. Conversely if glucose rises significantly after feeding and then falls peak activity of the insulin is too late; generally this is less of an issue.

In patients that are inconsistent eaters then 25% of their portion can be given prior to injecting insulin and 75% 45-60 minutes after insulin injection.

Impaired absorption

Slow absorption is a potential problem of ultralente insulin. Insulin analogues were developed to give more consistent absorption kinetics but it is uncertain how well this has been achieved.

Insulin absorption is also affected by external temperature, circulation and exercise.

Personally I feel that slow absorption can be more of an issue in some patients than generally reported associated with

- Overweight → obese patients where the injection is sometimes subcutaneous and sometimes into fat
- Patients that are hypotensive or hypovolaemic often due to their instability reducing peripheral circulation.

Solution intramuscular injection to assess the glucose response – if there is a marked difference between SC and IM injection then impaired absorption is likely.

Binding of insulin by anti-insulin antibodies

Anti-insulin antibodies are detectable in a subset of dogs receiving insulin approximately half of dogs on bovine insulin compared to 1/8 on porcine insulin. The significance of anti-insulin antibodies in terms of diabetic control is unclear. Cat insulin is not homologous to any of the available insulin type hence anti-insulin antibodies might be expected and have been demonstrated in 14-37% of cats. No correlation between the presence of antibodies and poor glycaemic control has so far been evident.

Obesity

Contrary to the situation in people, in dogs there is no evidence that visceral obesity contributes to insulin resistance so weight loss *per se* will not improve diabetic stabilisation. Obesity in cats has been shown to increase insulin resistance.

Interpreting glucose curves in unstable or poorly responsive diabetes

A variety of standard changes in glucose curves are reported and are useful as a starting point for some individuals however not all cases follow these trends. It should also be remembered that hypoglycaemia can occur very quickly and may be missed by hourly sampling (Fig. 1-4).

Common curves are illustrated below with some indications of potential response to dose change. As previously stated it is important to define the criteria for success before doing multiple curves so that the aim of testing is achieved; it is also easy for clients to become very number fixated rather than patient wellness focussed.

Figure 1 (a) Data as measured (b) Joining the dots (c) Alternative explanation

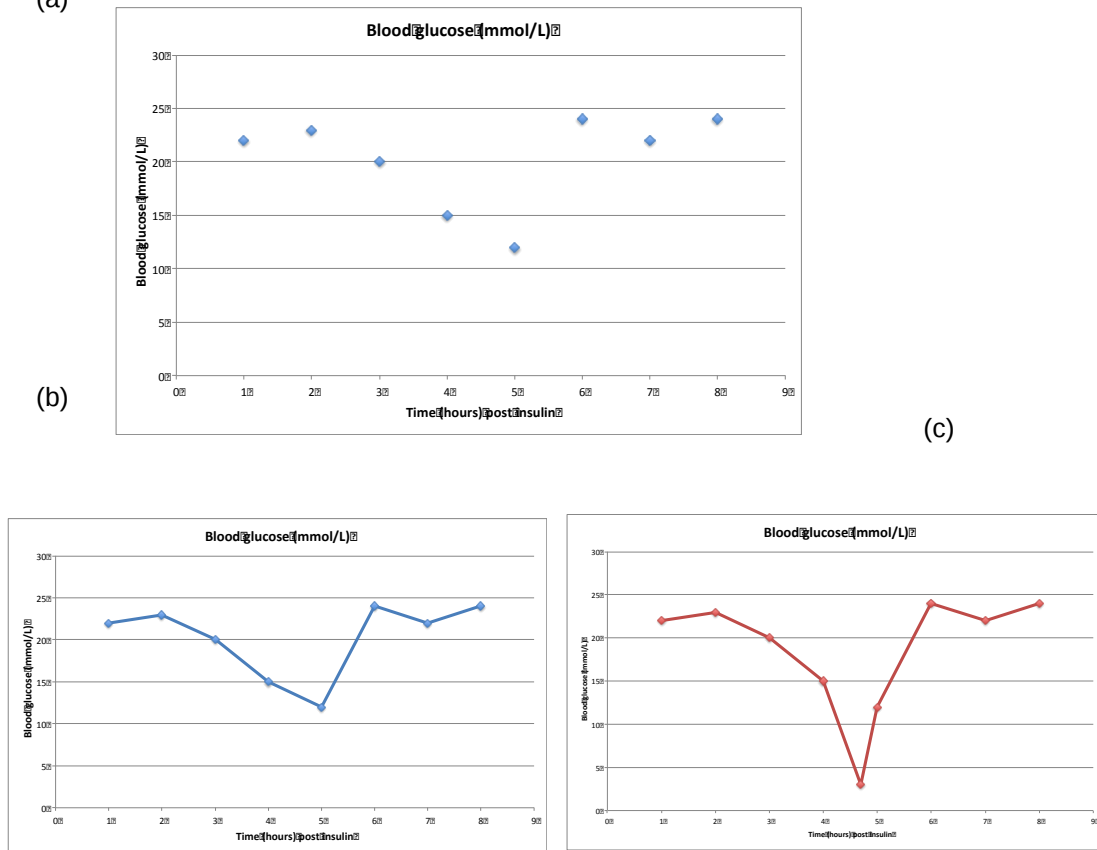


Figure 2
A dose of 1.5iU

Caninsulin in a cat has insufficient effect and also insufficient duration of action. In this case increasing the dose to 2 iU had a beneficial effect on both these factors.

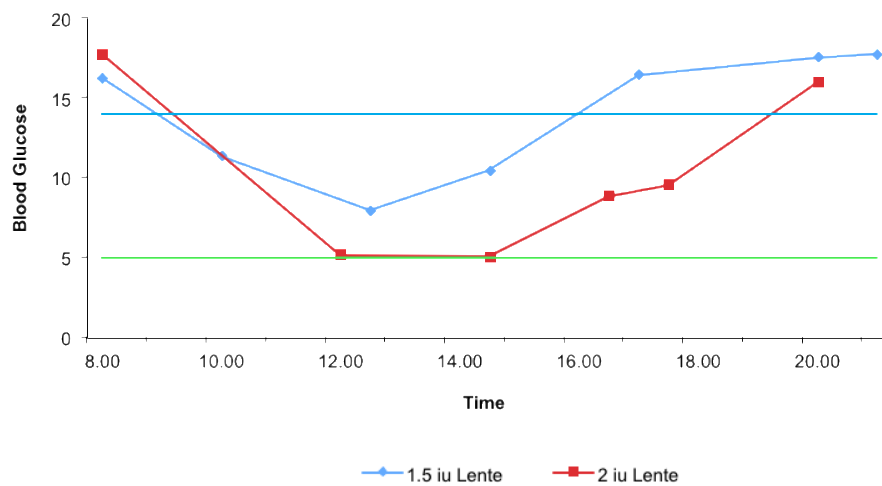


Figure 3 - In this example Caninsulin has a rapid onset but a short duration of action. Changing to PZI produces a more acceptable curve, with a slower onset of activity but a longer duration of action

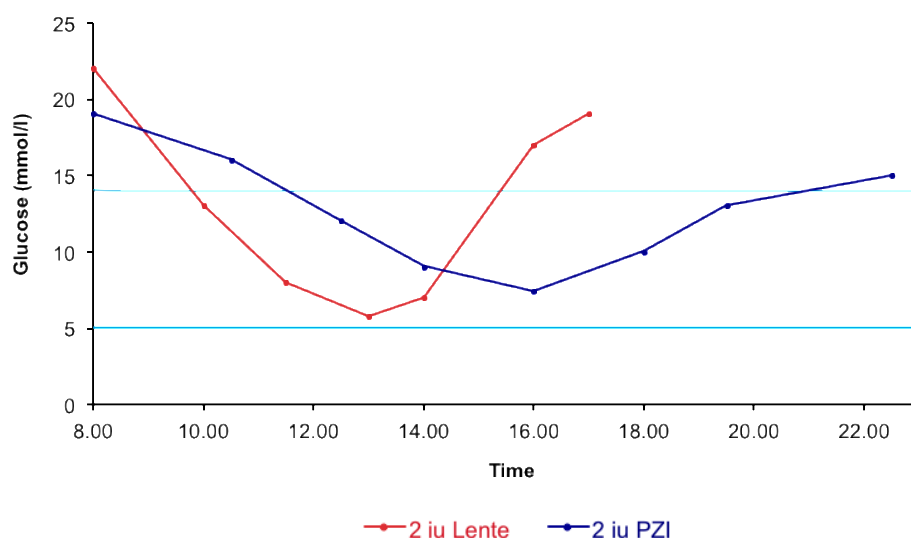
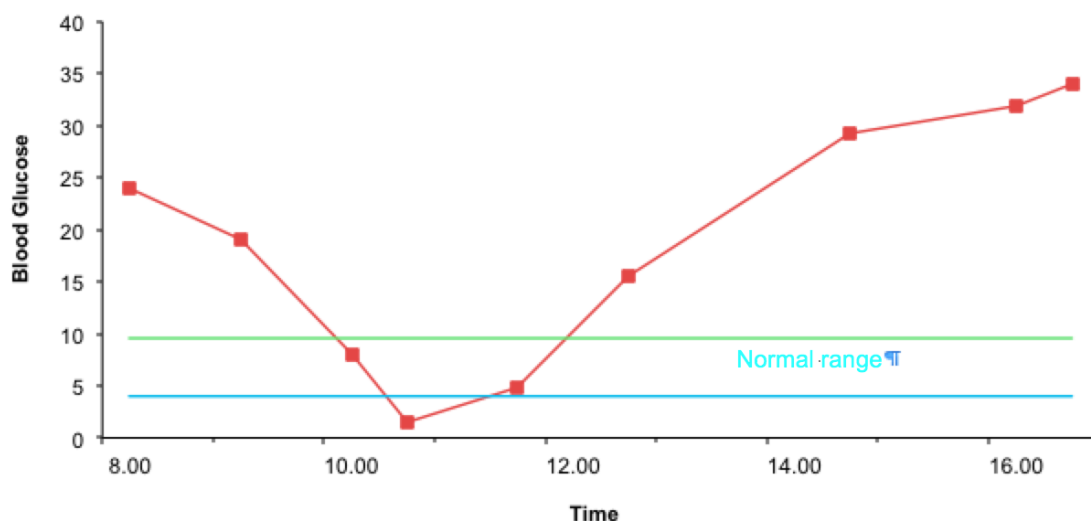


Figure 4 - An example of Somogyi overswing. The dose of insulin is too high and produces a rapid fall in blood glucose. When the dog becomes hypoglycaemic protective physiological mechanisms are activated which reverse the hypoglycaemia and cause hyperglycaemia.



Some important factors to consider are

- 1) Glucose curves are often not the same day → day
 - a. Ideally they should be for a full 24 hours if general patterns are required
 - b. Mini-curves may be valuable to answer specific questions e.g. what time post insulin does the nadir occur and how profound is it.
 - c. Be careful of joining the dots especially if testing is relatively infrequent – see figure 1
 - d. Reliability and reproducibility of glucometers – if you have more than one in the practice they should be numbered and the same one used throughout a curve (figure 5).
- 2) Handheld glucometers estimate blood glucose and should be used more to illustrate trends than to give absolute values.
- 3) Spot glucose testing unless hypoglycaemia is suspected is virtually useless unless specific goals have been set e.g. serially monitoring the nadir.
- 4) Often the critical events happen at night.
- 5) The stress of hospitalisation and blood sampling may significantly alter the curve.
 - a. Consider at home testing.

- 6) Continuous glucose monitoring may be a better solution allowing days of data to be collected.
 - a. Guardian system.
 - b. Freestyle Libre system.

Fructosamine and glycosylated haemoglobin

Fructosamine is a measure of glycosylated proteins principally albumin and is more widely available than glycosylated haemoglobin which is more commonly used in man.

Fructosamine level reflects average glucose levels over the past 1-3 weeks (depending on the half-life of the glycosylated protein) and is not affected by acute increases in blood glucose; this is particularly useful in cats prone to stress-associated hyperglycaemia when blood sampled. To some extent fructosamine can also be used to suggest that a patient is having prolonged periods (hours) of hypoglycaemia.

Fructosamine is used as a marker for recent diabetic stabilisation but should not be used alone as a sole measure of monitoring and managing diabetic patients. Serial monitoring can sometimes poorly correlate with other clinical parameters of stability. In the author's experience fructosamine results can end up being more confusing than useful.

Changing insulin therapy in unstable or poorly responsive diabetics

As far as possible changes in insulin therapy should be based on the results of glucose curves. If this is not possible for technical or financial reasons other parameters can be used such as fructosamine level, urine glucose concentration or water consumption but these are in general less reliable or easy to interpret.

In most cases changing the dose is appropriate usually by 0.5-1iU per dose and then reassess in 3-7 days for changes in response. In large and giant breed dogs changes of 2-3iU/dose may be appropriate.

In some cases despite testing it remains unclear as to whether instability is due to over or under-dosing, in such situations it is usually appropriate to reduce the dose.

As anti-insulin antibodies as a cause of a lack of response is rare changing to a different species of insulin is rarely justified.

Where duration of insulin action is significantly outside of the dose interval then changing insulin type is appropriate. If duration is too long (i.e. the second phase on Caninsulin is coinciding with the rapid phase of the next dose) changing to a biphasic insulin of different proportional activity or considering Isophane insulin may be necessary. Too short a duration of action is most commonly seen in cats when changing to PZI or glargine insulin is appropriate.

On rare occasions combining insulin types, as often occurs in man, may be an option to provide a constant background level with shorter acting insulin to deal with post prandial rises.

Diabetic remission in cats

Diabetic remission is becoming increasingly common in cats with one study suggesting that up to 85% of cats will go into remission with intensive management. This seems a relatively optimistic figure suggesting that all type II diabetic cats have reversible disease in reality most studies have shown rates that are closer to 40%. It important to also remember that as glycaemic control is re-established then progressively lower doses of insulin will be required. Diabetic remission takes weeks to months to occur. For most cats this requires intensive monitoring that is often best undertaken at home. The aim is to bring insulin down to within or close to the reference range for as much of the time as possible. For the first few weeks this may not be possible but any significant lowering will reduce the glucotoxicity and lipotoxicity on the islet cells.

The optimum approach to inducing diabetic remission has not been established and whether there are advantages of combining neutral insulin as additional injections through the day to manage glucose spikes is unknown.

Clearly the more aggressive the attempts to manage blood glucose are the greater the risk of overswing and hypoglycaemic episodes. However, no single factor predicts remission and successful remission has been documented with a variety of insulin types and protocols (Gostelow *et al* 2014)

Of cats that achieve remission a proportion of them remain pre-diabetic having abnormal fasting $\pm$ impaired glucose tolerance testing with one study (Gottlieb *et al* 2015) reporting 30% of cases relapsing and requiring insulin over a 9 month period from remission.

It is estimated that around one third of cats that go in to remission will relapse within 9 months.

Managing the unstable diabetic on a tight budget

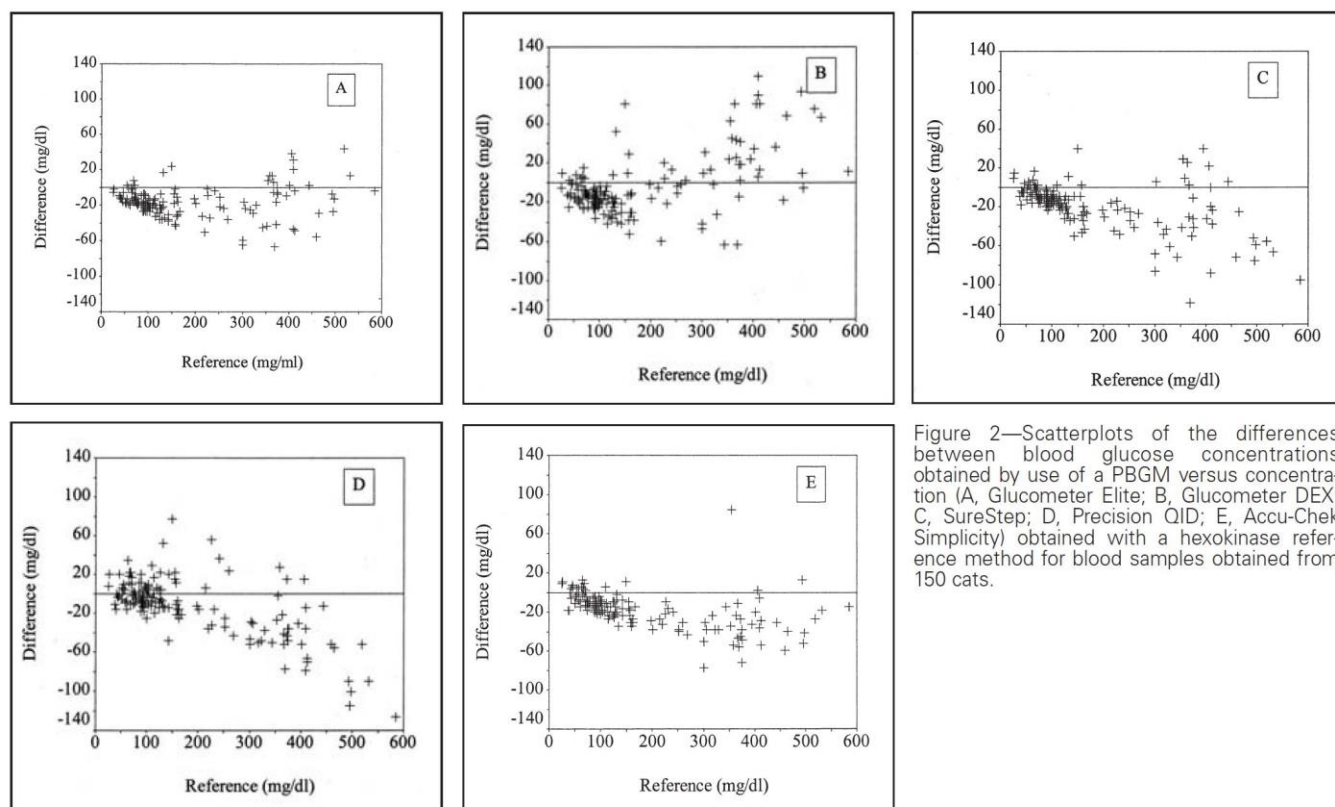
Aims

- 1) To reduce the risk of hypoglycaemic episodes
- 2) To prevent development of ketosis or ketoacidosis
- 3) To improve quality of life – reduce PU/PD/PP, maintain body weight

Approach to stabilisation

- a) Maximise consistency of the routine
 - i. Weigh food, give same treats daily
 - ii. Consistent amounts and timing of exercise
 - iii. Consistent feeding and insulin timing
- b) Ask the owner to keep a detailed diabetic diary for their pet
- c) Fully assess the effect of any change in insulin – at least 7 days between changes
 - i. Make small progressive changes in insulin dose as it is easier to monitor trends
 - ii. If in doubt reduce insulin dose – over-swing is more common than resistance
- d) Monitor water intake (this is still possible in multi-pet households assuming other pets drink a similar amount daily) as this has been shown to be a sensitive indicator of diabetic stabilisation i.e. if water consumption falls then diabetes is more stable.
- e) Weigh regularly (every 2-4 weeks) – try and achieve a BCS of 4-5/9 and maintain stable body weight → reasonable sign of diabetic stability (some overswing cases will gain weight despite relatively marked instability).
- f) Owner dipping urine at home – afternoon samples are the best as morning samples tend to have glycosuria and push insulin dose up. Early afternoon samples, if negative, suggest patient has been hypoglycaemic that morning especially if later sample/morning samples show high glucose.
- g) At home monitoring of blood glucose
 - i. Make sure you have a plan so the owner does not adopt a random sampling method making results difficult to assess

Figure 5 Comparison of handheld blood glucose monitors and laboratory reference values



From Wess & Reusch 2000

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