Interpretation and management of blood glucose above target on waking (fasting hyperglycaemia)

For many years it was believed that high blood glucose (BG) levels first thing in the morning might be driven by the body's stress response to hypoglycaemia during the night. This became known as rebound hyperglycaemia (and technically as the Somogyi effect after Michael Somogyi who suggested it in 1937). A reduction in bedtime background insulin (BI) was promoted as the solution. More recent research has not identified this phenomenon and so any DAFNE graduate suffering from frequent morning high blood glucose should consider other options for changing their insulin treatment.

Studies using Continuous Glucose Monitoring (CGM) suggest that a rise in fasting blood glucose overnight is due to basal insulin running out in the morning, combined with the DAWN effect (see appendix for details). The suggested actions, which should be discussed with your DAFNE health care professional include:

- With low or low-normal BG (below 5.5mmol/l) in the morning suspect night time hypo. Undertake 3am BG test (should be above 4.5mmol/l) to clarify overnight BG pattern.
- Understand that it is common to sleep through episodes of hypoglycaemia.
- Hypos may occur at other points in the night, if the pattern persists consider testing at different times on different nights.
- It is recommended that BI doses should be administered on retiring (going to bed) and rising (first thing on getting up) as long as there is a gap of at least 7 hours between doses. This will allow for an overlap of doses (see graph 1 appendix 1) in the morning when insulin requirements are highest.
- Reduction of night time BI after exercise or alcohol should be undertaken according to DAFNE guidelines to avoid hypos.
- Consider increasing BI if 3 am BG is safely above 4.5mmol/l; avoid inducing hypos in the early part of the night with increased BI. Always check BG at 3am pre- and post BI changes.
- Consider changing to twice daily analogue BI if not already being used; the flatter insulin profile and longer action time can be advantageous and may assist if night time hypos persist/cannot be resolved by adjustment of the dose or timing of the night time BI.
- most clinicians feel that Detemir rather than Glargine is the most appropriate analogue to choose if changing from isophane, but there is as yet no evidence to prove this."

Further details of the evidence base for this changed approach are contained in appendix 1.

Appendix 1

Interpretation and Management of Fasting Hyperglycaemia

For many years it was believed that high blood glucose (BG) levels first thing in the morning in those with Type 1 diabetes might be driven by the stress response to hypoglycaemia during the night to which the correct response would be a reduction in bedtime background insulin (BI). Most published evidence, particularly from clinical studies does not support this hypothesis concerning what is termed 'rebound hyperglycaemia' or the 'Somogyi effect'. This document explains how the latter hypothesis came about; why it is no longer valid; and gives insight into the dawn phenomenon.

The Somogyi effect

In 1938, Michael Somogyi postulated that fasting hyperglycaemia may be attributable to counter-regulatory hormone response to asymptomatic (i.e. without symptoms) nocturnal hypoglycaemia (low blood glucose). His postulation implied that the counter regulatory response is strong enough to overcome the hypoglycaemic effect of basal insulin in the night and raise the blood glucose above normal on waking. His hypothesis was based on a clinical finding of what was described as "unmanageable diabetes" in 8 patients who alternated between severe hypoglycaemia and extreme glycosuria (i.e. when glucose is present in urine).

How were type 1 diabetes patients treated back then?

The first patient had been experimentally treated with insulin in 1922. When Eli Lilly began production of insulin purified from beef and pork sources in 1923, it is unlikely that the predictability of action was like the insulins we are familiar with today. Home blood glucose monitoring was not available; the only method was chemical testing of urine for glucose, which lacks the immediacy and accuracy of present day testing methods. The standard treatment was twice daily soluble insulin, titrated up to a dose sufficient to prevent glycosuria. Consequently, some patients ended up on large doses of insulin (>200 units/day) which resulted in recurrent hypoglycaemia. In these patients Somogyi observed that nights with no glycosuria were invariably followed by heavy glycosuria the following morning. He found that a drastic reduction in insulin resolved both the hypoglycaemia and the following glycosuria. In his relatively small sample of eight patients, one was reduced from 110 units/day to 16 units/day, whist two others came off insulin altogether suggesting they may have had Type 2 diabetes.

Where are we now, 77 years on?

Continuous glucose monitoring now gives greater insight into blood glucose management overnight and there is consequently more evidence to help interpret blood glucose levels and understand the counter regulatory response. Most published evidence, particularly from clinical studies, does not support the Somogyi effect.

During the night, due to sleep and lying flat, the hormonal response to hypoglycaemia is suppressed. No-one knows why and research continues into different sleep stages. In type 1 diabetes the effect is more marked, probably because most adults with type 1 diabetes when duration is over 5 -10 years, have suppressed hormone defences already.

In both type 1 and type 2 diabetes, patterns of hypoglycaemia at night are very different from the day, often very prolonged (3-5 hours) and most are asymptomatic.

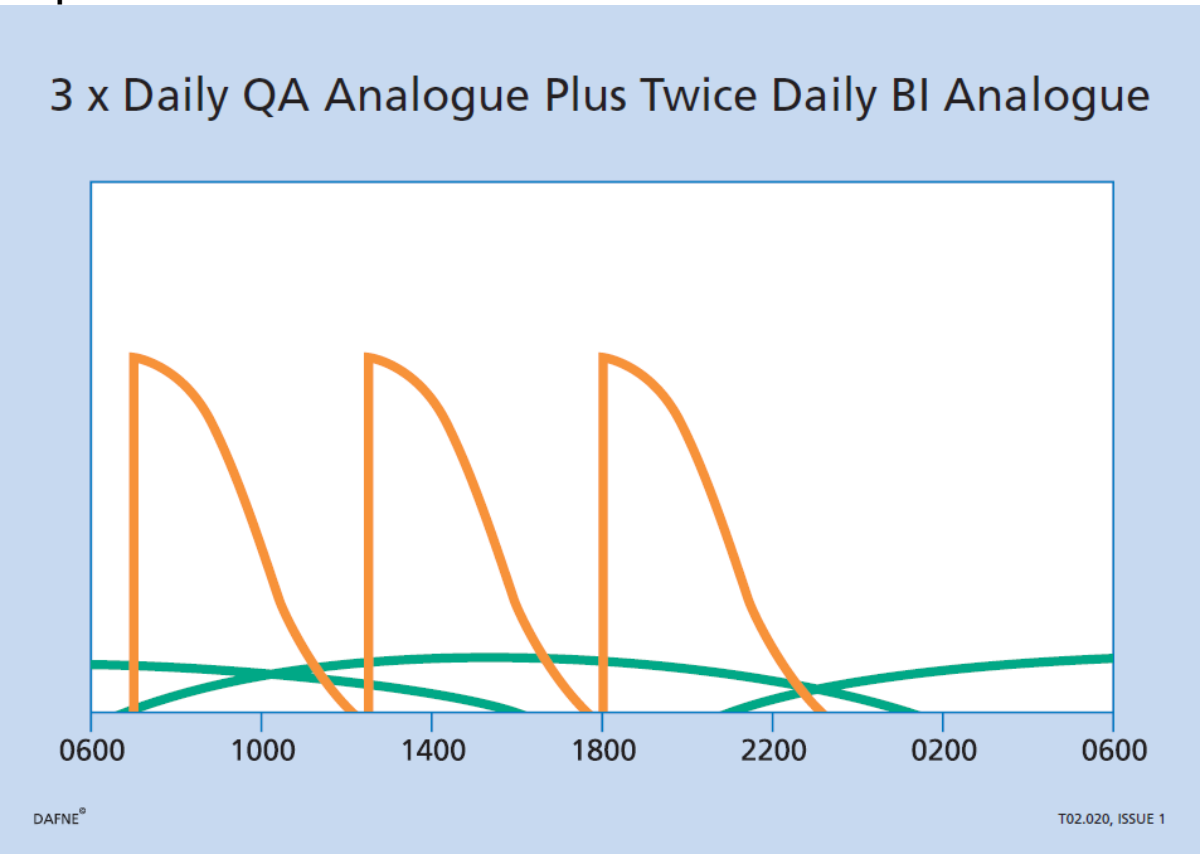
Dawn Phenomenon

In someone without diabetes, overnight glucose levels remain constant due to the balance between glucose output by the liver and glucose uptake by the cells, due to a small and consistent secretion of insulin. In the night, glucose production in the liver falls in the early part of the night because of a fall in counter regulatory hormones (cortisol, growth hormone, catecholamines). After 4 am, surges in growth hormone trigger liver glucose production and there is an increase in insulin production between 4-8 am, so holding glucose levels steady.

Someone with type 1 diabetes is dependent on injected insulin which cannot mimic physiological insulin production, falling in the early part of the night and rising between 4-8 am. Dependent on the BI used, dose and timing, insulin levels can be at their highest in the earlier part of the night and begin to fall at a time of increased requirements (4 am onwards) leading to a rise in BG – the dawn phenomenon.

Graph 1 illustrates how, by using twice daily BI taken on rising and retiring the overlap in insulin action times in the morning can help to counteract the dawn phenomenon.

Graph 1



Rebound hyperglycaemia as proposed by Somogyi is extremely rare. The rise in glucose before waking up is due to basal insulin running out in the morning, combined with the dawn phenomenon.

Table 1
Supporting evidence

Publication	Findings	Implication for management
Hoi-Hansen et al (2005) CGM 262 patients with type 1 diabetes	218 episodes of asymptomatic hypoglycaemia during 594 nights of observation Fasting glucose levels <7mmol/l associated with significantly greater risk of nocturnal hypos Mean fasting glucose was 5mmol/l lower on nights with hypo than after nights with no hypo	Importance of 3am testing to detect asymptomatic hypos Aim for the top end of DAFNE targets when aiming to avoid night time hypos (hypo awareness restoration) Lower fasting blood glucose (FBG) is more likely to indicate nocturnal hypo than higher FBG
Guillod et al (2007)	Failed to demonstrate any relationship between nocturnal hypoglycaemia and high fasting glucose	A high FBG is most likely to be due to lack of insulin, too low a dose or running out
Kaufman et al (2002); Guillod et al (2007)	Overnight monitoring of adults and children has revealed an incidence of nocturnal hypoglycaemia of 20-45%. Most episodes go unrecognised, with individuals remaining asleep with glucose levels below 2mmol/l	Silent night time hypos are common. Include 3-4am testing and adjustment of night time BI (particularly after exercise or alcohol)
Choudhary et al (2007) 89 patients with type 1 diabetes	No instances of nocturnal hypoglycaemia associated with a fasting glucose of >7mmol/l Nocturnal hypoglycaemia was associated with low fasting blood glucose levels. Fasting BG <5mmol/l evidence of nocturnal hypos on 94% of nights. Dawn phenomenon seen in 25% of participants.	Aim for top end of DAFNE targets to avoid night time hypos (hypo awareness restoration) Check 3-4am BG if FBG low/low normal Reduce night time BI if indicated Dawn phenomenon may be more common than thought previously Encourage twice daily BI on rising and retiring, consider bd analogue BI

Publication	Findings	Implication for management
	High bed time BG is associated with night time hyperglycaemia Lowest (not necessarily low) overnight sensor glucose was evenly distributed over the night 00.00-02.00 35% 02.00-04.00 16% 04.00-06.00 29%	Encourage correction to target of high BG pre bed If you suspect overnight hypos try testing at times in addition to 3am (on different nights)