Interpretation and Management of Fasting Hyperglycaemia in adults with Type 1 diabetes using MDI insulin regimen

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. A reduction in bedtime background insulin (BI) was promoted as the solution. This document explains why this practice should no longer be promoted, and explains an evidence-based approach to the management of fasting hyperglycaemia.

What was this belief based on?
The Somogyi effect or rebound hyperglycaemia.

In 1938 Michael Somogyi postulated that fasting hyperglycaemia may be attributable to a counter-regulatory hormone response (particularly the release of adrenaline) to asymptomatic nocturnal hypoglycaemia.

It implies that the counter-regulatory response is strong enough to overcome the glucose lowering effect of basal insulin in the night and raise the blood glucose to levels much above normal on waking.

When was this proposed?
At a meeting of the St Louis Medical School in 1938, 77 years ago, published 1959.

What is the evidence?
Based on a description of “unmanageable diabetes” in 8 patients who alternated between severe hypoglycaemia and extreme glycosuria.

How were these patients treated?
In 1922 the first patient in the world received insulin therapy. Eli Lilly began production of insulin purified from beef and pork sources in 1923. The action profile of early insulin would have been relatively unpredictable; unlike the insulins we are familiar with today.

Home blood glucose monitoring was not available; the only method was chemical testing of urine for glucose.

Standard treatment was twice daily soluble insulin titrated up to a dose sufficient to prevent glycosuria.

Consequently some patients ended up on large doses (>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 sample of eight patients, one was reduced from 110 units/day to 16 units/day, two others came off insulin altogether suggesting they may have had Type 2 diabetes.
Summary
Dr Somogyi, a biochemist, was working
- in the new field of insulin treatment for diabetes
- with the first mass produced insulin within 15 years of its introduction
- with the first generation of patients who could be kept alive by treatment with insulin
- with a small group of 8 people
- with participants who may not have had Type 1 diabetes
- using early urine testing which lacks the immediacy and accuracy of current blood glucose testing.

Where are we now, 77 years on?
Most published evidence, particularly from clinical studies does not support the hypothesis. The Somogyi effect appears to play little part in raising blood glucose above normal in routine clinical practice.

CGM gives greater insight into blood glucose management overnight.

There is more evidence to help interpret blood glucose levels and understand the counter regulatory response.

What do we know now about hormone levels overnight?
The Somogyi effect can only be clinically relevant if the counter-regulatory hormonal response is strong enough to overcome the glucose lowering effect of circulating insulin.

During the night, due to both sleep itself, and lying flat, the hormonal response to hypoglycaemia is suppressed. No-one knows why, research continues into different sleep stages.

In Type 1 diabetes the nocturnal suppressive effect is more marked probably because most adults with Type 1 diabetes for more than 5-10 years already have impaired hormone defences to hypoglycaemia.

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

These factors combined explain why it is extremely rare for the stress response to nocturnal hypoglycaemia to cause a raised fasting blood glucose.

The CGM studies suggest that a rise in fasting blood glucose overnight is due to basal insulin running out in the morning, combined with the DAWN effect, discussed in more detail below.
### What does research suggest today?

<table>
<thead>
<tr>
<th>Publication</th>
<th>Findings</th>
<th>Implication for practice</th>
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<tbody>
<tr>
<td>Hoi-Hansen et al (2005) CGM 262 patients with type 1 diabetes</td>
<td>218 episodes of asymptomatic hypoglycaemia during 594 nights of observation. Fasting glucose levels &lt;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.</td>
<td>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 FBG is more likely to indicate nocturnal hypo than higher FBG.</td>
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<td>Guillod et al (2007)</td>
<td>Failed to demonstrate any relationship between nocturnal hypoglycaemia and high fasting glucose.</td>
<td>A high FBG is most likely to be due to lack of insulin, too low a dose or running out.</td>
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<td>Kaufman et al (2002); Guillod et al (2007)</td>
<td>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.</td>
<td>Silent night time hypos are common. Encourage 3-4am testing and adjustment of night time BI (particularly after exercise or alcohol).</td>
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<td>Choudhary et al (2007) 89 patients with type 1 diabetes</td>
<td>No instances of nocturnal hypoglycaemia associated with a fasting glucose of &gt;7mmol/l. Nocturnal hypoglycaemia was associated with low fasting blood glucose levels. Fasting BG &lt;5mmol/l evidence of nocturnal hypos on 94% of nights.</td>
<td>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. Encourage correction to target of high BG pre bed.</td>
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<td>If you suspect overnight hypos suggest testing at times in addition to 3am (on different nights).</td>
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Dawn phenomenon seen in 25% of participants.

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%
Causes of fasting hyperglycaemia

Yellow trace: The patient experienced symptoms of hypo, and treated at 0430. If we didn’t know this it could be interpreted as a rebound high.

Red trace: The patient went to bed high and remained high as they were unwilling to treat due to the hypo the previous night.

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Implications for practice
- Focus on accurate CP counting at the evening meal, especially if eaten late.
- Highlight the usefulness of 3am testing.
- Encourage hypo treatment in line with DAFNE guidance. In most cases 1 ½ to 2 CPs rapid acting carbohydrate is enough to treat a hypo without following up with additional CPs, even at night.
- Explain the rational for correction of high BG pre bed – high BG will stay high.
**Causes of Fasting Hypoglycaemia**
**Tues 11 Jan (mmol/L)**

**Blue trace:** The patient went to bed with glucose around 10 and dropped. They had 3.5 hours hypo with no rise, until checked on waking, blood glucose only rose after they had eaten CPs.
If the Somogyi effect is a regular occurrence in clinical practice why didn’t this night time BG rise?

**Purple trace:** The patient stayed in target all night dropping until breakfast at 8am and again only rose after eating CPs

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**Implications for practice**
- With low/low normal BG (below 5.5mmol/l) in the morning suspect night time hypo and encourage 3am BG test (should be above 4.5mmol/l).
- Hypos may occur at other points in the night, if the pattern persists consider testing at different times on different nights.
- Encourage adjustment of night time BI after exercise or alcohol according to DAFNE guidelines to avoid hypos.
- Consider changing to analogue BI if night time hypos persist/cannot be resolved by adjustment of the dose or timing of the night time BI.
- Make course participants aware it is common to sleep through episodes of hypoglycaemia.
Additional traces of common patterns

Day 2

Again, the low followed by high on the first trace at 3am is due to treatment of the hypo with CPs, it is likely the hypo has been over treated.

The low on the second trace lasts 4-5 hours and only rises when the patient has breakfast, which suggests in line with the overall evidence that asymptomatic night time hypos are common and the Somogyi effect is not clinically significant. These traces mirror those of the previous patient.

Dawn phenomenon

In someone without diabetes glucose levels overnight 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 4am surges in growth hormone trigger liver glucose production and there is an increase in insulin production between 4-8am 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 4-8am. 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 (4am onwards) leading to a rise in BG – the dawn phenomenon.
This trace shows an example of dawn phenomenon.

The patient was on Levemir – 12 units AM and 6 units PM; QA insulin 2:1 for breakfast, 1:1 for lunch and dinner.

The patient woke at 0630 and usually had breakfast and quick acting insulin around 0700, before leaving for work.

On all days, there is a rise in glucose between 0500 – 0700, before a meal is eaten.

The blue trace appears to show a hypo with a rise afterwards, the lowest glucose is around 3.3 just below 3.5mmol/l (definition of hypo). Following the trace back shows that was the night when the patient started lowest, and may have been below the 6.5mmol/l DAFNE recommended target. Other nights have the same downslope between 0000 – 0500 and then rise from a nadir of about 7 on the red and black traces to about 15 before breakfast. The pattern is the same, the lowest reading being dependent on the starting BG level pre bed.

These traces may be misinterpreted as the Somogyi effect or rebound hyperglycaemia when the are in effect due to a lack of BI at a time of rising BG.

**Implications for practice**

- Check the timing of BI doses, on rising and retiring is recommended as long as there is a gap of at least 7 hours between doses. This will allow for an overlap of doses in the morning when insulin requirements are highest.
- Consider increasing BI if 3am 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.
- Discuss the advantages of changing to twice daily analogue BI if not already being used; the flatter insulin profile and longer action time can be advantageous.