The Somogyi effect: Fact or fiction?

Pratik Choudhary, Simon Heller

The Somogyi effect, also termed "rebound hyperglycaemia", describes the concept of nocturnal hypoglycaemia resulting in high fasting glucose levels due to the release of adrenaline and other counter-regulatory hormones in response to the hypoglycaemia. The proposed solution is to reduce the evening insulin dose – an action that is clearly counterintuitive when faced with a high glucose measurement. A belief in rebound hyperglycaemia still exerts a firm hold on the minds of diabetes professionals and others who advise people with diabetes on insulin adjustment, and consequently among the people with diabetes themselves. The concept was strongly challenged more than 30 years ago and its existence continues to be questioned. This review explains the pathophysiology behind the concept and reviews the research undertaken to determine whether the idea has any clinical relevance.

Despite strong evidence that keeping blood glucose levels close to "normal" reduces the risk of diabetic complications (DCCT [Diabetes Control and Complications Trial] Research Group, 1993; UKPDS [UK Prospective Diabetes Study] Group, 1998), few people with diabetes achieve this level of glycaemic control. Many are trained to adjust insulin and food intake to maintain tight glucose targets; however, largely due to the limitations of subcutaneous insulin delivery, those who aim for normal glucose levels may experience hypoglycaemia (DCCT Research Group, 1993).

In the authors' experience, people with diabetes find it particularly difficult to control their glucose level first thing in the morning. Fasting glucose levels have been shown to contribute significantly to HbA_{1c} levels (Peter et al, 2001). Most insulin algorithms ask individuals to adjust bedtime doses of long-acting insulin to achieve fasting glucose levels between 4 and 7 mmol/L (DAFNE [Dose Adjustment for Normal Eating] Study Group, 2003; Hermansen et al, 2006; Yki-Järvinen et al, 2000; 2007). A major barrier to achieving these levels is fear of developing hypoglycaemia during the night (Bastyr et al, 2000; Cryer, 2008; *Box 1*).

Box 1. Clinical vignette.

Laura is a 27-year-old administrator with type 1 diabetes of 12 years' duration. She underwent structured education (Dose Adjustment For Normal Eating) 2 years ago and is treated with a basal–bolus regimen. Her fasting blood glucose concentrations tend to be between 8 and 12 mmol/L and she has been unable to get her HbA_{1c} below 8%. In the past, she has tried to increase her bedtime dose of long-acting insulin, but is scared of "going low in the night" after a previous episode of nocturnal hypoglycaemia. She has read that high blood glucose levels in the morning could mean that levels are low at night and become high in the morning because of something called "rebound hyperglycaemia" – she asks her diabetes team if this could be an explanation.

Article points

1. Fasting hyperglycaemia is common in diabetes, as is overnight hypoglycaemia.
2. The Somogyi effect, or "rebound hyperglycaemia", proposes that overnight hypoglycaemia leads to fasting hyperglycaemia due to the release of counter-regulatory hormones.
3. People with diabetes and professionals are wary of increasing overnight insulin doses because of fear of nocturnal hypoglycaemia.
4. In clinical practice, fasting hyperglycaemia is much more likely to be due to inadequate insulin levels.
5. A 3 am glucose level is useful in guiding the best choice and dose of overnight insulin replacement.
6. Long-acting insulin analogues can reduce the risk of nocturnal hypoglycaemia.

Key words

- Diabetes
- Nocturnal hypoglycaemia
- Fasting hyperglycaemia
- Somogyi effect
- Dawn phenomenon

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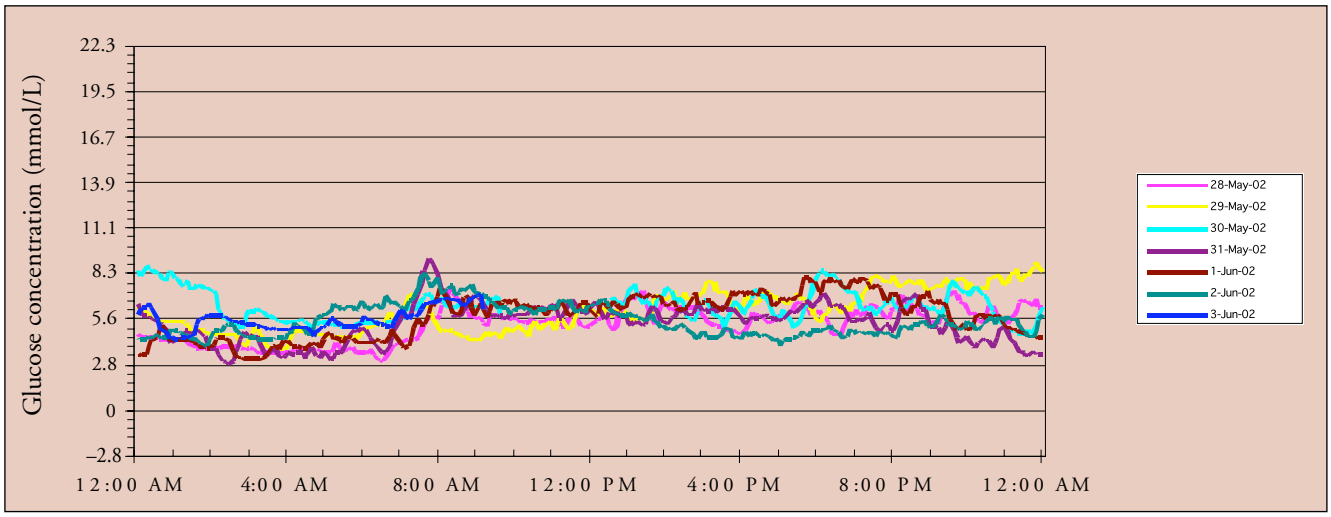

Figure 1. Continuous glucose monitoring trace in an individual without diabetes.

Page points

1. In people without diabetes, the most important factor preventing a low blood glucose concentration is the ability of the beta-cells to "switch off" insulin release completely when glucose levels fall below normal.
2. In contrast, people with diabetes who inject insulin continue to be exposed to raised concentrations until the insulin is completely absorbed.
3. Hypoglycaemia leads to cognitive impairment at a blood glucose concentration of 3 mmol/L, and very low blood glucose levels can result in permanent cerebral damage.

Vulnerability of insulin-treated people to hypoglycaemia

In people without diabetes, plasma glucose concentration is tightly regulated by a series of physiological mechanisms that have evolved to maintain glucose delivery to the brain. The most important factor preventing a low blood glucose concentration is the ability of the beta-cells to "switch off" insulin release completely when glucose concentrations fall below normal. In contrast, people with diabetes who inject insulin continue to be exposed to raised concentrations until the insulin is completely absorbed.

The clinical changes provoked by the onset of hypoglycaemia in individuals treated with hypoglycaemic agents highlight the importance of a regular supply of glucose to the brain and the protective responses that have evolved to maintain it. Hypoglycaemia leads to cognitive impairment at a blood glucose concentration of 3 mmol/L, and very low blood glucose levels can result in permanent cerebral damage (Heller and Macdonald, 1996). However, individuals are protected in part by the release of counter-regulatory hormones and activation of the autonomic nervous system. The release of glucagon, cortisol and catecholamines stimulates glucose release from the liver, while peripheral physiological changes caused by autonomic activation produce symptoms that prompt the individual to ingest carbohydrate (Cryer et al, 2003).

Nocturnal glucose homeostasis

Individuals without diabetes

Even during a prolonged period of fasting through the night, glucose levels in people without diabetes remain constant (*Figure 1*) because of the equilibrium that exists between hepatic glucose output and peripheral glucose uptake due to a small but consistent secretion of insulin.

During the night, hepatic glucose production initially falls as a result of reduced release of counter-regulatory hormones such as cortisol, growth hormone and catecholamines, and then rises after 4 am following surges in growth hormone secretion (Bolli et al, 1984a). In response, there is a compensatory increase in insulin levels between 4 am and 8 am to keep the plasma glucose concentration constant.

Individuals with type 1 diabetes

People with type 1 diabetes, who have no functioning beta-cells, are completely dependent on exogenous insulin. Intermittent injections of subcutaneous insulin cannot reproduce the physiological situation in which low levels of insulin are continuously secreted by the beta cells directly into the portal vein. Circulating insulin concentrations then begin to fall at a time of rising insulin requirements, leading to a rise in blood glucose, known as the "dawn phenomenon".

Conventional human long-acting insulin injected at bedtime produces gradually rising insulin levels, which peak at around 3 am

– a time when insulin requirements are at their lowest (Lepore et al, 2000). Circulating insulin concentrations actually begin to fall at a time of rising insulin requirements, owing to the dawn phenomenon (Trumper et al, 1995).

Long-acting insulin analogues (insulin glargine or insulin detemir) have a flatter pharmacokinetic profile and thus insulin levels tend to be more stable through the night, although both have some limitations in providing ideal basal insulin replacement (Heise et al, 2007).

Individuals with type 2 diabetes

People with type 2 diabetes are insulin resistant, and although insulin secretion is often maintained in the early years after diagnosis, this is insufficient to suppress hepatic glucose production. This is coupled with substantial cortisol and growth hormone release overnight; as a result, fasting hyperglycaemia is also common in this group (Carroll et al, 2002). Many people with type 2 diabetes are treated with a twice-daily mixed insulin regimen. If taken quite early, it is conceivable that the evening dose could provide suboptimal control of morning glucose levels. These factors may explain why people with type 2 diabetes who have not eaten since an early evening meal wake with high glucose levels.

Nocturnal hypoglycaemia

Nocturnal hypoglycaemia is a feared complication of insulin therapy and is particularly common in people with type 1 diabetes. Overnight monitoring in adults and children has revealed an incidence of 20–45% (Kaufman et al, 2002; Guillod et al, 2007). Most episodes go unrecognised, with individuals remaining asleep with glucose levels below 2 mmol/L.

Nocturnal hypoglycaemia has been implicated in overnight death, although this is very rare (Heller, 2002). Nevertheless, a single severe episode is a frightening experience for both the individual and his or her family, and understandably can result in subsequent reluctance to pursue tight glucose targets (Cryer et al, 2003).

In people with type 2 diabetes a combination of factors contribute to the risk of nocturnal hypoglycaemic episodes (Jones et al, 1998):

- A long period between meals.
- The pharmacodynamics of basal insulin.
- Previous hypoglycaemia which can blunt hormonal responses to subsequent hypoglycaemia.
- Reduced counter-regulation during sleep.

Severe nocturnal hypoglycaemia is rare in people with type 2 diabetes, but symptomatic hypoglycaemic episodes are not uncommon, particularly in those who have been instructed to aim for near-normal glucose levels first thing in the morning (Riddle et al, 2003; UK Hypoglycaemia Study Group, 2007).

Other potential explanations for high fasting glucose levels

As described above, a high fasting glucose in a person with diabetes may simply be due to inadequate insulin levels as the effect of injected insulin wears off. However, two metabolic situations that might contribute, namely the Somogyi effect and the dawn phenomenon, also need to be considered (*Figure 2*).

The Somogyi effect

In 1938, at a meeting of the St Louis Medical School, Dr Somogyi, a biochemist of Hungarian extraction, described:

> *"extreme fluctuations in the blood sugar level, and progressively increasing unstability of diabetic patients as a direct result of the administration of excessive amounts of insulin … we have failed to recognise the cause and effect relationship between hypoglycaemia and hyperglycaemia, and by administering insulin doses sufficiently large to cause hypoglycaemias, we produced more severe hyperglycaemias."* (Somogyi, 1938)

This was based on the clinical finding of what was described as "unmanageable diabetes" in eight patients who alternated between severe hypoglycaemia and extreme glycosuria. Doses of twice-daily soluble insulin had been increased in an attempt to abolish glycosuria and some patients ended up on large doses (>200 units/day), which resulted in recurrent severe hypoglycaemia. In these patients, Somogyi observed that nights with

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4. Long-acting insulin analogues (insulin glargine or insulin detemir) have a flatter pharmacokinetic profile and thus insulin levels tend to be more stable through the night.

Page points

1. A high fasting glucose in a person with diabetes may be due to inadequate insulin levels, the Somogyi effect or the dawn phenomenon.
2. However, much of the evidence used to justify these competing explanations has been obtained from studies that may not reflect the clinical situation.
3. The Somogyi effect is only clinically relevant if the counter-regulatory hormonal response is strong enough to overcome the glucose-lowering effect of circulating insulin.
4. Severe hypoglycaemia can occasionally induce a powerful hormonal reaction and transient insulin resistance, but overnight studies show that most nocturnal episodes that develop spontaneously provoke little if any counter-regulatory hormone release, particularly if the individual is asleep.

no glycosuria were invariably followed by heavy glycosuria and often ketonuria the following morning. He found that a drastic reduction in insulin (in one case from 110 units/day to 16 units/day) resolved both the hypoglycaemia and the following glycosuria.

He surmised that asymptomatic hypoglycaemia in the early part of the night leads to glycosuria in the morning, and proposed that "hypoglycaemia begets hyperglycaemia" (Somogyi, 1959). He hypothesised that hypoglycaemia leads to an outpouring of adrenaline and cortisol, which results in glycosuria. This concept has become ingrained in clinical teaching and practice.

The dawn phenomenon

In 1975, Deckert and Lorup found that during experimental studies in adults with type 1 diabetes, blood glucose levels rose in the morning despite a constant insulin infusion overnight, and coined the term "dawn phenomenon" to describe this effect (Deckert and Lorup, 1976).

As described above, normal circadian increases in the secretion of catecholamines, cortisol and growth hormone in the early part of the night are reflected in a 30% increase in plasma insulin levels between 4 am and 8 am in people without diabetes, and blood glucose levels remain stable (Bolli et al, 1984a; Schmidt et al, 1984). Thus, the term refers to the rise in blood glucose in people with diabetes, who are unable to increase insulin levels.

The "dawn phenomenon" is particularly observed in people with type 1 diabetes, who often exhibit an exaggerated surge in growth hormone (Campbell et al, 1985). Blocking cortisol does not affect the dawn phenomenon (Bright et al, 1980), whereas inhibiting growth hormone release with somatostatin largely obliterates the effect (Campbell et al, 1985).

Clinical relevance of experimental observations

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Some groups have induced hypoglycaemia experimentally and reported subsequent raised fasting glucose levels (Bolli et al, 1984b), whereas others have not been able to detect an inverse relationship between low overnight glucose values

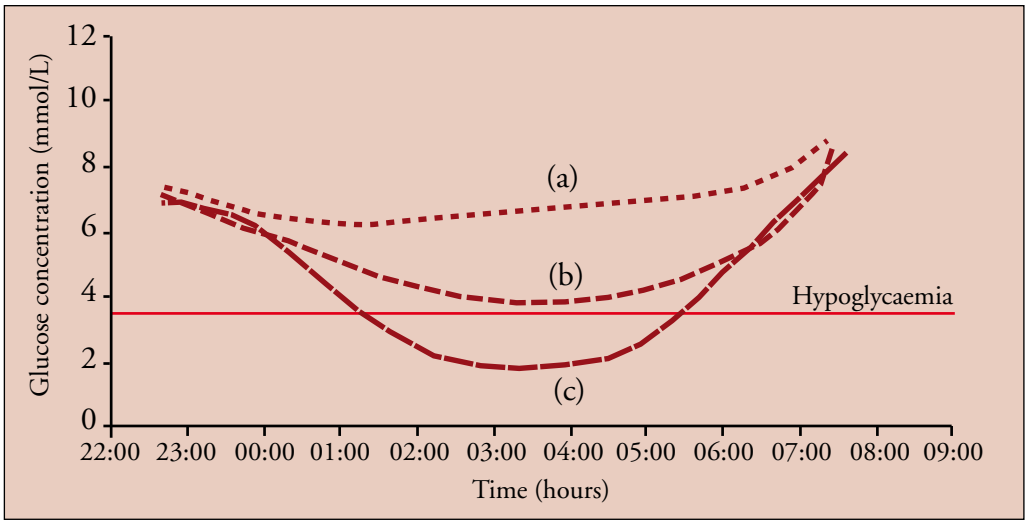

Figure 2. A Diagrammatic representation of possible causes of high fasting glucose concentrations in people with diabetes: (a) inadequate insulinisation; (b) the dawn phenomenon; (c) the Somogyi effect.

and a high value the following morning. The data are therefore conflicting (Gale et al, 1980; Tordjman et al, 1987; Perriello et al, 1988; Holl and Heinze, 1992).

The advent of continuous glucose monitoring has enabled investigators to explore the effect of low overnight glucose levels in more detail. Høi-Hansen et al (2005) found 218 episodes of asymptomatic hypoglycaemia during 594 nights of observation. Fasting glucose levels below 7 mmol/L were associated with a significantly greater risk of nocturnal hypoglycaemia. Mean fasting blood glucose was 5 mmol/L lower on nights with hypoglycaemia than after nights with no hypoglycaemia. Guillod et al (2007) also failed to demonstrate any relationship between nocturnal hypoglycaemia and high fasting glucose.

In a more recent study, our group has found a very similar relationship (Choudhary et al, 2007). Nocturnal hypoglycaemia was associated with low fasting blood glucose levels, and in people with type 1 diabetes there were no instances of nocturnal hypoglycaemia associated with a fasting glucose of >7 mmol/L. When fasting glucose was below 5 mmol/L, there was a 70% likelihood of nocturnal hypoglycaemia on the previous night. The dawn phenomenon was seen in 25% of participants. These data suggest that the Somogyi phenomenon had little clinical relevance in the individuals studied.

Clinical implications

The dawn phenomenon does appear to contribute to a high fasting glucose concentration, particularly in people with type 1 diabetes, and results from inadequate insulin delivery. In some cases, careful increases in basal insulin on the evening before may provide adequate morning glucose control, but this may be limited by overnight hypoglycaemia.

It is important to ask people with diabetes to check their blood glucose between 3 am and 4 am in order to determine the cause of high fasting glucose levels and identify the dawn phenomenon if present. Where nocturnal hypoglycaemia is a persistent problem the use of continuous subcutaneous insulin infusion pumps allows insulin infusion to be increased halfway through the night; this may be effective in overcoming the dawn phenomenon (Geffner et al, 1983).

The Somogyi effect appears to play little part in increasing blood glucose concentration in routine clinical practice. Most of the data from studies exploring its relevance in the clinical rather than the experimental setting suggest that asymptomatic nocturnal hypoglycaemia is more likely to result in low fasting glucose levels on the following morning. High glucose concentrations following symptomatic nocturnal episodes are therefore most likely to be associated with over-treatment with oral carbohydrate.

Conclusion

It is important for healthcare professionals working in primary care to be aware that high fasting glucose levels are usually due to inadequate overnight insulin replacement (Choudhary et al, 2007; *Box 2*). People with diabetes should be reassured that there is a low probability of overnight hypoglycaemia in this setting, and be encouraged to titrate up their overnight insulin doses. Long-acting insulin analogues are often useful in reducing the risk of nocturnal hypoglycaemia (Heller, 2008). Readings taken at around 3 am (although a little impractical) are useful in reassuring people with diabetes and also in identifying those with a strong dawn phenomenon. ■

Page points

1. Where nocturnal hypoglycaemia is a persistent problem the use of continuous subcutaneous insulin infusion pumps allows insulin infusion to be increased halfway through the night; this may be effective in overcoming the dawn phenomenon.
2. The Somogyi effect appears to play little part in increasing blood glucose concentration in routine clinical practice.
3. Evidence from studies in the clinical setting suggests that asymptomatic nocturnal hypoglycaemia is more likely to result in low fasting glucose levels.
4. High glucose levels following symptomatic nocturnal episodes are therefore most likely to be associated with over-treatment with oral carbohydrate.

Box 2. Authors' recommendations for clinical practice, based on experience and data discussed within this article.

- Recognise that low fasting glucose levels are associated with nocturnal hypoglycaemia.
- Many studies suggest an upper limit for target fasting glucose levels; it is important to also consider a lower limit of 5 mmol/L.
- A 3 am glucose test, and occasionally continuous glucose monitoring, may be helpful in determining the cause of a high fasting glucose level and identifying the dawn phenomenon.
- The Somogyi effect is rare. Asymptomatic nocturnal hypoglycaemic episodes are unlikely to produce a sufficiently strong counter-regulatory response to raised blood glucose.
- Concern about the Somogyi effect should not prevent, where appropriate, an increase in the evening dose of long-acting insulin in response to high fasting glucose levels.

Please note that the above are intended as general recommendations. Readers should ensure that management decisions are individualised according to the circumstances of specific patients.

"It is important for healthcare professionals working in primary care to be aware that high fasting glucose levels are usually due to inadequate overnight insulin replacement"

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