

Morning Insulin Requirements

Critique of Dawn and Meal Phenomena

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Morning insulin resistance has frequently been invoked to explain early-morning increases in both basal and breakfast-associated insulin requirements in diabetic patients. This increase in insulin requirements and plasma glucose from 0600 to 0900, when compared with midnight to 0600, has been termed the dawn phenomenon. We believe that the increased need for insulin in the morning has been misinterpreted. Data are reviewed that suggest the major perturbation overnight is a sleep-associated fall in hepatic glucose output, with a return to basal production rates on arousal in the morning. Moreover, the apparent increased insulin requirement for breakfast compared with lunch or supper (meal phenomenon) appears to be related more to lack of residual insulin effect from a preceding meal than to any putative morning insulin resistance. Thus, we found little evidence to support morning insulin resistance as a cause of either the dawn phenomenon (more appropriately designated the sleep phenomenon) or the meal phenomenon. A proper understanding of these phenomena is essential to the management of diabetic patients receiving insulin. Diabetes 38:273-77, 1989

Appropriate insulin therapy requires an appreciation of factors responsible for the diurnal variation in insulin requirements. In recent years, much attention has been devoted to suspected morning insulin resistance. The most widely publicized manifestation of this resistance is the dawn phenomenon, which refers to the increase in insulin requirements from 0600 to 0900. A less well recognized corollary of this phenomenon is the increased insulin requirement for breakfast compared with

lunch and supper. The major thrust of this perspective is to provide alternate interpretations for the reported increase in morning insulin requirements. Our considered judgment from a review of our data and those of others is that the dawn phenomenon is related more to a sleep-associated decrease in nocturnal insulin requirements than to any putative insulin resistance at dawn. Similarly, the increased insulin requirement for breakfast is more apparent than real because of the reduced requirements for the other meals due to residual insulin activity.

Elevations in overnight and early-morning blood glucose concentrations had been noted as early as 1924 (1) and 1967 (2). However, several technological advances led to widespread recognition and interest in the phenomenon during the past decade. In 1976, Deckert and Lorup (3), utilizing a constant insulin-infusion pump, showed that blood glucose tends to rise at dawn. Later it was noted by Schmidt et al. (4), who used a continuous glucose-monitoring apparatus, that plasma glucose was highest in diabetic patients between 0600 and 0900. Finally, the phenomenon seemed best documented in studies conducted with a closed-loop insulin-infusion device (Biostator) (5-9). The latter studies indicated that insulin requirements from 0600 to 0900 were greater than those from 2400 to 0600. The term *dawn phenomenon* to describe the early-morning glucose rise was first used by Schmidt et al. (10).

Although first observed in type I (insulin-dependent) diabetic patients, the dawn phenomenon has also been demonstrated in type II (non-insulin-dependent) diabetic patients and nondiabetic individuals (11). The magnitude of the increased insulin requirement at dawn varies considerably among subjects and even from day to day in the same subject (6). For this reason, caution has been recommended in implementing insulin prescriptions that might take this phenomenon into account (12).

Several potential explanations for the dawn phenomenon have been considered. Initially, investigators attempted to relate the increased insulin need at dawn to the circadian elevation in plasma cortisol. However, failure of dexameth-

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asone or metapyrone treatment to diminish the early-morning rise in blood glucose did not support that hypothesis (13,14). Other hormonal insulin antagonists that have been considered to play a role in the phenomenon are glucagon, catecholamines, and growth hormone. Glucagon and catecholamines are considered unlikely candidates because of their trivial diurnal variation (11,13). Some investigators have suggested that growth hormone may be responsible for the phenomenon. Campbell et al. (15) have shown that administration of somatostatin, which inhibits the nocturnal rise in growth hormone, eliminated the dawn phenomenon, whereas when somatostatin and growth hormone were administered together, insulin resistance at dawn was again observed. Recently, Davidson et al. (16) published data suggesting that anticholinergic blockade of nocturnal growth hormone release attenuated morning glucose elevations. Other studies have not supported a role for growth hormone in the dawn phenomenon (17,18). A circadian change in insulin clearance has also been proposed as an explanation for the increased insulin requirement at dawn (19,20). The latter observations may have been influenced by a technical artifact produced by the Biostator (21–23).

The Biostator artifact refers to heat-induced insulin aggregation during prolonged transit time through the pump module at low infusion rates (21–23). The artifact does not occur until after ~5 h of operation of the Biostator, during which the temperature of the pump module increases to ~39°C. The resultant insulin aggregate is biologically inactive; therefore, more insulin is required to maintain the blood glucose concentration at the target level. Because many of the dawn-phenomenon studies were designed to start the Biostator at 2200 and involved low overnight insulin infusion rates, it seems likely that in some of these studies, insulin inactivation may have occurred toward dawn, resulting in apparent increased insulin requirements.

Although the Biostator artifact may have distorted the magnitude of the phenomenon, we do not mean to imply that an increase in insulin requirements does not occur at dawn compared with midnight. Biostator studies with an albumin-containing insulin solution, thereby eliminating the artifact (24), or studies with a Harvard pump for insulin delivery (19,22) have also demonstrated rising plasma glucose values at dawn in diabetic subjects. In addition, studies without an insulin-infusion device have shown an increase in plasma glucose and immunoreactive insulin (IRI) at dawn in patients with type II diabetes (25) and in normal subjects (11,26). Note, however, that similar overnight studies by other investigators have failed to demonstrate such an increase in plasma IRI at dawn in normal subjects (27,28; this issue, p. 285).

We believe that the increase in blood glucose or insulin requirements in diabetic subjects at dawn reflects the increase in hepatic glucose output (HGO) that occurs on arousal compared with the reduced HGO during sleep. Observations reported by us in this issue indicate a dramatic reduction in HGO of ~30% during sleep (p. 285). In these studies on 17 subjects (11 asleep, 6 awake), HGO from 0400 to 0600 in subjects who slept overnight was only $69 \pm 5\%$ of the presleep basal value at midnight (2400), compared to $92 \pm 3\%$ in subjects who were kept awake ($P < .01$). This sleep-associated reduction in HGO occurs despite dimin-

ished insulin secretion and unchanged plasma glucagon and glucose levels, conditions that, if anything, should result in increased HGO.

Data by Bolli et al. (11) in normal humans indicate a similar decrease in HGO at night with a return toward basal production at dawn. Studies in diabetic humans have also demonstrated an increase in HGO before dawn (15). We believe that these studies indicate that a major, if not the only, factor responsible for increased insulin requirements at dawn is the juxtaposition of the sleep period, when HGO is reduced, with the period of arousal at dawn, when HGO returns toward basal levels. We therefore suggest that the emphasis for the phenomenon be placed on the sleep period rather than the arousal period. To continue to refer to the dawn phenomenon (an attitude we suspect this article will not change) is like attributing a rise in body temperature during the day to a low-grade infection.

In our studies in normal humans the overnight fall in glucose appearance (R_a or HGO) was equally matched by a fall in glucose utilization (R_d), and plasma glucose did not change. At dawn, the increase in R_a and R_d were again equally matched, and no increase in plasma IRI was observed. In this regard, it is interesting that several other studies in normal subjects have failed to demonstrate an increase in either plasma glucose or IRI at dawn (27,28; this issue, p. 285). In diabetic subjects an increase in morning plasma glucose and morning insulin requirements has been more consistently reproduced and probably occurs as a result of a pathological mismatch between the increase in R_a and the increase in R_d on arousal in diabetic subjects.

Another important aspect of morning insulin requirements is the increased insulin required for breakfast. In early studies with continuous subcutaneous insulin infusion (CSII) in type I diabetic patients, Tamborlane et al. (29) reported 40–55% greater insulin requirements for breakfast than for lunch or dinner. This observation agrees with observations of greater plasma insulin increases with breakfast than with other meals in nondiabetic subjects (30–32). It has been known among diabetologists that patients need more regular insulin before breakfast than before other meals. This increased insulin requirement for breakfast has been incorporated into algorithms for diabetic patients using pumps or intensive conventional therapy (33–35).

We have demonstrated increased insulin requirements for breakfast in type I diabetic patients by examining the amount of insulin delivered via the Biostator in response to ingestion of isocaloric meals of similar composition (36). Because of the rapid transit of insulin through the pump module when large amounts of insulin are required, the Biostator artifact does not pertain to studies examining meal insulin requirements. Our study indicated a 34% increase in insulin requirements for breakfast compared with an isocaloric lunch or supper.

Service et al. (37), using a somewhat different design, did not find increased insulin requirements at breakfast but did find a beneficial effect of a large meal in terms of lowering insulin requirements for subsequent meals. It is not clear why these studies did not demonstrate greater insulin requirements for breakfast than for other meals. It may have been related to the fact that insulin infusion rates were increased just before breakfast to control for the early-morning

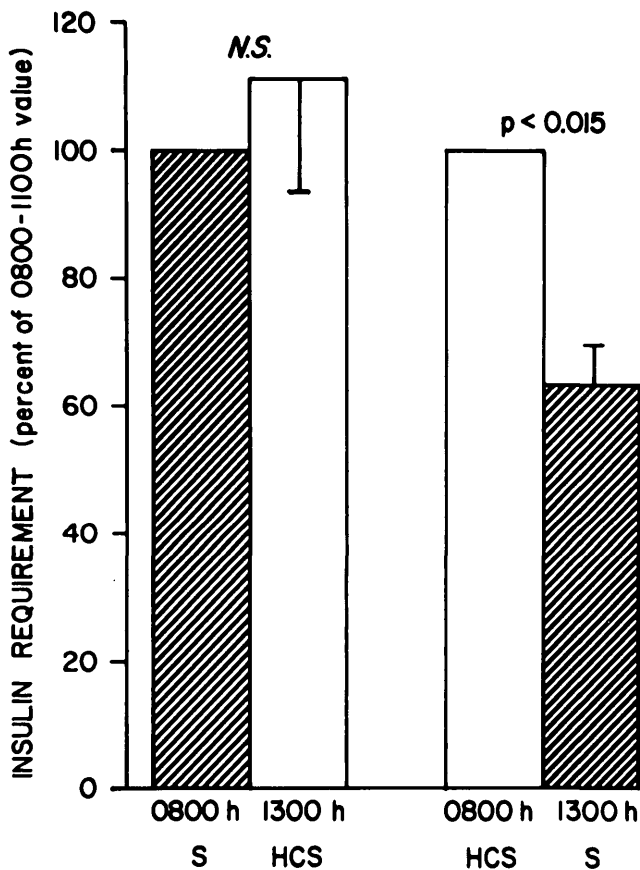


FIG. 1. Insulin requirements in 4 type I (insulin-dependent) diabetic patients given either sucrose (S, hatched bars) or hydrogenated corn syrup (HCS, open bars). On consecutive days and in random order, patients were fed either 120 kcal S at 0800 followed by 120 kcal HCS at 1300 or HCS at 0800 followed by S at 1300. Insulin requirements ($\text{mU} \cdot \text{kcal}^{-1} \cdot 3 \text{ h}^{-1}$) from 0800 to 1100 and from 1300 to 1600 were determined with closed-loop insulin-infusion system (Biostator). Insulin requirements ($n = 4$) have been normalized to 0800–1100 value of each study day and are expressed as means \pm SE.

rise in plasma glucose (dawn or “sleep” phenomenon). The effects of this increased insulin infusion may have persisted during breakfast, thus lowering breakfast insulin requirements.

We have referred to the increased insulin requirement for breakfast as a corollary of the dawn phenomenon (36). If the dawn phenomenon is not a result of morning insulin resistance but is simply a return of HGO to basal levels during the awake state, it is difficult to attribute the increased insulin requirement for breakfast to morning insulin resistance. Therefore, we have sought other explanations.

Insight into this problem occurred during a study in which we examined insulin requirements for a slowly absorbed carbohydrate (hydrogenated corn syrup) versus that required for a rapidly absorbed carbohydrate (sucrose) in type I diabetic patients (Fig. 1). When the slowly absorbed carbohydrate was given at 0800 (breakfast), insulin requirements for the second carbohydrate at 1300 (lunch) were reduced. If the rapidly absorbed carbohydrate was given at 0800, insulin requirements for the second carbohydrate challenge were not reduced. The lente (slowly absorbed) carbohydrate caused prolonged insulin delivery by the Biostator compared with the simple sugar (sucrose), and we postulate

that residual insulin action occurring in close temporal proximity to ingestion of the second meal may have reduced insulin requirements for that meal. This observation may be related to the Staub-Traugott effect (38).

We have recently had an opportunity to examine this hypothesis in normal humans with sucrose alone and sucrose with guar to produce the lente carbohydrate effect (39). These studies indicated that the ingestion of sucrose with guar (lente carbohydrate) at breakfast results in 1) prolonged elevations of plasma insulin and glucose until shortly before ingestion of the second carbohydrate challenge at lunch and 2) diminished plasma insulin and glucose responses for the second carbohydrate challenge. Conversely, when sucrose alone was given for breakfast, plasma glucose and insulin returned to baseline within 2 h, and the plasma insulin and glucose responses for the second meal were undiminished. Service et al. (37) invoked a similar explanation for the observation that a large meal reduced the insulin requirement for a subsequent meal. Although insulin levels had returned to normal before the subsequent meal in their studies, residual insulin activity from a slowly equilibrating biologically active compartment was proposed.

These data support our contention that decreased insulin requirements for lunch and supper compared with breakfast may be related to prolonged insulin elevation and effect after ingestion of a slowly absorbed meal. The fact that these mealtime differences are not observed when rapidly absorbed carbohydrates are ingested support this hypothesis. As with the dawn phenomenon, the emphasis on the meal phenomenon may have been misplaced. The emphasis should be on the reduction in insulin requirements for lunch and supper rather than on an increased requirement for breakfast. At the least, these observations indicate that the greater insulin requirement for the traditionally calorie-poor breakfast meal is not related to a diurnal change in insulin resistance.

In summary, we believe that both the dawn phenomenon and the meal phenomenon have been misinterpreted. It is

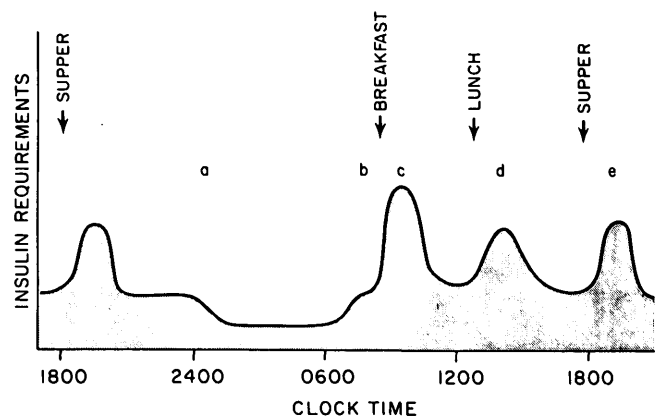


FIG. 2. Schema of daily insulin requirements. Insulin requirements before and during sleep and after breakfast, lunch, and supper. **a:** Decreased metabolic activity during sleep results in decreased hepatic glucose output (HGO) and decreased insulin requirements. **b:** Increased metabolic activity with arousal results in increase in HGO to basal level and increased insulin requirements. **c:** Increased insulin requirement for breakfast due to low residual insulin activity overnight. **d,e:** Decreased insulin requirement for lunch or supper compared with breakfast due to persistent insulin effect from previous meal. **Shaded area, sleep; open area, arousal.**

not necessary to postulate a diurnal change in insulin clearance or insulin resistance. Rather, simpler more physiological explanations exist to explain these phenomena (Fig. 2). Previous studies have ignored the role of normal sleep physiology in the pathogenesis of the dawn phenomenon, although Gale (40) hinted at this possibility in an editorial. A reduction in HGO occurs during sleep with a return toward normal on arousal at dawn, resulting in increased insulin requirements at dawn compared with the sleeping hours. The wide inter- and intraindividual variations observed with the dawn phenomenon may be related to the variable ability of subjects to sleep in the experimental laboratory. The fact that some physicians have found that the increase in plasma glucose at dawn can be attenuated by increasing predawn insulin delivery only implies that insulin needs are greater on awakening than during sleep (41,42). In our experience with insulin pumps, we have found a greater need to adjust infusion rates downward overnight rather than to increase them before dawn. Similarly, the greater insulin requirement for breakfast may only reflect the decreased insulin requirements for lunch and supper related to the persistent insulin elevation and action from the previous meal. In the diabetic patient the empirically determined insulin prescription takes into account the prolonged insulin effect needed to process a slowly absorbed meal.

The distinctions that the dawn phenomenon is due to a decrease in nocturnal insulin requirements rather than morning insulin resistance and that the increased insulin requirement for breakfast is due to decreased insulin needs for subsequent meals rather than to insulin resistance at breakfast represent more than semantic points. They are essential to understand the physiology responsible for these phenomena and to develop innovative methods of insulin delivery that take these phenomena into account. We hope that the interpretations outlined herein will lead to enhanced appreciation of the factors contributing to these phenomena by researchers and clinicians.

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