

## Effects of Growth Hormone on Diurnal Insulin Sensitivity in Normal and Type 2 Diabetic Patients and Animal Models

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### Abstract

This review addresses the effects of growth hormone on diurnal insulin sensitivity in normal, patients with type 2 diabetes mellitus (T2DM) and animal models described in our previous studies. Results confirmed the presence of diurnal insulin sensitivity, or greater insulin sensitivity in the morning, in normal subjects. The exact cause of this circadian rhythm in plasma glucose levels in healthy subjects has not been established, and nocturnal surges in growth hormone secretion remain a possible explanation. Results showed that growth hormone is an important factor controlling the diurnal variation of glucose tolerance and insulin sensitivity in rats. Data from our previous study provided direct evidence that the role of growth hormone in regulating insulin sensitivity in healthy subjects may be related to changes in the metabolic clearance rate of insulin and the metabolism of non-esterified fatty acids. A different circadian rhythm for plasma glucose appears to be present in patients with T2DM with nadirs in the early evening and peaks in the early morning, indicating greater insulin sensitivity in the evening. As in normal subjects, the exact cause of these circadian rhythms in the plasma glucose levels of patients with T2DM provided direct evidence that the reduction in insulin sensitivity may be due to the nocturnal surge of growth hormone in the early morning hours.

**Keywords:** Circadian rhythm; Dawn phenomenon; Diurnal variation; Insulin sensitivity; Normal subjects; Type 2 diabetes; Growth hormone

### Introduction

“Dawn phenomenon” was first described in 1981 as an abrupt increase in fasting levels of plasma glucose, insulin requirements, or both, in the early morning between 05:00 and 09:00 hours, without antecedent hypoglycemia [1]. This tendency for glucose to rise in the early morning hours in subjects with diabetes also reflects an increase in insulin infusion during the euglycemic insulin clamp test [2]. The frequency and reproducibility of dawn phenomenon were reported in T1DM and T2DM patients using insulin clamp studies [3], and the physiology of glucose homeostasis at night was studied in normal, nondiabetic subjects [4,5]. Differences in the frequency of dawn phenomenon were more evident in T2DM subjects older than age 70 years than in subjects younger than age 70 years, indicating that dawn phenomenon is present in adults aged 70 and older [6]. Monnier et al. [7] reported an additional observation on the dawn phenomenon in a large group of patients with T2DM and quantified its role in overall plasma glucose control. This type of morning rise in plasma glucose has also been found in diabetic patients who were treated with diet alone or diet plus sulfonylureas, leading researchers to suggest that factors such as treatment and duration of diabetes may contribute to the pathogenesis of dawn phenomenon [8].

Growth hormone has been reported to induce insulin resistance in healthy subjects [9]. The serum level of growth hormone shows a

nocturnal surge during nighttime slow-wave sleep [10]. The physiology of glucose homeostasis in normal, nondiabetic subjects exhibits remarkably flat, constant levels of plasma glucose and plasma insulin concentrations overnight, with a modest, transient increase in insulin secretion just before dawn [2,4] to restrain hepatic glucose production [4] and prevent hyperglycemia. Thus, normal subjects do not exhibit fasting hyperglycemia largely because they secrete insulin to prevent fasting hyperglycemia. One study shows that a nocturnal surge in growth hormone secretion is primarily responsible for the diurnal variation in glucose tolerance along with other counter-regulatory hormones such as cortisol, glucagon, and epinephrine [11]. Nevertheless, the use of synthetic glucocorticoid and recombinant growth hormone has transformed clinical practice and improved our understanding of the biological effects of these factors on insulin sensitivity in humans. However, more physiological, cellular and molecular studies employing the same observational rigor and insightful physiological reasoning are still needed to characterize in detail the targets for glucocorticoid and growth hormone effects on insulin sensitivity in humans [12]. Our previous study [13] showed that human growth hormone replacements have normalized insulin sensitivity in human growth hormone-deficient adults, which may be related to the reduction of total body fat. Results of another previous study [14] showed that time of day may influence glucose regulation in patients with T2DM. These findings suggest that diurnal insulin sensitivity may be related to a growth hormone-induced increase in insulin secretion in the early morning for the maintenance of normoglycemia [9,11-13].

Although the effects of growth hormone on insulin sensitivity have been suggested, the physiological role of growth hormone in dawn phenomenon in normal subjects and T2DM patients remains unclear. An animal study was conducted to evaluate diurnal changes in glucose tolerance and insulin sensitivity in normal rats and rats with reverse light-dark cycle using an oral glucose tolerance test and an intraperitoneal insulin tolerance test [15]. Results showed that the light-dark cycle, food intake, and growth hormone are all important factors controlling the diurnal variation of glucose tolerance and insulin sensitivity in rats [15]. A hypothesis was tested that growth hormone plays a critical role in regulating the morning rise in plasma glucose in both healthy subjects and T2DM patients without prior evidence of human growth hormone or insulin treatment [16]. The results provide direct evidence that the role of growth hormone in regulating insulin sensitivity in healthy subjects may be related to changes in the metabolic clearance rate of insulin and the metabolism of non-esterified fatty acids [16]. And that the reduction in insulin sensitivity may be due to the nocturnal surge of growth hormone in T2DM patients in the early morning hours [17].

### Core Tip

Diurnal insulin sensitivity is found in rats, normal subjects and T2DM patients, although it occurs in the opposite direction in normal subjects and T2DM patients. Growth hormone is involved in this diurnal insulin sensitivity in rats, normal subjects and T2DM patients.

### Diurnal Insulin Sensitivity in Normal Subjects and Patients with T2DM

A diurnal variation in glucose tolerance and insulin sensitivity in response to a glucose load has been reported in normal subjects [18]. In addition, glucose tolerance has been reported to be lower and insulin response slower when glucose is given orally either in the afternoon or evening than when it is given in the morning [18]. Similar diurnal insulin sensitivity has been reported in response to an intravenous glucose load [19]. The relatively impaired glucose tolerance observed in the afternoon or the evening is associated with a delayed insulin response to the glucose load, which is probably due to decreased sensitivity of pancreatic  $\beta$  cells to glucose [20]. Growth hormone concentrations are known to vary considerably throughout the day in normal subjects [4,21-23]; however, the physiological role of growth hormone-induced diurnal variation in glucose tolerance and insulin sensitivity remains unclear. Patients with T2DM appear to have a different circadian rhythm for plasma glucose, indicating greater insulin sensitivity in the evening.

In summary, diurnal insulin sensitivity exists in healthy subjects and patients with T2DM [14]. Although growth hormone has been suggested to have an effect on insulin sensitivity, the physiologic role of growth hormone in the dawn phenomenon in healthy subjects and T2DM patients remains unclear.

### Effects of Growth Hormone on Dawn Phenomenon in Rats

Daily fluctuations in plasma glucose concentrations are not random but describe a clear 24 h rhythm. Taking into account the 12 h shift that occurs due to different activity patterns between humans and rodents (i.e., humans are day-active; rodents, such as mice and rats, are night-active), rodents show similar diurnal variations in hormones involved in glucose metabolism and in energy substrates. Plasma concentrations of glucose and insulin are higher in the dark period

than in the light period [24]. The feeding schedule is a key factor influencing the diurnal variations in plasma glucose and insulin responses to an oral glucose load in rats, which may occur in day time or night time hours [25]. In the present study, although the responses of plasma glucose and insulin were undoubtedly influenced by variations in feeding patterns, it was difficult to measure the extent of such variation. It has been demonstrated that primates are able to synchronize cycles of eating and fasting with several diurnal rhythms, including the rhythmic changes of urinary excretion of water and potassium [26]. This synchronization has also been demonstrated in rat plasma corticosterone levels [27,28], sensitivity of glucose metabolism to insulin in rat soleus muscle [29], melatonin [30], B apolipoprotein [31] and plasma vasopressin and osmolality levels [32]. Thus, it is likely that the sensitivity of pancreatic  $\beta$ -cells to glucose is higher during the feeding time in the diurnal cycle. However, the mechanism responsible for the growth hormone-induced diurnal variation in glucose tolerance and insulin sensitivity remains unclear. In order to investigate the mechanism responsible for diurnal variation in insulin sensitivity, insulin-stimulated glucose uptake was measured in isolated adipocytes with and without growth hormone preincubation. Approximately 30% of insulin stimulated glucose uptake was suppressed when adipocytes were pretreated with growth hormone [15]. These results indicate that growth hormone has a superimposed role on the diurnal variation of glucose tolerance and insulin sensitivity [15]. Results of the present study are consistent with findings of daily rhythmic changes in the rates of absorption of saccharides in rat small intestine [33]. Feeding at an unusual time of day (inactive phase) desynchronizes peripheral clocks and causes obesity and metabolic disorders by inducing leptin resistance, hyperphagia, physical inactivity, hepatic fat accumulation and adiposity [34].

Common circadian-related gene variants are associated with increased risk for metabolic alterations, including in T2DM patients. Study results suggest that lower carbohydrate intake and normal sleep duration may ameliorate cardiometabolic abnormalities conferred by common circadian-related genetic variants. Recommendations applicable to the general population regarding diet-specific higher carbohydrate and lower fat composition and normal sleep duration should continue to be emphasized among individuals with the identified circadian-related gene variants [35]. Growth hormone is a major metabolic homeostatic factor that is secreted in a circadian pattern, but whether it is synthesized rhythmically is unknown. This is the first evidence that human growth hormone synthesis follows a diurnal rhythm and that dynamic associations exist between the circadian machinery and a component of a chromosomal structure of the human growth hormone 1 locus that is essential for efficient expression [36].

### Effects of Growth Hormone on Dawn Phenomenon in Healthy Adults

One possible factor affecting the diurnal variation in glucose tolerance is the nocturnal surge in growth hormone [4], even though that surge does not appear to be an important regulator of carbohydrate tolerance the following morning [37]. Results of one study [11] show that a nocturnal surge in growth hormone secretion is primarily responsible for the diurnal variation in glucose tolerance along with other counter-regulatory hormones such as cortisol, glucagon, and epinephrine. Many study findings have suggested that diurnal insulin sensitivity may be related to a growth hormone-

induced increase in insulin secretion in the early morning to maintain normoglycemia [9,11-13]. In contrast to the well-established effects of excess growth hormone, little is known about the impact, if any, of physiologic changes in plasma growth hormone concentration throughout the day. Therefore, we investigated the role of physiologic changes in plasma growth hormone concentration in healthy subjects, expecting then that the administration of octreotide, a growth hormone secretion inhibitor, would disturb the diurnal variation. On the other hand, if growth hormone were administered, we would expect the diurnal variation to be moved forward. The modified insulin suppression test was conducted to evaluate insulin sensitivity. A higher value of steady-state plasma glucose (SSPG) indicated lower insulin sensitivity, and a lower value of SSPG indicated higher insulin sensitivity [20,38]. The results suggest that insulin sensitivity in healthy subject is decreased in the evening compared with that in the morning [16]. The effects of growth hormone may be related to changes in the metabolic clearance rate of insulin and the metabolism of non-esterified fatty acids in healthy subjects [16].

A sustained increase in serum growth hormone has been shown to cause insulin resistance in healthy subjects [39] and patients with T2DM [17]. Results of our animal study showed that (1) male Sprague-Dawley rats exhibit diurnal variation of glucose tolerance and insulin sensitivity, with greater tolerance and lower insensitivity at 24:00 than 12:00 hours, corresponding with a greater food intake during the dark cycle; and (2) inhibition of insulin-stimulated glucose uptake by growth hormone may have a superimposed and amplifying effect on the diurnal variation of growth hormone [15]. A study using radioactive isotopes and insulin clamp techniques demonstrated that improved glucose tolerance after treatment for acromegaly might be due specifically to a decrease in peripheral insulin resistance [40]. Results of another study showed that dawn phenomenon was effectively prevented by applying a bedtime intranasal long-acting somatostatin analog [41]. Adult patients with growth hormone deficiency are insulin resistant, which is probably related to increased adiposity, reduced lean body mass, and impaired physical performance that temporarily worsens with the initiation of growth hormone treatment [13]. Conversely, despite an increased lean body mass and decreased fat mass, patients with acromegaly are consistently insulin resistant and become more sensitive after appropriate treatment [42]. Recently, low-dose growth hormone exposure was reported to evoke acute insulin resistance that subsided after 5 hours, suggesting that such time-dependent reversibility should be considered when assessing the influence of growth hormone on glucose homeostasis [43]. Nonetheless, although the dawn phenomenon has been attributed to a decrease in insulin sensitivity induced by a nocturnal spike in growth hormone secretion [44], some investigators suggest that an early morning increase in the metabolic clearance rate of insulin, rather than a decrease in insulin sensitivity, is the primary cause of the dawn phenomenon [45]. Debate is ongoing about whether overnight changes in the metabolic clearance rate of insulin play a role in the pathogenesis of the dawn phenomenon. It has also been suggested that the metabolic effects and metabolic clearance rate of insulin of exogenous growth hormone depend upon the time of day of administration [46].

As with growth hormone, several hormones that play important roles in the regulation of carbohydrate metabolism, including catecholamine, glucagon, and cortisol, also has diurnal rhythms. Theoretically, those diurnal rhythms can result in either an increase in glucose production or a decrease in glucose utilization. Although it has been proposed that an early morning rise in cortisol constitutes a

mechanism for increased glucose production, neither metyrapone blockade [47] nor dexamethasone suppression [48] has been shown to preclude the need for increased insulin delivery during the dawn period. Thus, glucagon and catecholamines are probably not involved in the pathogenesis of the dawn phenomenon [48].

Biochemically, the effects of growth hormone are complex and much research has focused on the mechanism behind the influence of growth hormone on insulin resistance. Authors of a recent study [49] pointed out that both growth hormone and insulin are key hormones regulating metabolism and growth, each activating different signaling pathways. As such, growth hormone and insulin can interact with each other to regulate cellular metabolism. In turn, we can then postulate that growth hormone and insulin can interact directly by signaling “crosstalk” and that insulin regulation of growth hormone signaling is associated with the duration of exposure to insulin. Although evidence suggests that chronic administration of excessive growth hormone can interfere with the activation of specific pathways by insulin [49,50], several other proteins have also been shown to be involved in the mechanisms underlying growth hormone-induced insulin resistance. For example, the results of Xu and Messina [49] and Domenici et al. [50] showed that insulin-like growth factor-1 (IGF-1) participates in the control of insulin sensitivity and plays an important role in the hormone balance between growth hormone and insulin.

### **Effects of growth hormone on dawn phenomenon in type 2 diabetes**

T2DM patients appear to have a different circadian rhythm for plasma glucose with nadirs in the early evening and peaks in the early morning, indicating greater insulin sensitivity in the evening. However, the exact cause of this circadian rhythm in the plasma glucose levels of T2DM patients has not been established. Data from our previous study [17] provided direct evidence that the reduction in insulin sensitivity in T2DM patients may be due to their nocturnal surge of growth hormone in the early morning hours.

In diabetes mellitus, fasting hyperglycemia is associated with higher mean daytime plasma glucose levels and subsequent poor overall glycemic control. The dawn phenomenon, also called the dawn effect, describes an abnormal early morning increase in plasma glucose—usually occurring between 02:00 and 08:00 hours in people with diabetes, and typically between 04:00 and 08:00 hours in people without diabetes. A surge for growth hormone released by the body occurs in the middle of the night and is followed by a surge in cortisol, which effectively cranks up glucose production in the liver to prepare the body for daytime activity after a period of fasting. However, in patients with T1DM whose pancreas does not make insulin, and in patients with T2DM whose liver may not respond to insulin sufficiently to stop glucose production (insulin resistance), changes in glucose metabolism during sleep can have a profound effect on morning plasma glucose levels. The term “dawn phenomenon” was introduced in 1981 by Schmidt et al. [1] to describe hyperglycemia or an increase for insulin needed to maintain normoglycemia, occurring during the early morning hours. Subsequently, based on the results of published studies [51-55] and clinical experience, investigators suggested that the magnitude of the dawn increase in plasma glucose level should be more than 10 mg/dL, or the increase in insulin requirement should be at least 20% of the overnight nadir, in order to fulfill quantitative criteria for the occurrence of the dawn phenomenon.

However, substantial evidence supports the impairment of early morning sensitivity to insulin in T2DM patients [56,57], suggesting that insulin resistance may be responsible for dawn phenomenon in diabetes. During the overnight period preceding or coinciding with the development of the dawn phenomenon, circulating glucagon levels remain unchanged, whereas levels of cortisol, catecholamines, and growth hormone all increase [3,54,55,58]. The early morning increase in cortisol level occurs concomitantly with the dawn rise in plasma glucose concentration. Nevertheless, several lines of evidence suggest that cortisol does not mediate the dawn phenomenon. The most conclusive evidence includes the well-described delay in the hyperglycemic action of cortisol and the lack of inhibition of the dawn phenomenon after pharmacologic suppression of cortisol secretion [47,48]. Sympatho-adrenal involvement in the dawn phenomenon also appears unlikely. Studies have shown that overnight combined  $\alpha$ - and  $\beta$ -adrenergic blockade does not cause significant changes in glucose production or utilization [11]. Thus, nocturnal increments in cortisol and catecholamines are unlikely candidates for producing a dawn rise in glucose levels. Most investigators, however, concur that growth hormone may be the primary mediator of the dawn phenomenon [44,59-61]. The tissues and/or the biochemical pathways involved in specific metabolic effects of growth hormone in humans have not been characterized precisely [62]. However, it is known that the hyperglycemic effect of growth hormone (as seen with the dawn phenomenon) is not due to hypoinsulinemia, but rather to increased insulin resistance [39]. Administration of growth hormone leads to substantial impairment of both hepatic and peripheral insulin sensitivity after an approximate 4-hour latency period in normal subjects [63]. This delay is consistent with the timing of the overnight peak in growth hormone secretion and the later onset of the dawn phenomenon. The relative contribution of increased glucose production and decreased glucose utilization to growth hormone-induced insulin resistance is unclear. Although post-absorptive peripheral utilization of glucose is low, a further suppression of glucose uptake by muscle is typically seen immediately after exposure to growth hormone. Moreover, Møller et al. [63] demonstrated that overnight administration of large doses of growth hormone in normal subjects stimulates gluconeogenesis, as determined by incorporation of labeled carbon into glucose. Thus, both decreased peripheral uptake of glucose and increased glucose production seem to be involved in the hyperglycemic effect of growth hormone. At the molecular level, it is currently unclear to what extent alteration of gene expression of glucose transporters and key glucoregulatory enzymes are involved in the growth hormone-induced impairment of insulin activity in humans.

IGFs are produced by the liver under the influence of growth hormone. Free IGF-1 exhibits glucose-lowering effects by inhibiting the secretion of growth hormone (thereby improving insulin sensitivity) and by acting at the insulin receptor (where it is only 6% as potent as insulin). IGFBP-1 is a binding protein produced by the liver and the kidneys. Although most IGF-1 in the serum is bound to IGFBP-3, the level of IGFBP actually controls the amount of circulating free IGF-1. When IGFBP-1 levels are high, levels of biologically active free IGF-1 are correspondingly low. The administration of exogenous IGFBP-1 promptly increases the level of glucose in animals [64]. Increased levels of IGFBP-1 and decreased levels of IGF-1 are also associated with decreased  $\beta$ -cell function in patients with T2DM [65] and correlate with impaired glucose tolerance in the non-diabetic population [66,67]. The overnight increase in IGFBP-1, which is due to impaired hepatic insulin sensitivity, may decrease the glucose-lowering

effects of free IGF-1 and be partially responsible for the dawn phenomenon in diabetic patients. More studies are needed to further clarify this relationship.

### Clinical applications for diabetes therapy

The dawn phenomenon is an important cause of early morning hyperglycemia and may occur in patients with diabetes regardless of age or glycemic control. The most likely underlying pathogenic mechanism is growth hormone-induced insulin resistance at the liver and peripheral tissues. Although the dawn phenomenon is not caused by insulin deficiency, effective insulin delivery can minimize its hyperglycemic effects. Strategies to prevent the dawn phenomenon should be tailored to the individual patient and should balance the risks of undesirable overnight hypoglycemia against optimal correction of fasting hyperglycemia [68].

Even though the impact of dawn phenomenon seems to be slightly lower in individuals on oral anti-diabetic drugs [69], study results indicate that the oral anti-diabetic drugs do not adequately control the dawn phenomenon, even when given in combination therapy [70]. Sulphonylureas are less than ideal due to risk of hypoglycemia in the afternoon or evening when the dose is increased to counteract the hyperglycemia of dawn phenomenon. Incretins are designed to elegantly improve postprandial periods, not fasting periods [71]. Sodium glucose co-transporter 2 (SGLT2) inhibitors are a new class of glucose-lowering agents developed for the treatment of T2DM. Depending on the agent and dosage used, SGLT2 inhibitors reduce fasting plasma glucose and are also associated with modest reductions in weight and systolic blood pressure [72]. The evening replacement of basal insulin, which abolishes the dawn phenomenon by restraining hepatic glucose production and lipolysis [73], is an effective treatment as it mimics the physiology of glucose homeostasis in the presence of cardiovascular risk factors along with impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes [74]. Basal insulin may be initiated to prevent an increase in hemoglobin A1c >7.0% and reduces new-onset diabetes [74] by reducing nocturnal hyperglycemia and the dawn phenomenon [75]. Self-monitoring of preprandial glucose values at the three main mealtimes can predict the presence/absence of the dawn phenomenon, and permits reliable assessment of its magnitude without requiring continuous overnight glucose monitoring [76]. In summary, despite the extensive number of published studies, the dawn phenomenon remains of research interest and importance. The dawn phenomenon must be taken into consideration when making treatment decisions in patients with T2DM.

### Conclusion

Diurnal insulin sensitivity is present in rats, normal subjects and T2DM patients, although in the opposite direction in normal subjects and T2DM patients. The dawn phenomenon is an important cause of early morning hyperglycemia and may occur in patients with diabetes regardless of age or glycemic control. Growth hormone is involved in this diurnal insulin sensitivity in rats, normal subjects and T2DM patients.

### Conflict of Interest

The authors have no conflicts of interest relative to the work described herein. No financial support was received for the study, nor do the authors have any relevant commercial relationships.

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