Research Article

A review of the current literature and guidance for treatment of the dawn phenomenon and glycemic variability

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Abstract

Background: The dawn phenomenon and glycemic variability have been readily identified in both type 1 and type 2 diabetes. Though extensive research exists, much remains unclear regarding the exact mechanism, frequency, and magnitude of the dawn phenomenon as well as the role of glycemic variability and the clinical impact as it relates to complications. Without concrete data on clinical implications, guidance for practitioners on appropriate treatment has been limited, especially in type 2 diabetes.

Methods: A MEDLINE search (1966-2015) was conducted using the dawn phenomenon and glycemic variability as key words. Identified articles were limited to English and evaluated by others to determine inclusion based on the topics of pathophysiology, incidence, complications, and with emphasis on treatment. References in obtained articles were also review for additional article inclusion.

Results/Conclusion: Conflicting evidence continues to exist on the exact cause, frequency, and impact of glycemic variability and the dawn phenomenon. Several studies have attempted to determine the need for treatment and best practices for doing so; however no consistencies have been established. The negative consequences of hypoglycemia after treatment often outweigh benefits of eliminating glycemic variability. This review establishes current patterns as well as areas for new research.

Key words: the dawn phenomenon; glycemic variability; type 1 diabetes; type 2 diabetes; dysglycemia; macrovascular; microvascular; hypoglycemia

Introduction

As early as 1924, providers managing diabetes have noticed a specific period of dysglycemia in the early morning hours when patients showed elevated blood glucose without a preceding incident of hyper- or hypoglycemia [1,2]. In 1981, Schmidt and colleagues labeled this observation, the dawn phenomenon [1,2]. Since then, the dawn phenomenon has been defined as either early morning hyperglycemia, an increase in early morning insulin requirements in order to maintain normoglycemia, or both and has been identified in both patients with varying pathophysiological causes for diabetes and is recognized as an example of glycemic variability (GV) [3-8]. The impact of GV over time can result in poor glycemic control and is a suggested factor associated with diabetic micro-and macrovascular complications, including retinopathy, neuropathy, nephropathy, and cardiovascular disease (CVD); however, controversy exists surrounding the overall frequency and clinical implications of the dawn phenomenon and GV [3,4,7,9-13]. Currently, guidelines from the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) provide little direction for providers in terms of whether treatment is required for this dysglycemia and what treatment is most effective [14,15].

The objective of this review is to evaluate the available evidence surrounding the dawn phenomenon as a part of glycemic variability addressing its pathophysiology, clinical implications, and treatment strategies.

Methods

A MEDLINE search (1966-2015) was conducted using

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the dawn phenomenon and glycemic variability as key words. Identified articles were limited to English and evaluated by others to determine inclusion based on the topics of pathophysiology, incidence, complications, and with emphasis on treatment. References in obtained articles were also review for additional article inclusion.

Results

Pathophysiology

As the most easily identifiable period of GV, the dawn phenomenon has been studied frequently to ascertain the pathophysiology in order to understand the impact and need for treatment. However, even with extensive research, the exact mechanism by which the dawn phenomenon occurs is not fully understood. Individuals without diabetes have a circadian change in insulin secretion and plasma level, which rises in the early morning, peaks midday, and declines in the evening [16]. Therefore, a true dawn phenomenon is not seen in these individuals as the increase in insulin released adequately suppresses the increase in early morning blood glucose levels [4,6,9,17,18].

It has been proposed that an increase in growth hormone, secreted by the anterior pituitary, may be connected to an increase in early morning blood glucose [4,19]. In 1985, surges in growth hormone were prevented through intravenous injections of somatostatin plus replacement glucagon [19]. Neither glucose production, nor glucose levels increased; however, the addition of growth hormone to the somatostatin infusion caused a reappearance of early morning hyperglycemia. Studies have found that patients with type 1 diabetes and growth hormone deficiency, either inherent or induced via administration of a somatostatin analogue, do not experience the dawn phenomenon, thus providing more evidence that growth hormone may be a culprit [4,20,21].

Though hyperglycemia as it relates to growth hormone is not fully understood, it is evident that the relationship relates to insulin resistance as following administration of growth hormone both hepatic and peripheral insulin sensitivity is impaired for approximately 4 hours [4, 22]. This time frame is consistent with the overnight increase in growth hormone and subsequent occurrence of the dawn phenomenon. It is known that growth hormone predominately acts through the hepatic production of insulin like growth factors (IGF) and when exposed to growth hormone, levels of insulin like growth factor 1 (IGF-1), glucose, ketone bodies, and insulin are increased [23]. IGF-1 and insulin-like growth factor-binding protein-1 (IGFBP-1) are produced within the liver and free IGF-1 inhibits the secretion of growth hormone, in turn improving insulin sensitivity. Increased levels of IGFBP-1 and subsequent decreased levels of IGF-1 have been shown to decrease β-cell function in type 2 diabetes and correlate with impaired glucose tolerance in the non-diabetic population [4,24]. It may be plausible that the cascade of overnight impaired hepatic insulin

sensitivity that leads to increased IGFBP-1 and decreased IGF-1 is responsible at least in part, for the dawn phenomenon [4].

In conclusion, though several proposed mechanisms exist behind why the dawn phenomenon and glycemic variability occurs, the exact cause is likely multifactorial, making research and treatment difficult. At this time, the strongest ties appear to be with growth hormone and IGF-1.

Treatment strategies based on underlying pathophysiology

Initial research evaluating appropriate treatment strategies for the dawn phenomenon focused on utilization of drug therapy as a method to correct possible hormonal causes based on the suspected pathophysiology. Davidson and colleagues performed with administration of oral methscopamine, an anticholinergic agent that suppresses sleep-induced growth hormone secretion, in patients with type 1 diabetes [25]. Patients were on continuous infusion insulin that was adjusted based on glucose readings throughout the night. While the authors did not disclose all the statistically analyzed data, they reported that the growth hormone response and peak concentration were significantly reduced and, as such, concluded that growth hormone suppression may be a possible treatment for the dawn phenomenon [25]. Limitations included use of the continuous infusion insulin that was updated based on glucose readings which may not be reproducible in clinical practice and author disclosure that insulin infusion rates may vary between devices used [25].

Shih and colleagues also studied the role of growth hormone in the dawn phenomenon in patients with type 2 diabetes [26]. Patients enrolled in the study received octreotide, a growth hormone secretion inhibitor. Patients were observed for 16 hours, with FBG, fasting serum insulin, IGF-1, and non-esterified fatty acids monitored. Increased levels of growth hormone resulted in insulin sensitivity reduction in patients with type 2 diabetes and the dose of octreotide was not sufficient to suppress growth hormone and insulin secretion [26]. Limitations include utilization of growth hormone suppression for the treatment of the dawn phenomenon which may result in undesirable effects in some patients, particularly younger patients dependent on it for proper growth.

In conclusion, growth hormone does not appear to be the only hormone involved in the pathogenesis of the dawn phenomenon, which makes it an incomplete treatment. Results of these studies are summarized in **Table 1.**

Incidence

The incidence is important to establish the clinical relevance of establishing treatment options. As the dawn phenomenon is the most well defined period of glycemic variability, incidence has been reported and studied, whereas less is known about the incidence of other periods of dysglycemia. The reported incidence of dawn phenomenon is similar between patients with type 1 diabetes and type 2 diabetes, 54% and 55%, respectively [4].

Reference	Patient Population	Study Design and Duration	Mean HgbA1c	Treatment	Parameters Significantly Improved	Parameters Not Significantly Improved
Davidson (26)	8 T1DM	Prospective, open-label, cross sectional study Two 12hour studies	N/A	Oral methscopolamine	GH peak concentration reduced (no p value)	Catecholamine secretion, serum levels of cortisol
Shih (27)	15 T2DM Taipei patients	Prospective, open-label, cross-sectional study Pretreatment medications given and then observation for 16 hours NS, GH, and octreotide were separated by at least 3 days	7.5 +/-0.7	Pretreatment with NS or Octreotide 300mcg@1600 or 8IU GH @2300	FPG, FSI, NEFA, SSSI (p<0.17) at 8 hours with pretreatment with GH FPG (p<0.17) at 15 hours for GH and octreotide	Pretreatment with octreotide at 8 hours for FPG, FSI, NEFA, SSSI Pretreatment with GH and octreotide at 15 hours for FSI, NEFA, SSSI
Yagasaki (39)	62 Japanese T1DM	Open-label, non-randomized, cross sectional study	7.9	CSII vs glargine vs NPH Doses were individually given based on patient's prescribed dose	The dawn phenomenon more frequent in NPH (62.1%) compared to glargine (16.6%) (p<0.05) and compared to CSII (14.3%) (p<0.05)	IFGBP-1 levels increased 10 fold in NPH group and free IGF-1 decreased by half
Nicolajsen (40)	29 T1DM children and adolescent	Retrospective case study of two groups Data compared 1 year after change to CSII 2 groups: High HgbA1c (>8.8%) and other reason	>8.8	Change from basal/bolus to CSII with an average dose of 78% prepump dose Humalog	Difference in TDD after 1 year in units/kg/day for high HgbA1c 0.4 (p<0.001) and other reasons 0.2 (p=0.011) Decrease in HgbA1c in high HgbA1c group (p<0.001)	HgbA1c in other indications group
Bouchonville (41)	40 T1DM patients	Observational, longitudinal study 8 months 3 groups: multiple daily injections, continuous infusion programmers (basal rate change), continuous infusion non-programmers (no basal rate change)	7.6	Glargine or detemir Humalog through CSII pump device	Hypoglycemia 3.9% in programming group compared to 3.5% in non-programming group (p=0.001)	Frequency of the dawn phenomenon among programmers and non-programmers (p=0.47) Magnitude of the dawn phenomenon among programmers and non-programmers (p=0.07)
King (42)	49 T1DM	Prospective	7.6	Individualized regimens of lispro and glargine MDD optimized daily by a trained investigator based on CGM and BG testing 7 times daily Meals were fixed with 50% carbohydrate content	BG rise at 0400 h to 0730 h; 32% increase in BG (p=0.00149) with a peak at 1000 hours with a 47% increase in BG (p=0.000182) Correlation coefficient between amplitude of dawn phenomenon and C-peptide level was -0.37 (p<0.05);duration of diabetes was 0.309 (p<0.05)	Correlation coefficient between amplitude of dawn phenomenon and weight and HgbA1c

Carroll (10)	16 T2DM volunteers Various night studies were performed; 34 observations	Case study	8.1+/-1.9	Glipizide vs NPH vs MDD regular insulin vs overnight CSII Forced hypoglycemia	N/A	Cortisol, epinephrine, norepinephrine, BG, GH drawn with no significant differences
Monnier (28)	248 T2DM non-insulin treated	Prospective, non-randomized, non-blinded case control study	7.16	Diet vs insulin sensitizers (metformin, TZD) vs insulin secretagogues (sulfonylurea, DPP-IV inhibitor) vs insulin sensitizer plus insulin secretagogue	For overall population impact of the dawn phenomenon on HgbA1c level 0.39% (p=0.007) and 24 hour mean glucose value 12.4mg/dL (p=0.0009) Patients on diet alone impact of the dawn phenomenon on 24 hour mean glucose 16.7mg/dL (p=0.019) Impact of the dawn phenomenon on HgbA1c for insulin sensitizers 0.38% (p=0.037) and insulin secretagogues alone and in combination with sensitizers 0.5% (p=0.047)	Impact of the dawn phenomenon on HgbA1c level for diet alone and 24 hour mean glucose for insulin sensitizers and insulin secretagogues alone and in combination with sensitizers

Table 1: Summary of trial data for treatment of pathophysiology and dysglycemia.

Monnier and colleagues performed a study to determine if the age of an individual has an independent effect on the incidence of dawn phenomenon in patients with type 2 diabetes not on insulin therapy as had been suggested [27]. The prevalence of the dawn phenomenon ranged from 52-70% across the three age groups showing that age is not a predicting factor in the incidence of the dawn phenomenon.

A discrepancy in reporting dawn phenomenon incidence is the varying definitions used to define the condition. A few examples include increases in blood glucose of more than 10mg/dL, increases in blood glucose of 15-50mg/dL, or ≥20% increase in insulin requirements overnight [4,6,26, 28]. Another consideration is the inconsistency of not only the intra-day dysglycemia, but also the inter-day variation further justifying the need for research on dysglycemia as it relates to glycemic variability.

The impact of glycemic variability (GV)

Glycemic variability (GV) is defined as either intra- or inter-day (day to day) glucose variation [11,12,28]. Due to the impact it has on overall glycemic control, numerous methods have been utilized to assess the number and degree of glucose excursions that occur over time, and are summarized and defined in **Table 2** [29].

Utilizing the various methods for assessment of glycemic variability, the dawn phenomenon has been indicated to cause large day-to-day glucose variations impacting overall glycemic control [28,29]. In a non-controlled clinical trial, Schmidt and colleagues assessed if the dawn phenomenon influenced intra-day BG variation, using FAGE [30]. Of the 11 patients with type 1 diabetes, 10 demonstrated an increase in FAGE, which positively and significantly correlated with the morning postprandial BG peak. CV and MAGE were strongly correlated with high BG values during the morning (0900-1600 and 0900-1800, respectively), and to a lesser extent, lower BG values during the evening and night period. The glucose maximum was predominantly dependent on FAGE, contributing to more than half of the day's largest glucose excursion. This signifies that the dawn phenomenon accounts for the largest glucose excursion within a day, extending well into lunch postprandial BG values and is a causative factor for day-to-day glucose instability and variability [28,30]. Excessive post-breakfast glucose excursion, "extended dawn phenomenon," is characterized by worse glucose intolerance in the early morning than any other time of the day and subject to large day-to-day fluctuations [28,31]. This is supported by Monnier and colleagues who conducted a trial assessing the magnitude of the dawn phenomenon and it's impact on total glucose exposure using CGM in noninsulin-treated individuals with type 2 diabetes [31]. The magnitude of the dawn phenomenon, assessed by absolute median glucose increments from nocturnal nadir to pre-breakfast value did not differ statistically; however, the influence of the dawn phenomenon on day-to-day fluctuations was found to be statistically significant for HgbA1c and 24-h mean glucose values [28,31]. Further results of both studies are summarized in Table 2.

GV Measure	Definition	Advantages	Disadvantages
Standard deviation (SD)	Calculated by a 7-point SMBG.; Measures the dispersion from the mean; Positively associated with the mean value or CV	Straightforward and easily calculated ;Simplest method to assess intra-day variability; Commonly used ; Also provides a measure of interday GV depending on frequency	Can miss the number of glycemic swings within a 24-hour period, such as the dawn phenomenon
Coefficient of variation (CV)	Calculated by dividing the SD by the mean and multiplied by 100	Useful for comparisons between groups with different glucose tolerance	Can miss the number of glycemic swings ; Can miss the dawn phenomenon
Fasting ascending segment of the morning blood glucose excursion (FAGE)	Calculated by the glucose nadir typically between 2400 and 0600 and subtracted from the glucose value reached immediately before breakfast	Useful for determining presence of the dawn phenomenon and intraday BG variation	Requires continuous blood glucose monitoring ; Not extensively used the literature ; Only considers glycemic excursions during the fasting period
Mean amplitude of glycemic excursion (MAGE)	MAGE is defined as the arithmetic mean of the differences between BG peak and nadirs and vice versa, when both ascending and descending segments exceeded >1 SD of the BG for the same 24h period	Most extensively used in the literature ; Preferred method for assessing CGM data; Quantifies both upward and downward glucose fluctuations > 1 SD; Measure of intraday GV	Arbitrary definition of peak/nadir (> 1 SD); Excludes minor upward and downward glucose excursions of < 1 SD; Does not differentiate between the magnitude of glucose fluctuations ; Dependent on sampling frequency and is limited to individuals with everyday accessibility to CGM systems
Continuous overlapping net glycemic action (CONGA)	Calculates the difference between current glucose levels and glucose levels in previous n hours, with n varying from 1 to 8h; using the SD of these differences	Provides a precise measurement of intra-day variability using CGM data points over short-or long-term intervals More objective than MAGE; Able to capture smaller glycemic swings over shorter time intervals ; Does not require arbitrarily defined glucose peaks and nadirs	Specifically developed for CGM; Excludes frequent real-world use in patients with T2DM; Requires software for calculation Glucose differences are not normally distributed, which is necessary for calculating the SD; Which time segments will provide the most useful results have yet to be determined
Mean of daily blood glucose differences (MODD)	Calculated by the mean absolute value of the differences between paired blood glucose values in two consecutive days that occurred at the same time within a 24-hour period	Reflects the consistency and stability of interday glucose patterns	Requires software for calculation. Affected by different daily eating habits, mealtimes, and exercise can greatly affect MODD scores
BG (blood glucose); CGM (continuous glucose monitoring); SMBG (self-monitoring of blood glucose levels) [29]			

Table 2: Summary of glycemic variability (GV) measure [29].

How the dawn phenomenon impacts diabetes-related complications has yet to be determined as published studies are lacking an objective for this measure. The absence of a uniformly accepted measurement makes it difficult to determine when and what magnitude of glycemic variability is of clinical relevance and what, if anything, should be done to resolve it. Although epidemiological studies have attempted to determine these questions, the various assessment indicators used to examine the effects of glycemic variability and how it relates to the development of diabetes-related complications, make direct comparisons difficult and produce ambiguous conclusions. Subsequent analyses of the Diabetes Control and Complications Trial (DCCT) found no association between glycemic variability and micro- and macrovascular complications in patients with type 1 diabetes [32,33]. A study published by Bragd and colleagues was conducted in patients with type 1 diabetes and assessed glycemic variability as an independent risk factor for microvascular complications [36]. The authors found the SD was significantly related to peripheral neuropathy and a borderline predictor of incidence, concluding the nervous system may be particularly vulnerable to glycemic variability. Both the DCCT and the study conducted by Bragd and colleagues relied on SMBG data, and may have missed fluctuations

occurring between the measurements providing a less accurate measure of GV [32-34]. Further results are summarized in Table 2.

In contrast, Lin and colleagues conducted a study among patients with type 2 diabetes primarily on oral antidiabetic therapies and assessed if glycemic variability, evaluated by FBG-CV, can predict mortality independent of other risk factors [35]. After adjusting for mean FBG, mean HgbA1c, HgbA1c variation, and other risk factors, annual FBG-CV was an independently statistically significant predictor of all-cause and CVD mortality over a period of 5 years [35]. Hirakawa and colleagues examined the association between glucose inter-variability from visit-to-visit in HgbA1c and FBG in a cohort of the randomized control trial, Action in Diabetes and Vascular Disease: the Preterax and Diamicron MR Controlled Evaluation (ADVANCE) [36]. The trial included assessment of patients with type 2 diabetes by visit-to-visit glycemic variability as the SD of 5 measurements of FBG and HgbA1c. Visit-to-visit GV of FBG and HgbA1c were significantly associated with macrovascular, microvascular, combination of micro-and macrovascular, and mortality when an HbA1c ≤6.5% was targeted [36]. These results, summarized in Table 2, suggest that glycemic variability during a longer period of time is an important risk factor for vascular events and mortality and the impact may be equal to or even more than that of intraday glycemic variability.

Sartore and colleagues conducted a trial investigating the association between diabetic retinopathy and glycemic variability in patients with type 1 and type 2 diabetes [37]. Glycemic variability indicators were significantly higher in patients with type 1 diabetes, demonstrating more than a 2-fold risk of severe hyperglycemia compared to patients with type 2 diabetes. Further analysis revealed a significant association between diabetic retinopathy, duration of diabetes and intensive insulin treatment; and minimal significance between diabetic retinopathy and glycemic variability associated with SD and CONGA. Unfortunately, this study did not assess if the risk of diabetic retinopathy was associated with the magnitude, frequency, or duration of glycemic variability. Results are summarized in Table 2.

In conclusion, the growing debate in the literature on the magnitude with which glycemic variability contributes to the progression of microvascular and macrovascular complications still remains unclear; however, given the associated implications in the pathogenesis of diabetes complications, reductions in glycemic variability represent an important target for treatment and management. The dawn phenomenon is currently the most identifiable, most defined example of glycemic variability, and therefore may be a more concrete place to establish outcomes and treatment.

Treatment of dysglycemia with antidiabetic agents

Several studies have used current treatments for diabetes as a

means to treat the dawn phenomenon, and are perhaps, the most clinically useful data. A study by Yagasaki and colleagues assessed the differences in dawn phenomenon occurrence when patients with type 1 diabetes were treated with continuous infusion insulin, NPH, or insulin glargine [38]. Results, summarized in Table 1, indicated significantly greater occurrence of the dawn phenomenon in the NPH group with 62.1% of patients experiencing the dawn phenomenon compared to the insulin glargine group and the continuous insulin infusion group. Limitations of this study include the open-label design, exclusion of patients with type 2 diabetes, and potentially non-optimal insulin dosing prior to study completion; however, it does demonstrate that bedtime dosed NPH, with waning levels of insulin during the expected time of the dawn phenomenon hours, may not be an optimal treatment.

Nicolajsen and colleagues performed a study in children and adolescents analyzing the dawn phenomenon and insulin usage during a transition from basal/bolus regimens to continuous infusion insulin pump therapy [39.] Over one year, analysis showed that basal rates were overall decreased by 20% and bolus doses were decreased by 15-30% across groups. Additional results listed in Table 1. It also showed that children aged 3-9 required slightly higher basal settings from 2300-2400, whereas adolescents aged 15-21 needed higher basal rates from 0300-0700 based on the dawn phenomenon [39]. The results indicated that pump therapy should be considered as a treatment modality to account for changes in basal insulin needs as attributed to the dawn phenomenon. A limitation of this study is that it was only conducted in children and adolescents with type 1 diabetes limiting clinical extrapolation.

In contrast, Bouchonville and colleagues performed an extensive, controlled, observational 8-month longitudinal study of in patient with type 1 diabetes with CGM receiving continuous infusion insulin [40]. The study compared rates of the dawn phenomenon and hypoglycemia in patients divided into 3 groups; multiple daily injections, continuous infusion programmers with an increased basal rate of 35.1% between the hours of 0300 and 0700, and continuous infusion non-programmers that did not change basal rate. All patients utilized CGM with a total of 356 overnight observations analyzed. In these patients the dawn phenomenon occurred 38-63% of the time across groups, with no statistical difference in the number of times it occurred or the magnitude of change. Of note, hypoglycemia occurred more often in the programming group compared to the non-programmers and was statistically significant. In addition, 44% of the hypoglycemia readings were below 50mg/dL and considered severe. Additional results are summarized in Table 1; however, limitations include that it was not randomized and it did not account for lifestyle changes. There was also no explanation for the dawn phenomenon which occurred an average of 56% of the time, confirming that the incidence of the dawn phenomenon also fluctuates and varies within an individual as well as the population, and further shows the difficulty in assessing and treating glycemic variability [40].

This information contrasts the study conducted by Nicolajsen and colleagues as no improvement was seen in reducing the dawn phenomenon with increased insulin infusion and displayed significant increases in hypoglycemia that may lead to detrimental effects [40].

King and colleagues also displayed the negative consequences of adjusting a basal regimen for the dawn phenomenon in patients treated with once nightly insulin glargine [41]. Patients had daily follow up with insulin regimens optimized at each visit utilizing CGM, as well as, BG testing performed 7 times daily. Results, summarized in Table 1, indicated that blood glucose goals were reached except for 0400 and 0730 which both showed statistically significant increases of blood glucose by 32% and 47% respectively. Increases of greater than 30mg/dL occurred in 56% of subjects and greater than 10mg/dL in 73% of subjects. If insulin doses were titrated based on getting initial morning readings to goal, it resulted in hypoglycemia for the rest of the day [41]. The replicability of this study is low as it controlled for both food and insulin regimens that were adjusted daily by a trained investigator; however, it does corroborate Bouchonville's evidence, which basal insulin regimens adjusted to cover the dawn phenomenon may result in increased hypoglycemia.

Carroll and colleagues performed several small studies with 34 observations to assess the frequency of the dawn phenomenon and then further assess the impact of a variety of treatments on six individuals with type 2 diabetes [10]. The six patients were first observed on their current treatment, then after 6 weeks of treatment on glipizide, then after 6 weeks of bedtime NPH, then after 3 days of an intensive insulin therapy that included multiple daily injections of regular insulin, and finally, after continuous overnight intravenous infusion of regular insulin resulting in 16 total observations. Results included only 1 out of the 16 total observations meeting the criteria for the dawn phenomenon. Results summarized in Table 1. A separate observation conducted by Carroll and colleagues, forced hypoglycemia using insulin, and growth hormone values were drawn every 30 minutes [10]. In the forced hypoglycemia group, 9 out of 12 participants failed to have an increase in growth hormone secretion, which may explain why the occurrence of the dawn phenomenon was lower than expected in this group of individuals. No differences were noted in treatments in the type 2 diabetes patients; however, the occurrence of the dawn phenomenon was so small, data relating to the various treatment arms of 6 patients may not be attributable to larger populations [10]. In addition, patients with a known history of the dawn phenomenon were not selected which may have caused a selection bias.

Monnier and colleagues perhaps completed the most applicable research in patients with type 2 diabetes that looked at the comparison of diet alone (50% carbohydrate diet of weight based calorie intake), insulin sensitizers (metformin, TZD), insulin secretagogues (sulfonylurea, DPP-IV inhibitor), or insulin sensitizer plus insulin secretagogue in 248 patients monitored on CGM for two consecutive days [28]. Each patient with the dawn phenomenon was then matched to a patient not diagnosed with the dawn phenomenon with similar nocturnal nadir glucose values. HgbA1c and 24 hour mean glucose concentrations were measured in all patients. Results showed that a statistically significant difference in blood glucose confirming the dawn phenomenon occurred across both groups. Average change in blood glucose was 20mg/dL for the diet alone group, 15mg/dL for the sensitizer alone group, and 13mg/dL for the combination treatment group. When the dawn increase met criteria of 20mg/dL, both the HgbA1c and 24 hour mean glucose were statistically significantly higher in the dawn phenomenon group compared to the matched group, with results further summarized in Table 1. This study gives us some indication that treatment using insulin sensitizers alone and in combination with secretagogues can decrease the impact of the dawn phenomenon; however, they are insufficient at treating it completely.

Monnier and colleagues' most recent publication asks the question of how much dysglycemia due to glycemic variability is required before treatment should be in place [16]. Monnier reported an impact on HgbA1c of 0.4% by the dawn phenomenon. The data also shows that the dawn phenomenon does not occur in non-diabetic subjects due to endogenous insulin secretion change; however it is present in individuals with HgbA1c starting at 5.7% and to avoid hypoglycemia, recommends treatment of dysglycemia with metformin and incretin agents instead of insulin [9]. Summarized in Table 1.

In conclusion, no one treatment was found to be superior consistently across trials. Evidence also showed that over treating glycemic variability and the dawn phenomenon, likely related to intra-variability, could result in harmful hypoglycemia in some patients, thus further complicating treatment.

Discussion/Conclusion

The dawn phenomenon, an established period of glycemic variability, is a component of dysglycemia that remains an underappreciated risk factor in patients with diabetes. In over 30 years of research, the exact mechanism and best treatment modality are still unclear. HgbA1c is the gold standard used to evaluate glycemic control; however, HgbA1c is unable to capture the amplitude, frequency, and duration of glycemic fluctuations that can result in dysglycemia and glycemic variability. The amount of dysglycemia caused by the dawn phenomenon that warrants treatment to achieve optimal glucose control and prevent diabetes-related complications has not yet been determined. In spite of this, more guidance is needed to assist providers on the available options. Studies involving glycemic variability and the dawn phenomenon also need to evaluate micro- and macrovascular complications as endpoints to better articulate the role of therapies in preventing

these complications. As Monnier and colleagues reported, a 0.4% overall impact on HgbA1c is caused by the dawn phenomenon [16]. The United Kingdom Prospective Diabetes Study (UKPDS) showed that small changes in HgbA1c of 1% can lead to decreases in death by 21%, myocardial infarction by 14% and decreases in microvascular complications of 37% [16]. This indicates that even the small change in HgbA1c of 0.4% is likely having a significant impact.

Monnier and colleagues demonstrated some success in decreasing the dawn phenomenon with their identified insulin sensitizers and secretagogues, but the effect was not complete [16]. Based on available data, it appears the most appropriate recommendation at this time is the use of insulin, either by adjusting basal rates in patients with type 1 diabetes or by increasing basal insulin in patient with type 2 diabetes, but hypoglycemia has been an unfortunate side effect. This also leaves a gap in therapy guidance for patients with type 2 diabetes with a moderately elevated HgbA1c who are experiencing the dawn phenomenon and are not currently on insulin therapy. The ORIGIN Trial looked at this specifically when it studied the use of basal insulin glargine in patients with impaired fasting glucose, impaired fasting glucose in addition to cardiovascular risk factors, and newly diagnosed type 2 diabetes, to achieve a FBG target of less than 95mg/dL compared to patients receiving standard care in each of those disease states [42]. In the 12,537 patients studied over 6 years, results showed that there was no difference in cardiovascular outcomes in the glargine groups compared to the standard care group. It also resulted in statistically significant increases in severe hypoglycemia, defined as 54mg/dL or less, (1 vs 0.31 per 100 person years) and weight increases of 1.6kg compared to a decrease of 0.5kg in the standard treatment group. The authors concluded that this study did not provide support for early use of insulin glargine in patients with early dysglycemia, which includes the dawn phenomenon [42]. The current position statement for the ADA and the European Association for the Study of Diabetes has well established standardized treatment for hyperglycemia and also recognizes the consequences of not addressing it [14,16,42]. However, not enough guidance, based on lack of evidence, is given for how to treat glycemic variability, and more specifically, how to address the dawn phenomenon.

In conclusion, after analyzing the data, providers at this time should be identifying patients with the dawn phenomenon and glycemic variability through first screening individual blood glucose readings. CGM should be used in patients displaying a wide variety of inter- and intra-day variations to confirm the variations are not caused by preceding hypoglycemia. Providers should then work with patients on an individual basis to reduce glycemic variability and the dawn phenomenon with insulin sensitizers, insulin secretagogues, long acting insulin, and insulin pump settings; however, avoiding hypoglycemia should take precedent to eliminating transient hyperglycemia, GV, or the dawn

phenomenon at this time. Insulin should not be used for patients not requiring it for other areas of glycemic control.

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