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The altered circadian pattern of basal insulin requirements – an early marker of autoimmune polyendocrine syndromes in type 1 diabetes mellitus

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Objectives. The purpose of the present paper is to propose and introduce novel biomarkers of autoimmune polyendocrine syndromes that are relevant to the early diagnosis and optimal medical management of the patients who already suffer from type 1 diabetes mellitus.

Methods. We hypothesize and demonstrate on a case study that various organ-specific autoimmune endocrinopathies can result in lowered basal insulin requirements, leading to unexplained hypoglycemia.

Results. It can be hypothesized that hypothyroidism in patients with type 1 diabetes mellitus may deteriorate glycemic control and can lead to an increased rate of hypoglycemia, particularly the overnight and morning hypoglycemia. Thus, the decreased requirements for particularly overnight basal insulin can be an early marker of the autoimmune polyendocrine syndrome-3 with subclinical autoimmune thyroiditis in immune-mediated type 1 diabetes mellitus. Further, it could be proposed that unexplained hypoglycemia during the late afternoon or evening could be an early marker of the autoimmune polyendocrine syndrome-2 with subclinical autoimmune Addison disease in immune-mediated type 1 diabetes mellitus. As a result, an altered circadian pattern of basal insulin requirements can occur, characterized by a decreased late afternoon basal insulin rate.

Conclusions. After exclusion of other causes, the unexplained reoccurring hypoglycemia can be a remarkable feature of autoimmune polyendocrine syndromes in immune-mediated type 1 diabetes mellitus on intensive insulin replacement therapy.

Key words: type 1 diabetes mellitus, hypoglycemia, autoimmune polyendocrine syndromes, insulin, hypothyroidism, Addison disease

Type 1 diabetes mellitus (T1DM) is a lifelong, noncommunicable disorder, considered one of the most common endocrine and metabolic disorders in childhood. T1DM may occur at any age, although its onset is most common in childhood and adolescence. Out of 424.9 million people (8.8% of adults) estimated to have diabetes worldwide, T1DM affects 1.1065 million children and adolescents (IDF 2017).

T1DM develops as a result of absolute insulin deficiency predominantly due to autoimmune destruction of pancreatic beta-cells. Its manifestation is characterized by the sudden onset of severe hyperglycemia that can progress rapidly to diabetic ketoacidosis and death unless treated with insulin. Hyperglycemia is also a major modifiable contributor to development and progression of chronic diabetic

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complications. Encouraging evidence suggests that early and sustained improvements in glucose control with normal or nearly normal blood glucose levels may effectively delay the onset and slow the progression of chronic diabetic complications.(Nathan et al. 1993; Nathan 2014) At the same time, persons on tight control are at increased risk of hypoglycemia that can range from relatively mild to potentially life-threatening. Of importance, long-term follow-up studies show higher rates of microvascular complications and mortality among individuals with a history of brittle diabetes characterized by erratic or fluctuating glycemic control, associated with frequent, unpredictable and unexplained hypoglycemia, recurrent episodes of diabetic ketoacidosis or a combination of the two (Cartwright et al. 2011).

While the clinical presentation of hypoglycemia ("Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia," 2005; Seaquist et al. 2013) is often characteristic, the combination of deficient glucagon and epinephrine responses particularly in the individuals with long-standing T1DM causes defective glucose counterregulation (Cryer 2002). Since the neuroglycopenic symptoms of hypoglycemia are nonspecific, many episodes are less well recognized. It is widely estimated that about 19.5% of patients with T1DM suffer from hypoglycemia unawareness (Geddes et al. 2008), which is particularly dangerous at night. A more complex set of drivers of unexplained hypoglycemia can include potentially relevant pathomechanisms underlying undiagnosed autoimmune disorders, most commonly autoimmune hypothyroidism and hypocorticism. Autoimmune endocrinopathies can coexist in the same individuals and some of them are nosologically codified in the so-called autoimmune polyendocrine syndromes (Sperling and Yau 2000).

It can be conceivably hypothesized that the altered circadian pattern of basal insulin requirements can serve as an early marker of autoimmune polyendocrine syndromes in T1DM. The purpose of the present paper is to propose and introduce novel biomarkers of autoimmune polyendocrine syndromes that are relevant to the early diagnosis and optimal medical management of the patients who already suffer from T1DM. We hypothesize and demonstrate on a case study that various organ-specific autoimmune endocrinopathies can result in lowered basal insulin requirements, leading to unexplained hypoglycemia. The major goal is to ultimately optimize care and improve the outcomes for the patients with autoimmune endocrine diseases.

Classification of autoimmune polyendocrine syndromes. The classification of autoimmune polyendocrine syndromes (APS) has undergone some additional development since first proposed in 1980 by Neufeld and Blizzard (Neufeld and Blizzard 1980) and continues to evolve as knowledge expands. The initial classification (Neufeld and Blizzard 1980) designated four main types of the APS according to the types of diseases present in an affected individual: APS -1 characterized by the concomitant presence of at least two of three diseases: chronic mucocutaneous candidiasis, chronic hypoparathyroidism, and autoimmune Addison disease; APS-2 characterized by the obligatory occurrence of autoimmune Addison disease in association with autoimmune thyroid disease and/or immune-mediated type 1 diabetes mellitus; APS-3 characterized by the association of autoimmune thyroid disease with other endocrine and non-endocrine autoimmune manifestations excluding autoimmune Addison disease, hypoparathyroidism, and chronic candidiasis; APS-4 that includes all other possible combinations of two or more organ-specific autoimmune diseases that do not fall into APS-1, APS-2, or APS-3. Because autoimmune thyroid disease is the most prevalent autoimmune condition in the general population, APS-3 is the most frequently observed autoimmune polyendocrine syndrome. Although the APS-2 is a rare condition, its latent forms are much more frequent, particularly in subjects with a pre-existing autoimmune disease, e.g. T1DM. With slow-onset chronic Addison disease, significant low-level, nonspecific, but debilitating, symptomatology including hypoglycemia may occur.

If left undiagnosed, there may be serious and potentially fatal complications of untreated APS organ-specific autoimmune diseases – Addison disease, thyroid disorders, and T1DM – that highlight the need for their early detection and satisfactory treatment prior to morbidity and in some cases mortality.

Hypotheses

The altered fasting basal insulin requirements. In most adults (after the growth years), basal insulin requirements tend to peak during the early morning/predawn hours and then decline slowly throughout the day resulting in the expected bimodal curve shape. This is mainly due to the circadian production of growth hormone and cortisol that stimulate the liver to release glucose into the bloodstream. Basal insulin requirements depend on age, levels of

hormones, and residual endogenous insulin production in T1DM (Scheiner and Boyer 2005). It can be hypothesized that various organ-specific autoimmune endocrinopathies can result in lowered basal insulin requirements, resulting in unexplained hypoglycemia. Therefore, after exclusion of other causes, the unexplained reoccurring hypoglycemia can be a remarkable feature of APS in immune-mediated T1DM on intensive insulin replacement therapy.

The potential role of hypothyroidism in precipitating morning hypoglycemia. Thyroid hormones thyrotropin (TSH), free triiodothyronine (T3) and free thyroxine (T4) show a distinct circadian rhythm with a sinusoidal signal; TSH levels reach a maximum between 2:00 AM and 4:00 AM and a nadir between 4:00 PM and 8:00 PM (Russell et al. 2008). It has been established that hypothyroidism is a precipitating factor for hypoglycemia (Samaan 1989) Of importance, prolonged hypoglycemia due to exogenously administered insulin was reported in hypothyroid patients (Shah et al. 1975) It can be hypothesized that hypothyroidism, including its latent subclinical forms, in patients with T1DM may deteriorate glycemic control and can lead to an increased rate of hypoglycemia, specifically the overnight and morning hypoglycemia. Thus, the decreased requirements for particularly overnight basal insulin can be an early marker of the APS-3 with autoimmune Hashimoto thyroiditis in immune-mediated T1DM.

The unexplained late afternoon hypoglycemia in subclinical hypocorticism. Cortisol is a steroid hormone with a circadian rhythm secretion. In individuals without disease of the hypothalamus-pituitary-adrenal axis, plasmatic cortisol levels peak early in the morning between 4:00 AM and 8:00 AM and then decline slowly throughout the day with a nadir occurring in the late evening hours (Krieger et al. 1971). It could be proposed that unexplained hypoglycemia during the late afternoon or evening could be a sign of subclinical adrenocortical failure in immune-mediated T1DM. As a result, an altered circadian pattern of basal insulin requirements can occur. The pattern is characterized by a decreased late afternoon fasting basal insulin rate that can be an early marker of the APS-2 with subclinical autoimmune Addison disease in T1DM.

Evaluation of the Hypotheses

In the majority of patients with T1DM, the associated autoimmune disease follows the onset of diabetes. If our hypotheses are supported, we will be able to identify APS (APS-2 and APS-3) susceptible individuals based on detection of the altered circadian pattern of basal insulin requirements. Subsequently, screening for thyroid and adrenocortical autoantibodies will be performed. Specifically, the presence of antibodies against thyroglobulin, antibodies against thyroid peroxidase, and 21-hydroxylase autoantibody will be analyzed. Amongst autoantibody positive individuals, thyroid and adrenal function testing will follow.

To evaluate basal insulin doses, glucose monitoring during a fasting basal test is advised. Glucose monitoring can also provide healthcare providers with the information needed to identify glycemic patterns to adjust insulin. Presently, persons with T1DM can self-monitor blood glucose with fingersticks and a glucose meter, or monitor glucose concentrations nearly continuously using a continuous glucose monitor (CGM) if available.

The informed consent was obtained from the patient for being included in the study.

Preliminary results from a case study

A 30-year-old unmarried Caucasian woman diagnosed with type 1 diabetes at the age of 15 years presented to the outpatient clinic due to brittle diabetes. She complained of chronic fatigue and gave a long-standing history of recurring hypoglycemic episodes, including several moderate to severe nighttime and daytime hypoglycemias, one of which required hospital admission.

Besides the intensive insulin-treated T1DM, she also suffered from arterial hypertension well controlled with ramipril 2.5 mg once daily and had positive autoantibodies against thyroglobulin and thyroid peroxidase. Her medical history was otherwise unremarkable. The patient denied recreational drug use, did not smoke, and only drank alcohol occasionally. The patient was highly educated, regularly performed mild physical activity and maintained a reasonable diet. There was a family history of T1DM, arterial hypertension, and coronary artery disease.

The insulin regimen consisted of insulin pump therapy (Paradigm RT 522; Medtronic MiniMed, Northridge, CA) with short acting insulin analog lispro (Humalog; Eli Lilly, Indianapolis, IN) delivered at preset basal rates and administered in several premeal boluses. The total daily dose of insulin was around 40 IU.

The patient's HbA1C was 6.9% (52 mmol/mol) and BMI 21.5 kg/m^2.

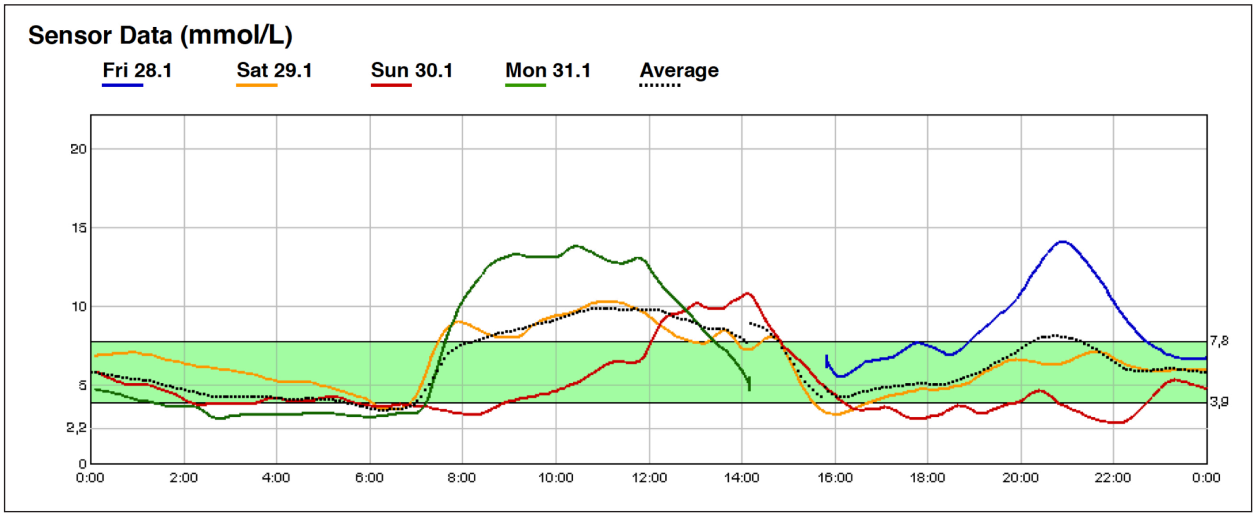

Figure 1. Continuous glucose sensor daily overlay report.

To capture all of the relevant information for glucose pattern analysis, a retrospective CGM study was scheduled. The subject was fitted with the iPro2 Professional CGM system (Medtronic MiniMed, Northridge, CA) that recorded blinded glucose values for diagnostic purposes. The patient was then asked to continue self-monitoring of blood glucose at home and keep good notes of anything that may have affected blood glucose readings. After 4 days of CGM, the data were reviewed upon their upload, and glucose profiles were analyzed with a health care professional.

Figure 1 depicts the first four days of glucose sensor tracings layered on top of each other for comparison (Sensor Daily Overlay Report). The CGM profiles revealed unrecognized prolonged nighttime hypoglycemic episodes during the second and third night of maximum duration more than 5 hours. The patient was not awakened by hypoglycemia. The episodes occurred without symptoms except for reports of morning headache. Hypoglycemia was confirmed by self-monitoring of blood glucose in the morning. No obvious predisposing cause was identified. Adjustments to the basal rate were proposed. The overnight basal rate was adjusted by 0.1 to 0.2 IU/h decrements to keep the overnight glucose levels within the desired range above 5.6 mmol/l (100 mg/dl). The patient was strongly advised to regularly check blood glucose at 2:00 AM. She was advised of the increased chances of having nocturnal hypoglycemia and was educated on how to prevent it. Because of the high titer of the antithyroid antibodies and presence of symptoms of hypothyroidism, thyroid tests were ordered as well as the ultrasound of the thyroid gland. The results were consistent with mild subclinical hypothyroidism defined by a slightly elevated serum TSH level (5 mIU/L) along with a normal T4 level. Thyroid ultrasound demonstrated diffuse hypoechogenicity indicating the presence of chronic thyroiditis. Based on these findings, levothyroxine replacement therapy was commenced at 50 ug/day. Regular diabetes and endocrine clinic follow-up visits were scheduled. The patient reported improvements in overnight glucose control with considerably reduced episodes of nighttime and morning hypoglycemia.

After one year, the subject presented to the clinic with complaints of persisting recurring late afternoon hypoglycemic episodes despite significant decreases in appropriate basal rates. No obvious predisposing cause was identified. She was in good health and asymptomatic. Her HbA1C was 6.8% (51 mmol/mol) and BMI 20.7 kg/m^2. The patient utilized the sensor-augmented insulin pump with the real-time CGM to minimize the risk of silent hypoglycemia and allow management decisions to be taken in real-time. The total daily dose of insulin was around 39 IU.

As shown in Figure 2, glucose alerts were used to prevent and limit the duration of imminent hyper- and hypoglycemic events. The figure also depicts the basal-bolus insulin requirements around the clock. Of importance, the CGM detected significant decreases in glucose levels in the late afternoon (at around 4:00 PM) consistent with self-monitored borderline hypoglycemia despite considerably decreased basal insulin rate in the afternoon (as low as 0.2–0.3 IU/h at 1:00 PM–5:00 PM). The subject was encouraged to

continue intensive self-monitoring of blood glucose and reviewing her basal rates on regular basis. To reduce the risk of late afternoon hypoglycemia, the patient was advised to eat a protein-rich snack mid-afternoon. The presence of 21-hydroxylase autoantibody was analyzed. Because of the autoantibody positive result (a low positive titer), adrenal function testing was performed. The results showed normal morning plasma adrenocorticotropic hormone and cortisol levels. The appearance of circulating adrenal autoantibodies directed against the enzyme steroid 21-hydroxylase indicated pre-clinical phase of the adrenal autoimmune process that may lead to adrenal insufficiency. One-year endocrine clinic follow-up visit was scheduled. The patient has been classified as affected by an APS-3.

Discussion

Despite the enormous advances in medicine over the past 100 years, the diabetes and its complications remain serious medical challenges. Setting and establishment of appropriate basal insulin levels are critical to intensive insulin therapy of T1DM. In most adults with T1DM, basal insulin requirements tend to peak during the early morning hours due to the dawn effect – a widely recognized phenomenon that results in an increased secretion of glucose by the liver. Basal insulin levels then gradually decrease throughout the day along with the decreasing levels of plasmatic cortisol. Previous studies have investigated the impact of age and gender (Scheiner and Boyer 2005), acute diabetic complications (Laimer et al. 2016), diabetes duration, and glycated hemoglobin (Bachran et al. 2012) on total daily basal insulin requirement and circadian distribution of basal insulin. Age is a well-recognized factor that determines the overall basal insulin requirements. Lower overall basal insulin requirements were found in the youngest (age < or =10) and oldest (age >60) groups (Scheiner and Boyer 2005). A bimodal distribution of basal insulin need was observed for all age-groups, but with variable age-dependent amplitudes, concluding that age of the patient is the primary factor that influences both total daily requirement and circadian distribution of basal insulin in insulin pump therapy (Scheiner and Boyer 2005). Despite this knowledge, the variability in the diurnal pattern of basal insulin requirements remains insufficiently defined in adult patients with T1DM.

Hypoglycemia, hypoglycemia unawareness, and unrecognized wide glucose excursions continue to be major obstacles to achieving the safe recommended long-term blood glucose control and an associated reduction in long-term complications in people with T1DM. Although the autoimmune comorbidities frequently occur in T1DM, their early pre-clinical stages remain often undiagnosed. To date, no studies have investigated the association between the altered circadian distribution of basal insulin and the autoimmune comorbidities in adults with immune-mediated T1DM.

The APS-2 is a complex multifactorial genetic disorder associated with specific human leukocyte antigens (HLA) risk haplotypes and non-HLA genes that determine the targeting of specific tissues by autoreactive T cells, which leads to organ specific autoimmunity as a result of this loss of tolerance. Both Addison disease and T1DM have overlapping genetic risk factors and share a common pathophysiology characterized by T-cell mediated destruction of the target organ. The APS-2 has a polygenic autosomal dominant inheritance pattern with variable expressivity and incomplete penetrance (Eisenbarth et al. 1979; Skordis and Maclaren 1988; Robles et al. 2002). Susceptibility is determined by multiple genetic loci that interact with environmental triggers and thus contribute to the loss of immune self-toler-

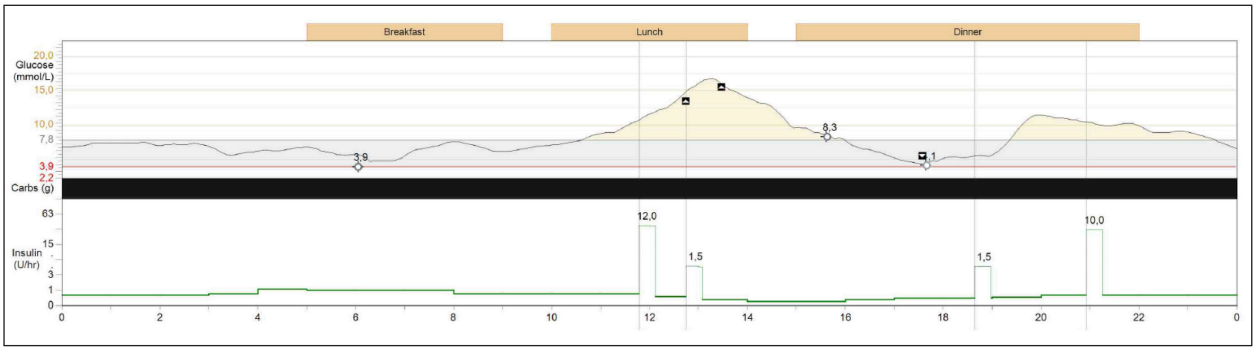

Figure 2. Real-time continuous glucose monitoring daily detail and insulin requirements.

ance. From the clinical point of view, T1DM is one of the most frequent component disorders of APS-2 and is often its first symptom; it commonly precedes the development of the clinically manifest adrenocortical insufficiency in most patients with APS-2 that usually develops years to decades apart. Adrenal autoantibodies appear months to years before the appearance of clinical signs of adrenal insufficiency and a preclinical phase of the disease can be recognized. The clinically overt APS-2 usually occurs in adults with a peak incidence in the fourth decade.

The APS-3 is the most frequently observed autoimmune polyendocrine syndrome because autoimmune thyroid disease is the most prevalent autoimmune condition in the general population and is common in T1DM as well.

The hypotheses presented herein have implications for future research and clinical practice. Establishment of proper basal insulin doses should be part of both the complex T1DM management and the monitoring for physiologic decompensation with a goal of treating prior to morbidity. An important goal in the prevention and management of organ-specific autoimmunity lies in identification of individuals at high risk of developing clinical disease. Our hypotheses provide a new approach to assigning a risk score for the development of APS in T1DM patients, considering circadian distribution of basal insulin requirements. The development of unexplained recurrent hypoglycemia should arouse suspicion of autoimmune hypothyroidism or adrenocortical insufficiency. Our approach gives useful information about the level of risk and recommended timing for clinical (age, preexisting disease/antibodies) and laboratory (autoantibody titers, hormone levels) evaluation.

Thanks to major advances in medicine in the past two decades, endocrine disease diagnosis has moved beyond the standard hormone measurements. A combination of clinical, novel genetic and immunological markers has allowed us to identify subjects at risk for the development of many autoimmune endocrine disorders. Novel diagnostic biomarkers of APS are critically needed. If the hypotheses presented herein are supported, we will determine surrogate markers and intermediate phenotypes for APS-2 and APS-3 disease progression – an enormous benefit to patients with T1DM.

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