Clinical Case Report

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Spontaneous and transient hyperglycemia before sleep in a patient with glaucomatous blindness and diabetes

A case reprt

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Abstract

Rationale: The peak of blood glucose was during 9 PM to 3 AM. There is a stable, spontaneous and short-term abnormal increase of blood glucose. The pathophysiological mechanism is unknown. It is speculated that the cause might be the imbalance of the glucose-regulating hormone that is caused by the disorder of the biological clock system.

Patient concerns: The case was a 73-year old man with bilateral glaucoma (only mild light perception) and was hospitalized to establish a viable hypoglycemic plan. He received 4 shots of insulin enhancement, oral meditation, pre-mixed insulin treatment during the 22 days. However, his blood glucose had been spontaneously increased from 9 PM to 3 AM which was the highest of the day, and then resumed by itself. Insulin intervention was effective.

Diagnosis: Glaucomatous blindness and diabetes, spontaneous and transient hyperglycemia before sleep.

Interventions: We used insulin aspart 3u when we found hyperglycemia three times at 9 PM and it was effective. Without intervention, blood sugar will automatically improve in the morning.

Outcomes: During the late night and early morning, there is a stable, spontaneous and short-term transit abnormal increase in blood glucose, which suggests the complexity of blood glucose adjustment.

Lessons: Due to the case specialty, we could not do the systematic review of the study. However, it improves the awareness of the abnormal periodically increase of blood glucose during the special periods, and provides with a reference for clinical research of dawn and dusk phenomenon. Multi-point blood glucose monitoring or dynamic blood glucose monitoring throughout the day is of great significance for the detection of special types of hyperglycemia.

Abbreviations: BMI =body mass index, CBC = complete blood count, SCN = hypothalamic suprachiasmatic nucleus.

Keywords: diabetes mellitus, glaucomatous blindness, hyperglycemia before sleep, reset of biological clock

1. Introduction

There are many types of spontaneous and transient hyperglycemia among diabetic patients. The "Dawn phenomenon" has been well-known by researchers and physicians. However, the "Dusk phenomenon" has not been paid attention yet. Our research team has been studying the "Dusk phenomenon" and proposed the clinical symptoms[1] and diagnosis[2] related to the phenomenon. It is a transient and spontaneous hyperglycemia happened at dusk (before and after dinner) among diabetic patients that are otherwise under adequate control with a post-lunch blood glucose with no hypoglycemic episodes.[1] At the beginning of studying the case, we thought that this sudden hyperglycemia at night was a delay for the dusk phenomenon. However, our subsequent observation revealed that although the hyperglycemia started at dusk, the peak of blood glucose was during 9 pm to 3 am. Combined with his nearly blindness, it is more likely a day and night turn over of the glucose regulation. It has a great clinical and theoretical value to explore the mechanism of spontaneous and transient hyperglycemia.

2. Case presentation

A 73-year-old male was admitted to our hospital for "polydipsia and emaciation for 2 years, disturbance of glucose homeostasis after glaucoma surgery for 10 days" on April 4th, 2016.

Informed written consent was given for participation in this study, which was approved by the health ethics board of the Affiliated Cixi Hospital, Wenzhou Medical University. Two years ago, the patient presented with "polydipsia, emaciation and fatigue" and was diagnosed as "type 2 diabetes mellitus". He had

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fairly good glycemic control by taking Gliclazide Modified Release

Tablet 60 mg once daily and Acarbose 50 mg 3 times daily. Half a month ago, he underwent glaucoma surgery in the right eye and received glucocorticoid therapy, which led to markedly increased blood glucose. Oral medications were switched to a regimen of insulin aspart 3 units 3 times daily and insulin glargine 7 units once daily. However, the patient was still unable tomaintain a constant blood glucose level and was transferred to our hospital. His medical history was remarkable for bilateral glaucoma, which progressed to blindness in the left eye for 10 years. His right eye with only light perception for 4 years underwent surgery recently due to extreme pain. At presentation, body mass index (BMI) was 20 kg/m^2. He had total blindness in the left eye and only light perception in the right eye. Physical examination was unremarkable otherwise. On admission, random blood glucose was 20.8 mmol/L. Results of laboratory tests (e.g., complete blood count (CBC), Urinary ketone body (-), liver and kidney function tests, electrolytes, thyroid functions) were unremarkable. The patient was diagnosed as "1. Type 2 diabetes mellitus, 2. Absolute glaucoma (left eye), 3. Post-operative glaucoma (right eye)". An intensified insulin therapy was designed for glycemic control during the first 10 days. The dose was reduced rapidly as soon as the patient was able to maintain stable blood glucose levels. A rare phenomenon was observed (Fig. 1). The blood glucose started to rise gradually before dinner. Then there was a sharp increase in blood glucose at 9:00 PM, which was initially considered to be "extended dusk phenomenon". Additional 3-unit insulin aspart was administered to achieve satisfactory glycemic control (Fig. 2). If left untreated, blood glucose level would remain high until 3:00 AM. After that, the glucose level fell dramatically of itself and reached the lowest during fasting period. The regimen was optimized, consisting of insulin aspart (5 units, 3 units, and 3 units) and insulin glargine (3 units once daily). However, the patient had trouble with injections due to poor sight and insisted on switching back to oral medications. Repaglinide (1 mg) was orally administered three times daily for 2 days, which resulted in a sharp increase in blood glucose level throughout the day. The peak was also reached at 9:00 PM. To get better glycemic control, the patient was persuaded into switching to twice-daily premixed insulin for 10 days. The dose of insulin aspart 30 was progressively titrated to 7 units before breakfast and 6 units before dinner. The overall glycemic control was satisfactory except that blood glucose level at 9:00 PM was still poorly controlled. The patient refused additional injection before sleep. Regular endocrinologist follow-up was instituted after discharge. The length of stay was 22 days. The patient managed to follow a strict diet plan but seldom took exercises due to poor sight. He maintained a stable mood during his hospital stay.

3. Discussion

The patient's blood glucose was sensitive to insulin. His blood glucose was well controlled when insulin was applied except the period of bedtime and midnight (Fig. 1). Since the night shift physicians were not all endocrine specialists, we used insulin aspart 3u when we found hyperglycemia 3 times at 9 PM and it was effective (Fig. 2). Later, we changed to the oral medicine and the blood glucose was rebounded sharply. Then we changed to pre-mixed insulin, the blood glucose was well controlled again, except the bedtime period. However, among all those treatment methods, there had no significant effect on hyperglycemia just before bedtime (Fig. 1).

Our research team have found that, some patients with type 1 and type 2 diabetes had spontaneous hyperglycemia just before

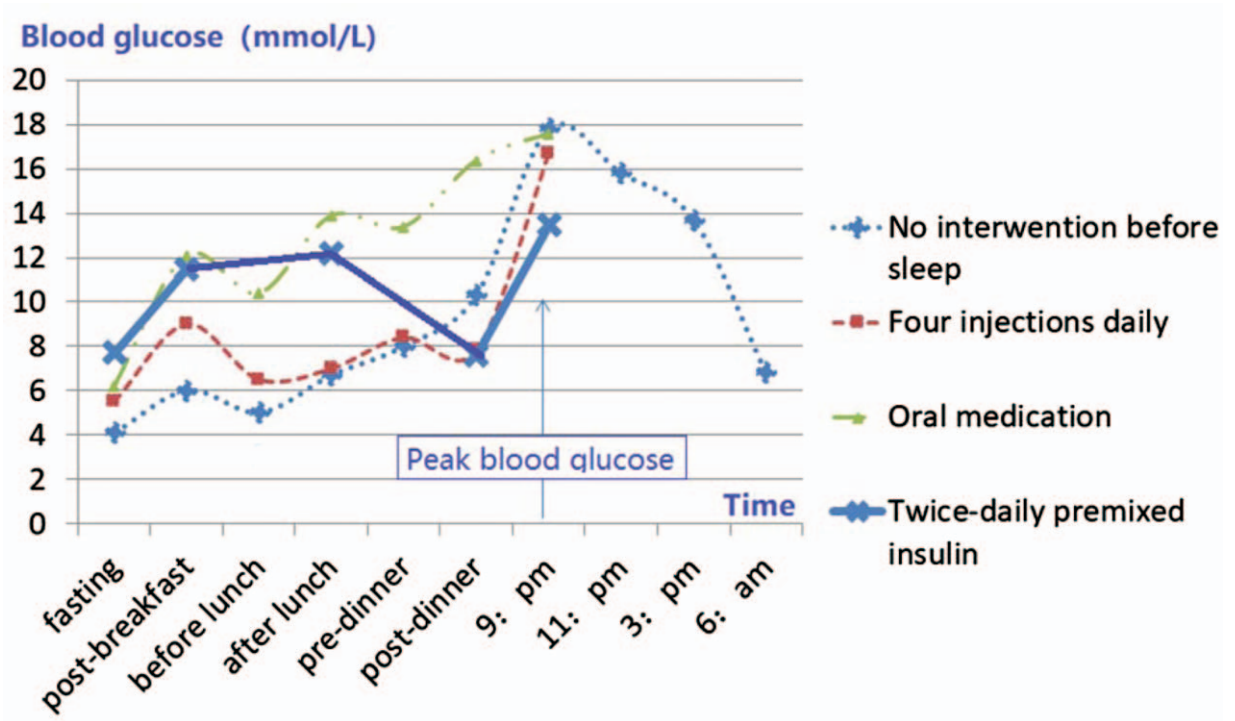

Figure 1. The fluctuation of blood glucose under different treatment conditions. The peak blood glucose was 9 PM by 4 injections daily, Oral medication, Twice-daily premixed insulin. No intervention before sleep (4 injections daily) blood glucose level would remain high until 3:00 AM. After that, the glucose level fell dramatically of itself and reached the lowest during fasting period.

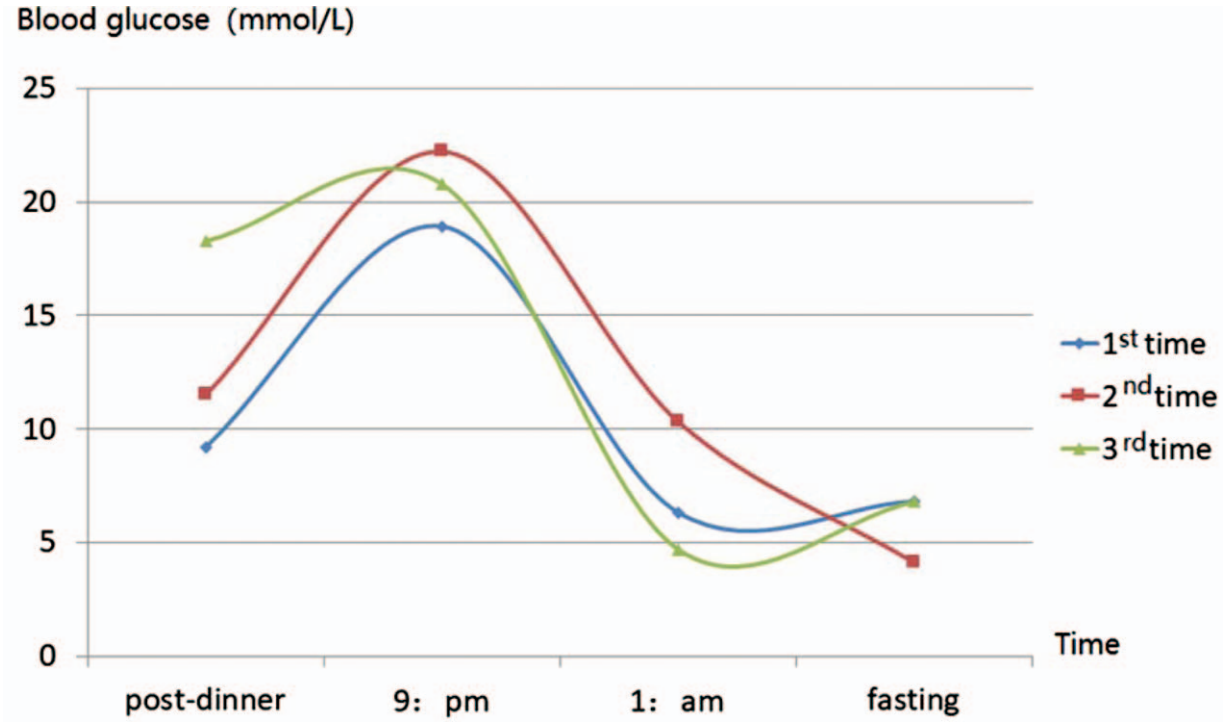

Figure 2. The effect of insulin intervention (3-unit insulin aspart before sleep) on blood glucose levels. Everytime additional 3-unit insulin aspart was administered to achieve satisfactory glycemic control.

dinner time and could be extended to bedtime. We call it "dusk phenomenon".[1] This case is a very special one. Due to near blindness, he is dependent on the surroundings and has a simple lifestyle. But at the same time, he has a high expectation to control blood glucose. The case had a good treatment compliance and been confirmed no extra meal during the treatment. The trend of increased blood glucose started before dinner with small elevation. According to the fact that his blood glucose was higher before dinner than 2 hours after lunch, we initially judged it as "dusk phenomenon".[1,2] And we thought that there was a delay of dusk phenomenon when his glucose was suddenly rise sharply from 9 PM. However, it was found later that throughout the hospital stay with 22 days, the abnormal hyperglycemia was existed stably, from 9 AM to 3 AM (high blood glucose began to fall after 1 AM). The time of peak blood glucose is usually the lowest period in the regular population. It is difficult to explain with the delay of the dusk phenomenon, and it is more like a form of day and night blood glucose flipping.

In addition, it has been reported that a diabetic patient with cerebrovascular disease had the severe abnormality of blood glucose from 11 PM to 3 AM[3] that the glucose was only controlled after applying the insulin pump with short-term but large dose base amount. Those cases are existed periodically and are definitely not induced by diet or hypoglycemia. For those "heterogeneous blood glucose phenomena", previous studies have not been involved. A new hypothesis needs to be proposed.

We propose a better explanation that the blood glucose regulation and response system might have periodic fluctuation under the influence of human biological clock that will lead to the absolute or relative deficiency of insulin, which causes the blood glucose to rise and fluctuate. There are generally two factors of the sudden hyperglycemia during the steady stage: 1) the lack of insulin; 2) the increase of glycemic hormone and the corresponding increase in insulin resistance. As patients with diabetes, the insulin deficiency and the increase of glycemic hormone should be the main causes. The cyclical fluctuation of glycemic hormone in a non-stressed state might be due to the periodicity of human biological clock.

In the 18th century, the biological clock was first proposed. Subsequent research has shown that almost all living organisms exhibit both physiological activities and extrinsic behaviors with their own rhythms.[4,5] A study from Schibler found that in adult rats, the liver transcriptional activator DBP has an obvious circadian rhythm. In the morning, DBP could not been detectable in the liver nucleus while in the afternoon, DBP number rose sharply. This fluctuation is a transcription of "free running".[6] It is suggested that the efficiency of genes in different time periods is different. A systematic study from Hogenesch of 12 mice tissues found that just before dawn and dusk, the genetic expression increased significantly. The most active tissue in the liver, and other issues related to glucose metabolism have the similar phenomena including kidney, brown fat, white fat, skeletal muscle and adrenal gland.[7] Panda and others, studied hamadryas that are much closer to human beings, showed that up to 81.7% of protein-coding genes have daily rhythmical expression which peaks at dawn and dusk. It is also revealed that the central and peripheral tissues' difference between diurnal and nocturnal animals.[8] These evidences could explain the mechanism of diabetic dawn and dusk phenomena. In addition, the "dawn phenomenon" study found that the insulin sensitivity had a circadian rhythm.[9,10] Those findings suggest that the periodic blood glucose changes among our diabetic patients might be associated with genetic expression difference due to the biological clock fluctuation.

We noticed that this patient was a glaucoma patient with nearly blind eyes for many years. The reason of blindness in glaucoma is a persisted increase in intraocular pressure that destroys the eye nerves. The photoreceptor of retina of the eye is the window of the phase shift caused by the photoperiod. Previous studies showed that removal of bilateral eyeballs in rats could affect the circadian rhythm of rats.[11] It is speculated that the injury of ocular nerve in this case might change the circadian rhythm or circadian clock system of the retina, hypothalamic suprachiasmatic nucleus and pineal gland, to generate the reset of the biological clock that might be related to this special case. Due to the case specialty, we could not do the systematic review of the study. However, it improves the awareness of the abnormal periodically increase of blood glucose during the special periods, and provides with a reference for clinical research of dawn and dusk phenomenon.

Limitations of this case:

1. Due to the limitation of examination conditions of the hospital, no glycemic hormone tests were performed. Only blood glucose level was monitored.
2. The best treatment for this case should be insulin pump, which was rejected by the patient.
3. Blood glucose control should be carried out with continuous 9 PM insulin injection, which was not accomplished due to the debatable opinions among the doctors.
4. Without the patient's previous blood glucose data, there is no definite evidence to conclude whether there is a direct link between the patient's peculiar blood glucose condition and the symptoms of glaucoma and blindness.

Author contributions

Data curation: Si-na Du.
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Writing – review & editing: Wei Li.

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