



# Excessive Postprandial Sleepiness in Two Young Adults Effectively Treated with Antidiabetic Medications

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Sleep Sci

## Abstract

We herein describe the cases of two young Japanese adults who presented with excessive daytime sleepiness (EDS). Based on their history, the postprandial nature of the sleepiness was suspected, although the patients themselves were not aware of the association. Oral glucose tolerance tests (OGTTs) reproduced the sleepiness and showed the patterns of insulin resistance (IR) compatible with type-2 diabetes mellitus (T2DM) in one patient and glucose intolerance in the other. There was no evidence of chronic hyperglycemia in either patient. Antidiabetic medications resulted in the disappearance of EDS in both patients; in one, a repeat OGTT revealed improved IR. We suggest that postprandial somnolence can present with EDS, and it can be effectively treated with antidiabetic medications, and that the OGTT can be useful in identifying IR, which may be the underlying cause of the excessive postprandial somnolence.

## Keywords

- ▶ postprandial period
- ▶ disorder of excessive somnolence
- ▶ oral glucose tolerance test
- ▶ insulin resistance

## Introduction

Excessive daytime sleepiness (EDS, difficulty staying awake in situations requiring alertness) is frequently encountered in medical, neurological, and psychiatric practices and is often difficult to diagnose correctly. Common causes of EDS include sleep deprivation, primary sleep disorders (such as narcolepsy, obstructive sleep apnea (OSA), and idiopathic hypersomnia), and psychiatric disorders such as depression.<sup>1,2</sup> Obesity/weight gain and metabolic disorders (such as diabetes mellitus, DM) are often associated with sleep complaints, including EDS.<sup>3-5</sup> In the general population, EDS has shown a U-shaped relationship between age and incidence, being more prevalent in young (< 30 years of age) and elderly (> 75 years of age) patients.<sup>4,5</sup> The occurrence of

postprandial somnolence or sleepiness is well known and generally considered to have relatively little pathological significance.<sup>6</sup> Recently, however, the positive relationship between diet, especially diets with high carbohydrate or sugar intake, and EDS has been increasingly recognized, although its mechanism(s) remains unclear.<sup>7</sup> We herein report the cases of two patients with EDS secondary to excessive postprandial somnolence, which could be effectively treated with antidiabetic medications.

## Case Reports

### Patient 1

A 24-year-old Japanese male patient presented with a 3-month history of EDS. Initially, he was able to stay awake at work, but after two months, the urge to sleep was so strong that he often fell asleep at his desk, causing a progressive deterioration of his job performance as a manufacturing

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**Table 1** Results of the 75g oral glucose tolerance test (OGTT).

		Patient 1		Patient 2
		Before	After	Before
Insulin (in $\mu\text{U/mL}$ )	Fasting	5.6	5.3	7.8
	30 minutes	24.2	31.5	60.6
	60 minutes	31.9	36.9	65.1
	90 minutes	45.8	38.5	80.2
	120 minutes	59.6	28.1	88.1
	180 minutes	18.2	4.6	66.5
	240 minutes	9.9	4.7	8.9
Glucose (in mg/dL)	Fasting	87	95	83
	30 minutes	153	185	146
	60 minutes	211	187	162
	90 minutes	232	151	148
	120 minutes	224	126	139
	180 minutes	131	58	98
	240 minutes	88	89	49
Urine sugar (in mg/dL)	Fasting	—	—	—
	60 minutes	—	—	—
	120 minutes	200	—	—

**Notes:** A 240-minute OGTT was performed instead of the conventional 120-minute OGTT. In patient 1, a second OGTT was performed 6 months after the initiation of treatment, when the patient was asymptomatic for EDS.

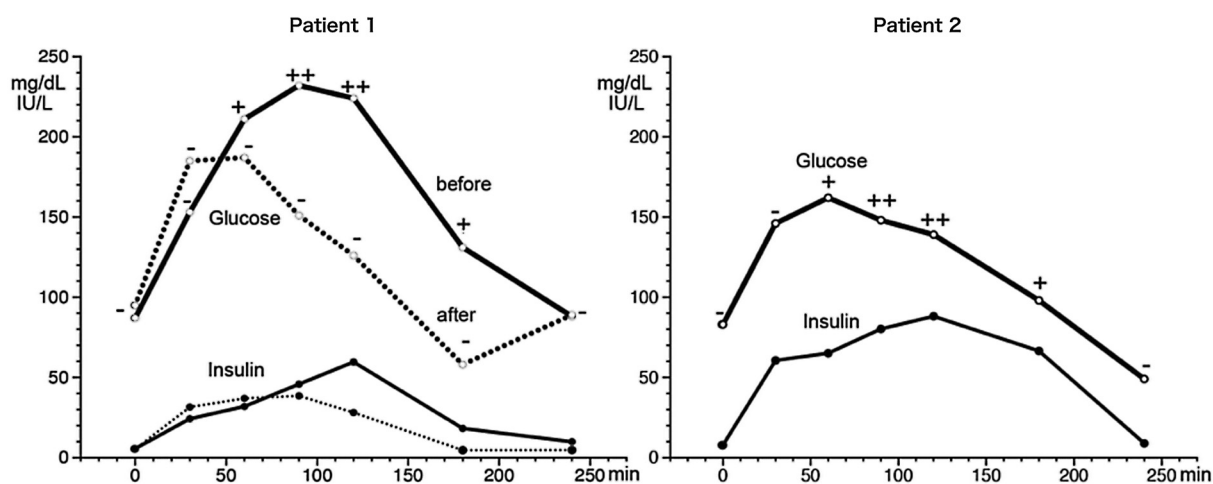
designer. He was advised to take a sick leave to get full medical and psychiatric attention. He underwent polysomnography at another hospital, which showed an apnea-hypopnea index (AHI) of 2.2 (normal: < 5) events per hour. He had used caffeine, modafinil, and methylphenidate in an

effort to improve his EDS, without benefit. The medical and family histories of the patient were unremarkable. He did not drink alcohol or use habitual medications.

Upon examination, his height was of 174.6 cm and he weighed 77.2 kg, with a body mass index (BMI) of 25.3 kg/m<sup>2</sup>. The results of general and neurological examinations were unremarkable. The score on the Epworth Sleepiness Scale (ESS) was of 9. Metabolic panels were unremarkable, including the levels of thyroid hormones, thyroid stimulating hormones (TSHs), serum cortisol, adrenocorticotropic hormone (ACTH), prolactin, and antidiuretic hormone. The level of hemoglobin A1c (HbA1c) was of 5.4% (normal range 4.6% to 6.2%). The brain magnetic resonance imaging (MRI) scan and electroencephalogram (EEG) were unremarkable.

A more detailed history suggested that the sleepiness of the patient could be postprandial. He became most sleepy at around 10 am to 11 am and 2 pm, except when he was physically active. When he tried delaying breakfast by 2 hours, he became sleepy 2 hours later. With a carbohydrate-free diet, his sleepiness decreased. We performed a 240-minute 75-g oral glucose tolerance test (OGTT), instead of the conventional 120-minute OGTT. The patient became sleepy during the OGTT; his glucose reached 224 mg/dL at 120 minutes, which was associated with a 10.6-fold increase in insulin from the fasting state (**Table 1**, **Fig. 1**). The homeostasis model assessment of insulin resistance (HOMA-IR) was of 1.2 (normal: < 1.6) and the insulinogenic index was of 0.28 (normal: < 0.4).

We initiated treatment with 10 mg/day of empagliflozin, a sodium-dependent glucose cotransporter 2 (SGLT-2) inhibitor. At the follow-up visit after one month, the patient reported that the symptoms of EDS had almost disappeared. The ESS score at that visit was of 4. He returned to his original job, and his performance was said to be back to baseline. He continued to be well on the same medication for the next five



**Fig. 1** Serum glucose and insulin changes during the OGTT. In patient 1 (*left*), the maximum glucose level was of 224 mg/dL at 120 minutes, compatible with T2DM. *Dashed lines*: the results of a repeated OGTT performed six months after the initiation of treatment for DM. He did not become sleepy, and the results showed improved IR; there were reductions of a 47% and 53% in glucose and insulin values at 120 minutes respectively compared to before treatment. In patient 2 (*right*), glucose values were within the normoglycemic range, but there was a delayed and marked elevation in insulin values, reaching the peak at 120 minutes, indicating IR. Delayed reactive hypoglycemia (49 mg/dL) was apparent at 240 minutes, when she was no longer too sleepy. Notes: (-) to (++) indicate the degree of sleepiness recorded by the patients during the OGTT: (-) not sleepy, (+) mildly sleepy, (++) very sleepy.

months. At that point, we performed a second OGTT, which revealed improved glucose tolerance compared to the level before the treatment (►Table 1, ►Fig. 1). At 2 years and 3 months after the presentation, the patient remained free from EDS while on the same medication.

### Patient 2

A 29-year-old Japanese female patient was referred by a psychiatrist due to possible narcolepsy. Three months earlier, she had begun to experience daytime sleepiness at work and at home. When driving to work as a company secretary, she often felt an irresistible urge to sleep and had to pull over to the side of the road to take a short nap or let the drowsiness pass. After having lunch, she often fell asleep at her desk. She even frequently fell asleep in the shower after dinner. She reported that she had had a few episodes of sleep paralysis and one episode suggestive of a cataplexy. At her presentation, her ESS score was of 17.

She had been diagnosed with autism spectrum disorder and an adjustment disorder, and received monthly counseling by a certified clinical psychologist. She otherwise had no medical history. She did not drink alcohol and was not on any habitual medications. Her family history was significant in that her mother and brother had type-2 diabetes mellitus (T2DM).

Upon examination, the height of the patient was of 158 cm, and her weight was 58.5 kg, with a BMI of 23.4 kg/m<sup>2</sup>. The results of the general and neurological examinations were unremarkable. The results of a metabolic panel were normal, including free thyroxine, TSH, ACTH, cortisol, growth hormone, and prolactin levels. The HbA1C was of 5.5%. On modified portable sleep apnea testing, her respiratory event index (REI) was of 4.9 (normal: < 5). Her EEG and brain MRI findings were unremarkable. The cerebrospinal fluid (CSF) sample,

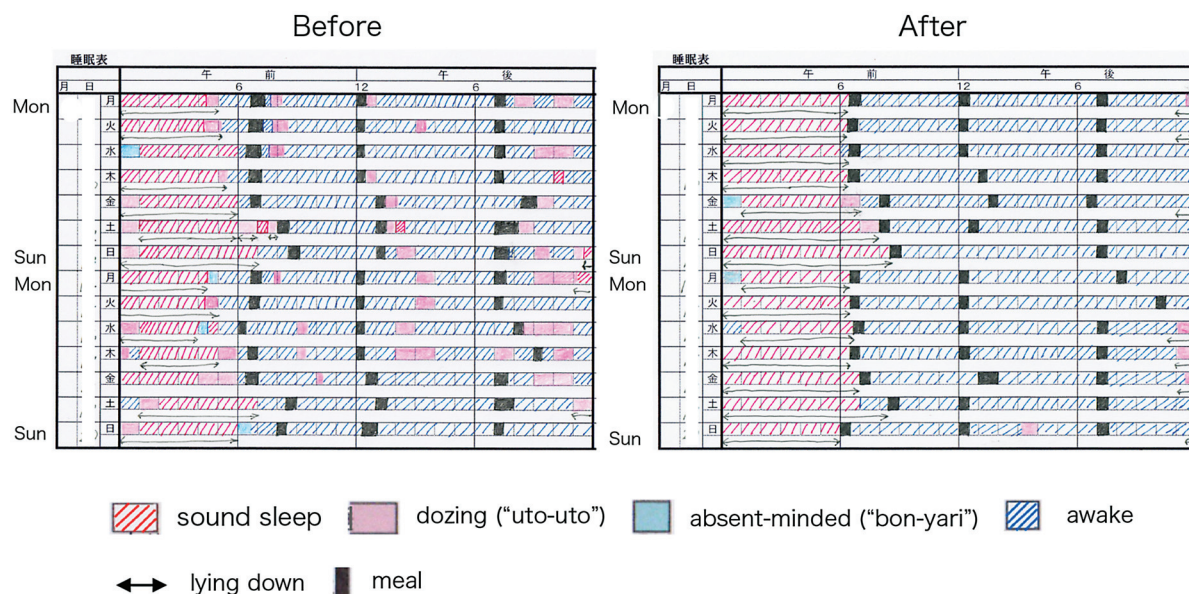
taken 2 hours after a meal, showed an orexin level of 381.6 (normal: > 110) pg/mL.

Based on the clinical history suggestive of postprandial sleepiness and the family history of T2DM, we performed a 240-minute 75-g OGTT. The patient became sleepy during the test. The result showed normal glucose values and an 11.3-fold increase in insulin at 120 minutes from the fasting state (►Table 1, ►Fig. 1). The HOMA-IR was of 1.59 (normal: < 1.6), and the insulinogenic index was of 0.83 (normal: < 0.4). We initiated treatment with 3x/day 50 mg miglitol, an  $\alpha$ -glucosidase inhibitor. At the follow-up clinic visit 4 weeks later, the patient reported a marked reduction of daytime sleepiness and had no further episodes of falling asleep in the shower (►Fig. 2). Her ESS score was of 9. At 2 years and 3 months after her presentation, she has remained free from EDS while on the same medication. She stopped seeing the clinical psychologist and got married.

### Discussion

The two young adults herein reported presented with EDS, and based on their histories, we suspected a postprandial somnolence; they were unaware of this before their presentation, most likely because their sleepiness tended to develop more than 1 hour, or often approximately 2 hours after meals, and this time-lag may have made their self-awareness of the association difficult. In this regard, it is interesting to note that Lowden et al.<sup>8</sup> have reported that postprandial sleepiness reaction could be induced 3 to 4 hours after a meal, especially after a high carbohydrate diet during 24-hour constant wake conditions.

It is of note that, in patient 1, despite the fact that daytime sleepiness significantly impaired his daily work, and had required medical attention, his ESS score was of 9 and was



**Fig. 2** The sleep diary entries self-recorded by patient 2 for 2 weeks, before (left) and 2 months after the initiation of the treatment for DM (right). Before the treatment, daytime sleepiness (pink) tended to occur at various intervals after the meals (30 minutes to 2.5 hours). After treatment, the sleepiness nearly disappeared. The sleep diary format was downloaded from the home page of the World Premier International Institute for Integrative Sleep Medicine (WPIIIS), University of Tsukuba, Japan (<http://kaminsho.jp/sleepdiary.html>) and partially modified.

not suggestive of EDS (score > 10). However, this rating scale may present subjective-objective discrepancy.<sup>9,10</sup>

Postprandial somnolence or sleepiness occurs with various etiologies, including hyperglycemia, but its mechanism and whether hyperglycemia itself causes sleepiness are largely unclear.<sup>6</sup> We performed OGTTs on our patients, which did reproduce sleepiness, but unexpectedly revealed a pattern of insulin production to the glucose load suggestive of insulin resistance (IR). Based on the current diagnostic criteria for DM,<sup>11</sup> the OGTT pattern of patient 1 was compatible with T2DM. However, the measurements of fasting blood sugar (FBS) and HbA1C were repeatedly normal, which precluded the definite diagnosis of T2DM. In patient 2, on the other hand, her OGTT glucose values fell within the normal range, as did her FBS and HbA1C values. However, at 60 minutes during the OGTT, the glucose level of the patient was of 162 mg/dL, exceeding the > 155 mg/dL threshold that has been regarded as a strong predictor of the future development of T2DM.<sup>12</sup> In addition, according to the classification of IR proposed by Wang et al.,<sup>13</sup> which is based on the patterns of the mean concentrations of insulin and glucose during an OGTT in a large cohort, the pattern of patient 1 corresponds to that of new-onset T2DM, and the pattern of patient 2 corresponds to that of impaired glucose tolerance (IGT).

It has been shown that T2DM and obesity are independent risk factors for the development of EDS, and individuals with these factors have a greater tendency to develop sleep disorders such as OSA.<sup>2,3,5</sup> Weight gain is also a strong predictor of EDS in non-obese patients.<sup>5</sup> Our patients were not obese and had no history of weight gain. It is not certain, however, whether our patients could develop T2DM in the future; therefore, further follow-up seems necessary.

In both patients, primary sleep disorders such as idiopathic hypersomnia (IH) and narcolepsy types 1 and 2 were suspected. It should be noted that a multiple sleep latency test (MLST), which has been recommended in the diagnosis of central sleep disorders, was not performed in either of the present patients, although, in patient 2, we were able to rule out narcolepsy type 1 based on her normal CSF orexin levels.<sup>14</sup> However, the fact that EDS disappeared in both patients, associated with substantial reduction in their ESS scores after the treatment with antidiabetic medications – which could also improve postprandial hyperglycemia<sup>15,16</sup> –, argues against the diagnosis of primary sleep disorders.

Pyykkönen et al.<sup>17</sup> have suggested a possible role of IR in mediating postprandial sleepiness; they reported that when subjects without T2DM with/without sleep-related complaints underwent an OGTT, those with sleep complaints showed higher fasting and 120-minute insulin and higher 120-minute glucose compared with controls. These authors<sup>17</sup> have also suggested that IR is a characteristic of individuals with sleep complaints whose OGTT values fall within the normoglycemic range. A possible role of IR in mediating EDS has also been suggested in patients with OSA syndrome.<sup>18–20</sup> Otake et al.<sup>20</sup> have reported that the prevalence of T2DM was higher in OSA patients than in controls. In

their study,<sup>20</sup> 62% of Japanese patients with OSA were newly diagnosed as having IGT or T2DM. On the other hand, the relationship between diet, especially diets with high intakes of carbohydrates or sugars, and EDS has been increasingly recognized. Xi et al.<sup>7</sup> have reported that, among Chinese adolescents, excessive intake of free sugars was positively associated with EDS, although the exact mechanisms responsible for the sleepiness remain speculative.

In both of our patients, the OGTT revealed the pattern of IR consistent with T2DM and IGT respectively.<sup>13</sup> In patient 1, a repeat OGTT when the patient was free from EDS revealed a marked reduction in insulin secretion without inducing sleepiness. In patient 2, strong sleepiness occurred during the OGTT, but her glucose values were within the normoglycemic range during the test. Moreover, it should be noted that, in both patients, the HbA1c values were repeatedly normal, despite the fact that they had EDS. Taken together, our present observations agree with the notion that IR, or an overproduction of insulin to the glucose load, may contribute more to EDS than hyperglycemia.

It should be noted that IR is generally assessed at a steady state (after overnight fasting), so that the simple HOMA-IR is most used, which was within normal range in both of our patients. However, overproduction of insulin (hyperinsulinemia) after glucose load can be also regarded as a state of IR. Such form of IR might be difficult to assess with HOMA-IR.

The cases herein reported show that postprandial somnolence can present with EDS. Because the patient may not be aware of the association of meal and sleepiness, it is important to take this into account when taking their medical history. If excessive postprandial somnolence is suspected as a cause of EDS, we suggest performing a four-hour OGTT with simultaneous measurement of insulin instead of the usual two hours to check for delayed insulin hypersecretion. If this is present, diabetic medications to suppress postprandial insulin overproduction may be therapeutic.

## Conclusion

Postprandial somnolence can present with EDS, and it can be effectively treated with antidiabetic medications. The OGTT can be useful in detecting IR, which may be the underlying cause of the excessive postprandial somnolence.

### Informed Consent

The signed consent form is retained by the corresponding author.

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### Conflict of Interests

The authors have no conflict of interests to declare.

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