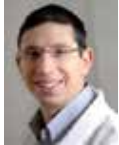


# Nocturia and Diabetes

## Diagnosis and Management



Jeremy Gilbert,  
MD, FRCPC, Assistant  
Professor, University of  
Toronto, Endocrinologist,  
Sunnybrook  
Health Sciences Centre,  
Toronto, ON.

### *Abstract*

*Reduced sleep duration and quality can affect slow wave sleep (SWS) or restorative sleep, which is associated with an increased risk of developing type 2 diabetes mellitus. In patients who have been diagnosed with type 2 diabetes mellitus, treating nocturia and the associated deterioration of sleep duration and quality is particularly important to avoid the worsening of symptoms and the potential development of serious complications. Low-dose sublingual desmopressin (25 µg for adult women or 50 µg for adult men) has proven effective in reducing nocturia with the goal of improving SWS.*

***Key words:** type 2 diabetes mellitus (T2DM), sleep duration, sleep quality, sleep hygiene, slow wave sleep (SWS), optimal glycemic control, desmopressin*

### Introduction

Type 2 diabetes mellitus (T2DM) is the most common type of diabetes in adults, accounting for approximately 90-95%<sup>1</sup> of cases, and thus will be the focus of this discussion. It is characterized by hyperglycemia, insulin resistance, and relative impairment in insulin secretion. The prevalence of type 2 diabetes mellitus has risen alarmingly in recent years in large part because of rising rates of obesity and sedentary lifestyle.<sup>2</sup> Type 2 diabetes can lead to significant morbidity and mortality via its microvascular and macrovascular complications.

Patients with undiagnosed type 2 diabetes mellitus might not report any symptoms. If they do experience symptoms, they can include: intense thirst, polyuria, blurred vision, and fatigue.

Polyuria, or urine output exceeding 3 L/day in adults, may occur in individuals with type 2 diabetes mellitus. This is mainly related to poor glycemic control resulting in the kidneys' inability to reabsorb the large glucose load. As a consequence, glucose is excreted in the urine in a process called glucose-induced osmotic diuresis. Water follows glucose, resulting in amplified water in the kidneys and increased urine

output. Polyuria can occur during the day and night; urinary frequency at night is called nocturia.

### Risk Factors (clinical)

Risk factors for type 2 diabetes mellitus include:

#### Family history

Patients with a first-degree family member diagnosed with type 2 diabetes mellitus have a two- to three-fold higher chance of developing this condition than the general population. This elevated rate climbs to a five- to six-fold probability of developing type 2 diabetes mellitus if there is both a maternal and paternal history of the disease.<sup>3</sup>

#### Ethnicity

Individuals from certain ethnic backgrounds have a higher risk of being diagnosed with type 2 diabetes mellitus. Some examples of ethnic groups with a high risk of developing type 2 diabetes include Asian, Hispanic, Aboriginal, and African American populations.<sup>4,5</sup>

#### Obesity

An increase in BMI is a very important risk factor associated with an increase in diabetes prevalence. Certain environmental factors such as diet and exercise are modifiable and can strongly influence the BMI.

### Risk Factors (environmental)

#### Sleep (quantity and quality)

Impaired quantity and quality of sleep may predict the risk of devel-

oping type 2 diabetes mellitus.

Research shows that compared with a baseline of approximately eight hours per day of sleep, short ( $\leq 5$  to 6 hours/day) and long ( $> 8$  to 9 hours/day) sleep durations were significantly associated with an increased risk of type 2 diabetes. Research shows that difficulty initiating and maintaining sleep were also associated with an increased incidence of type 2 diabetes mellitus.<sup>6</sup>

Another study of more than 23,000 participants found that short sleep duration ( $< 6$  hours/day versus 7 to  $< 8$  hours/day) was associated with an increased risk of various chronic diseases, including type 2 diabetes mellitus.<sup>7</sup>

Short sleep duration may increase the risk of type 2 diabetes mellitus because it decreases melatonin secretion. One observational study has demonstrated that lower melatonin secretion is associated with a higher risk of developing type 2 diabetes mellitus.<sup>8</sup> The relationship between slow wave sleep and diabetes will be discussed in greater detail below.

#### Activity/Exercise

A sedentary lifestyle and physical inactivity are associated with obesity, an increased BMI, and a higher risk of developing type 2 diabetes mellitus. Research has shown that physical inactivity appears to increase the risk of type 2 diabetes mellitus, even when there is no significant weight gain and in individuals with a normal BMI. A recently published study found that low aerobic capacity and muscle strength at 18 years of age



#### Key Point

*Type 2 diabetes mellitus (T2DM) is an increasingly common chronic disorder.*

was associated with an increased risk of type 2 diabetes 25 years later.<sup>9</sup>

### Smoking

Smoking is correlated with an increased risk of developing type 2 diabetes mellitus, with current smokers having an elevated risk versus non-smokers. Moreover, the combination of smoking in individuals with type 2 diabetes increases the prevalence and severity of many of the complications of type 2 diabetes.

### Diet

The consumption of red or processed meats, refined grains, and sugar-sweetened beverages are all associated with a higher risk of type 2 diabetes mellitus. People can reduce their risk of type 2 diabetes mellitus or those already diagnosed with type 2 diabetes mellitus can improve glycaemic control and blood lipids by consuming a diet rich in whole grains, fruits, vegetables and legumes. The consumption of red and processed meat, refined grains, and sugar-sweetened beverages should be reduced as much as possible. Alcohol consumption should also be moderate.<sup>10</sup>

## Complications Associated with Type 2 Diabetes Mellitus

It is essential that type 2 diabetes mellitus be diagnosed as early as possible and controlled through lifestyle modification, and possibly medications, to avoid the following complications:

- Coronary heart disease
- Cerebrovascular disease

- Peripheral vascular disease
- Retinopathy
- Nephropathy
- Neuropathy

The effect of sleep duration and quality on patients with type 2 diabetes mellitus

### Sleep Duration

Sleep plays a very interesting role for individuals diagnosed with type 2 diabetes mellitus. Slow wave sleep (SWS) or deep sleep (stages 3 and 4 or stage N3) is characterized by slow, high amplitude delta waves and non-rapid eye movements (NREM). SWS is thought to be the most physically restorative of the sleep stages. One study found that the quantity of SWS was significantly lower in individuals diagnosed with type 2 diabetes mellitus.<sup>11</sup> This decreased SWS combined with the tendency of individuals with type 2 diabetes mellitus to experience nocturia coupled with hyperglycemia means that sleep architecture can be severely compromised.

A second study examined the association of nocturia and type 2 diabetes mellitus. It found that nocturia, when nighttime waking to void was  $\leq 2$  times, affected next day physical activity. Subjects from the study reported diminished levels of physical activity during daytime hours following a night of sleep interrupted by nocturia episodes.<sup>12</sup> This finding is concerning, given how useful exercise is in controlling weight, BMI, and glucose values.

### Sleep Quality

A third study observed that SWS is associated with hormonal changes



#### Key Point

*Type 2 diabetes mellitus (T2DM) rates have risen in recent years in proportion to rising obesity rates, increasing BMIs, and ever more sedentary adult populations.*

that affect glucose regulation. When researchers suppressed SWS in young, healthy, adult study participants where total sleep time remained the same, they found there was a significant decrease in insulin sensitivity. However, the participants did not display adequate compensatory insulin release. As a result, reduced SWS is associated with decreased insulin sensitivity. This observation could indicate an association between impaired SWS and an increased risk of developing type 2 diabetes, although more research is needed.<sup>13</sup>

### Treatment of Nocturia in Type 2 Diabetes Mellitus Patients

Sleep duration and quality potentially play an important role in type 2 diabetes mellitus prevention and management. As such, any reduction in sleep hygiene in the general population should be identified as soon as possible and treated with efficacy. In patients already diagnosed with type 2 diabetes mellitus, the benefit of treating nocturia to restore proper sleep patterns becomes even more valuable.

#### Behavioural Modification

First-line treatments for nocturia require patient behaviour modification, are relatively easy to integrate into daily routine, and can include the following:

- Restriction of fluid intake (especially caffeine and alcohol) before bedtime
- Daily pelvic floor muscle or Kegel exercises
- Toilet scheduling—regulation of voiding during the day

- Bladder training—to help decrease the frequency of urination
- Afternoon naps—assist in fluid being absorbed into the bloodstream; the individual can then void the bladder upon waking
- Compression stockings—can also help with daytime fluid absorption into the bloodstream

#### Optimal Glycemic Control

In individuals with type 2 diabetes mellitus, improving glycemic control may be helpful in reducing nocturia and polyuria. It is extensively recognized that optimal glycemic control leads to prevention of or delay in the development of microvascular complications and can diminish macrovascular events.

#### Pharmacological Treatment

Behavioural modification and glycemic control might still be insufficient to counter nocturia associated with type 2 diabetes mellitus. With the goal of minimizing waking to void during the night and thus ensuring a sufficiently long period of rest which includes quality SWS, clinicians may prescribe low-dose sublingual desmopressin (25 µg for adult women or 50 µg for adult men).

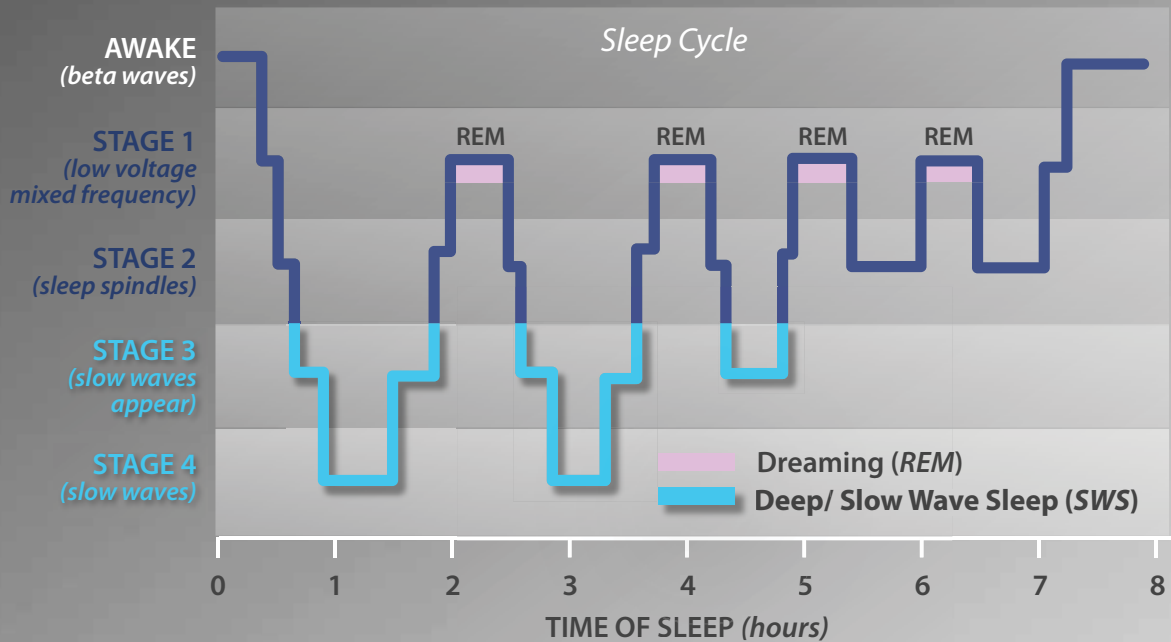
Desmopressin has proven effective in reducing the number of awakenings to void during the night in people with type 2 diabetes mellitus who report polyuria.<sup>14</sup> It has also reduced or eliminated nocturia in patients with different chronic



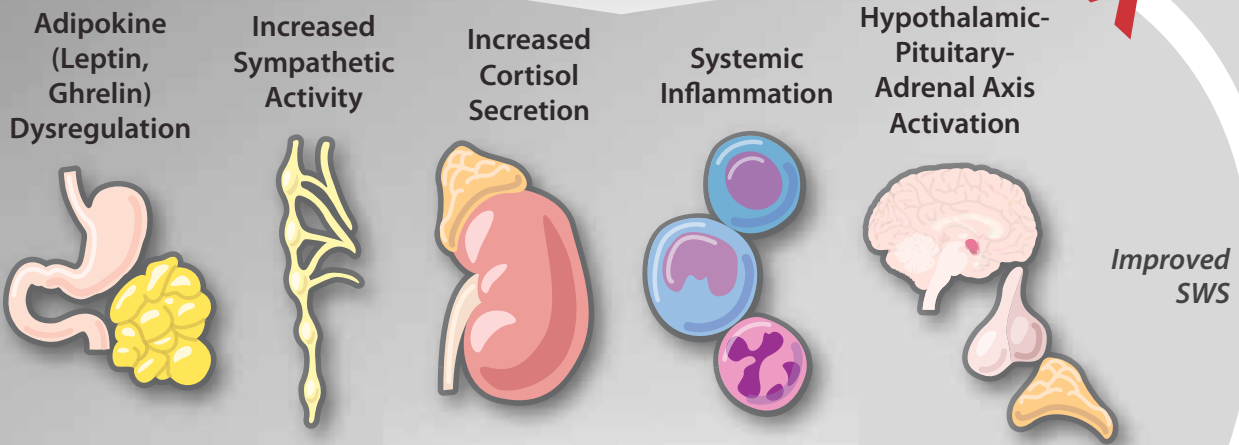
#### Key Point

*Research has demonstrated that reduced sleep duration and quality can affect slow-wave sleep (SWS), which is associated with an increase to the risk of developing type 2 diabetes mellitus.*

# Nocturia and Type II Diabetes Mellitus



Decreased SWS



Increased Insulin Resistance

Glucose Intolerance

TYPE II DIABETES MELLITUS

Treatment of Nocturia with Desmopressin



## Key Points

Type 2 diabetes mellitus (T2DM) is an increasingly common chronic disorder.

Type 2 diabetes mellitus (T2DM) rates have risen in recent years in proportion to rising obesity rates, increasing BMIs, and ever more sedentary adult populations.

Research has demonstrated that reduced sleep duration

and quality can affect slow-wave sleep (SWS), which is associated with an increase to the risk of developing type 2 diabetes mellitus.

In patients with type 2 diabetes mellitus, treating nocturia and deteriorated sleep duration and quality may be useful to reduce symptoms of hyperglycemia and potentially reduce the development of serious complications.

conditions that are associated with nocturia, including type 2 diabetes mellitus.<sup>15</sup>

Side effects from low-dose desmopressin are, for the most part, minor and temporary. They include:

- Headache (38%)
- Hyponatremia (9%)
- Insomnia
- Dry mouth
- Hypertension
- Abdominal pain (10%)
- Peripheral oedema
- Nausea (12%)<sup>15</sup>

The most serious of these side effects, hyponatremia, is most common in men over 65 years of age. The primary predictor for hyponatremia in people taking low-dose desmopressin is increasing age. Serum sodium monitoring at baseline and during treatment is recommended to reduce the risk of developing hyponatremia.<sup>15</sup>

## Conclusion

Type 2 diabetes mellitus is a chronic condition characterized by hyperglycemia, insulin resistance, and rela-

tive impairment in insulin secretion. It is becoming increasingly common as obesity rates rise. Research has shown that reduced sleep duration and quality can affect SWS or restorative sleep, which in turn can increase the risk of developing type 2 diabetes mellitus. In patients already diagnosed with type 2 diabetes mellitus, the benefit of treating nocturia and the associated deterioration of sleep duration and quality becomes even more important. Low-dose sublingual desmopressin (25 µg for adult women or 50 µg for adult men) has proven effective in reducing nocturia with subsequent improvement of SWS and with the hope of ameliorating the health of individuals with type 2 diabetes.

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## Key Point

*In patients with type 2 diabetes mellitus, treating nocturia and deteriorated sleep duration and quality may be useful to reduce symptoms of hyperglycemia and potentially reduce the development of serious complications.*



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## Clinical Pearls

The initiation of SWS coincides with the hormonal changes that affect glucose regulation.

When researchers suppressed SWS in young, healthy, adult participants, they found a significant decrease in insulin sensitivity.

Low-dose sublingual desmopressin (25 µg for adult women or 50 µg for adult men), in addition to optimal glycemic control, has proven effective in reducing nocturia in patients with type 2 diabetes mellitus.

When nocturia events are decreased or eliminated, SWS is improved.