

## Remarks in metformin and sleep disorders in diabetic patients

Sir,

We read with interest the Wiwanitkit S and Wiwanitkit V's manuscript entitled "Metformin and sleep disorders."<sup>[1]</sup> It is a valuable brief review about the adverse effects of metformin, a widely used antidiabetic medication, on sleep of diabetic patients. They skillfully reviewed briefly the main sleep problems, such as insomnia, sleepwalking, dreams, and sleep apnea, which are induced by metformin, but we think there are some challengeable issues that are be considered in this topic.

The role of metabolism of glucose in sleep disorders should be considered, although this relationship can be explained reciprocally.<sup>[2]</sup> Some biomarkers, such as adipokines, can confirm this relationship between sleep disorders and glucose metabolism. Moreover, metformin as an insulin sensitizer can affect sleep via altering glucose metabolism. Metformin improves the neural glucose resorption and it can affect the nervous system health, and therefore affecting sleep quality.<sup>[3]</sup> Also, metformin does not induce hypoglycemia and this is one of its advantages in comparison to the other glycemic control agents. Hypoglycemia induces a patients' sense of fatigue and ill-being but metformin users are safe from hypoglycemia.

On the other hand, sleep apnea syndrome can affect the glucose metabolism and reduce the response to the lowering weight agents, such as metformin.<sup>[4]</sup>

Today, it is clarified that sleep architecture can affect by brain activity via Toll-like receptor family function. Sartorius *et al.* demonstrated that "Toll-like receptor protects brain from a fat-mediated impairment in insulin action, and by

an IL-6/osteopontin-dependent mechanism."<sup>[5]</sup> Therefore, metformin through influencing the fat metabolism and sensitizing cells to insulin can affect this mechanism. Other metabolic effects of metformin on brain and sleep architecture carry out via some challenging pathway (such as lactate production), which has to be focused on to confirm. Also, metformin monotherapy improves  $\beta$ -cell function and so can improve the neuronal glucose metabolism by enhancing the insulin production. There are some evidences about the role of some interleukins and biologic signals, such as tumor necrosis factor- $\alpha$ , interleukin-6, adiponectin, and leptin in association between sleep and glucose metabolism.<sup>[6]</sup> These mentioned biologic substances also are affected by insulin resistance reducing medications, especially metformin.

Also, in this minireview the association between weight, sleep disorder, and metformin was not discussed. Many diabetic patients have overweight and the relationship between obesity and sleep disorders, such as obstructive sleep disorders, narcolepsy, and chronic insomnia, was clarified previously.<sup>[7]</sup> Weight loss was confirmed as one of the main treatment of obstructive sleep apnea and insomnia. Besides, metformin can cause weight loss and so it can be effective on the sleep disorders by reducing the weight.

With a closer and more meticulous look, we can find the role of oxidative stressors in this association. Oxidative stressors and antioxidants (such as GSH-Px and MDA) increase in diabetes mellitus and also in sleep disorders.<sup>[8,9]</sup> In addition, reduction in oxidative stress can be associated with diabetes and sleep disorder control. It is already known that metformin can regulate oxidant/antioxidant balance and therefore regulates sleep disorders.<sup>[9]</sup>

Finally, the role of vitamin B12 in mental health and so sleep is specified.<sup>[10]</sup> Moreover, vitamin B12 was used in a few trial studies to treat the sleep disorders. On the other hand, the effect of metformin therapy on the vitamin B12 level of diabetic patient was approved.<sup>[11]</sup> Therefore, metformin may lessen the sleep disorders in diabetic patients via enhancing vitamin B12 supply.

It seems that there are not enough evidences about the effects of metformin on the sleep disorders and more long-term trials and cohort studies are needed in this regard.

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## REFERENCES

1. Wiwanitkit S, Wiwanitkit V. Metformin and Sleep Disorders. *Indian J Endocrinol Metab* 2012;16(supp1):S63-4.
2. Klingenberg L, Sjodin A, Holmback U, Astrup A, Chaput JP. Short sleep duration and its association with energy metabolism. *Obes Rev* 2012 Mar 22. [In Press]
3. Gupta A, Bisht B, Dey CS. Peripheral insulin-sensitizer drug metformin ameliorates neuronal insulin resistance and Alzheimer's-like changes. *Neuropharmacology* 2011;60:910-20.
4. Borel AL, Leblanc X, Almeras N, Tremblay A, Bergeron J, Poirier P, *et al.* Sleep apnoea attenuates the effects of a lifestyle intervention programme in men with visceral obesity. *Thorax* 2012 Mar 6. [In Press]
5. Sartorius T, Lutz SZ, Hoene M, Waak J, Peter A, Weigert C, *et al.* Toll-like receptors 2 and 4 impair insulin-mediated brain activity by interleukin-6 and osteopontin and alter sleep architecture. *Faseb J* 2012;26:1799-809.
6. Padilha HG, Crispim CA, Zimberg IZ, De-Souza DA, Waterhouse J, Tufik S, *et al.* A link between sleep loss, glucose metabolism and adipokines. *Braz J Med Biol Res* 2011;44:992-9.
7. Fischer MK, Martinez D, Cassol CM, Rahmeier L, Vieira LR. Immediate and overnight recumbence-dependent changes of neck circumference: Relationship with OSA severity in obese and nonobese subjects. *Sleep Med.* 2012;13:650-5.
8. Franco CM, Lima AM, Ataide L Jr, Lins OG, Castro CM, Bezerra AA, *et al.* Obstructive sleep apnea severity correlates with cellular and plasma oxidative stress parameters and affective symptoms. *J Mol Neurosci* 2012;47:300-10.
9. Abdulkadir AA, Thanoon IA. Comparative Effects of Glibenclamide and Metformin on C-Reactive Protein and Oxidant/Antioxidant Status in Patients with Type II Diabetes Mellitus. *Sultan Qaboos Univ Med J* 2012;12:55-61.
10. Okawa M, Takahashi K, Egashira K, Furuta H, Higashitani Y, Higuchi T, *et al.* Vitamin B12 treatment for delayed sleep phase syndrome: A multi-center double-blind study. *Psychiatry Clin Neurosci* 1997;51:275-9.
11. Kos E, Liszek MJ, Emanuele MA, Durazo-Arvizu R, Camacho P. The Effect of Metformin Therapy on Vitamin D and B12 Levels in Patients with Diabetes Mellitus Type 2. *Endocr Pract.* 2012;18:179-84.

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