

September 10th, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name:).

Title: Effect of Obstructive Sleep Apnea on Type 2 Diabetes Mellitus; A Comprehensive Literature Review

Author: Srikant Nannapaneni, MBBS, MPH; Kannan Ramar, MBBS, MD; Salim Surani, MD, MPH, MSHM< FACP, FCCP, FAASM

Name of Journal: *World Journal of Diabetes*

ESPS Manuscript NO: 4153

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer 1: Nannapaneni et al. reviewed the current articles and summarize the information about the effects of obstructive sleep apnea on type 2 diabetes and its associated complications. This is interesting and well organized manuscript. However, there are some comments should be noticed. Major comments: 1. In this review, the authors listed diabetic retinopathy, diabetic nephropathy and diabetic neuropathy, which are all belongs to diabetic microvascular complications. However, diabetic macrovascular complications, such as diabetes induced heart and brain vessel diseases were not mentioned. Please list them in this review. If there is no relationship between obstructive sleep apnea and diabetic macrovascular complications, the title of this review should be “..... and its associated microvascular complications:”. Minor comments: 1. For abstract part. What’s “CPAP” mean? Please give the full name. 2. For “Relationship between obstructive sleep apnea and complications of diabetes mellitus” part. The authors claimed that “Long standing poorly controlled T2DM is associated with the development of complications such as retinopathy, nephropathy, neuropathy and vascular disease”. This sentence is not exactly right. Because diabetes induced retinopathy, nephropathy and neuropathy are all vascular diseases. 3. For “Diabetic retinopathy” part. Please discussion more about the mechanism underling the effects of obstructive sleep apnea on diabetic retinopathy.

Response: We appreciate the reviewer’s comment. The emphasis of this article is mainly on the microvascular complications of Type 2 Diabetes Mellitus (T2DM). In the abstract we have added all the microvascular complications of T2DM as suggested by the reviewers. In addition, we have modified the abstract to differentiate between the microvascular and macrovascular complications of T2DM. Title of the article also has been amended to reflect the microvascular complications of T2DM. The pathophysiological mechanism of diabetic retinopathy has been enhanced to reflect the comment by the reviewer.

Reviewer 2: The review article by Nannapaneni et al regarding the effects of OSA in type 2 diabetes is well written, in a comprehensive way, and the review of the literature is acceptable. They should include some articles regarding the influence of OSA on cardiovascular complications, i.e.: Diabetes Metab Res Rev. 2013 Mar;29(3):227-34; Clin Exp Pharmacol Physiol. 2012 Dec;39(12):995-1003 The authors should also consider to include a recent review on the effects of CPAP on type 2 diabetes

Response: We greatly appreciate the reviewer's comment on the inclusion of articles relevant to this article. We have incorporated material from these articles in to the document and have updated the references with the suggested articles.

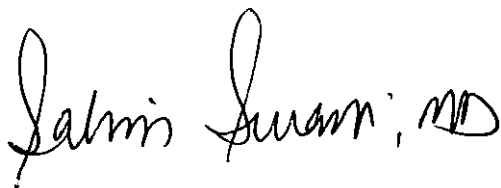
Reviewer 3: This is a well written review article attempting to establish a direct link between sleep apnea and type 2 diabetes. The biochemical link is that sleep apnea leads to hypoxia, which elevates blood glucose levels. While elevations in sympathetic activity, oxidative stress and blood glucose are key features of diabetes, hypoxia does not lead to enhanced fatty acid metabolism, which requires aerobic metabolism. Thus, the supposition that insulin resistance will arise from enhanced fatty acid metabolism is incorrect. Moreover, elevations in angiotensin II is an important features of diabetes, which is not mentioned in the review. Therefore, while there is clearly an association between sleep apnea and diabetes, a causative relationship seems unlikely. Nonetheless, a review focusing on the association between sleep apnea and diabetes has merit.

Response: We appreciate the reviewers comment on the pathophysiological mechanism of OSA induced complications in individuals with T2DM. We agree that hypoxia does not lead to enhanced fatty acid metabolism and our review of the pathophysiology does not incorporate this pathway. Angiotensin II as a mediator of nephropathy in T2DM is mentioned in the section on Diabetic Nephropathy. We also agree that Angiotensin II levels are elevated in individuals with T2DM and especially in patients with Diabetic Nephropathy. Additionally, there is literature pointing to the increased level of Angiotensin II levels in individuals with untreated OSA (Kizawa, Nakamura et al. 2009) and an improvement of the levels post treatment. By inference, it is conceivable that Angiotensin II levels are elevated in individuals with T2DM and co-existing OSA. But we could not find specific literature on looking in to this relationship.

Kizawa, T., Y. Nakamura, et al. (2009). "Pathogenic role of angiotensin II and oxidised LDL in obstructive sleep apnoea." The European respiratory journal **34**(6): 1390-1398.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Diabetes*



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