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Name of Journal: *World Journal of Diabetes*

ESPS Manuscript NO: 28682

Manuscript Type: Original Article

ANSWERING REVIEWERS

To,
The Editor
World Journal of Diabetes

Dear Sir

The authors appreciate the kind efforts of the Reviewers in pointing out a number of lacunas that we overlooked. Accordingly the manuscript has been revised in light of the suggestions of Reviewers.

Please find enclosed the edited manuscript in Word format (file name: 28682-revised manuscript.doc)
along with the reply to Reviewers comment.

With best of regards

Prof. A.K.Tripathi

Name of journal: World Journal of Diabetes

ESPS manuscript NO: 28682

Title: Role of angiotensin converting enzyme (ACE) and angiotensinogen (AGT) gene

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polymorphisms on ACE inhibitor-mediated antiproteinuric action in type 2 diabetic nephropathy patients

Reviewer's code: 03490249

Major comments:

1. In page 3 lines 8-9 and page 11 lines 7-8, it is not clear whether it is statistically significant in the increase response in TT genotype of AGT M235T.

Answer: Authors are thankful to the reviewer for pointing out the inadvertent mistake of not mentioning the significance. Macro-albuminuric patients with TT genotype are more responsive to therapy in terms of % of patients benefitted; however, the response is not significant statistically. This information has now been incorporated in the text at page 3 line 9 and page11 lines 16-17.

2. In page 3 line 10 and page 8 lines 19-20, how the authors define the 'response' as 30% reduction in albuminuria?

Answer: The decrease in urinary ACR was calculated by using the following formula. Decrease in urinary ACR% = (baseline value - follow up value) X100/ baseline value. This information has now been included under "Clinical response" head of "Material and Methods". Page 6, line 9-10, the selection of 30% reduction in ACR as response point is based on few articles and National Kidney Foundation (NKF) guidelines [references- 13, 14].

3. In page 6 line 5-6, authors should describe the distribution of dosage of ramipril, 5 to 20 mg/day in the patients with type 2 diabetes.

Answer: Majority of patients (n=217) received 5mg ramipril once daily. Two equal doses at 12 hourly interval were given to patients receiving >5mg ramipril/day.

4. Recent therapies such as GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT2 inhibitor may reduce the proteinuria in the patients with diabetic nephropathy. Authors should describe the pharmacological interventions, oral anti-diabetic drugs, GLP-1 mimics and insulin, in the enrolled patients.

Answer: The details of intake of oral-diabetic drugs and insulin in the enrolled patients were mentioned in demographic & clinical data Table 1. None of the patients were on GLP-1 receptor agonists, DPP-4 inhibitors and SGLT2 inhibitor treatment.

5. In page 8 lines 11-12, did authors check the family history of CKD (chronic kidney disease) or diabetic nephropathy?

Answer: All the enrolled patients were checked for family history of CKD and diabetic nephropathy. However, only 5 patients had family history of CKD.

Minor comment

1. In Table 2, it is not clear which parameters are significantly different between baseline and 6 months. Please list all P values in the table. Similarly, authors should show P values in Table 3, Table 5 and Table 6.

Answer: All necessary corrections have been incorporated according to the above suggestions.

Reviewer's code: 03313513

Comment 1. A brief mention of direct renin-inhibitors (aliskiren) might be provided. One or two tables summarizing the results of the studies quoted, might improve readability.

Answer: Considering that we studied the antiproteinuric efficacy of ACE inhibitor only we did not mention direct renin-inhibitors as it may be out of place.

Comment 2. Some revision of language style and spelling is required

Answer: The whole manuscript has been checked thoroughly with regard to language and spelling.

Reviewer's code: 03641631

Comment 1. This is a well-designed, performed and written clinical study for the evaluation of the effect of angiotensin converting enzyme insertion or deletion (ACE I/D) polymorphism on the serum levels of soluble receptor for advanced glycation end-products (sRAGE) and other oxidative-glycation biomarkers in type 2 diabetic patients with and without microalbuminuria. The authors investigated the potential genetic and biochemical risk factors for diabetic nephropathy.

Answer: In this manuscript we examined the antiproteinuric efficacy of ACE inhibitor therapy in DN patients with regard to ACE I/D and AGT M235T polymorphisms and

not on “soluble receptor for advanced glycation end-products (sRAGE) and other oxidative-glycation biomarkers in type 2 diabetic patients with and without microalbuminuria”. Possibly there is some kind of a mix-up.