

Thessaloniki 1st February 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16024-review.doc).

Title: Low T3 syndrome and long-term mortality in patients on maintenance hemodialysis. Is there an association with inflammation?

Authors: Stylianos Fragidis, Konstantinos Sombolos, Elias Thodis, Stylianos Panagoutsos, Euthymia Mourvati, Maria Pikilidou, Aikaterini Papagianni, Ploumis Pasadakis, Vasilios Vargemezis.

Name of Journal: *World Journal of Nephrology*

ESPS Manuscript No: 16024

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 reviewers:

REVIEWER 1

Thank you for kindly reviewing and accepting our manuscript.

REVIEWER 2

Thank you for your thoughtful suggestions regarding our manuscript. All the potential modifications were made according to your comments. To answer specifically your queries:

- a. The title has changed and the question was deleted.
- b. We have remarked that our cohort consisted of chronic hemodialysis patients in the title and abstract, as well as in the body of the manuscript and conclusions.
- c. The introduction was significantly shortened.

- d. Blood samples from patients of the first and second shift were drawn in the same time frame. Following your suggestion, a statistical re-evaluation of our results was performed excluding the patients of the third shift from whom samples were taken in the evening at 15.00 pm. However, the results remained actually unaltered, probably due to the very small patient number of the third shift (only 6% of the patients). Nevertheless, this is now clearly stated in the discussion section.
- e. We totally agree that in our study the association of low free T3 syndrome with inflammation was too weak and this issue was deepened in the discussion section.
- f. An English language revision was performed.
- g. All typing errors in the references were corrected

REVIEWER 3

Thank you for your thoughtful suggestions regarding our manuscript. All the potential modifications were made according to your comments. To answer specifically your queries:

- a. A power analysis was performed to determine the number of subjects in each group required to detect significant differences in survival after a 7 year follow-up and this is now stated in the Statistical analysis section.
- b. The two patients groups were unequal in number due to the fact that patients consecutively entered the study and the prevalence of non thyroidal illness syndrome in our population was relatively low probably due to the very strict inclusion and exclusion criteria. Nevertheless, according to the conducted power analysis the number of patients in each group was sufficient to detect statistical significant differences. The above is now stated in the Statistical analysis section.
- c. We totally agree that low T3 group was sicker with lower serum albumin and increased prevalence of diabetes and cardiovascular disease. In univariate Cox regression analysis, albumin was not significantly associated with survival ($p=0.178$). In addition, in the low T3 multivariate model an adjustment for serum albumin, as you have suggested, was performed which did not influence the results. Of note, although the low T3 group had significantly lower serum albumin compared to normal T3 group, only 8 patients (14%) of the former group had serum albumin

below the lower laboratory normal range and none had albumin lower than 3 g/dl.. The above is consistent with the presence of a very low grade of inflammation in our patient population and a relatively good nutritional status. Finally, our results showed an association between history of CVD and diabetes with survival. However, in multivariate analyses low free T3 was a more powerful predictor of survival than diabetes but not than CVD. All the above are now presented in the Results section.

d. The Discussion was extended to include interpretation of our results and recommendations.

5. Euthyroid sick syndrome (ESS), was included in the Discussion section. Of note the terms ESS and non thyroidal illness syndrome are used interchangeably in the literature for patients with severe chronic illnesses and low T3 values without any identifiable primary thyroidal disease.

e. References and typesetting were corrected.

Thank you again for reviewing and editing our manuscript for possible publication in the *World Journal of Nephrology*.

Sincerely yours,



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