

Format for ANSWERING REVIEWERS

October 10, 2014



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 12547-Review).

Title: Type 1 diabetes and polyglandular autoimmune syndrome: A review

Authors: Martin P. Hansen, Nina Matheis, and George J. Kahaly

Name of Journal: *World Journal of Diabetes*

ESPS Manuscript No: 12547

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

- 1) The manuscript was completely edited by the AmEditor Certificate Service (please refer to the attached certificate)
- 2) The format has been updated
- 3) The revision has been made according to the suggestions of the reviewers
- 4) References and typesetting were corrected

We thank the Editorial Board of the *World Journal of Diabetes* and the two Reviewers for their most constructive criticism. Their well-taken points and suggestions will significantly improve the scientific level and the clarity of the revised manuscript. We have tried to comply with all comments of the Reviewers and will point by point respond (in bold) to the individual questions and proposals of the Reviewers.

REVIEWER I

Point 1) should all of [the patients with type 1 diabetes] be screened for associated autoimmune diseases? Who should be screened, when should screening be performed, how frequently should patients be screened, what parameters should be used to screen patients?

Authors' reply: Per request of the Reviewer, we have now added a figure illustrating the recommended serological and functional screening for associated autoimmune glandular and non-glandular diseases in patients with type 1 diabetes of recent onset as well as every two years in the further follow-up (please kindly refer to new figure three, page 33).

Point 2) this reviewer would like to know whether screening is really useful?

Authors' reply: Several longitudinal studies of both patients with type 1 diabetes and their first-degree relatives have shown the high prevalence of associated autoimmune thyroid disease leading to the classical phenotype of the polyglandular autoimmune syndrome (PAS) type III. Autoimmune adrenal failure (Addison's disease), autoimmune type A gastritis and celiac disease are also frequently registered in patients with type 1 diabetes. Regular screening (every two years) is recommended in patients with type 1 diabetes, most specially in those with multiplex families involving other family members or first-degree relatives also showing endocrine autoimmunity as well as in patients and families of patients with PAS. (Please kindly refer to page 9, lines 15-16)

Point 3) Do patients with PAS have a different genetic background?

Authors' reply: Yes indeed. Compared to healthy persons and to patients with monoglandular autoimmune disease, especially those with autoimmune thyroid disease, patients with PAS show significantly different genotypes and haplotypes, please refer to: 1) Villano MJ & al., autoimmune thyroiditis and diabetes: dissecting the joint genetic susceptibility in a large cohort of multiplex families. J Clin

Endocrinol Metab 2009 Apr; 94(4):1458-66; 2) Dittmar M & al., Genetics of the autoimmune polyglandular syndrome type 3 variant. Thyroid 2010 Jul; 20(7):737-43.); 3) Flesch BK & al., HLA class II haplotypes differentiate between the adult autoimmune polyglandular syndrome types II and III. J Clin Endocrinol Metab 2014 Jan; 99(1):E177-82; 4) Weinstock & al. al., Tissue Antigens 2011 Apr; 77(4):317-24)

Point 4) Do papers exist showing that insulin doses need to be reduced in the hypothyroid phase? In clinical practice, this reviewer has never encountered this. The authors mention that insulin dose should be reduced by 25%.

Authors' reply: Hypothyroidism leads to a reduction of both glucose resorption in the duodenum as well as of glucose release from the liver. Also, due to decreased appetite and intake of calories the risk of hypoglycemia is significantly enhanced; please refer to 1) Brenta G, Diabetes and thyroid disorders. Brit J Diabetes Vascular disease 2010; 10: 172-177; 2) Duntas L & al., the interface between thyroid and diabetes mellitus. Clin Endocrinol 2011; 75: 1-9; 3) Kadiyala R & al., Thyroid dysfunction in patients with diabetes: clinical implications and screening strategies. Int J Clin Pract 2010; 64: 1130-1. Please kindly refer to page seven, lines 9-18)

In his clinical practice as diabetologist specialized on endocrine autoimmunity in a tertiary referral academic diabetes outpatient clinic, the senior author does encounter an increased risk of hypoglycemia in overt hypothyroidism and does reduce the insulin dosage by ~20-25% till reaching biochemical euthyroidism within 3-4 weeks

Point 5) Does hyperthyroidism really contribute to a clinically meaningful rise in glycaemia in adult T1DM patients?

Authors' reply: Again, hyperthyroidism increases glucose resorption and hepatic glucose release leading to hyperglycemia and especially in patients with type 1 diabetes to insulin resistance and an increased release of fatty acids causing ketoacidosis. Please refer to 1) Brenta & al, Diabetes and thyroid disorders. Brit J Diabetes Vascular diseases 2010; 10: 172-177; 2) Perros & al, Frequency of thyroid

dysfunction in diabetic patients: value of annual screening. Diab Med 1995; 12: 622-627; 3) Lambadiari & al., thyroid hormones are positively associated with insulin resistance early in the development of diabetes. Endocrine 2010; 39: 28-32. Please kindly refer to page seven, lines 21-29.

The senior author also adapts the insulin dose in patients with overt hyperthyroidism and type 1 diabetes for approximately 3-4 weeks till reaching biochemical euthyroidism with the help of antithyroid drugs.

Point 6) Do the authors advise to screen for them [pituitary antibodies] in T1DM?

Pituitary autoantibodies are measured in a few research labs only and standardization or commercializations of correspondent assays are not available yet. Further, the relevance and significance of these autoantibodies has not been clarified yet. Therefore the measurement of the pituitary antibodies cannot be recommended currently. (Please kindly refer to new figure 3, page 33)

REVIEWER II

We thank the Reviewer for his kind words and for praising the review manuscript

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

Sincerely yours

George J KAHALY, MD, PhD
Department of Medicine I
Johannes Gutenberg University Medical Center
Langenbeckstreet 1, Mainz 55131, Germany
Fax: +49 – 6131 – 17-3460
E-mail: Kahaly@ukmainz.de