JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
LETTER TO THE EDITOR

Administration of thiamazole for Graves' disease might trigger the onset of type 1 diabetes

A 61-year-old woman consulted a local physician due to palpitation, weight loss and hyperhidrosis. She was referred to Saitama Medical University Hospital, Moroyama, Saitama, Japan, with a diagnosis of thyrotoxicosis (thyroid-stimulating hormone <0.01 μIU/L, free triiodothyronine 17.43 pg/mL, free thyroxine 4.87 ng/dL). Her mother had a history of thyroid disease. Because of the positive anti-thyroid-stimulating hormone receptor antibody (35.2 IU/L), she was diagnosed with probable Graves' disease, and treatment with thiamazole (30 mg/day) was started. Her postprandial blood glucose was 150 mg/dL and glycated hemoglobin 6.2%; the degree of glucose intolerance at this point could be explained solely by the thyrotoxicosis. Two weeks later, she started to experience excessive thirst, polydipsia and polyuria, and visited our outpatient clinic 1 month later. Her blood glucose level had increased up to 429 mg/dL and glycated hemoglobin 12.0%. In contrast, her thyroid function was rather suppressed (free triiodothyronine 1.78 pg/dL and free thyroxine 0.70 ng/dL). Her fasting C-peptide level was 0.58 ng/dL, glutamic acid decarboxylase antibody 13.5 U/mL, insulin autoantibody 1.3 U/mL and islet antigen 2 antibody 2.0 U/mL; the patient was diagnosed as having type 1 diabetes. She possessed the *HLA DRB1*09:01* allele that confers susceptibility to type 1 diabetes in Japanese people. Furthermore, we assessed insulin-peptide B11-25 reactive T-cell response by using the enzyme-linked immunospot assay and found spots positive for interferon-γ, suggesting the existence of insulin peptide reactive T helper 1 cells. Importantly, her glutamic acid decarboxylase and islet antigen 2 antibody titers increased up to 1182.5 U/mL and 12.0 U/mL, respectively 3 months after the onset of type 1 diabetes (Figure S1), supporting our belief that the autoimmune reaction seemed to have started after the administration of thiamazole. Thiamazole was discontinued and potassium iodide was administered temporary, then the patient was treated by radioisotope.

To the best of our knowledge, so far there has been no report regarding the "trigger" of type 1 diabetes by thiamazole. The fact that obvious decline of the patient's thyroid function within 1 month after the administration of thiamazole, and the paradoxically significant rise in her blood glucose and glycated hemoglobin level within the same period of time suggests the "trigger" of type 1 diabetes by thiamazole (Figure 1). It is well known that Graves' disease and type 1 diabetes can occur concurrently. In such cases, a high glutamic acid decarboxylase antibody titer is usually observed at the onset of diabetes, and the most susceptible human leukocyte antigen type is reportedly *HLA DRB1*04:05*[1]. Also, it is well known that insulin autoimmune syndrome can be induced by thiamazole. Disulfide bonds are essential for structural stability of insulin, and modified by thiamazole, which contains the sulfhydryl group. Reportedly[2], drugs such as thiamazole, which contain the sulfhydryl group, modify insulin to be recognized as an autoantigen. Considering very recent reports[3,4], which have shown that modified antigens are essential targets in pancreatic lesions of type 1 diabetes, we assume that thiamazole could modify insulin, leading to triggering autoreactivity to the pancreatic islets, and resulting in the onset of type 1 diabetes, although we cannot deny the

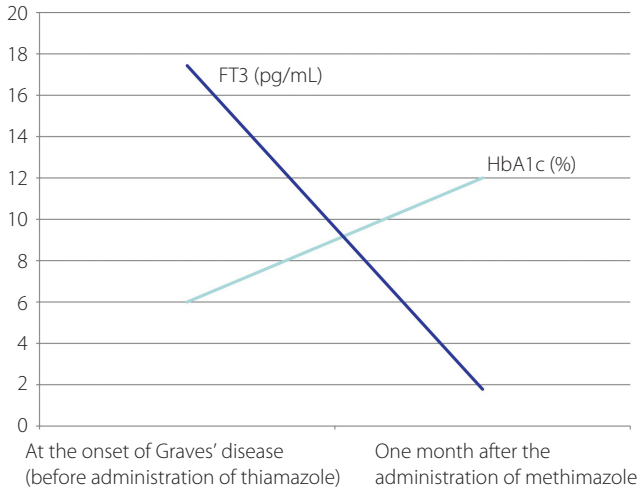

Figure 1 | Change in the levels of free triiodothyronine (FT3) and glycated hemoglobin (HbA1c) at the onset of Graves' disease and 1 month after the administration of thiamazole.

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Received 25 September 2017; revised 10 November 2017; accepted 27 November 2017

possibility that Graves' disease itself might contribute to the onset of type 1 diabetes.

We believe that our observation in this patient could contribute to our knowledge of the pathophysiology of the onset of type 1 diabetes.

DISCLOSURE

AS has received lecture fees from Novo Nordisk Pharma, Sanofi and Eli Lilly Japan. MN has received lecture fees from Sanofi, Novo Nordisk Pharma, Mitsubishi Tanabe Pharma, Daiichi Sankyo, Eli Lilly Japan, MSD, Sanwa Kagaku Kenkyusho, Ono Pharmaceutical Co. Ltd, Takeda Pharmaceutical Co. Ltd, Astellas, Kowa Pharmaceutical Co. Ltd, Taisho Toyama Pharmaceutical Co. Ltd, Kissei Pharmaceutical Co. Ltd, Meiji Seika Pharma Co. Ltd, Kyowa Hakko Kirin Co. Ltd, ABBVie Inc. Johnson & Johnson K.K., Novartis Pharma K.K. and Shionogi & Co., Ltd., and has received research grants from Astra Zeneca, Takeda Pharmaceutical Co. Ltd, Daiichi Sankyo, Mitsubishi Tanabe Pharma and Kyowa Hakko Kirin Co. Ltd. GM, YH, AS, TI, RN, YM, SY, YO, MI and II declare no conflict of interest.

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Doi: 10.1111/jdi.12784

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1| Change of autoantibody titer.