Association Study of the Thyroid Peroxidase Gene in Autoimmune Thyroid Diseases

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Introduction: The etiology of autoimmune thyroid diseases (AITDs), such as Graves' disease (GD) and Hashimoto's thyroiditis (HT), is largely unknown. However, genetic susceptibility is believed to play a major role. Recently, a case-control association study performed in Croatia showed a significant association of the single nucleotide polymorphism (SNP) rs11675434 near thyroid peroxidase (TPO) with HT, and also with thyroid autoantibodies against TPO (TPOAb) levels. High TPOAb levels are present in 90% of patients with HT and serve as a clinical marker for the detection of early AITD/HT. Therefore, we conducted a case-control study to determine the genetic association of the rs11675434 near TPO with AITD in a cohort of the Japanese population. **Methods:** We genotyped the rs11675434 near TPO in 457 Japanese patients with AITD (286 with GD, 171 with HT) and 242 matched Japanese control subjects. The SNP was analyzed using TaqMan probe method, and association study was performed using the χ^2 and Fisher's exact tests with Yates correction. **Results:** Both GD and HT showed no significant associations. Moreover, when patients with GD were stratified according to Graves' ophthalmopathy (GO) (n=96), there were no allelic associations with GO, although there were weak associations between GO and controls (P=0.0494, Odds ratios (ORs)=0.3102). **Conclusions:** Our finding suggest that the rs11675434 near TPO may not contribute to the risk of AITD in the Japanese population, although the study was in insufficient and underpowered sample size.

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THYROID AUTOIMMUNITY, COVID-19 & THYROID DISEASE

At Last the Explanation for Increased Spontaneous Miscarriages in Thyroid Autoantibody Positive Pregnant Women

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In women who are pregnant, the presence of thyroid autoantibodies is associated with an increased rate of miscarriage in the first trimester, with multiple reports averaging ~17% compared with ~8% in autoantibody negative women. During pregnancy immune tolerance is altered to allow implantation of the semi-allogeneic fetus and T-regulatory cells (Tregs), which play a major role in such tolerance, have been shown to increase during pregnancy, reaching a peak in the second trimester. A deficiency in this Treg response has been widely associated with spontaneous miscarriages. While it is known that the number of Tregs in patients with autoimmune thyroid disease (AITD) is decreased there are no data on pregnant women with AITD. In this study, we examined both the number and function of Tregs in pregnant women with (n=26) and without (n=41) thyroid autoantibodies (anti-Tg and/or anti-TPO) as well as healthy non pregnant women (n=25). Tregs were measured by flow cytometry of isolated CD4+, CD25+ and FoxP3+ T-cells. We found that the total number of CD4+CD25+FoxP3+ ^{high} Tregs was significantly increased in pregnancy consistent with previous reports (from 11% to 22%, p<0.024). Furthermore, this increase in Tregs was less in pregnant women with thyroid autoantibodies (mean of 12%). In addition, studies of phosphorylated signal transducer and activator of transcription-5a (pStat-5a) as a marker of Treg function, showed that while Tregs were activated in pregnancy, their activity per cell was diminished in the pregnant antibody positive women with a frequency:MFI ratio of 201 compared to 316 in the negative group. These data demonstrate that pregnant women with thyroid antibodies have a reduced Treg response to pregnancy, both in number and function, and offer a likely explanation for the increased miscarriage rate in such patients.

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Characterization of Thyroid Disease Prevalence Among Transgender and Gender-Diverse Patients

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Objective: Transgender and gender-diverse individuals are at risk of insufficient treatment of endocrine diseases due to a number of barriers to care. There are currently no data evaluating the prevalence of thyroid disease in this population, and it is unknown if gender-affirming hormone therapy affects treatment of thyroid disease in these individuals. **Methods:** Utilizing a registry of 676 patients over 18 years of age who were seen in our Transgender and Intersex Specialty Care Clinic from 2015-2019, we identified 554 individuals seeking medical therapy for gender dysphoria/incongruence. Of these, 56 patients were taking thyroid hormone or antithyroid medications or had a coded diagnosis of thyroid disease; 2 were excluded as they were receiving thyroid hormone as adjunctive therapy for refractory depression. 54 patients were therefore analyzed with respect to thyroid disease (TD+), and compared to those 498 patients without thyroid disease (TD-) with regard to average vital signs, demographics, and presence of common comorbidities. **Results:** Fifty percent of our TD+ patients were recorded female sex at birth, and 98% were Caucasian. TD+ patients were much more likely to have essential hypertension (OR 5.99), to use tobacco (OR 2.23), and to be overweight or obese (OR 2.16) than TD- patients. Due to the evolving natural history of disease, some TD+ patients belonged to multiple categories: 48 patients, 26 trans feminine and 21 trans masculine, had hypothyroidism, of whom 41 had overt hypothyroidism and 2 patients had subacute thyroiditis that progressed

to the hypothyroid phase of illness. 5 patients (3 trans masculine and 2 trans feminine) demonstrated hyperthyroidism, 4 of whom had Graves' Disease. 2 patients had multinodular goiter, both trans masculine. 2 patients had thyroid malignancies, both trans feminine, of whom one had proven follicular thyroid carcinoma and the other had unspecified thyroid malignancy. Among hypothyroid patients, there was a slight non-significant trend toward increased thyroid hormone requirements while receiving treatment with estradiol or testosterone. **Conclusion:** To our knowledge, this represents the first attempt to characterize the prevalence of various thyroid disease states in the gender diverse population. Our data corresponded to a prevalence of hypothyroidism of approximately 8.7%, which is higher than previously published estimates of 3-5% in the general population. Whether this represents actual increased prevalence or assessment bias is uncertain. It is important for all health professionals who care for gender diverse people to identify and appropriately treat thyroid disease, and to monitor thyroid function closely if gender-affirming hormone therapy is initiated.

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Comparison of Block and Replace Regime and Titration Regime in Graves' Disease

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In Graves' disease (GD), medical treatment is still the cornerstone in its management and there were some studies done on comparison of the block and replace regime and titration regime of the antithyroid drugs (ATDs). In Myanmar, titration regime is mostly practiced for management of GD. In daily clinical practice, frequent hospital visits are needed in titration regime and loss of follow-up is an obstacle in patients treated with titration regime. A hospital based randomized clinical trial was conducted and aimed to compare the proportion of attainment of euthyroid status between block and replace regime and titration regime in patients with recently diagnosed GD. A total of 117 patients; 58 patients in block and replace regime and 59 patients in titration regime, who met the inclusion criteria were included. The results showed that euthyroid status was observed in increasing trend during the study period for both regimes but there was no significant difference of achieving euthyroid status between the regimes at the end of 12 months. Regarding side effects of ATDs, skin rash and pruritus were more frequently occurred during the first 3 months of ATDs but no significant difference was noted between the regimes at the end of study. There was also no case of serious side effects such as agranulocytosis and hepatotoxicity up to the end of 12 months. The results of the study pointed out that block and replace regime was comparable to dose titration regime in attaining euthyroid status. As a conclusion, block and replace regime can be applied as an alternative option where titration regime is not feasible. **Reference:** (1) Abraham *et al*., 2005; A systematic review of drug therapy for Graves' hyperthyroidism. *Eur J Endocrinol*. 153: 489-98. (2) Vaidya *et al*., 2014; Block & replace regime versus titration regime of antithyroid drugs for the treatment of Graves' disease: a retrospective observational study. *Clinical Endocrinology*. 81: 610–613.

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Does Primary BCG Vaccination Prevent Autoimmune Hypothyroid Disease?

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Autoimmune thyroid disease (AITD) involves autoimmune destruction of thyrocytes marked by the presence of anti-TPO and/or anti-TG antibodies. In autoimmune diseases, an immunomodulatory role of BCG vaccination has been reported with decreased autoantibody production and induction of regulatory T cells (Tregs). We hypothesize that the loss of efficacy of BCG vaccine in adulthood might be associated with the appearance of AITD. To evaluate the protective efficacy of primary BCG vaccination, we assessed the anti-mycobacterial responses, thyroid function, and antithyroid autoimmune responses in autoimmune subclinical hypothyroid (SCH) (n=39) and non-autoimmune SCH (n=25) subjects. The anti-mycobacterial responses were determined by the Mantoux test and by BCG induced *in-vitro* proliferation of peripheral blood mononuclear cells in terms of proliferation index (PI). The immunophenotyping of autoreactive CD8+ T cells recognizing TPO derived epitopes was performed by flow cytometry using APC labelled dextramers by flow cytometry in patients with HLA-A*02 and HLA-A*24 alleles. We observed that the autoimmune SCH group had more subjects with a negative Mantoux reaction (less than 5mm) (61.5% vs 33.3%, p= 0.01). The PI with BCG stimulation was similar in both groups (2.55±0.31 vs 2.51±0.41, p = 0.667). The correlations (r) between Mantoux test and PI in autoimmune SCH and non-autoimmune SCH were, insignificant. The autoimmune SCH group had more subjects with diffused thyroiditis (43% vs 13%, p= 0.02). The SCH subjects with the presence of a BCG scar (n=11) had lower TSH (μIU/ml) (7.94±1.67 vs 6.75±1.56, p= 0.026) levels and lower frequencies of TPO-reactive CD8+ T cells (3.35±0.72% vs 1.77±0.98%, p= 0.061), as compared to subjects with the absence of a BCG scar (n = 53). The SCH subjects with positive Mantoux test (more than 10mm) demonstrated similar titres of anti-TG antibody (IU/ml) [(230 (56.71-508.90) vs 85.5 (15-345.9), p= 0.055] and anti-TPO antibody (IU/ml) [29.9 (5-135) vs 12 (5-83), p= 0.665)] as compared to those with a negative Mantoux test. The TPO-reactive CD8+ T cells and anti-TG antibody titres had a negative correlation in autoimmune SCH (r= -0.695, p=0.038) and non-autoimmune SCH (r= -0.642, p=0.024) subjects. Next, we observed a similar frequency of TPO-reactive CD8+ T cells in non-autoimmune and autoimmune SCH subjects (8.40±3.74% vs 9.02±4.17% p= 0.937). The absence of anti-TPO or anti-TG antibody did not rule out the presence of any underlying autoimmunity. The persistence of the protective effects of either BCG