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Serum BAFF and thyroid autoantibodies in autoimmune thyroid disease

Jiunn-Diann Lin MD [a,b,c], Yuan-Hung Wang PhD [a,d], Wen-Fang Fang MD [e], Chia-Jung Hsiao MS [a], Amarzaya Chagnaadorj MD [a], Yuh-Feng Lin MD [a,f], Kam-Tsun Tang MD [g], Chao-Wen Cheng PhD [a,*]

[a] Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, ROC
[b] Division of Endocrinology, Department of Internal Medicine, Shuang-Ho Hospital, Taipei Medical University, New Taipei City, Taiwan, ROC
[c] Division of Endocrinology and Metabolism, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, ROC
[d] Department of Medical Research, Shuang-Ho Hospital, Taipei Medical University, New Taipei City, Taiwan, ROC
[e] Department of Family Medicine, Shuang-Ho Hospital, Taipei Medical University, New Taipei City, Taiwan, ROC
[f] Division of Nephrology Department of Internal Medicine, Shuang-Ho Hospital, Taipei Medical University, New Taipei City, Taiwan, ROC
[g] Division of Endocrinology and Metabolism, Department of Internal Medicine, Veterans General Hospital, Taipei, Taiwan, ROC

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ABSTRACT

Background: This study investigated the association of serum B-lymphocyte activating factor (BAFF) levels with autoimmune thyroid disease (AITD) in a Chinese population.
Materials and methods: We enrolled 221 patients with AITD [170 patients with Graves' disease (GD), 51 patients with Hashimoto's thyroiditis (HT)], and 124 healthy controls. Serum BAFF levels, thyroid function and thyroid autoantibody (TAb) levels, including of thyroid-stimulating hormone receptor antibody (TSHRAb), anti-thyroid peroxidase antibody (Anti-TPO Ab), and antithyroglobulin antibody (ATA), were measured at baseline.
Results: Serum BAFF levels were higher in the GD, HT, and AITD groups than in the control group. Significant correlations were observed between BAFF and TSHRAb levels ($r = 0.238$, $p = 0.018$), between BAFF and Anti-TPO Ab levels ($p = 0.038$), and between BAFF and ATA titers ($p = 0.025$) in women but not in men. In addition, serum BAFF levels were significantly associated with free thyroxine ($r = 0.430$, $p = 0.004$) and TSHRAb ($r = 0.495$, $p = 0.001$) levels in women with active GD but not in those with inactive GD.
Conclusions: Serum BAFF levels are increased in GD, HT, and AITD. The correlation between serum BAFF and TAb levels exhibits a dimorphic pattern, particularly in active GD.

1. Introduction

Autoimmune thyroid disease (AITD) is the most common autoimmune disease (AID) in the general population [1,2] and includes Graves' disease (GD) and Hashimoto's thyroiditis (HT). GD is characterized by the generation of a B-cell immune response resulting in the formation of thyroid-stimulating hormone (TSH) receptor antibody (TSHRAb), which causes thyroid follicular cell hyperplasia and increases thyroid hormone production. By contrast, HT is mainly triggered by a T-cell-mediated immune reaction, followed by the destruction of thyroid follicular cells and finally the occurrence of overt hypothyroidism [3]. In addition, HT development is associated with B lymphocyte activation and autoantibody formation; thus, thyroid autoantibodies (TAbs) can be detected in most patients with HT [1].

B lymphocytes are essential for maintaining a normal humoral immune reaction through the promotion of antibody formation [4]. However, because of the dysregulation of polyclonal activation, production of autoantibodies, and costimulation of autoreactive T cells, B cells have a pathogenic role in the development of AIDs [5]. B-lymphocyte activating factor (BAFF) has a critical role in regulating the maturation, proliferation, and differentiation of B cells and prolonging the survival of B cells [6,7]. BAFF transgenic mice develop hypergammaglobulinemia and have phenotypes similar to those of autoimmune lupus-like disease, including the presence of autoantibodies to nuclear antigens and immune complex deposits in the kidney [8]. This evidence indicates that BAFF acts as a stimulator of immunoglobulin production in AIDs. A high serum BAFF level has been correlated with several human AIDs including systemic lupus erythematosus (SLE), rheumatoid arthritis, and Sjögren's syndrome [9,10,11]. In addition, serum BAFF levels have been associated with serum autoantibody levels in AIDs [10,12].

Several studies have reported a relationship between AITD and BAFF expression. Fabris et al. reported that the plasma BAFF level was higher in patients with GD and HT than in healthy controls [13]. Moreover, Vannucchi et al. reported that serum BAFF level was increased in

Abbreviations: AITD, autoimmune thyroid disease; Anti-TPO Ab, anti-thyroid peroxidase antibody; ATA, antithyroglobulin antibody; BAFF, B-lymphocyte activating factor; GD, Graves' disease; HT, Hashimoto's thyroiditis; TAb, thyroid autoantibody; TSHRAb, thyroid-stimulating hormone receptor antibody.

* Corresponding author at: Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, 250 Wuxing St., Taipei 110, Taiwan, ROC.
E-mail address: ccheng@tmu.edu.tw (C.-W. Cheng).

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Table 1
Demographic characteristics of the Graves' disease (GD), Hashimoto's thyroiditis (HT), and control groups.

	Control (124)	GD (170)	HT (51)	AITD (221)
Age (y)	46 ± 12	45 ± 13[c]	51 ± 14[b]	46 ± 13
Women/Men (women %)	76/48 (61.3)[c,d]	121/49 (71.2)[c]	45/6 (88.2)[a,b]	166/55 (75.1)[a]
Smoking (%)	15.1[d]	24.6[c]	10.0[b]	21.2[a]
Family history of thyroid disease (%)	4.0[b,c,d]	29.4[a]	19.1[a]	27.0[a]

Age is expressed as the mean ± SD.
AITD, autoimmune thyroid disease (GD + HT).
[a] $p < 0.05$ vs. the control group.
[b] $p < 0.05$ vs. GD.
[c] $p < 0.05$ vs. HT.
[d] $p < 0.05$ vs. AITD.

patients with GD; however, the level decreased after immunosuppressive therapy [14]. Campil et al. demonstrated that BAFF protein expression in infiltrating lymphocytes was higher in AITD than in multinodular goiter tissues [15]. In our recent study, we reported that rs2893321, a BAFF single-nucleotide polymorphism variant, affected susceptibility to the development of GD and AITD [16]. All these studies have suggested the involvement of BAFF in the pathogenesis of AITD. However, whether serum BAFF level is associated with the clinical manifestations of GD and HT remains unclear.

2. Materials and methods

2.1. Patients

The serum samples of 221 patients with AITD, including 170 patients with GD and 51 patients with HT, aged >20 y, were collected by the Division of Endocrinology, Internal Department, Shuang-Ho Hospital (New Taipei, Taiwan) from January 2013 to September 2014. The blood samples of 124 patients without AITD or other AIDs and aged >20 y were obtained by the Health Screening Center of Shuang-Ho Hospital from May to August 2014. Patients with AITD and healthy controls were excluded if they were aged <20 y, pregnant, alcoholic, or had a history of drug intoxication. The study protocol was approved by the Joint Institutional Review Board of Taipei Medical University, and all the patients provided written informed consent prior to participation.

GD was diagnosed if one of the following criteria was met: (1) presence of a low TSH level, normal or high free thyroxine (FT4) level, and TSHRAbs; (2) presence of thyrotoxicosis without TSHRAbs but increased or normal diffuse thyroid uptake of I^{131}; or (3) a proven diagnosis by another hospital, as indicated by medical records. HT was diagnosed on the basis of the presence of a Hashimoto autoantibody (either an anti-thyroid peroxidase antibody [Anti-TPO Ab], antithyroglobulin antibody [ATA], or both) and hypoechogenic thyroid parenchyma on a thyroid sonogram.

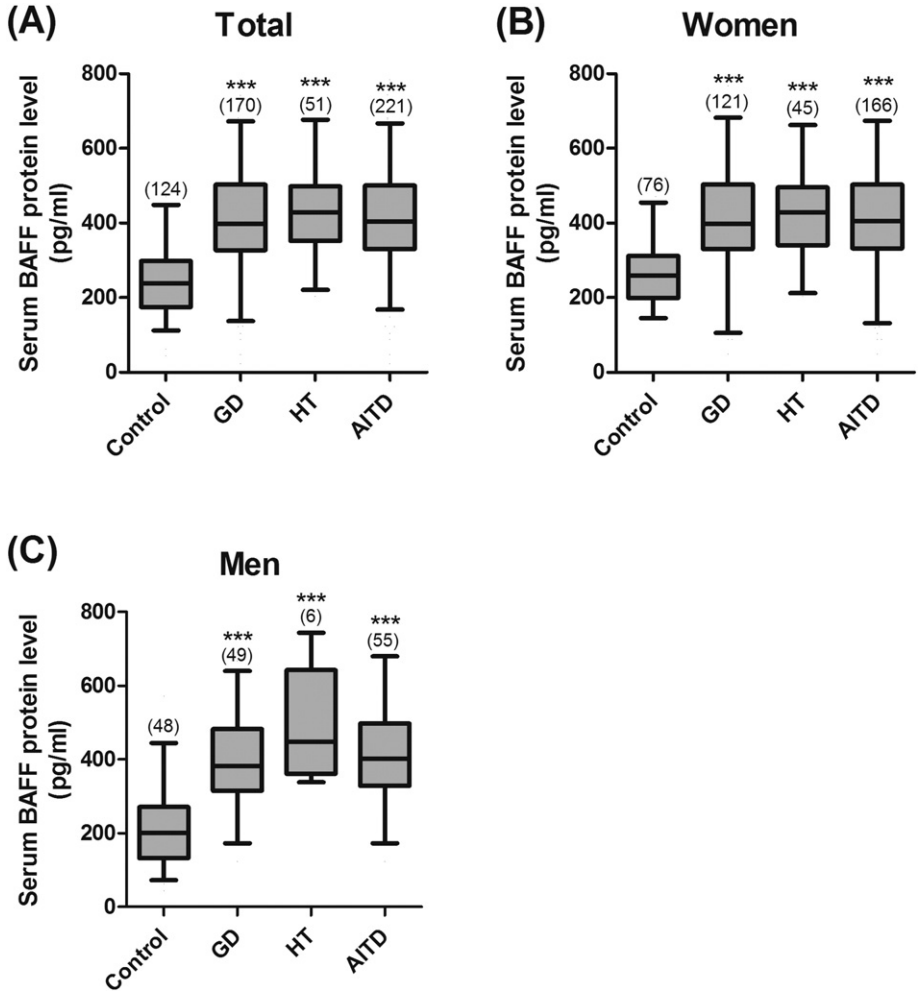

Fig. 1. Comparison of serum B-lymphocyte activating factor (BAFF) levels in each group. GD, Graves' disease; HT, Hashimoto's thyroiditis; AITD, autoimmune thyroid disease (GD + HT). The number in the column indicates the number of patients. Data are presented as box plots (median, 25th–75th percentile). ***$p < 0.001$ compared with the controls.