

## Review Article

# Thyroid dysfunction: an autoimmune aspect

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**Abstract:** Auto immune thyroid disease (AITD) is the common organ specific autoimmune disorder, Hashimoto thyroiditis (HT) and Grave's disease (GD) are its well-known sequelae. It occurs due to loss of tolerance to autoantigens thyroid peroxidase (TPO), thyroglobulin (Tg), thyroid stimulating hormone receptor (TSH-R) which leads to the infiltration of the gland. T cells in chronic autoimmune thyroiditis (cAIT) induce apoptosis in thyroid follicular cells and cause destruction of the gland. Presences of TPO antibodies are common in HT and GD, while Tg has been reported as an independent predictor of thyroid malignancy. Cytokines are small proteins play an important role in autoimmunity, by stimulating B and T cells. Various cytokines IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13, IL-14, TNF- $\alpha$  and IFN- $\gamma$  are found in thyroid follicular cells which enhance inflammatory response with nitric oxide (NO) and prostaglandins.

**Keywords:** Autoimmunity, antibody, cytokines, lymphocytes, thyroid peroxidase, thyroglobulin

### Thyroid and autoimmunity

Thyroid dysfunction is a common health problem prevalent in individuals aged > 60 years. Its symptoms often appear gradually and are commonly misdiagnosed. The most common thyroid problems are the underactive thyroid, overactive thyroid, and thyroid nodules [1, 2]. Epidemiological studies have associated the subclinical condition of thyroid dysfunction with adverse clinical outcomes [3, 4].

AITD arises due to decreased immune susceptibility to thyroid auto antigens. AITD comprises GD and cAIT, which are characterized by hyperthyroidism and hypothyroidism respectively [5]. The organ specific autoimmune disease includes infiltration of the thyroid by lymphocytes which are auto-reactive to thyroid antigens, presence of circulating thyroid autoantibodies, immunological overlap with other autoimmune diseases, a story of familiar occurrence, mainly in females [6]. According to American Thyroid Association large numbers of patients develop thyroid nodules by the age of 60, although majority of these nodules are benign [7]. The Whickham study recorded 9.3% of women and 1.2% of men to have serum TSH

concentrations > 10 mIU/l [1]. Tg, TPO and TSH-R are the three main thyroid auto-antigens present in both kind of disease. Presence of TPO antibodies was significantly associated with thyroid failure with increasing age, mainly in women [8].

### Mechanism of thyroid autoimmunity

Thyroid autoimmunity is found mainly associated with lymphocytic infiltration caused by the loss of immune tolerance to auto-antigens and reactivity of the thyroid, which in turn produce antibodies specific for clinical manifestations of GD and cAIT respectively. Moreover, T cells in cAIT induce apoptosis in thyroid follicular cells, leading to the destruction of the gland [9].

Antigen-presenting cells (APCs) (macrophage, dendritic cells) belonging to major histocompatibility complex (MHC) class II, especially dendritic cells, accumulate within the thyroid gland and present specific thyroid antigens to lymphocytes, which leads to activation and proliferation of auto-reactive B and T lymphocytes. Thus, activated antigen-specific T-helper CD4+ lymphocytes induce the formation of cytotoxic CD8+ T cells, and activate B cells, which pro-

duce autoantibodies. The destruction of thyroid parenchyma is due to gland infiltration by cytotoxic T cells [6, 10].

Sachaguchi S and Schevach EM reported lack of T regulatory cells in humans and mice results in various systemic autoimmune disorders such as thyroiditis, multiple sclerosis, inflamed ovaries etc [11, 12]. Activated organ specific CD4<sup>+</sup> T cells recruit B cells by fixing complete immune response through autoantibodies [13]. CD4<sup>+</sup> T are the main infiltrating cells in AITD. Three different types of CD4<sup>+</sup> T lymphocytes has been noted; Th1, Th2, Th17. The progress of Th cells proceeds in association with MHC Class II molecules by APC (dendritic cells) [14]. HT is a result of Th1 immune response which triggers the cell mediated immunity and follicular cell death by apoptosis [15, 16]. The humoral response by Th2 increases B cell antibody production which results in activated anti-apoptotic molecules resulting death of cytotoxic lymphocytes and infiltrating thyroid tissue. In GD cytokine production is commonly known by Th2 subtype of CD4<sup>+</sup> T lymphocytes [17]. Also, Andrew GG reported epithelium and other elements of thyroid play important role in defining the pattern of inflammation and tissue remodeling in GD [18]. Nanba et al. first described the presence of Th17 cells in patients with GD [19]. Nagayama Y described the pathogenesis of GD by Th17 subtypes [20]. In a study, increased number of Th17 cells were seen in blood (with increased RORC2 gene expression responsible for differentiation of Th17), and also in thyroid tissue of HT patients, but not in GD [21].

### **Auto-antibodies involved in pathological process**

In auto immune thyroid disease raised levels of antibodies against TPO, TG, TSH-R are commonly found [22]. Thyroid autoimmunity is known as a result of TPO and Tg cross reactivity. Increased anti-Tg antibodies are observed in HT and GD patients, but also in 10-20% of healthy women [23]. In a study by Vasileiadis et al. reported anti-thyroid antibodies (both anti-TPO antibodies and anti-Tg antibodies) showed a relationship with HT patients thus confirming an association between anti-thyroid antibodies and thyroid cancer [24].

TPO antibodies are membrane bound on thyrocytes and the key enzyme for iodination and

coupling reaction in thyroid hormone synthesis [25]. Presence of TPO antibodies are higher in women of child bearing age [26]. Stagnaro A. et al. demonstrated the noticeable association between thyroid auto-antibodies (TPO, Tg) and increased risk of miscarriage or preterm delivery [27]. In various studies presence of TPO antibodies without overt thyroid dysfunction was significantly associated with a 3- to 5-fold increase in miscarriage rate [28-31]. Prevalence of anti TPO antibodies is higher in autoimmune hypothyroidism and Grave's disease. Tg antibodies are found in less than 60% of patients with lymphocytic thyroiditis and 30% of GD [32, 33]. Kim et al. reported positive serum Tg antibodies as an independent predictor for thyroid malignancy regardless of the presence of AITD [34].

TSH-R is common in GD and atrophic thyroiditis [35]. In GD, thyroid stimulating antibodies bind to the receptor and stimulate the thyroid cell to produce excessive amount of thyroid hormones resulting in hyperthyroidism [36].

### **Cytokines contribution in AITD**

Cytokines are small proteins synthesized by variety of cell types, and significantly contribute in immune system. These are membrane bound, soluble proteins focusing on the receptors over the nearby cells. Their major function is to regulate immune response and initiate autoimmunity. Moreover, they affect the function of other cells, hematopoiesis, mediate inflammation, wound healing. Cytokines initiate inflammatory response, by stimulating T and B cells [18, 34, 37]. Cytokines are involved in the initiation, consequences of immune response and key role in pathogenesis of AITD, directly target thyroid follicular cells by modulating epithelial cell growth and function [38, 39].

Various studies have demonstrated the presence of pro-inflammatory IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13, IL-14, TNF- $\alpha$  and IFN- $\gamma$  in thyroid follicular cells [40, 39]. In the presence of antigen, under cell mediated immunity macrophages and T cells differentiate into T helper cells (Th1, Th2, Th17, also Th3), thus produce variety of pro inflammatory cytokines. Th1 under cellular response secrete (IL-1 $\beta$ , IL-12, IFN- $\gamma$ , TNF- $\alpha$ ) [41]. Nanba et al. reported much Th1 cells in extreme HD patients than in mild [19]. Dendritic cells (DC) bridge

innate and acquired and thus generate pro inflammatory cytokines. IL-12, IFN- $\gamma$ , TNF- $\alpha$  play an important role in initiating adaptive immune response [42]. IL-1 $\beta$  has variety of effects on other cells, like it can alter cell signaling, migration, cytokine production, break peripheral tolerance and implicate autoimmune disease.

Not only the pro-inflammatory cytokines provoked AITD or an inflammatory response, they alone can prevent the experimental autoimmune thyroiditis, suggested by Rasmussen et al. [38].

Th2 under humoral response secrete IL-4, IL-5, IL-6, IL-10, IL-13 and Th17 produce IL-17, IL-21, IL22. Th17 cells differentiate in presence of TGF- $\beta$  with IL-6 [43] or IL-21 [44]. Figureoavega et al. reported increased levels of IL-17, IL-22 were observed in HT patients than GD patients [21]. Contrarily, Horie et al. reported that Th17 cells can also induce GD depending upon the genetic background [45].

A subtype of CD4+ T cells is Th3 which reveals a protective role against the incidence of autoimmune disease [41]. Cytokines enhance inflammatory response with the production of nitric oxide (NO) and prostaglandin; when thyroid follicular cells get stimulated by IL-1, IFN- $\gamma$ , TNF- $\alpha$  [38,46]. In a thyroid tissue immune histochemical study IFN- $\gamma$  present in cells infiltrating the thyroid gland, IL-1 in thyroid endothelial cells, and increased IL-1, IL-6, TNF- $\alpha$  in follicular cells. IL-1 $\beta$ , IL-6, TNF- $\alpha$  generates inflammation and autoimmunity. IFN- $\gamma$ , TNF- $\alpha$  restricts the growth of the cell without affecting its activity [47].

### Conclusion

The role of cytokines in AITD presents a tedious picture and remains unclear. The anti-thyroid antibodies and cytokines present in peripheral blood reveals information in the pathogenesis of AITD. But additional studies are required to understand the effect of cytokines on various immune components.

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### Disclosure of conflict of interest

None.

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