

Importance of cytolytic activity and dietary iodine in the pathogenesis of postpartum thyroiditis

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The incidence of lymphocytic thyroiditis (LT) has increased since the introduction of iodine prophylaxis, and LT is claimed to represent an adverse reaction to iodine. This theory is supported by animal studies as well as experimental studies in humans. In pregnancy iodine turnover is increased. During the immunological rebound period occurring postpartum the thyroid autoantibodies increase, and may lead to postpartum thyroiditis (PPT). The iodine content within the gland may be important for this reaction. *In vitro* it has been shown that iodine inhibits the cAMP-dependent events of the thyroid cell function, but iodine may also stimulate the intrathyroidal immuno-competent cells leading to cytokine synthesis. Cytokines have been shown to interfere with the thyroid cell function. Iodine may thus trigger the autoreactive attack and enhance the local autoantibody production, which plays a primary pathogenic role for development of PPT.

Key words: cytokines; iodine; lymphocytic thyroiditis; postpartum thyroiditis; thyroid antibodies.

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Lymphocytic thyroiditis

Autoimmune thyroid diseases are inflammatory disorders, which can be classified according to the thyroid function (5). A general histological feature is the lymphocytic infiltration forming lymphoid follicles with infiltration of plasma cells. In the chronic variants (Hashimoto's thyroiditis, atrophic thyroiditis) the histological features show germinal centres, in contrast to the reversible variant (silent thyroiditis) also called lymphocytic thyroiditis (LT). Besides the lymphocytic infiltration in the thyroid parenchyma, the thyroid follicles are destroyed and preformed thyroid hormones are released resulting in hyperthyroidism which lasts up to 4 months (37).

The incidence of LT has increased significantly over the last 20 years. It has been suggested that lymphocytic infiltration of the thyroid and LT might represent adverse reactions to iodine, because the increase of LT was coin-

cident with the introduction of iodine prophylaxis (28). Further, an increased number of lymphocytes has been demonstrated in thyroid glands removed from patients treated with iodine for hyperthyroidism (16, 36). Moreover, acute thyroiditis from excess of iodide and increase of thyroid autoantibodies with and without occurrence of transient hyperthyroidism have been demonstrated in otherwise immunologically normal persons in a previous goitrous area 3-6 months after acute administration of iodized oil. Finally, high dietary intake of iodide seems to be associated with high incidence of papillary carcinoma in contrast to areas of endemic goitre, where dietary intake of iodide is known to be low. There seems to be a geographic variation in the prevalence of thyroiditis related to difference in iodine intake. However, other explanations as ingestion of beef contaminated by thyroid tissue, leading to transient thyrotoxicosis has been reported (18).

Animal studies

The suggestion that dietary iodine may lead to development of autoimmune LT, has been further confirmed by studies in animals. Increased levels of iodine as well as dietary iodide induced thyroid infiltration and autoantibodies specific for thyroglobulin and thyroid hormones in genetically susceptible chicken (4, 34). In diabetes-prone Biobreeding Worcester rat iodine increases the incidence of lymphocytic thyroiditis and the levels of serum thyroglobulin antibodies, but leads only to hypothyroidism, when the thyroid reserve is reduced by hemithyroidectomy (1, 2). After iodine ingestion, the thyroglobulin becomes highly iodinated with an increased immunogenicity leading to a striking increase in levels of antibodies (34).

Human studies

After iodide ingestion the content of iodide increases in the thyroid gland. After oxidation, organabsorption and coupling to iodothyronines, the thyroid hormones are synthesized. However, acute iodide in excess inhibits these processes, which has been called the Wolff-Chaikoff effect (35). The inhibitory effect is probably partially overcome by an increase in TSH secretion. This compensatory TSH response may prevent hypothyroidism in normal subjects during long-term administration of iodide. After chronic iodide in excess the hormone formation resumes normality, called the escape or adaptation phenomenon.

It is well known that excess iodine in man can precipitate hypothyroidism in many patients with chronic LT (Hashimoto's thyroiditis). Radioactive iodine turnover is increased with a depletion of thyroidal iodine stores. It has been postulated that iodine-induced hypothyroidism in these patients is due to a combination of diminished thyroid reserve due to follicular destruction and a mild defect in the organabsorption of iodine to the gland. In contrast to the chronic variant of autoimmune LT, the radioactive iodine uptake is suppressed in transient LT. The normal serum iodide in these cases indicates that the disease is not due to

iodine excess. The urinary iodine is elevated in the hyperthyroid phase and fell on recovery suggesting that thyroid iodine is released during the destruction-induced thyrotoxic phase, while the low iodine excretion in the subsequent hypothyroid phase may reflect compensatory thyroidal iodine conservation (22). Extremely low iodine uptake, low thyroidal iodine clearance, and low conversion rate support the concept that iodine trapping and hormone synthesis are temporarily depressed in transient LT. Measurement of thyroidal iodine content has shown a decrease, which may last several years (33).

Postpartum thyroiditis

In pregnancy iodine turnover is increased secondarily to a higher glomerular filtration rate and renal iodine clearance. This causes a decrease in the proportion of iodine accumulated by the thyroid gland and may induce relative iodine deficiency leading to goitre development. Accordingly, it has been found that thyroid volume, by ultrasonic determination, increases 30 % during pregnancy, indicating a goitrogen effect of pregnancy, which could be explained by iodine deficiency (31). The formation of goiter during pregnancy has been disputed, and especially in North America development of goiter is uncommon. As this area is iodine sufficient, goitre development would not be expected. This geographical variation further suggests an influence of iodine.

During pregnancy there is an immunological suppression with an immunological rebound phenomenon during the postpartum period. In some women a transient LT develops during this period, called postpartum LT (PPT). Whether iodine plays a primary role in the immunological events underlying LT occurring postpartum is debatable. The incidence in Japan with high dietary iodide intake (3) is nearly the same as in Sweden with a possible borderline iodine deficiency (20), while the high incidence in England (15) can be due to high prevalence of thyroid autoantibodies (Table 1). However, it has been proposed that a high thyroid iodine content at the time of the initial

immunological attack may lead to more pronounced destruction and thereby thyrotoxic phase (22).

Thyroid antibodies

The increase in antibodies during the immunologic rebound period may be the triggering factor in susceptible individuals, contributing to the high incidence after delivery. This increase is confined to thyroid microsomal antibodies (MAb), whereas other IgG antibodies mostly remain unchanged postpartum (23). There is a close association between MAb level in the individual woman and the incidence and degree of hypothyroidism (24). Moreover, pregnancy constitutes a considerable risk for development of Graves' disease within 1 year after delivery, suggesting that the immune modulatory events following pregnancy in general are important for the development of autoimmune thyroid disease (24). Whether autoantibodies cause or are a result of PPT is unresolved. However, the incidence of PPT correlates with the incidence of antibodies, suggesting that the autoantibodies are primary for development of PPT (Table 1).

Table 1

Number of women screened for presence of microsomal thyroid autoantibodies (MAb) in pregnancy and the relation to occurrence of postpartum thyroiditis in reports published

	No. screened	No. affected	Pos. MAb	Affected women
Amino et al. (3)	507	28 (5.5)	28/479 (5.8)	25/28 (89)
Jansson et al. (20)	406	30 (6.5)	30/430 (7)	23/30 (77)
Freeman et al. (14)	212	7 (3.3)	6/212 (2.8)	2/7 (28)
Nikolai et al. (29)	238	16 (6.7)	27/23 (11.3)	15/16 (94)
Fung et al. (15)	232	49 (21)	117/901 (13)	37/49 (76)

Figures in brackets are % of total number screened.

Genetic aspects

A genetic predisposition has been postulated for development of the different variants of LT. It has been suggested that susceptibility to development of organ-specific autoimmunity is linked to certain HLA-D/DR alleles, and it has been suggested that they all arise from a genetic predisposition in combination with an adverse reaction to iodine. As the HLA system might be important for control of the events responsible for antibody formation, the relationship between HLA alleles and pattern of autoantibodies in autoimmune thyroiditis is of interest. In PPT Farid & Bear (12) found that DR3 was confined to those appearing with thyrotoxicosis and DR4 to those with hypothyroidism, while Jansson et al. (22) found that genes coding for the DR4 antigen may have a regulatory influence on MAb production. Table 2 suggests a HLA-D restriction and genetic specificity of the proliferative response to the relevant antigens, and in analogy to animal studies there might be genetically determined low- and high-responders with respect to organ-specific autoantibodies.

Lymphocyte function

That local autoantibody production plays a primary pathogenic role in the development of

Table 2

Relation between the HLA-antigen and thyroid autoantibodies in the different variants of autoimmune thyroiditis. The thyroid stimulating antibodies (TSAb), TSH receptor binding inhibiting immunoglobulins (TBII) and growth stimulating antibodies (TGI) are confined to thyrotoxicosis, while thyroglobulin antibodies (TgAb) and thyroid microsomal antibodies (MAb) are confined to hypothyroidism

	HLA-antigen	Autoantibodies
Graves' disease	B8 D/DR3	TSAb, TBII, TGI
Hashimoto's thyroiditis	D/DR5	TgAb, MAb, TGI TBII
Atrophic thyroiditis	B8 D/DR3	TgAb, MAb
Silent thyroiditis	DR3	TgAb/MAb
Postpartum thyroiditis	DR3, DR4, DR5	MAb

PPT is shown in studies of the phenotypic distribution of thyroid infiltrating lymphocytes in LT. Jansson et al. (21) found in PPT increased helper/suppressor T cell ratio and increased B cells in both the thyrotoxic and hypothyroid phase and only a small number of infiltrating T lymphocytes with the cytotoxic phenotype. However, recent functional studies have shown that a considerable proportion of the thyroid infiltrating T cells *in vivo* are activated suppressor cytolytic T cells with NK activity (9). Further, the predominant HLA-DR positive T cell seems to be the suppressor T cell, and the suppressor T cells are either cytotoxic T cells or precursors of cytotoxic cells (7). These findings have been further extended by cloning technique. The cloned T cell lines derived from patients with chronic LT were cytotoxic (8). Moreover, these cells produce large amounts of IFN- γ , release IL-2 upon mitogen stimulation, and display cytolytic activity (27). Finally, a relationship between IFN- γ and NK activity in T cell clones has been demonstrated (11). As IFN- γ induces MHC class II antigens on thyrocytes and induces IL-1 production by antigen-presenting cells, a regulatory role for NK and NK-like cells in antibody production has been postulated (10). The MHC class II antigen expression of human thyroid cells is sensitive to low levels of lymphokines (30), and the intrathyroidal T cell population may serve as a source of lymphokines. Further, it has been shown that IL-1 β suppresses the thyroid cells (25). The secretion of thyroglobulin and cAMP is suppressed even by low doses of recombinant IL-1 β , and formation of follicles and glycogen accumulation in response to TSH is suppressed. These effects are augmented by IFN- γ (26). Moreover, rIFN- γ can probably induce LT in susceptible animals without presence of thyroglobulin antibodies (32). These data therefore strongly suggest that cytokines and cytolytic activity are important factors in the pathogenesis of PPT.

Experimental studies

Knowledge of the basal effects of iodide has been obtained using thyroid membranes, slices

and isolated thyroid follicle cells. Both *in vivo* and *in vitro* studies have shown that iodine inhibits the stimulation of thyroid adenylate cyclase activity by TSH and other cAMP stimulators. This effect is dependent on iodide organabsorption. Iodine also inhibits the glucose transport system by reducing the number of glucose carriers in the plasma membrane (13) as well as thyroidal iodide transport and hormone synthesis and secretion (6). On the other hand, iodide stimulates cell cycle-related events in thyroid cells as it elevates *c-myc* mRNA levels and stimulates ^3H thymidine incorporation and mitotic activity in the absence of TSH or other growth factors (19).

Lithium does, to some extent, have a similar effect on the thyroid gland as iodide. Although lithium does not have any effect on the extent of thyroiditis or induce anti-Tg antibody production in normal rats (17), lithium elicits many effects on the immune function which have been mainly attributed to the effect on the cAMP-dependent events. Among these are induction of cytokine synthesis, and stimulation of suppressor T cells, and it is possible that lithium acts as a nonspecific cytotoxic agent. The effect of iodide on the lymphocytic infiltrating cells in the thyroid gland has not yet been studied. However, iodide accumulates in the thyroid gland and exerts its effect specifically on the thyroid cell, but iodide may resemble lithium and affect the local immune competent cells. Iodide may thus induce cytokine synthesis and stimulate the suppressor T cell and thereby lead to cytotoxicity which triggers the autoreactive attack.

Conclusion

In conclusion, there is no evidence of iodine-induced cytotoxicity in PPT. However, high urinary iodine excretion in the thyrotoxic phase indicates cell destruction. Furthermore, iodide can induce LT in susceptible subjects, and there exists a genetic predisposition in PPT and relationship with MAb. Recent studies in LT have shown that cytokine and cytolytic activity seems to be important in the autoimmune process. In analogy with a similar agent, lithium, it

is therefore proposed that iodide acts on the intrathyroidal immune competent cells leading to cytokine synthesis and stimulation of suppressor T cells with cytolytic activity.

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