High prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome

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Abstract

Objective: To investigate the prevalence of autoimmune thyroiditis (AIT) in patients with polycystic ovary syndrome (PCOS).

Design: Over a period of 30 months, 175 patients with PCOS were recruited to a prospective multicenter study to evaluate thyroid function and morphology; 168 age-matched women without PCOS were studied as a control group.

Methods: PCOS was defined as a- or oligomenorrhea, hyperandrogenism and exclusion of other disturbances of estrogen or androgen synthesis. All laboratory parameters were determined with automated immunoassays. Thyroid morphology was assessed by ultrasound.

Results: PCOS patients were characterized by an increased LH/FSH ratio, low progesterone, elevated testosterone and a high prevalence of hirsutism (PCOS 83%, control 3%; mean hirsutism score 12 ± 5 and 3 ± 2 respectively), but no differences in estrogen levels were found. Thyroid function and thyroid-specific antibody tests revealed elevated thyroperoxidase (TPO) or thyroglobulin (TG) antibodies in 14 of 168 controls (8.3%), and in 47 of 175 patients with PCOS (26.9%; P, 0.001). On thyroid ultrasound, 42.3% of PCOS patients, but only 6.5% of the controls (P, 0.001) had a hypoechoic tissue typical of AIT; while thyroid hormone levels were normal in all subjects, PCOS patients had a higher mean TSH level (P, 0.001) and a higher incidence of TSH levels above the upper limit of normal (PCOS 10.9%, controls 1.8%; P, 0.001).

Conclusion: This prospective study demonstrates a threefold higher prevalence of AIT in patients with PCOS, correlated in part with an increased estrogen-to-progesterone ratio and characterized by early manifestation of the disease.

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Introduction

Chronic autoimmune thyroiditis (AIT, Hashimoto’s thyroiditis) is a common disease and the most prevalent cause of hypothyroidism in areas with sufficient iodine intake. Its two major forms, goitrous and atrophic AIT, are both characterized by gradual thyroid dysfunction. Nearly all patients have high serum levels of antibodies against one or more thyroid antigens, lymphocytic infiltration of the thyroid, and a typical hypoechoic pattern on thyroid ultrasound (1).

The cause of AIT is thought to be a combination of genetic susceptibility and environmental factors. AIT clusters in families, either alone or in combination with Graves’ disease, and these two autoimmune thyroid disorders may evolve into one another. Genetic susceptibility to AIT is also obvious from its increased frequency in patients with Down’s and Turner’s syndrome (2). The prevalence of AIT has been correlated with the HLA DR3 and DR5 genes (3) and certain alleles of CTLA-4, a T-cell surface molecule involved in T-cell activation (4). However, the development of AIT cannot be predicted from susceptibility genes alone.

Environmental factors contributing to the development of AIT are viral infections, stress and sex steroid hormones, of which the latter appear to be the most important (5). Compared with men, the five- to tenfold higher prevalence of AIT in women has been correlated to their high estrogen levels, which are implicated as enhancers of humoral immunity, while androgens and progesterone are thought to be protective as natural immune suppressors (6). The striking preponderance of autoimmune diseases has also been shown in several animal models, in which estrogens promote, whereas androgens abrogate, B-cell-mediated autoimmune diseases (7, 8). Autoimmune responses are also controlled by complex interactions of cytokines, exemplified by the predisposition to autoimmunity...
Anovulation was ascertained by low progesterone levels (no cycles in the past 6 months) or oligomenorrhea (cycles lasting longer than 35 days), clinical or laboratory hyperandrogenism and the absence of any adrenal disorders, such as rheumatoid arthritis, has been correlated with a high estrogen-to-androgen ratio (11).

To date, no systematic analysis of thyroid function in women with polycystic ovary syndrome (PCOS) has been undertaken. PCOS is the most common endocrine disorder in women of reproductive age, affecting about 5 to 10% of all premenopausal women (12, 13). As patients with PCOS are oligo- or anovulatory and deficient in progesterone secretion, they usually have an increased estrogen-to-progesterone ratio. Thus, we hypothesized that they are more susceptible to the development of AIT. We now present a multicenter prospective study confirming an increased prevalence of AIT in PCOS.

Subjects and methods

Study participants

All consecutive patients with hypertrichosis and a- or oligomenorrhea visiting the outpatient clinics of the Departments of Medicine of the Ludwig-Maximilians-University in Munich or of the University of Essen between January 2000 and July 2002 were considered for our study. PCOS was defined as chronic amenorrhea (no cycles in the past 6 months) or oligomenorrhea (cycles lasting longer than 35 days), clinical or laboratory hyperandrogenism and the absence of any adrenal or pituitary disorder. Clinical hyperandrogenism was defined as hypertrichosis (Ferriman–Gallway score > 7) (14) and/or acne (15), and/or androgenic pattern alopecia (16). Biochemical hyperandrogenemia was defined by elevated testosterone (> 2.0 nmol/l). Anovulation was ascertained by low progesterone (< 1.5 μg/l). A luteinizing hormone (LH)-to-follicle-stimulating hormone (FSH) ratio above 2 was considered elevated. In those patients who were not virgins, transvaginal pelvic ultrasound was performed by gynecologists and the presence of cystic ovaries established according to the method of Fox and Hull (17).

Other reasons for hyperandrogenism were excluded by adrenocorticotropin-stimulated 17-OH progesterone and, if hypercortisolism was clinically suspected, by dexamethasone suppression test and/or 24-h urine cortisol excretion.

For age-matched controls, female patients visiting our outpatient clinics because of problems not related to PCOS with normal menses and not seeking advice for thyroid dysfunction were investigated for AIT.

Measurement of laboratory parameters

Free thyroid hormone, thyrotropin (TSH), LH, FSH, insulin, estradiol, progesterone and testosterone were measured by an automated commercial luminescence immunoenzyme assay system (ACS 180, Bayer AG, Ludwigshafen, Germany). Blood glucose was measured by an automated commercial hexokinase method on a Dimension RXL (Dade-Behring, Schwalbach, Germany). The sensitivity of the assays and the intra- and interassay coefficients of variation (5% and 8% respectively) were controlled by routine external quality control surveys (German Association of Clinical Chemistry). HOMA-insulin resistance was calculated as (fasting insulin (mU/l) · fasting glucose (mmol/l)/22.5) (18). Thyroperoxidase (TPO) and thyroglobulin (TG) antibodies were determined by commercial immunometric assays (Byk-Sangtec, Munich, Germany or Brahms, Berlin, Germany) and considered positive when above 100 U/ml. In 298 of the 343 samples (87%) antibodies were measured with both tests, and the correlation coefficient was r = 0.93 with a P value < 0.001.

Thyroid ultrasound

Ultrasound of the thyroid was performed using a 7.5 MHz transducer with Duplex sonography (Munich: Sonoline Elegra, Siemens, Erlangen, Germany; Essen: Quadroline 505, General Electric, Frankfurt, Germany). The thyroid was considered hypoechogenic when its signal was equal or below the echogenicity of the surrounding neck muscles.

Statistical analysis

Differences of findings between PCOS patients and controls were evaluated with Student’s t-test and chi-square test.

Results

A total of 316 patients with hypertrichosis and oligomenorrhea were screened. PCOS was ascertained in 175 patients, all of which gave informed consent and agreed to participate in the study. The 141 excluded patients did not fulfill the PCOS criteria but instead suffered from idiopathic hirsutism (n = 122) or from heterozygous adenogenital syndrome (n = 19). The characteristics of both PCOS patients and controls are shown in Table 1. In all PCOS patients, by definition, chronic a- or oligomenorrhea was present. Hypertrichosis (Ferriman–Gallway score > 7) was present in 159 (91%) patients. Laboratory parameters characteristic for PCOS were significantly different in patients and controls: testosterone was above 2.0 nmol/l in 121 patients (69%); the LH-to-FSH-ratio was elevated above 2.0 in 138 (79%); progesterone was below...
1.5 μg/l in 166 (95%); HOMA-insulin resistance was above 2.0 mU·mmol/l in all patients. Accordingly, mean levels of these parameters were also significantly different (Fig. 1). However, estradiol levels were not different in PCOS patients and controls. Interestingly, although the difference was small, TSH levels were significantly elevated in PCOS (Table 1, Fig. 1). Polycystic ovaries (PCO) were documented in 97 (68%) of 143 patients. In 32 patients, transvaginal ultrasound could not be performed because they were virgins or refused the examination.

From 175 patients, 47 (26.9%) had elevated TG and/or TPO antibodies, but only 14 (8.3%) of the controls exhibited this (Fig. 2). An even higher percentage of PCOS patients (42.3%; controls 6.5%) had a hypoechoic ultrasound pattern, compatible with AIT (1). From these, 8 PCOS patients had an enlarged thyroid with a volume >18 ml (the upper limit of normal thyroid size in adult women). The prevalence of a small thyroid (<8 ml) was not significantly different with 13.1% in PCOS and 7.1% in controls. Twenty-two (12.8%) of PCOS patients were under L-thyroxine replacement because of previously detected AIT with overt or subclinical hypothyroidism, while three (1.8%) otherwise healthy controls were under L-thyroxine replacement to prevent goiter growth without actually having been previously evaluated by thyroid ultrasound or thyroid function testing. Another two PCOS patients but no controls had been thyroidectomized because of Graves’ diseases. One PCOS patient suffered from insulin-dependent diabetes in addition to AIT, indicative of polyglandular autoimmune disease. Taken together, 36 PCOS patients had both elevated thyroid antibodies and a hypoechoic ultrasound

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**Table 1** Characteristics of healthy controls and PCOS patients. Values are means±s.d. (range).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n = 168)</th>
<th>PCOS (n = 175)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.8±7.4 (15–52)</td>
<td>28.4±6.5 (16–47)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.5±7.1 (17–51)</td>
<td>30.0±7.9 (18–58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LH (U/l)¹</td>
<td>3.8±3.1 (0.5–15.0)</td>
<td>12.3±8.9 (0.4–6.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FSH (U/l)¹</td>
<td>4.1±2.5 (0.6–21.5)</td>
<td>4.9±1.8 (0.6–11.5)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LH-to-FSH ratio¹</td>
<td>1.0±0.5 (0.2–2.9)</td>
<td>2.5±1.8 (0.2–17.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Testosterone (nmol/l)¹</td>
<td>1.0±0.5 (0.3–2.1)</td>
<td>2.6±1.2 (0.4–9.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estradiol (ng/dl)¹</td>
<td>6.7±5.9 (2.5–33.3)</td>
<td>6.3±4.4 (2.5–29.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Progesterone (μg/l)¹</td>
<td>8.5±4.9 (0.5–16.1)</td>
<td>1.0±0.8 (0.4–4.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR (mU·mmol/l)</td>
<td>2.4±1.3 (1.0–7.1)</td>
<td>4.4±1.1 (0.5–19.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thyroid volume (ml)</td>
<td>12.4±4.4 (5–26)</td>
<td>14.8±11.2 (4–125)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypoechoic US (%)</td>
<td>6.5</td>
<td>42.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TSH (mU/l)</td>
<td>1.4±0.6 (0.5–3.4)</td>
<td>2.0±1.0 (0.4–6.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Free thyroxine (pmol/l)</td>
<td>14.9±2.4 (10–23)</td>
<td>14.1±2.5 (9–24)</td>
<td>NS</td>
</tr>
<tr>
<td>TPO antibodies (U/l)</td>
<td>10±18 (0–88)</td>
<td>123±328 (0–2860)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG antibodies (U/l)</td>
<td>4±17 (0–123)</td>
<td>113±312 (0–2770)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI, body mass index; HOMA-IR, HOMA-insulin resistance; US, ultrasound; NS, not significant.

¹ Subjects on contraceptives or antiandrogens were excluded.

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**Figure 1** Laboratory values in PCOS patients (shaded bars) and healthy controls (open bars). Parameters characteristic for PCOS (testosterone, nmol/l; LH/FSH ratio; progesterone, μg/l; HOMA-insulin resistance (HOMA-IR), mU·mmol/l; all P < 0.001) were found to be significantly different in patients and controls, while no difference in estradiol levels (ng/dl) was found. TSH levels (mU/l) were significantly elevated in PCOS patients (P < 0.001).

**Figure 2** Prevalence of thyroid-specific signs and symptoms in PCOS patients and controls. In PCOS patients, positive thyroid antibodies (TPO/TG Ab +), a hypoechoic ultrasound (US) pattern and hypothyroidism requiring thyroid hormone replacement (T4) were more prevalent than in controls (P < 0.001), while no significant difference in thyroid volume was found.

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pattern, indicating manifest AIT. These patients included all subjects with a previous diagnosis of AIT, all patients with a small thyroid and all patients on L-thyroxine medication. In contrast, only 11 controls had both elevated thyroid antibodies and a hypoechoic ultrasound, amounting to a more than threefold higher incidence of manifest AIT in young PCOS patients compared with the age-matched controls.

While the diagnosis of PCOS coincided with a higher prevalence and elevated levels of thyroid-specific antibodies, their presence or absence did not have a major influence on the characteristics of the PCOS patients (Table 2). The antibody-positive patients were slightly older but had the same degree of obesity as the controls. As expected, a higher proportion of antibody-positive PCOS patients had a hypoechoic ultrasound pattern, but thyroid volume, TSH levels and free thyroxine (T4) levels were not different. While LH and FSH levels alone were not different, the LH-to-FSH-ratio was higher in antibody-positive patients. Furthermore, no significant differences were found in testosterone, estradiol, progesterone and HOMA-insulin resistance (Table 2).

Discussion

Family studies have indicated a genetic susceptibility to PCOS. Polycystic ovaries and hyperandrogenemia are present in approximately 50% of sisters of affected women. Increased androgen secretion and insulin resistance persist in cultured theca cells and skin fibroblasts respectively from women with PCOS; this finding suggests that these are intrinsic, presumably genetic, defects. Insulin resistance and elevated low-density lipoprotein levels also cluster in sisters of women with PCOS, consistent with genetic traits. Moreover, brothers of women with PCOS have insulin resistance and elevated dehydroepiandrosterone sulfate levels, which supports a genetic basis for these findings. Family-based studies of linkage and association have implicated several genes in the pathogenesis of PCOS (19, 20). The high prevalence of affected individuals and the wide range of related phenotypes can be explained by the interaction of a small number of key genes responsible for most of the endocrine and metabolic symptoms, with environmental risk factors (either during prenatal or postnatal life) converting an occult PCOS into a clinically manifest syndrome (20, 21).

Table 2 Influence of thyroid antibody status on characteristics of PCOS patients. Values are means±s.d. (range).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Antibody negative (n=128)</th>
<th>Antibody positive (n=47)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.5±6.3 (16–47)</td>
<td>30.9±6.4 (16–43)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.7±8.1 (18–58)</td>
<td>31.0±7.1 (20–53)</td>
<td>NS</td>
</tr>
<tr>
<td>Thyroid volume (ml)</td>
<td>14.3±6.4 (5–45)</td>
<td>15.9±17.4 (4–125)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypoechoic US (%)</td>
<td>32.3</td>
<td>63.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TSH (mU/l)</td>
<td>2.0±1.6 (0.4–6.2)</td>
<td>21.1±1.0 (0.8–3.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Free thyroxine (pmol/l)</td>
<td>14.1±2.5 (9–24)</td>
<td>14.0±2.1 (9–21)</td>
<td>NS</td>
</tr>
<tr>
<td>LH (U/l)²</td>
<td>11.9±8.1 (0.4–50.7)</td>
<td>13.3±10.5 (3.1–69)</td>
<td>NS</td>
</tr>
<tr>
<td>FSH (U/l)²</td>
<td>5.0±1.8 (0.6–11.5)</td>
<td>4.6±1.6 (1.6–9.0)</td>
<td>NS</td>
</tr>
<tr>
<td>LH-to-FSH ratio³</td>
<td>2.3±1.2 (0.7–7.4)</td>
<td>3.1±2.7 (0.7–17.3)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Testosterone (ng/dl)³</td>
<td>2.7±1.3 (0.4–9.0)</td>
<td>2.5±1.0 (0.7–4.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Estradiol (ng/dl)³</td>
<td>6.4±4.5 (2.5–29.0)</td>
<td>6.0±3.9 (2.6–20.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Progesterone (µg/l)³</td>
<td>0.9±0.7 (0.4–4.0)</td>
<td>1.0±0.9 (0.4–4.6)</td>
<td>NS</td>
</tr>
<tr>
<td>HOMA-IR (mU·mmol/l)³</td>
<td>4.4±3.8 (0.5–17.3)</td>
<td>5.8±5.3 (0.6–19.6)</td>
<td>NS</td>
</tr>
</tbody>
</table>

BMI, body mass index; HOMA-IR, HOMA-insulin resistance; US, ultrasound; NS, not significant.

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in 81 of 547 subjects (14.8%) aged 27 to 58 years living in an urban area with relatively low iodine intake (28), thus higher than the prevalence of 6.5% in our control sample but still well below the 42.3% of hypoechoic thyroid ultrasound pattern in our PCOS sample. Anti-TPO antibodies were positive in 72 subjects of this Brazilian study (13.2%), but again, the sample was, on average, 20 years older than our controls.

While there has been no previous systematic analysis of thyroid function in PCOS, several case reports have reported data supportive of our findings. In a Chinese population, an exaggerated TSH and a blunted TRH response during thyrotropin-releasing hormone (TRH) testing, indicative of latent hypothyroidism, were reported in a group of PCOS patients with an LH-to-FSH ratio > 3, but not in a group of PCOS patients with a ratio < 3 (29). Earlier reports from Italy (n = 5) (30) and Russia (n = 25) (31) have also reported elevated basal or TRH-induced TSH levels in PCOS patients, while similar TSH levels as the control group were reported in a study from the UK (32) and in a study from Turkey (33). Acanthosis nigricans, a finding common in patients with insulin resistance and also in PCOS, has been reported to have a positive correlation with hypothyroidism (34). Other cases of thyroid disease or AIT in patients with PCOS have been reported from Italy (35), Japan (36) and India (37).

The reason for the high incidence of AIT in PCOS is open to speculation. It might be assumed that, as both susceptibility to AIT (38) as well as PCOS (19, 39) have a genetic background, and both are clustered in families, there is some common genetic defect. Both disorders seem to have an oligo-genetic background. AIT is supposed to be related to variants in the HLA and CTLA-4 genes. In contrast, PCOS is related to genetic predispositions for insulin resistance (40), especially defects in insulin signaling pathways (41), genetic variants in LH (42), follistatin and to CYP11A, a gene coding for P450 cholesterol side chain cleavage (43). To date, a common genetic background has not been found.

However, other autoimmune disorders are also more common in PCOS and related disorders. A high prevalence of autoimmune reactions has been reported in 108 Estonian women with reproductive failure including PCO, PCOS (n = 3), endometriosis and unexplained infertility. One or more common autoantibodies were found in 40.7% of patients’ sera and 14.8% of control sera, of which anti-nuclear antibodies (ANA) and smooth-muscle antibodies (SMA) were most frequently detected, while TPO antibodies were only slightly more prevalent (44). Antiovarian antibodies of all isotypes (immunoglobulin (Ig) G, IgA, IgM) were significantly higher in PCOS patients than in age-matched controls and almost as high as in patients with primary ovarian failure in a study by Fenichel et al. (45). An increased frequency of abnormal immunologic tests was also found among Caucasian women experiencing reproductive failure. Most common were anti-phospholipid antibodies (APA, 40%), while 9% of the patients had either TG antibodies or TPO antibodies (46). In a study from South Africa, anti-ovarian autoantibodies localized to the granulosa cells were detected in four of eight PCOS patients. In analogy to thyroid and adrenalin endocrinopathies characterized by hypersecretion of hormones, the authors speculated on a possible pathogenetic mechanism of PCOS involving stimulatory antibodies (47). PCOS patients were also reported to have an increased prevalence of lupus erythematosus (48). With regard to thyroid function and the prevalence of thyroid antibodies in PCOS, these studies suffer from their small sample size.

It may be speculated that the imbalance of normal to high estrogens and low progesterone levels, the so-called ‘unopposed estrogens’ thought to be responsible for the apparent increase in prevalence of AIT during the menopause (6), also account for the higher prevalence of AIT in PCOS. Estrogens are known to increase interleukin (IL)-4 expression in TH2 cells. IL-1 in monocytes, IL-6 in T-cells and interferon gamma in TH1 cells. During normal menstrual cycles in young women, IL-6 is elevated in the follicular phase and decreased in the luteal phase, and inversely correlated to progesterone levels (10). Hence, the immune stimulatory activity of estrogens seems to be counteracted by progesterone. As patients with PCOS have no or nearly no progesterone because of anovulatory cycles, the immune system in these patients seems to be overstimulated, which may propagate autoimmune disease. Autoimmune oophoritis (47, 49) and a high prevalence of antiovarian antibodies (45) have already been shown in patients with PCOS. In our patients, low progesterone levels would appear to be the likely culprit, as the estradiol levels were not different in PCOS and controls. Also, measures aimed to re-establish ovulatory cycles would be likely to prevent the development of AIT in PCOS patients. Although androgens are known to protect from autoimmune disease, the mildly elevated androgens in PCOS (compared with the much higher male androgen levels) do not appear to protect PCOS patients from the development of AIT.

On the other hand, the presence of thyroid antibodies in euthyroid women has been reported to be associated with an adverse outcome in an in-vitro fertilization–embryo transfer programme (50). Furthermore, hypothyroidism worsens PCOS by further decreasing sex hormone binding globulin levels, increasing the conversion of androstenedione to testosterone and aromatization to estradiol and reducing the metabolic clearance rates of androstenedione and estrone. Since thyroid hormones are involved in the gonadotropin-induced estradiol and progesterone secretion by human granulosa cells, hypothyroidism will interfere with ovarian function and fertility (51). Animal studies
and case reports of PCOS patients with myxoedema also suggest a link between hypothyroidism and the spontaneously occurring ovarian hyper-stimulation syndrome (52) and ovarian cyst formation (53). Correction of hypothyroidism, when present, would certainly form an important aspect in the management of PCOS.

In conclusion, this prospective study demonstrates a threefold higher prevalence of AIT in PCOS. Our data suggest that all patients with PCOS should be screened for thyroid function and thyroid-specific autoantibodies even without evidence of overt thyroid dysfunction, as it is known that patients with TPO and TG autoantibodies are likely to develop thyroid dysfunction later in life.

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