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Are Autoimmune Thyroid Dysfunction and Depression Related?*

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ABSTRACT

The objective of this study was to examine the relationship between autoimmune thyroid disease and depression in perimenopausal women. Thyroid function [TSH, free T_4, and thyroid peroxidase antibodies (TPO-Ab)] and depression (using the Edinburgh Depression Scale) were assessed cross-sectionally together with other determinants of depression. The subjects were 583 randomly selected perimenopausal women (aged 47–54 yr) from a community cohort of 6846 women. The main outcome measures were the occurrence of thyroid dysfunction (abnormal free T_4 and/or TSH or elevated levels of TPO-Ab) and the concomitant presence of depression according to the Edinburgh Depression Scale. Neither biochemical thyroid dysfunction nor menopausal status was related to depression. Apart from several psycho-social determinants (the occurrence of a major life event, a previous episode of depression, or financial problems), an elevated level of TPO-Ab (≥100 U/mL) was significantly associated with depression (odds ratio, 3.0, 95% confidence interval, 1.3–6.8). We conclude that women with elevated TPO-Ab levels are especially vulnerable to depression, whereas postmenopausal status does not increase the risk of depression. (*J Clin Endocrinol Metab* **83:** 3194–3197, 1998)

SEVERAL clinical signs and symptoms of thyroid dysfunction are similar to depression, and depression may be provoked by underlying overt hypothyroidism (1–3). T_4 replacement increases central 5-hydroxytryptamine activity and reduces depressive symptoms (4). Depressed in-patients have an increased incidence of (sub)clinical thyroid dysfunction, and women suffering from postpartum depression have a higher prevalence rate of elevated thyroid peroxidase antibody (TPO-Ab) levels, an important marker of autoimmune thyroid disease (5–8). Moreover, the occurrence of stressful life events (an important determinant of depression) is a risk factor for the development of thyroid dysfunction, particularly Graves' disease (9, 10). Most, if not all, of these studies have reported a correlation while only (and often retrospectively) investigating an association at an univariate level. However, the origin of depression is multifactorial, which means that when looking at the effect of one variable on depression, the influence of other determinants of depression should simultaneously be taken into account (11). One explanation of the suggested relationship between stress and thyroid disease could be that stress causes depression, which, in turn, causes or exacerbates autoimmune thyroid disease.

We have investigated cross-sectionally the relationship between thyroid dysfunction and depression in a community cohort of perimenopausal women in whom, apart from thyroid function, several determinants related to depression were assessed.

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Subjects and Methods

Subjects and sample size

Between September 1994 and September 1995, all women between 47–54 yr of age (n = 8503) living in the city of Eindhoven in the southeast Netherlands were invited for screening of bone mineral density (BMD). Screening occurred at the Diagnostic Center (Eindhoven, The Netherlands) and at the St. Joseph Hospital (Veldhoven, The Netherlands), a suburb of Eindhoven. During the visit for BMD screening, detailed menstrual, gynecological, and general medical histories as well as the use of medication were determined by paramedical assistants. Blood samples were collected and stored. The women were asked to complete several questionnaires at home and to return these within 1 week of screening. For methodological reasons (use of self-rating scales, racial aspects related to osteoporosis), only Dutch Caucasian women [n = 8098, of whom 6648 (78%) participated in the study] were included in the analysis; 6116 (92%) of these women returned the questionnaires, of whom 4975 (81%) correctly completed the self-rating scales. A 1 in 2 random sample was selected for the assessment of thyroid status (n = 2584). Assuming a prevalence of depression of 25% and of elevated TPO-Ab titers of 10% (type I error (α) of 0.05 and a power of 0.80), a minimum of 548 women would be needed to detect a relative risk of at least 2.0 for TPO-Ab in relation to depression. Therefore, from these 2584 women, a 1 in 4 random sample was drawn, resulting in 583 women in whom thyroid status, depression, and determinants of depression were assessed.

As well as the subject's own informed consent, permission for the study was obtained from the medical ethics committee at the St. Joseph Hospital (Veldhoven, The Netherlands).

TABLE 1. Characteristics of the samples of Dutch Caucasian perimenopausal women (47–54 yr)

	A	B	C
No. of women	4975	2584	583
Mean age (yr) of women (SD)	50.0 (2.1)	50.2 (1.9)	49.9 (2.2)
Educational level [no. (%)]			
Primary school	648 (13)	311 (12)	58 (10)
Secondary school	1890 (38)	904 (35)	216 (37)
Low college degree	1840 (37)	1111 (43)	239 (41)
High college degree	498 (10)	206 (8)	52 (9)
Academic degree	99 (2)	52 (2)	17 (3)
Gynecological status [no. (%)]			
Women on hormone replacement therapy (HRT)	1194 (24)	568 (22)	151 (26)
Menstruation pattern in women not receiving HRT			
Premenopausal	646 (13)	362 (14)	70 (12)
Perimenopausal	1492 (30)	723 (28)	181 (31)
Postmenopausal	1044 (21)	594 (23)	128 (22)
Women with hysterectomy	945 (19)	439 (17)	116 (20)
Women with oophorectomy	398 (8)	155 (6)	41 (7)
Parity			
No pregnancy	547 (11)	232 (9)	70 (12)
Primipara	796 (16)	490 (19)	99 (17)
Multipara	3632 (73)	1921 (74)	414 (71)
Lifestyle habits [no. (%)]			
Currently smoking	1890 (38)	878 (34)	210 (36)
Regular alcohol intake	2537 (51)	1266 (49)	280 (48)
Thyroid parameters [no. (%)]			
Clinical hyperthyroidism		16 (0.6)	3 (0.5)
Clinical hypothyroidism		13 (0.5)	2 (0.4)
Subclinical hyperthyroidism		54 (2.1)	15 (2.5)
Subclinical hypothyroidism		98 (3.8)	23 (4)
TPO-Ab ≥100 U/mL		245 (9.5)	58 (10)
Euthyroidism on drug therapy		23 (0.9)	6 (1)
Previous treatment of hyperthyroidism		62 (2.4)	13 (2.2)
EDS scores (mean, SD)	7.3 (5.9)	7.1 (6.1)	7.2 (6.2)
Depression (≥12 on EDS)	1194 (24)	543 (21)	134 (23)

A, Characteristics of the women who completed all screening questionnaires (n = 4975); B, characteristics of randomly selected women in whom thyroid parameters were assessed (n = 2584); C, characteristics of the women in whom thyroid function and depression parameters were assessed (n = 583).

Measurements

Depression. Depression was assessed using the Edinburgh Depression Scale, originally called the Edinburgh Postnatal Depression Scale, which is a 10-item self-rating scale; the reliability, sensitivity, and specificity of this scale for detecting depression have been proven in postpartum women (12–14). Recently, the Edinburgh Postnatal Depression Scale has been validated for use in nonchild-bearing women and has shown accurate psychometric characteristics resulting in another nomenclature: the Edinburgh Depression Scale (EDS) (15). A score of 12 or higher on the EDS was defined as depression. Because this study was part of a larger longitudinal study program of depression in perimenopausal women, after screening, a subgroup of 320 women was subsequently visited at home, and a syndromal diagnosis of depression was made during an interview using the Research Diagnostic Criteria (16). Again, the EDS was completed and showed appropriate psychometric characteristics: a predictive value, sensitivity, and specificity for detecting (syndromal) depression of 71%, 68%, and 92%, respectively.

Thyroid function. Thyroid function was assessed by the measurement of free T_4 (fT_4; reference range, 8–26 pmol/L; Abbott, North Chicago, IL), TSH (reference range, 0.4–6 mU/L; Abbott), and TPO-Ab (Autozyme Tab, Cambridge Life Sciences, Cambridge, UK). The coefficients of variation for fT_4 were 6.8%, 8.2%, and 6.7% at concentrations of 6.4, 18, and 30 pmol/L, respectively; those for TSH were 9.8%, 4.8%, 3.9%, and 3.1% at concentrations of 0.06, 0.75, 6.8, and 30 Mu/L, respectively; and that for TPO-Ab was 9.6% at a concentration of 231 U/mL. Moreover, personal and family histories of (previous) thyroid dysfunction were assessed during the screening for BMD. Clinical thyroid dysfunction was defined by the presence of both abnormal TSH and fT_4 concentrations, whereas subclinical thyroid dysfunction was defined by abnormal TSH concentrations with normal fT_4 levels. A TPO-Ab level of 100 U/mL or higher was defined as positive.

Determinants of depression. The determinants of depression, assessed in the group of 583 women who completed the EDS and in whom thyroid function was evaluated, included educational level, previous history of depression in the woman herself or in her first degree relatives, life-style habits (current smoking and alcohol intake), marital state, working outside the home, financial problems, and the occurrence of a major life event (11). Data analysis refers to this cohort of 583 women.

Statistical analysis

Statistical analysis was performed using the Statistical Products and Service Solutions (SPSS, Evanston, IL). The relationship between thyroid dysfunction and depression was investigated by multiple logistic regression analysis, with a high score on the EDS (≥12) as the dependent variable.

Results

The characteristics of the women in the various cohorts are shown in Table 1. The demographic features, gynecological status, life-style habits, and thyroid parameters were equally distributed in the total cohort (n = 4975), in the cohort of women in whom thyroid function was assessed (n = 2584), and in the cohort of women (n = 583) in whom the questions being studied were analyzed.

According to the EDS (≥12), the prevalence of depression

was equally distributed in the three cohorts (24%, 21%, and 23%, respectively; Table 1). Subset analysis in pre-, peri-, and postmenopausal women did not reveal any difference in prevalence rates of TPO-Ab and depression.

Of the 583 women in whom both thyroid function and determinants of depression were assessed, 3 (0.5%) had clinical hyperthyroidism, 2 (0.4%) had clinical hypothyroidism, 15 (2.5%) had subclinical hyperthyroidism, 23 (4%) had subclinical hypothyroidism, and 58 (10%) had high TPO-Ab levels (≥100 U/mL). An additional 6 women (1%) were euthyroid due to thyroid hormone therapy, and 13 (2.2%) were euthyroid due to previous treatment for hyperthyroidism. Several independent thyroid-related and psycho-social variables were entered into a multiple logistic regression analysis, using a high score on the EDS (≥12) as the dependent variable (Table 2). The occurrence of financial problems, caring for parents, a previous episode of depression in the woman's life, the occurrence of a major life event, and an elevated concentration of TPO-Ab (≥100 U/mL) were all significantly and independently related to depression. Thyroid dysfunction (either clinical or subclinical) was not related to depression and neither was menopausal status.

Discussion

The characteristics of the various study groups are similar, indicating that the group of women studied is representative of the total community-based cohort of perimenopausal women. Most studies investigating the relationship between menopausal state and depression failed to use a standardized assessment of depression or to show evidence that the study group was representative of the general population of perimenopausal women (17). In the present study, neither the presence of perimenopausal complaints nor the menopausal status of the women was related to depression, which suggests that changes in hormone concentrations of estrogens and progesterone (as reflected by an irregular menstruation pattern) do not make a woman more susceptible to depressive symptoms (17). Postnatal women also failed to show a relationship between abrupt changes in estrogens and progestagens after child-bearing and the occurrence of depression (18).

TABLE 2. Multiple logistic regression analysis (n = 583), with depression (score ≥12 on the EDS) as the dependent variable

Variable	O.R.	95% CI
Psycho-social factors		
High educational level	1.9	0.5–5.9
Marital state	1.3	0.4–5.4
Previous episode of depression	4.8	2.3–6.9
Depression in family	3.1	0.8–7.8
Occurrence of major life event	2.1	1.2–4.6
Financial problems	3.3	1.8–6.2
Caring for parents	2.7	1.5–4.8
Working outside home	1.9	1.3–3.8
Gynecological state		
Regular menstruation pattern	1.4	0.5–6.2
Multiparity	1.7	0.6–4.2
Hot flushes	1.5	0.4–4.1
Sweating at night	1.3	0.6–4.2
Hormonal substitution	1.4	0.8–1.5
Uterus extirpation	1.6	0.7–2.1
Thyroid parameters		
Clinical hyperthyroidism	6.1	0.6–19.8
Clinical hypothyroidism	7.9	0.8–16.4
Subclinical hyperthyroidism	3.3	0.7–10.5
Subclinical hypothyroidism	2.9	0.9–8.9
TPO-Ab titer ≥100 U/mL	3.0	1.3–6.8

Recent epidemiological studies on the occurrence of depression in the general population revealed a 1-yr (period) prevalence of 7–11% (19, 20). In postnatal women, a (period) prevalence of 10–15% has been shown (18), and several studies of perimenopausal women have indicated a (period) prevalence in the community of 16–21% and even of 36% at perimenopausal clinic (19–21). Apparently, although our study did not show any correlation between perimenopausal status and depression, women of this age seem to be especially vulnerable to depression.

This is the first study to show that women with a high concentration of TPO-Ab are at risk for depression (odds ratio, 3.0; 95% confidence interval, 1.3–6.8), a relationship that still exists after adjustment for other (psycho-social) determinants of depression. There are several postpartum studies and studies of a general psychiatric population that also report a correlation between depression or a rapid cycling mood disorder and TPO-Ab status (although at an univariate level), whereas others failed to find a relationship (7, 8, 22, 23). Because there is general agreement that the origin of depression is multifactorial, possible biological explanations of depression should be studied together with the influence of other psychological aspects, such as educational level, socio-economic status, the occurrence of major life events, and a family history of depression (11).

Up to 10% of fertile women have elevated levels of TPO-Ab, and once an individual is TPO-Ab positive, he or she will tend to remain so for the rest of his/her life and will be at high risk of developing clinical thyroid dysfunction in the future (3, 24). Recommendations have been made for screening women during or after pregnancy to detect TPO-Ab-positive cases, who are at risk of developing thyroid dysfunction during pregnancy, postpartum, or later in life (25). This study would add another argument for screening for TPO-Ab during pregnancy, because of the significant association with later depression.

The cross-sectional design of our study does not resolve the problem of whether autoimmune thyroid dysfunction (as reflected by the presence of TPO-Ab) precedes depression or *vice versa*. The only way to address this would be to undertake a longitudinal study, during which subjects would be followed for a long period of time. Pregnant women would be an appropriate study population; 10% have elevated levels of TPO-Ab (and remain positive for the rest of their lives), and the prevalence of depression is high, with a lifelong cumulative incidence of depression of at least 20% (18–20).

We conclude that depression, although not related to menopausal status, has a high prevalence in perimenopausal women in the community. The psycho-social determinants of depression are no different from those found for depression in general. The presence of one biological stable marker (TPO-Ab) is associated with and may make women more vulnerable for depression.

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