Psychiatry and Clinical Neurosciences 2009; **63**: 305–313 doi:10.1111/j.1440-1819.2009.01938.x

Regular Article

Thyroid hormones affect recovery from depression during antidepressant treatment

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Aims: The aim of the present study was to evaluate whether thyroid hormonal changes during menopause may affect the development and the course of major depressive disorder.

Methods: Thirty-nine female patients ($n = 17$ in pre-menopause; $n = 22$ in post-menopause) with major depressive disorder based on Diagnostic Statistical Manual of Mental Disorders (4th edition) criteria and who were euthyroid and not on hormonal replacement therapy, participated in a prospective, 6-week, open-label naturalistic study. The Hamilton Depression Rating Scale-17 item, the Montgomery-Åsberg Depression Rating Scale, the Clinical Global Impression scale and the Cognitive Failure Questionnaire were administered at baseline, week 1, week 3, and week 6. Levels of thyroid stimulating hormone, total thyroxine and total triiodothyronine were collected at baseline visit.

Results: In the whole sample, particularly in pre-menopausal women, levels of thyroid stimulating hormone-potential markers of subclinical hypothyroidism were correlated with those of less severe but more resistant depressive form. Conversely, total thyroxine levels were correlated with a more severe depression, but high levels of this hormone favored the response to antidepressants. Overall, a diagnosis of subclinical hypothyroidism was associated with a poor response to antidepressant treatment. Finally, total triiodothyronine levels were associated with better cognitive functioning, though they did not influence improvement occurring with recovery.

Conclusions: Our study suggests that thyroid hormones may have an impact on severity and efficacy of antidepressant treatment. However, our result should be considered with caution and merely as a suggestion due to some methodological limitations. Hence further studies are required to better ascertain the role of thyroid hormones in depression after menopause.

Key words: antidepressant treatment, correlation, depression, thyroid hormone.

THYROID STATUS MARKEDLY affects mood and the development of mood disorders.[1] Defect in thyroid function may lower the threshold for depression, while excess of thyroid hormone can contribute to a state of tense dysphoria.[2] Approximately 10% of depressed patients are considered as having subclinical hypothyroidism and altered thyroid function may influence the course of affective disorders.

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Received 20 March 2008; revised 10 December 2008; accepted 16 December 2008.

Thyroid hormones are thought to influence mood status via post-receptor mechanisms through signal transduction pathways in the brain. Indeed, there is substantial evidence that thyroid hormone interacts with norepinephrine and serotonin function in several brain areas, especially hippocampus, frontal lobe and amygdale.[3] This influence may be generalized to widely recognized targets of antidepressant therapies.[4]

In some cases, a positive correlation between elevated levels of thyroxine (T4) and the onset of response to antidepressants has been reported.[5] Indeed, thyroid hormones favor antidepressant efficacy[6] and hypothyroidism may play a role in some treatment-resistant depressive disorders.[7] Furthermore, there is evidence that overt and subclinical hypothyroidism may be a predisposing factor for cognitive impairment and dementia.[8] In non-treated depressed patients, high thyroid-stimulating hormone (TSH) levels, markers of hypothyroidism, were found correlated to lower global and regional cerebral blood flow and lower glucose metabolism.[9] Interestingly, TSH and T4 levels were gender-specifically associated with current depression in the young adult population (lower TSH for men and higher T4 levels for women), indicating a need for more investigations into whether these depression-associated changes represent distinct endophenotypes of depression.[10]

The prevalence of biochemical or subclinical hypothyroidism in women increases steadily with age, rising from 10% to 20% in the postmenopausal age range of 55 and above.[11] The lower endogenous estrogen level associated with menopause has been associated with a decrease in thyroid functioning.[12–15] Nevertheless, the published reports regarding the effects of estrogen on thyroid function in postmenopausal women are still in debate. It has been reported that levels of estradiol do not affect the levels of thyroid hormones.[16,17] However, treatment with estrogens for menopausal symptoms seems to have pronounced effects on thyroid hormonal levels and it has been recently associated with mean pituitary height in postmenopausal women.[18]

It has been found that TSH levels are increased by estrogens or selective estrogen receptor modulators treatment (SERM) in some studies[18–22] but not in others.[23–25]

In post menopausal women, estrogen treatment has also been reported to increase total thyroxine (T4),[22–24,26–28] while other studies failed to support those findings.[20,25,29] In addition, free triiodothyronine (T3) levels were found to be reduced in post-menopausal women as compared to those of pre-menopausal women[30] and estrogen treatment also seems to increase levels of total T3.[22,24,28] However, other studies did not replicate changes in differences in total T3.[20,23,25]

Given that there is an interaction between gender and thyroid hormones, hormonal changes occurring with menopause may affect the development and the course of mood disorders in women. In fact, in our previous investigation,[31] we found that depressed menopausal women without adjunctive hormonal therapies responded to antidepressant treatment to a lesser degree than pre-menopausal women. This effect was not only explained by the old age of menopausal women, as previously reported,[32,33] but it was also correlated with high follicle stimulating hormone (FSH) levels in this group of patients.

Considering that thyroid function seems to be reduced after menopause, in the present study we aimed to investigate the differential role of thyroid hormonal levels on depressive symptomatologies and the response to antidepressants in female patients with major depressive disorder (MDD), according to the presence/absence of menopause. We expected clinical markers of subtle hypothyroidism to reduce response to treatments, particularly in post-menopausal women.

SUBJECTS AND METHODS

Design

The study was designed as a prospective, 6-week, open-label naturalistic study for comparison of antidepressant response in pre-menopausal versus post-menopausal women with MDD.

Subjects

Demographic and clinical features characterizing the samples have been described previously.[31] Briefly, post-menopausal women were different from pre-menopausal women only by being older at their first illness episode (54.7 ± 10.1 vs. 34.2 ± 7.0); age at onset was neither correlated with severity of depression at any stage of the follow up, nor with thyroid hormonal levels. In the whole sample, 10 patients (31.25%) were at their first depressive episode (five non-menopausal and five post-menopausal women).

The subjects consisted of 39 Korean female patients who were diagnosed with MDD, according to the DSM-IV criteria.[34] All patients were recruited based on an advertisement at the Depression Clinical Research Unit of Kangnam St. Mary's Hospital, which is a teaching hospital located in Seoul, Republic of Korea. Post-menopause was defined as amenorrhea for more than twelve months,[35] while premenopausal women were defined by the absence of significant vasomotor symptoms or menstrual irregularity; if irregular cycles were reported, we included women younger than 37.[35]

Exclusion criteria were: serious suicide risk, pregnancy, lactation, recent participation in another study in the previous 30 days, psychotherapy initiated in the last 6 months, substance use disorder in the last 6 months, any other current occurrence or past history of Axis I disorders other than MDD such as psychotic disorders and bipolar disorders, Axis II disorders, significant medical conditions such as malignancy, hysterectomy, or oophorectomy. Furthermore, subjects with a diagnosis of thyroid dysfunction[36] were excluded after consultation with an endocrinology specialist (manifestation of both clinical symptoms of hypothyroidism or hyperthyroidism and abnormal thyroid hormone values), as well as women receiving estrogens and/or thyroid hormonal therapies. The study was strictly reviewed and approved by the Institutional Review Boards at Kangnam St. Mary's Hospital and all subjects provided written informed consent prior to participating in the study and after having all of the study procedures explained to them.

Psychiatric diagnosis

The AXIS I diagnosis was evaluated by the consensus between the two board-certified psychiatrists upon the study entry,[31] according to the DSM-IV criteria, using a Structured Clinical Interview for DSM-IV Axis I disorders-Research Version, performed by evaluators separately, on two different occasions.[37]

Medications

Currently available antidepressants (e.g. selective serotonin reuptake inhibitors; serotonin and norepinephrine reuptake inhibitors; noradrenergic and specific serotonin antidepressant and tricyclic antidepressant, etc) were recommended to be dosed using a flexible titration strategy within approved dosage guidelines based on each manufacturer's package inserts, with consideration of the individuals' clinical response and tolerability. No other psychotropic medications were permitted during the study with the exception of hypnotics for insomnia and benzodiazepines for anxiety. No patient included was concomitantly treated with mood stabilizer drugs. Over-the-counter medications were only allowed as needed, for example acetaminophen. Patients already in treatment with psychotropic drugs at the intake underwent a one-week washout of previous medications.

Since different antidepressant drugs require different dosages, we uniformed doses according to the Antidepressant Treatment History Form[38] and we calculated for each woman the citalopram equivalent dose received during the six-weeks of follow up.

Assessments

At baseline, all patients were evaluated for depressive severity using the Hamilton Depression Rating Scale-17 item (HAMD),[39] the Montgomery-Åsberg Depression Rating Scale (MADRS)[40] and the Clinical Global Impression Severity scale (CGI-S);[41] the Cognitive Failures Questionnaire (CFQ)[42] was also administered to evaluate cognitive functioning. The CFQ is a subjective test designed to investigate 'failures of perception, memory and motor function'; it consists of 25 questions regarding common lapses of cognitive function including memory, perception and attention. Each question is scored 0 to 4 depending on frequency of occurrence, as rated by the subject. High scores relate to increasing frequency of cognitive lapses. All women were prospectively followed up for six weeks during antidepressant treatment and evaluated with the HAMD, the MADRS, the CGI-S, the Clinical Global Impression –Improvement scale (CGI-I)[41] and the CFQ at week 1, 3 and 6.

Non-fasting blood samples for hormone assays were collected at the intake, before treatment administration. In non-menopausal women samples were taken during their lutheal phase, in order to avoid increased levels occurring during the preovulatory phase.[43] Levels of follicle stimulating hormone (FSH), luteinizing hormone (LH) and estradiol (E2) were tested. Assays of hormonal levels were conducted with the immunoradiometric method using commercially available kits (FSH, BioSourceFSH-IRMA Kit; LH, Biosource LHsp-IRMA Kit; E2,

Biosource E2-RIA-CT Kit, Biosource Europe S.A. Nivelles, Belgium). Levels of TSH, T4 and T3 were tested. Assays of hormonal levels were conducted with the immunoradiometric method using commercially available kits (T3, IMMUNOTECH Total T3 RIA kit; T4, IMMUNOTECH Total T4 RIA kit; TSH, IMMUNOTECH TSH RIMA kit, IMMUNOTECH Radio VA 1-102 27, Prague, Czech Republic). The reference levels of T3, T4 and TSH were 0.78–1.82 ng/mL, 4.68–12.4 mg/dL and 0.17–4.1 mIU/L, respectively.

Statistical analysis

Statistical analyses were performed with the 'Statistica' software (StatSoft). Clinical and demographic features in pre-menopausal and post-menopausal women were analyzed with the χ^2-test, the Student's *t*-test and the Pearson product–moment correlation analysis. The associations between hormonal levels with baseline depressive scores or rate of improvement at week 6 from the baseline were analyzed with the ANCOVA, to control for potential confounders such as age and single versus recurrent MDD. The association between hormonal levels and response to antidepressant treatment in terms of both symptomatology and cognitive functioning was analyzed by the repeated measures of ANCOVA, including covariates. Categorical response to treatment (≤50% reduction from the baseline in the scores of HAMD) was analyzed by the multivariate regression analysis, including covariates. Multivariate regression was also employed to analyze simultaneously the effect of thyroid hormones on depressive severity and treatment outcome indexes.

With a standard level of significance ($\alpha = 0.05$), in our sample we had a post-hoc sufficient power (0.80) to detect only large effect sizes ($d = 0.82$), corresponding to a difference between pre-menopausal and post-menopausal women of 4.95 points on both final HAMD and MADRS scores, of 0.7 points on CGI-S scores, of 0.6 on CGI-I scores, and of 15.2 points on CFQ scores (explained variance range: 14.2–14.5%). Because of the small sample size we had a low statistical power (a priori: 0.46), thus smaller influences exerted by the thyroid hormones on recovery from depression with antidepressant treatment may have been largely missed.

RESULTS

Thyroid hormones in pre- and post-menopausal women

Thyroid hormone levels were not associated to age at menarche, age at first delivery, or age at menopause (in post-menopausal women). TSH and T4 levels were not different between pre- and post-menopausal women, while T3 levels were slightly higher in post-menopausal women (Table 1) and they were correlated with age ($r = 0.34$, $P = 0.036$).

In the whole sample, only four patients (≥TSH of 4.1 mIU/L) showed sub-clinical hypothyroidism (high levels of TSH and normal values of T4 and T3) (three pre-menopausal and one post-menopausal); no women showed signs of sub-clinical hyperthyroidism. There was no significant difference between pre- and post-menopausal women (χ^2-test = 3.78, d.f. = 2, $P = 0.15$) and diagnosis of sub-clinical

Table 1. Thyroid hormonal levels in pre- and post-menopausal women

	PRMW ($n = 17$)	POMW ($n = 22$)	Range of thyroid hormone level ($n = 39$)	t-value (d.f. = 38)	*P*-values
FSH (IU/L)	4.6 ± 2.2	62.6 ± 27.8	–	8.6	<0.0001
LH (IU/L)	4.9 ± 3.2	16.7 ± 8.4	–	5.5	<0.0001
E2 (pg/mL)	153.6 ± 108.0	40.4 ± 25.5	–	−4.8	<0.0001
TSH (mIU/L)	1.6 ± 1.4	2.1 ± 1.9	0.25–9.77	−0.8	0.45
T4 (mg/dL)	7.1 ± 1.4	8.3 ± 2.1	5.03–11.9	−2.0	0.056
T3 (ng/mL)	0.8 ± 0.1	1.0 ± 0.3	0.71–1.78	−2.7	0.011

Data represent mean ± standard deviation.
E2, estradiol; FSH, follicle stimulating hormone; LH, luteinizing hormone; POMW, post-menopausal women; PRMW, pre-menopausal women; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

thyroid disorder was not associated with any other demographic and clinical variable.

Thyroid hormones and depression

Correlation between baseline depressive scores and thyroid hormonal levels, controlling for age and medical status, are reported in Table 2. TSH levels were correlated with less severe depression at the intake in the whole sample and in pre-menopausal women. Conversely, T4 levels were associated with a more severe baseline symptomatology, in the whole sample, in post-menopausal women and, as a trend, in pre-menopausal women as well. T3 levels were not associated with depressive severity in both groups.

Including both TSH and T4 levels in a multivariate regression, T4 levels showed a major impact on depressive severity (MADRS: $R = 0.35$, $\beta = 0.36$, $P = 0.039$; CGI-S: $R = 0.35$, $\beta = 0.44$, $P = 0.008$). Inclusion of T3 levels did not change results. Analyzing separately pre-menopausal women, only marginal trends could be observed for T4 levels in pre-menopausal women (MADRS: $P = 0.006$, CGI-S: $P = 0.071$), while the effect was significant in post-menopausal women on MADRS scores ($R = 0.49$, $\beta = 0.45$, $P = 0.040$, as a trend on CGI-S: $P = 0.070$).

Thyroid hormones and response to antidepressant treatment

Correlation between final depressive scores and thyroid hormonal levels are shown in Table 2. In the whole sample and in post-menopausal women, no association could be observed, while in pre-menopausal women, TSH levels were associated with higher severity scores and, conversely, T4 levels were associated with lower severity.

Controlling for covariates, in the whole sample, TSH levels were associated with categorical response (on CGI-S) to treatment (multiple linear regression, $\beta = -0.39$, $P = 0.02$): high levels were associated with a poor response to the antidepressant. The inclusion of menopausal state in the model did not have an effect; however, analyzing separately pre- and post-menopausal women, the association remained significant only in pre-menopausal women (multiple linear regression, $\beta = -0.56$, $P = 0.037$).

In pre-menopausal women only, TSH levels were also negatively associated with improvement of symptoms during treatment (repeated measures ANCOVA, time x TSH levels on CGI-S: $F = 3.24$, d.f. = 3, $P = 0.034$) and with the rate of improvement from baseline (ANCOVA, TSH on HAMD: $F = 15.57$, d.f. = 1, $P = 0.003$).

Analyzing concurrently TSH and T4, respectively high T4 and low TSH levels were associated with less severe final depression (T4 on MADRS: $R = -0.80$, $\beta = -0.69$, $P = 0.0029$; TSH on CGI-S: $R = 0.53$, $\beta = 0.55$, $P = 0.046$) and absolute improvement from baseline (MADRS, T4: $R = -0.51$, $\beta = 0.90$, $P = 0.00019$; HAMD, TSH: $R = -0.51$, $\beta = -0.51$, $P = 0.023$), but in pre-menopausal women only. No such effects could be observed in post-menopausal women.

Table 2. Correlations between thyroid hormonal levels and depressive scores at the baseline and after 6 weeks of antidepressant treatment (controlling for age and medical status)

	Whole sample ($n = 39$)			Pre-menopausal women ($n = 17$)			Post-menopausal women ($n = 22$)		
	HAMD	MADRS	CGI-S	HAMD	MADRS	CGI-S	HAMD	MADRS	CGI-S
TSH (mIU/L)†	**−0.35**	−0.14	+0.15	**−0.58**	+0.14	+0.08	−0.23	−0.27	+0.17
T4 (mg/dL)†	+0.33	**+0.35**	**+0.35**	*+0.49*	+0.37	+0.42	+0.26	**+0.49**	+0.36
T3 (ng/mL)†	−0.18	−0.28	+0.06	−0.41	−0.22	−0.07	−0.14	−0.24	+0.11
TSH (mIU/L)‡	−0.01	−0.06	+0.15	**+0.50**	+0.49	**+0.55**	−0.16	−0.21	+0.02
T4 (mg/dL)‡	+0.03	+0.07	+0.04	−0.49	**−0.80**	−0.14	+0.06	+0.17	+0.03
T3 (ng/mL)‡	+0.07	+0.03	+0.29	+0.28	+0.42	+0.34	−0.07	−0.15	+0.24

†Correlations with baseline scores. ‡Correlations with final scores.
Bold characters represent significant correlations and italic characters indicate trends.
CGI-S, Clinical Global Impression-Severity scale; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

In the whole sample, T4 levels were associated with the improvement of symptoms during treatment, but in the opposite direction of TSH: high levels were associated with a better outcome (repeated measures ANCOVA: time x T4 levels on MADRS: $F = 3.22$, d.f. = 3, $P = 0.026$). Menopausal status did not have a significant effect; nevertheless, analyzing separately pre- and post-menopausal women, the association remained statistically significant only in pre-menopausal women (repeated measures ANCOVA: time x T4 levels on MADRS: $F = 5.66$, d.f. = 3, $P = 0.0034$). In pre-menopausal women, T4 levels were also associated with the rate of improvement from baseline (ANCOVA, T4 on HAMD: $F = 5.62$, d.f. = 1, $P = 0.039$, T4 on MADRS: $F = 37.36$, d.f. = 1, $P = 0.0001$) and with positive (categorical) response (multiple linear regression, on HAMD: $\beta = 0.51$, $P = 0.027$, on MADRS: $\beta = 0.88$, $P = 0.0001$).

Analyzing concurrently FSH and T4, both T4 and TSH levels influenced improvement during treatment in pre-menopausal women (repeated measures ANCOVA: time x T4 levels on MADRS: $F = 3.66$, d.f. = 3, $P = 0.022$; time x T4 on CGI-S: $F = 3.90$, d.f. = 3, $P = 0.035$). Such effects were not observable in post-menopausal women. T3 levels were not associated with response to antidepressant treatment in the whole sample, and separately in the two groups of patients.

Finally, clinically high levels of TSH (observed in three pre-menopausal women and one post-menopausal), which are considered markers of subclinical hypothyroidism (>4 mIU/L), were associated with a poor response (categorical) to antidepressant treatment (multiple linear regression, including age, medical condition as covariates, $\beta = -0.38$, $P = 0.027$).

Thyroid hormones and cognitive functioning during antidepressant treatment

At the baseline, controlling for age, medical status and baseline depressive scores, high T3 levels were associated with a better cognitive performance in the whole sample and in menopausal women (Table 3). Confounders did not have significant impact, and nor did menopausal status. TSH and T4 levels did not have significant effect at baseline.

Controlling for the same covariates and response to antidepressant treatment, in the whole sample, as well as separately in pre- and post-menopausal women, the improvement of cognitive functioning was not associated with thyroid hormonal levels, but only with response to antidepressant treatment (repeated measures ANCOVA, time x response to antidepressant in the whole sample: $F = 4.37$, d.f. = 3, $P = 0.006$).

Table 3. Correlations between thyroid hormonal levels and cognitive performances at the Cognitive Failure Test, at the baseline and after 6 weeks of antidepressant treatment (controlling for age, medical status and baseline depressive scores)

	Whole sample ($n = 39$)	Pre-menopausal women ($n = 17$)	Post-menopausal women ($n = 22$)
TSH (mIU/L)†	−0.23	0.11	−0.37
T4 (mg/dL)†	−0.10	−0.17	−0.02
T3 (ng/mL)†	**−0.40**	−0.09	**−0.50**
TSH (mIU/L)‡	−0.25	−0.13	−0.31
T4 (mg/dL)‡	−0.02	0.12	−0.039
T3 (ng/mL)‡	−0.31	−0.15	−0.37

†Correlations with baseline scores.
‡Correlations with final scores.
Bold characters represent significant correlations.
T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

DISCUSSION

The role of thyroid hormonal levels in mood disorders is well recognized.[1] As thyroid hormones interact with estrogens, and given the evidence of a reduced functioning of the thyroid in post-menopausal women, we investigated the role of thyroid hormones in depressive symptomatologies and response to antidepressant treatment in both pre- and post-menopausal women.

Results of our analyses indicated that baseline TSH levels, potential markers of subclinical hypothyroidism, may be correlated with a less severe form of depression. On the other hand, when looking at the response to antidepressants, high baseline TSH levels predicted a poorer response to treatment. Indeed, a diagnosis of sub-clinical hypothyroidism significantly predicted a poor response to antidepressants. Conversely, high baseline T4 levels, potential indicators of good thyroid functioning (all women being euthyroid and none diagnosed for overt or subclinical hyperthyroidism), were associated with a more severe form of depression, but also with a better outcome after treatment.

Overall, these results suggest that low thyroid functioning may cause subjects to experience depressive symptoms (which seems to be less severe as in euthyroid subjects) and this may lower the chance of response to antidepressant treatment. We can hypothesize that an important portion of symptomatology in patients with high TSH levels may be due to thyroid dysfunction, and is thus a differentially characterized depressive form. In particular, as regards treatment outcome, patients with subtle thyroid disease may benefit less from antidepressant treatment alone, while improving more significantly with adjunctive hormonal replacement therapy.[44] Accordingly, hypothyroidism has been associated with treatment-resistant depression.[7] On the other hand, depression in women with good thyroid functioning may be more severe, but in the presence of high levels of T4, the chances of recovery are much higher, in line with previous observations of a positive effect of T4 on response to treatment.[6]

However, we can not exclude the possibility of stratification bias. Indeed, treatment resistance may be influenced by many aspects and conditions, including genetics, psychopathological dimensions, medical condition, psychosocial and environmental factors and so on.

Finally, we found the outcome in terms of improvement of cognitive impairment not influenced by thyroid hormonal levels, but only by the concurrent improvement of depressive symptoms. Nevertheless, high T3 levels at the baseline, potential indicators of a good thyroid functioning, were negatively correlated with CFQ scores, thus favoring better cognitive functioning. This result is in line with previous evidence that suggests that overt and subclinical hypothyroidism may be a predisposing factor for cognitive impairment and dementia.[8]

Most of these results were stronger in pre-menopausal women than in post-menopausal women. We can hypothesize that, given the reported reduction of thyroid functioning in women after menopause, thyroid hormones could have more impact in pre-menopausal women than in post-menopausal women. However, we excluded from our study women with overt thyroid dysfunctions and this criterion may have biased the sample of menopausal women. It is likely that a great proportion of post-menopausal women, in which the effect of thyroid hormones may be stronger, have been excluded. This can also explain the unexpected result of higher hormonal levels in post-menopausal women. The exclusion of post-menopausal women with clinical thyroid dysfunctions may have resulted in a higher representation of women with particularly high thyroid functioning in the post-menopausal group. As there is a paucity of data in this field, specifically comparing the response to antidepressant in pre- and post-menopausal women in relation to thyroid hormones, and not treated with adjunctive hormonal therapies, further research on larger samples and including women with clinical thyroid dysfunction, is needed. Moreover, there is evidence that thyroid hormonal levels correlate with body-weight.[45] Unfortunately we did not collect this data and were thus unable to control for potential stratification bias.

Some other important limitations may underlie the present study. First, the small sample size substantially reduced the statistical power of our analyses and we were able to significantly detect only large effects exerted by clinical and hormonal indicators. Furthermore, to improve the possibility to detect differences, and given the preliminary nature of our analyses, we did not apply a Bonferroni correction, but this could have lead to false positives, thus the results should be taken with caution. Second, our pre- and post-menopausal women had some specific characteristics, which can limit the generalization of the results. Other than having high thyroid hormonal levels, our post-menopausal women were characterized by an older onset age, ranging from 35 to 74 years, with a median of 58 years. Even if the old age of these women may have impaired the assessment of previous episodes that occurred at a younger age, the sample is characterized by a late-onset depressive disorder and it is possible that the majority of post-menopausal women in our sample did not experience depressive episodes before menopause. However, age at onset did not affect depression severity or cognitive function. Furthermore, our pre-menopausal group had a high rate of subjects at their first depressive episode (approximately 50%). Thus, the specific composition of our pre- and post-menopausal subjects limits their representativeness and the results may not be reliable for earlier onset or recurrent post-menopausal women with MDD. Pre- and post-menopausal women were not different for the incidence of medical conditions; nevertheless, we took into account this variable as well, even though medical problems may be more severe in the older menopausal group. Finally, patients were treated with different antidepressants. However, the type of

antidepressant drug was not related to hormonal levels and the doses, uniformed as citalopram equivalents,[38] were not different in pre- and post-menopausal women.

In conclusion, our study suggests that thyroid hormones may have an impact on severity and efficacy of antidepressant treatment. However, our result should be considered with caution and merely as a suggestion due to some methodological limitations. Hence further studies are required to better ascertain the role of thyroid hormones in depression after menopause.

ACKNOWLEDGMENT

This study was supported by a grant from the Medical Research Center, Korea Science and Engineering Foundation, Republic of Korea (R13-2002-005-04001-0).

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