CLINICAL STUDY

Thyroid and adrenal axis in major depression: a controlled study in outpatients

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Abstract

Objective: Major depressive disorder has been associated with changes in the hypothalamus–pituitary–thyroid (HPT) axis and with hypercortisolism. However, the changes reported have been at variance, probably related to in- or outpatient status, the use of antidepressant medication and the heterogeneity of depression. We therefore conducted a controlled study in unipolar depressed outpatients who had been free of antidepressants for at least 3 months.

Design: We assessed endocrine parameters in 113 depressed outpatients and in 113 sex- and age-matched controls.

Methods: Patients were included if they had a major depression according to a Structural Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM), fourth edition (SCID-IV) and if they had a 17-item Hamilton rating scale for depression (HRSD) score of ≥ 16 . Endocrine parameters contained serum concentrations of TSH, (free) thyroxine, tri-iodothyronine, cortisol, thyroid peroxidase (TPO) antibody titre and 24-h urinary excretion of cortisol.

Results: The serum concentration of TSH was slightly higher in depressed patients as compared with controls ($P < 0.001$), independent of the presence of subclinical hypothyroidism and/or TPO antibodies ($n = 28$). All other HPT axis parameters were similar in both groups. The 24-h urinary cortisol excretion was similar in patients and controls. In atypical depression, serum cortisol was lower than in non-atypical depression ($P = 0.01$). Patients with neither melancholic depression nor severe depression ($\text{HRSD} \geq 23$) had altered endocrine parameters. Finally, serum TSH values could not be related to cortisol values.

Conclusion: When compared with matched control subjects, outpatients with major depression had slightly higher serum TSH, while urinary cortisol levels were similar. Furthermore, we observed lower serum cortisol in atypical depression than in non-atypical depression.

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Introduction

Major depressive disorder has been associated with changes in the hypothalamic–pituitary–thyroid (HPT) axis and the hypothalamic–pituitary–adrenal (HPA) axis. In the HPT axis a decrease in serum thyrotrophin (TSH), a blunted TSH response to thyrotrophin-releasing hormone (TRH) and an increase in serum free thyroxine (FT4) have been reported by various authors (for reviews see 1, 2). Furthermore, an increased prevalence of subclinical hypothyroidism and thyroid peroxidase (TPO) antibodies have been described (3, 4). Hypercortisolism in depression has been reported in many studies as reflected by elevated mean 24-h serum cortisol concentrations and increased 24-h urinary excretion of cortisol. In endocrine tests, such as the

dexamethasone-suppression test (DST), serum cortisol and adrenocorticotrophin concentrations are not suppressed in some 20–50% of patients (for review see 5).

These endocrine alterations may be of pathogenic relevance. Kirkegaard & Faber (1) proposed that the alterations in the HPT axis are caused by serotonin and/or norepinephrine deficiency in depression. Alternatively, Jackson (2) postulated that the changes in the HPT axis are due to the hypercortisolism in depressed patients. Various explanations have been put forward for the activation of the HPA axis in major depression, including glucocorticoid resistance and hypothalamic overdrive of corticotrophin-releasing hormone (CRH) (for review see 5). Furthermore, these changes are proposed to have clinical significance; Krog-Meyer *et al.* (6) described that a persistent blunting of the TSH response

after treatment predicted early relapse. Likewise, patients with resistance to the suppressive effects of dexamethasone on cortisol were reported to have higher relapse rates (7).

However, the reports on part of the endocrine changes in major depression are inconsistent: several authors do not find changes in the HPT axis (8–10) and not all studies report hypercortisolism in major depression (11–13). The inconsistency in the literature may be due to several factors. First, studies differ with respect to the in/outpatient status of the included patients. Studies on outpatient populations are less numerous, although outpatients comprise the majority of patients with major depression. Furthermore, in several studies patients were on antidepressant medication which may influence endocrine parameters (14–16), even after short-term discontinuation of these drugs (17, 18). The heterogeneity of depression is probably an important factor as well; several studies include unipolar as well as bipolar patients (19–22), and the prevalence of depression subtypes such as melancholic depression are often not mentioned. Some studies have indicated that endocrine alterations are more pronounced in bipolar and melancholic patients (23, 24). Additional factors are the absence of a control group, unclear sources of the reference values used (4, 10, 25) and small sample sizes (13, 26–28).

In view of the inconsistent studies and the potential clinical importance of endocrine changes in depression, we investigated HPT and HPA axis parameters in 113 outpatients with unipolar major depression who had been free of antidepressants for at least 3 months and in 113 age- and sex-matched control subjects. Furthermore, we evaluated whether changes in hormone levels were associated with atypical, melancholic or severe depression and if serum TSH was related to cortisol concentrations.

Subjects and methods

Subjects

The depressed patients took part in a randomised clinical trial evaluating the efficacy of thyroid hormone (triiodothyronine; T₃) addition to treatment with a selective serotonin reuptake inhibitor (SSRI), as described elsewhere (29). The Paroxetine (Seroxat) and T₃ (Cytomel) used in this trial were kindly supplied by Smith Kline Beecham (Middlesex, UK). In short, the study was carried out at two academic psychiatric outpatient clinics in Amsterdam, The Netherlands. To be eligible for the study the patients had to be between 18 and 65 years of age, fulfil the diagnostic criteria for major depressive disorder and, in cases of previous depressive episodes, be free of antidepressant medication for at least 3 months. Diagnosis of depression and its subtypes was performed by a Structural Clinical Interview for the Diagnostic (SCID) and Statistical Manual of Mental

Disorders (DSM), fourth edition (SCID-IV). Patients were required to have a score of at least 16 on the 17-item Hamilton rating scale for depression (HRSD), a commonly used questionnaire to rate depression severity. This study was approved by the medical ethical committee of the Academic Medical Centre (AMC) and the Free University Medical Centre. All 113 randomised patients provided written informed consent.

Exclusion criteria were bipolar disorder, substance abuse or dependence disorder for alcohol or drugs, clinically manifest thyroid or adrenocortical disease. Patients were not allowed to have taken corticosteroids, drugs interfering with thyroid hormone metabolism (e.g. amiodarone), thyroid hormone or psychotropic drugs during the last 3 months before inclusion, with the exception of low-dose benzodiazepine (equivalent to 30 mg oxazepam daily) and oestrogens.

Control subjects were recruited by advertisement between 1995 and 2000. These subjects took part in an ongoing project of the Department of Endocrinology and Metabolism of the AMC aimed at determining reference values for endocrinological parameters. Part of the results of this project has been published earlier (30, 31). Control subjects had self-declared good general health. Exclusion criteria were identical to the depressed patients except for some projects (30, 31) in which oestrogen medication was also an exclusion criterion. From the eligible 200 control subjects, 113 were age (± 5 years) and sex matched to the depressed patients. If several control subjects could be matched to one depressed patient, the control was randomly selected.

Procedure and hormone measurements

Subjects had an intravenous puncture for blood withdrawal in the morning (before 1000 h) at the AMC and were instructed to collect two separate, refrigerated 24-h urine samples. Serum, plasma and urine samples were kept at -20°C . Hormone assays were performed in the laboratory of endocrinology of the AMC. Serum T₄ and T₃ were measured by in-house RIA methods (32), with a detection limit of 5 nmol/l and 0.3 nmol/l respectively. The intra-assay coefficient of variation was 2–4% and 3–4% and the interassay coefficient of variation was 3–6% and 7–8% respectively. Free T₄ and TSH were measured by time-resolved fluoroimmunoassay (respectively Delfia FT₄ and hTSH Ultra; Wallac Oy, Turku, Finland), with a detection limit of 2 pmol/l and 0.01 mU/l respectively. The intra-assay coefficient of variation was 4–6% and 1–2% and the interassay coefficient of variation was 5–8% and 3–4% respectively. The reference range for serum TSH was 0.4–4.0 mU/l (33) and for FT₄ 10–23 pmol/l. Subclinical hypothyroidism was defined as an increased serum TSH and a normal serum FT₄. Subclinical hyperthyroidism was defined as a decreased serum TSH and a normal serum FT₄. Anti-TPO was measured by chemiluminescence immunoassay (LUMI-test anti-TPO; BRAHMS, Berlin,

Germany) with a detection limit of 30 kU/l. The intra-assay coefficient of variation was 3–7% and the inter-assay coefficient of variation was 8–12%. The cut-off value for a positive anti-TPO titre was 60 kU/l.

Cortisol levels were determined by luminescence enzyme immunoassay on an Immulite (Diagnostic Products Corporation, Los Angeles, CA, USA), with a detection limit of 30 nmol/l. The intra-assay coefficient of variation was 5.8% and the interassay coefficient of variation was 7.0%. Urinary cortisol was measured by an in-house high-performance liquid chromatographic method with a detection limit of 5 nmol/l. The intra-assay coefficient of variation was 6.5% and the inter-assay coefficient of variation was 10.5%. Of the two 24-h urine samples, total volume as well as concentrations of free cortisol and creatinine were measured. In 50 control subjects, cortisol concentrations of only one urine sample were measured. These concentrations were not different from the mean concentration of other controls. For all subjects, total creatinine excretion was measured to assess the completeness of the collection. If total creatinine excretion in the sample with the highest creatinine excretion was $\geq 150\%$ of the creatinine excretion of the other sample, both samples were excluded (30). Six patients withdrew from the study protocol before the collection of urine samples had taken place and an additional 13 patients did not collect urine samples correctly, leaving 94 patients for the analysis of cortisol in the urine. In the control group, 100 subjects collected urine correctly. In the remaining 84 pairs, comparisons of urinary cortisol levels were made between depressed and control subjects. Hypercortisoluria was defined as values being more than $2 \times$ S.D. of the control group yielding > 187 nmol/24 h.

Data analysis

The differences between groups for serum FT4, total T4, T3, cortisol and urinary cortisol were tested for statistical significance using the paired sample *t*-test. Serum total T4, T3 and cortisol were also analysed after exclusion of oestrogen medication, since oestrogens (e.g. anti-conceptive medication) increase serum total T4, T3 and serum cortisol. To exclude the possibility that use of low-dose benzodiazepines influenced our results, we performed the same analyses in patients free of benzodiazepines. For TSH, the difference between depressed patients and normal controls showed a non-normal distribution. Therefore, the Wilcoxon rank test was performed. For dichotomous paired variables (oestrogen and benzodiazepine medication, positive TPO antibodies, subclinical hyper- or hypothyroidism) the McNemar test was used. To see whether endocrine parameters were different in a subtype of depression, we compared atypical and melancholic depression with a group of patients with neither subtype. In this way, we prevented the

possibility that changes were due to inclusion of the other subtype in the comparison group. Changes between these subtypes in serum TSH (after log transformation), FT4 and cortisol were tested by the Student's *t*-test. Since urinary cortisol was not normally distributed, the Mann–Whitney U test was used for this comparison. The cut-off score for severe versus non-severe depression was 23 on the 17-item HRSD (34). For the correlation between serum TSH and serum cortisol, Pearson's correlation was used after log transformation of TSH. For the correlation between serum TSH and urinary cortisol, Spearman's correlation was used because of the non-normal distribution of urinary cortisol.

For all tests a *P* value < 0.05 was considered to reflect statistical significance.

Results

Sample characteristics

A total of 113 patients with depression met the criteria for eligibility and 113 control subjects were matched for age and sex. By definition, the age and sex of both groups were similar (Table 1). Significantly more subjects were present in the depressed group who took low-dose benzodiazepines (27% vs 1%; $P < 0.001$). Furthermore, more women in the depressed group used oestrogens (anti-conceptive medication or postmenopausal oestrogen replacement therapy) than in the control group (21% vs 4%; $P < 0.001$). The 17-item HRSD score indicated that most patients had a moderately severe depression. Thirty-two patients (28%) had melancholic and twenty-five (22%) had atypical depression. The depressed patient group included a considerable number of patients with chronic (44%) and recurrent (52%) depression.

Hormone values

Endocrine parameters are presented in Table 2. The serum concentration of TSH was slightly, but

Table 1 Demographic and clinical characteristics of patients and controls ($n = 113$).

	Patients	Controls
Age (mean $\pm$ S.D.)	47 $\pm$ 11	46 $\pm$ 12
Woman (<i>n</i> , %)	70 (62%)	70 (62%)
Benzodiazepines* (<i>n</i> , %)	30 (27%)	1 (1%)
Oestrogen use* (<i>n</i> , %)	24 (21%)	5 (4%)
17-item HRSD (mean $\pm$ S.D.)	21 $\pm$ 3	n.a.
Subtypes		
Melancholic (<i>n</i> , %)	32 (28%)	n.a.
Atypical (<i>n</i> , %)	25 (22%)	n.a.
Current episode (chronic (<i>n</i> , %))	50 (44%)	n.a.
Lifetime course (recurrent (<i>n</i> , %))	59 (52%)	n.a.

n.a. = not applicable.

* Depressed patients are significantly different from controls ($P < 0.001$).

Table 2 Endocrine parameters of patients and controls ($n = 113$).

	Patients	Controls	P
TSH (mU/l) (median, p^{10-90})	1.90 (0.93–4.26)	1.50 (0.85–2.72)	<0.001
TPO antibody and/or subclinical hypothyroidism# excluded (median, p^{10-90}) ($n = 85$)	1.70 (0.90–2.70)	1.40 (0.83–2.30)	<0.001
FT4 (pmol/l) (mean $\pm$ s.d.)	13.7 $\pm$ 2.0	13.7 $\pm$ 2.0	0.93
T4 (nmol/l) (mean $\pm$ s.d.)	112 $\pm$ 26	103 $\pm$ 18	0.002
Oestrogen use excluded (mean $\pm$ s.d.) ($n = 89$)	106 $\pm$ 23	100 $\pm$ 17	0.10
T3 (nmol/l) (mean $\pm$ s.d.)	2.2 $\pm$ 0.5	2.0 $\pm$ 0.4	0.001
Oestrogen use excluded (mean $\pm$ s.d.) ($n = 89$)	2.1 $\pm$ 0.4	2.0 $\pm$ 0.4	0.28
Positive TPO antibodies (n , %)	9 (8%)	11 (10%)	0.79
Subclinical hypothyroidism# (n , %)	12 (11%)	7 (6%)	0.33
Cortisol (nmol/l) (mean $\pm$ s.d.)	417 $\pm$ 153	439 $\pm$ 172	0.27
Oestrogen-use excluded (mean $\pm$ s.d.) ($n = 89$)	391 $\pm$ 139	413 $\pm$ 148	0.27
Urinary cortisol (nmol/24h)* (median, p^{10-90}) ($n = 84$)	63 (17–125)	59 (32–123)	0.56

The reference values for TSH were 0.40–4.00 mU/l (33). p^{10-90} , 10th and 90th percentile.

* Urinary cortisol values are from patients who collected urine samples correctly.

significantly, higher in depressed patients when compared with controls (median (10th and 90th percentile (p^{10-90})): 1.90 (0.93–4.26) vs 1.50 (0.85–2.72) mU/l; $P < 0.001$). This difference was still present when patients with subclinical hypothyroidism and/or subjects with TPO-positive antibodies were excluded. The difference in serum TSH persisted also after exclusion of subjects taking oestrogens (median (p^{10-90})): 1.80 (0.90–4.00) in depression vs 1.50 (0.90–2.50) mU/l in control subjects; $P = 0.003$) and low-dose benzodiazepines (median (p^{10-90})): 1.90 (0.93–3.99) in depression vs 1.45 (0.82–2.74) mU/l in control subjects; $P = 0.009$). Serum FT4 was unaltered in depressed patients. There was a higher serum total T4 and T3 in the depressed group, but this difference disappeared after exclusion of subjects taking oestrogens. Positive TPO antibodies occurred in 8% of the patients and in 10% of the control subjects ($P = 0.79$). The prevalence of subclinical hypothyroidism was 11% in patients with major depression and 6% in the control subjects ($P = 0.33$). None of these results was different in subjects who did not use benzodiazepines.

There was no alteration in serum cortisol in the depressed group, or in the 24-h excretion of cortisol

in the urine, regardless of whether subjects using oestrogens (urinary cortisol: median (p^{10-90})): 63 (14–137) in depression vs 63 (32–130) nmol/24 h in control subjects; $P = 0.86$) and benzodiazepines (urinary cortisol: median (p^{10-90})): 62 (19–124) in depression vs 61 (34–127) nmol/24 h in control subjects; $P = 0.98$) were excluded. In the depressed group, the prevalence of hypercortisolemia (2%) was similar to the control group (1%; $P = 1.00$).

Hormone values in subtypes of depression

Serum cortisol was significantly lower in patients with atypical depression as compared with non-atypical and non-melancholic depression (Table 3). This difference persisted after exclusion of patients taking oestrogens (means $\pm$ s.d.: 318 $\pm$ 124 and 420 $\pm$ 139 nmol/l respectively; $P < 0.01$), but it was not reflected in lower urinary cortisol excretion. Patients with melancholic depression showed similar hormone values when compared with non-melancholic and non-atypical depression. When we analysed the data according to severity of depression, we found no differences between severe and non-severe depression (Table 4).

Table 3 Endocrine parameters in subtypes of depression.

	A atypical depression ($n = 25$)	N neither subtype ($n = 56$)	M melancholic depression ($n = 32$)	N vs A P	N vs M P	A vs M P
TSH (mU/l) (median, p^{10-90}) ($n = 113$)	1.90 (1.06–4.70)	2.20 (0.90–4.26)	1.70 (0.85–4.15)	0.65	0.75	0.96
FT4 (pmol/l) (mean $\pm$ s.d.) ($n = 113$)	13.2 $\pm$ 2.4	14.0 $\pm$ 1.7	13.8 $\pm$ 1.9	0.27	0.63	0.18
Cortisol (nmol/l) (mean $\pm$ s.d.) ($n = 113$)	353 $\pm$ 143	437 $\pm$ 137	432 $\pm$ 176	0.01	0.87	0.07
Urinary cortisol* (nmol/24 h) (median, p^{10-90}) ($n = 94$)	64 (9–260) ($n = 22$)	59 (26–140) ($n = 46$)	65 (13–118) ($n = 26$)	0.87	0.08	0.29

* Urinary cortisol values are from patients who collected urine samples correctly.

Table 4 Endocrine parameters and severity of depression[#].

	Non-severe depression (n = 75)	Severe depression (n = 38)	P
HRSD (mean ± S.D.) (n = 113)	19 ± 2	25 ± 2	
TSH (mU/l) (median, p ^{10–90}) (n = 113)	1.80 (0.95–4.24)	2.20 (0.90–4.48)	0.46
FT4 (pmol/l) (mean ± S.D.) (n = 113)	13.7 ± 2.1	13.8 ± 1.9	0.82
Cortisol (nmol/l) (mean ± S.D.) (n = 113)	418 ± 161	415 ± 138	0.92
Urinary cortisol* (nmol/24 h) (median, p ^{10–90}) (n = 94)	63 (24–125) (n = 62)	63 (12–136) (n = 32)	0.77

[#] Severe depression was defined as having an HRSD score ≥ 23 (34).

* Urinary cortisol values are from patients who collected urine samples correctly.

Interaction between cortisol and serum TSH

There was no significant correlation between serum or urinary cortisol and serum TSH in depressed patients (R^2 0.03, $P = 0.08$ and $R^2 < 0.01$, $P = 0.79$ respectively), and this was independent of oestrogen use.

Discussion

The present study included a large population of solely unipolar depressed outpatients who were compared with age- and sex-matched controls. Diagnosis of subtypes of depression was performed by the Structural Clinical Interview for DSM, fourth edition (SCID-IV) to further investigate possible endocrine variances. Active screening for depressive symptoms in the control group was not performed. However, controls were included if they had self-proclaimed good general health and subjects using antidepressants were excluded. It seems unlikely therefore that major depression was prevalent in our group which would have greatly obscured our results.

Unexpectedly, the only difference we observed between patients and controls was a slightly higher serum TSH. Review articles have described rather a decreased serum TSH referring to studies on inpatients (discussed later) (1, 2). We are the first to compare age- and sex-matched patients and controls in such a large group of outpatients. We may therefore have been able to detect the subtle difference in outpatients described in the present study. Kirkegaard *et al.* (26) described that when depressed inpatients were compared with T4-treated hypothyroid patients, in whom T4 production rates were similar to the depressed patients, TSH was in fact inappropriately increased (0.90 mU/l in depressed patients and 0.11 mU/l in treated hypothyroid patients). Because of the absence of hypercortisolism in these outpatients, such inappropriate

higher TSH was possibly also revealed. Nevertheless, this finding should be replicated in future studies.

Our observation that most HPT or HPA axes parameters are unaltered in depressed outpatients is in contrast to a number of well-controlled studies reporting HPT axis alterations or hypercortisolism in depressed patients. On close reading of the literature it is striking that HPT axis alterations and hypercortisolism have almost exclusively been described in inpatients (19, 35–37) and to a much lesser extent in outpatients (9, 13). This suggests that the in/outpatient status is an important factor in the presence of endocrine alterations in major depression. Indeed, Rush *et al.* (23) found that both an abnormal DST and blunting of TSH response to TRH are approximately twice as prevalent in depressed inpatients as compared with depressed outpatients. Also in a meta-analysis on the DST in major depression, non-suppression rates were higher in inpatients (36%) than in outpatients (22%) (24). Thus, the in/outpatient status seems to be a determinant of the endocrine alterations described in depression. This is supported by studies describing the same endocrine alterations in patients with mania, schizophrenia and panic disorder as the changes described in depression (20, 38–42).

One can argue that the difference between in- and outpatients is due to a difference in the severity of depression. However, we did not find an association between baseline endocrine parameters and HRSD ratings, which is in line with other studies (13, 20, 38, 43). Post-dexamethasone cortisol concentrations have been related to depression severity (5), suggesting that the severity of depression is related to the DST, but not to hypercortisolism. In line with this, Nelson & Davis (24) and Brown *et al.* (44) showed that severe depression symptoms such as agitation and delusions were related to post-dexamethasone cortisol but not to baseline cortisol values.

The unaltered values in the present study cannot be due to the use of antidepressants. This is important, since antidepressants seem to have opposite effects on the described endocrine alterations in major depression, possibly even after short-term discontinuation of these drugs (16–18). In fact, this is the first large study in which patients were free of antidepressants for 3 months. Only one small study (13) ($n = 25$) measured 24-h serum cortisol concentrations and 24-h urinary cortisol in depressed outpatients, who were medication free for 3 months and reported no differences as compared with matched healthy subjects.

We evaluated whether endocrine alterations were present in patients with melancholic or atypical depression. We are the first to report lower serum cortisol in a large study wherein atypical depression was diagnosed according to international standards (45, 46). Gold & Chrousos (47) proposed that atypical depression is not only in clinical terms the opposite of melancholic depression but also in neuroendocrinological terms. In this model, melancholic depression is accompanied by a hyperactive stress response and, as a central component of the HPA axis, an activated CRH system. In contrast, atypical depression was proposed to go together with a CRH deficiency. These differences in CRH activity may explain part of the behavioural differences between melancholic and atypical depression (i.e. hypersomnia and hyperphagia in the former and hypersomnia and hyperphagia in the latter). Thus, the lower serum cortisol in atypical depression may reflect lower central CRH activity. With respect to melancholic depression, increased rates of cortisol non-suppression by dexamethasone in this subtype were reported in a meta-analysis by Nelson & Davis (24). However, this difference between melancholics and non-melancholics was reduced after correction for in/outpatient status. This may explain why, in the outpatient setting of the present study, we did not measure hypercortisolism in melancholic patients.

TSH is known to be suppressed by high serum cortisol (48). However, neither serum cortisol nor urinary cortisol was related to serum TSH levels in the present study. This is in line with another study reporting no relation between baseline serum cortisol and serum TSH in depressed inpatients (49).

In conclusion, our data indicate that several of the reported endocrine alterations in major depression are absent in outpatients. We propose that the alterations described in the literature are influenced by the out/inpatient status. Our data support an earlier finding, that the HPA axis is less active in atypical depression.

References

- 1 Kirkegaard C & Faber J. The role of thyroid hormones in depression. *European Journal of Endocrinology* 1998 **138** 1–9.
- 2 Jackson I. The thyroid axis and depression. *Thyroid* 1998 **8** 951–956.
- 3 Pop V, Maartens L, Leusink G, van Son M, Knottnerus A, Ward A, Metcalfe R & Weetman A. Are autoimmune thyroid dysfunction and depression related? *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 3194–3197.
- 4 Nemeroff C, Simon J, Haggerty J Jr & Evans D. Antithyroid antibodies in depressed patients. *American Journal of Psychiatry* 1985 **142** 840–843.
- 5 Holsboer F & Barden N. Antidepressants and hypothalamic–pituitary–adrenocortical regulation. *Endocrine Reviews* 1996 **17** 187–205.
- 6 Krog-Meyer I, Kirkegaard C, Kijne B, Lumholtz B, Smith E, Lykke-Olesen L & Bjorun N. Prediction of relapse with the TRH test and prophylactic amitriptyline in 39 patients with endogenous depression. *American Journal of Psychiatry* 1984 **141** 945–948.
- 7 Zobel A, Nickel T, Sonntag A, Uhr M, Holsboer F & Ising M. Cortisol response in the combined dexamethasone/CRH test as predictor of relapse in patients with remitted depression. a prospective study. *Journal of Psychiatric Research* 2001 **35** 83–94.
- 8 Haggerty J Jr, Simon J, Evans D & Nemeroff C. Relationship of serum TSH concentration and antithyroid antibodies to diagnosis and DST response in psychiatric inpatients. *American Journal of Psychiatry* 1987 **144** 1491–1493.
- 9 Sullivan P, Wilson D, Mulder R & Joyce P. The hypothalamic–pituitary–thyroid axis in major depression. *Acta Psychiatrica Scandinavica* 1997 **95** 370–378.
- 10 Engum A, Bjoro T, Mykletun A & Dahl A. An association between depression anxiety and thyroid function – a clinical fact or an artefact? *Acta Psychiatrica Scandinavica* 2002 **106** 27–34.
- 11 Rubin R, Poland R, Lesser I, Winston R & Blodgett A. Neuroendocrine aspects of primary endogenous depression. I. Cortisol secretory dynamics in patients and matched controls. *Archives of General Psychiatry* 1987 **44** 328–336.
- 12 Oldehinkel A, van dB, Flentge F, Bouhuys A, ter Horst G & Ormel J. Urinary free cortisol excretion in elderly persons with minor and major depression. *Psychiatry Research* 2001 **104** 39–47.
- 13 Young E, Carlson N & Brown M. Twenty-four-hour ACTH and cortisol pulsatility in depressed women. *Neuropsychopharmacology* 2001 **25** 267–276.
- 14 McCowen K, Garber J & Spark R. Elevated serum thyrotropin in thyroxine-treated patients with hypothyroidism given sertraline. *New England Journal of Medicine* 1997 **337** 1010–1011.
- 15 Barden N, Reul J & Holsboer F. Do antidepressants stabilize mood through actions on the hypothalamic–pituitary–adrenocortical system? *Trends in Neurosciences* 1995 **18** 6–11.
- 16 Schule C, Baghai T, Rackwitz C & Laakmann G. Influence of mirtazapine on urinary free cortisol excretion in depressed patients. *Psychiatry Research* 2003 **120** 257–264.
- 17 Kraus R, Hux M & Grof P. Psychotropic drug withdrawal and the dexamethasone suppression test. *American Journal of Psychiatry* 1987 **144** 82–85.
- 18 Dilsaver S & Greden J. Effects of antidepressant withdrawal on the dexamethasone suppression test. *Psychiatry Research* 1985 **14** 11–22.
- 19 Carroll B, Curtis G, Davies B, Mendels J & Sugerman A. Urinary free cortisol excretion in depression. *Psychological Medicine* 1976 **6** 43–50.
- 20 Baumgartner A, Graf K, Kurten I & Meinhold H. The hypothalamic–pituitary–thyroid axis in psychiatric patients and healthy subjects: parts 1–4. *Psychiatry Research* 1988 **24** 271–332.
- 21 Rubin R, Poland R, Lesser I & Martin D. Neuroendocrine aspects of primary endogenous depression – IV. Pituitary–thyroid axis activity in patients and matched control subjects. *Psychoneuroendocrinology* 1987 **12** 333–347.
- 22 Bauer M, Baur H, Berghofer A, Strohle A, Hellweg R, Muller-Oerlinghausen B & Baumgartner A. Effects of supraphysiological thyroxine administration in healthy controls and patients with depressive disorders. *Journal of Affective Disorders* 2002 **68** 285–294.
- 23 Rush A, Giles D, Schlessner M, Orsulak P, Weissenburger J, Fulton C, Fairchild C & Roffwarg H. Dexamethasone response,

- thyrotropin-releasing hormone stimulation, rapid eye movement latency, and subtypes of depression. *Biological Psychiatry* 1997 **41** 915–928.
- 24 Nelson J & Davis J. DST studies in psychotic depression: a meta-analysis. *American Journal of Psychiatry* 1997 **154** 1497–1503.
 - 25 Fava M, Labbate L, Abraham M & Rosenbaum J. Hypothyroidism and hyperthyroidism in major depression revisited. *Journal of Clinical Psychiatry* 1995 **56** 186–192.
 - 26 Kirkegaard C, Korner A & Faber J. Increased production of thyroxine and inappropriately elevated serum thyrotropin in levels in endogenous depression. *Biological Psychiatry* 1990 **27** 472–476.
 - 27 Coiro V, Volpi R, Marchesi C, DeFerri A, Capretti L, Caffarri G, Colla R & Chiopera P. Different effects of pyridostigmine on the thyrotropin response to thyrotropin-releasing hormone in endogenous depression and subclinical thyrotoxicosis. *Metabolism* 1998 **47** 50–53.
 - 28 Michelson D, Stratakis C, Hill L, Reynolds J, Galliven E, Chrousos G & Gold P. Bone mineral density in women with depression. *New England Journal of Medicine* 1996 **335** 1176–1181.
 - 29 Appelhof B, Brouwer J, Van Dyck R, Fliers E, Hoogendijk WG, Huyser J, Schene A, Tijssen JG & Wiersinga WM. Triiodothyronine (T₃) addition to paroxetine in the treatment of major depressive disorder. *Journal of Clinical Endocrinology and Metabolism* 2004 **12** 6271–6276.
 - 30 Bos Kuil M, Endert E, Fliers E, Prummel M, Romijn J & Wiersinga W. Establishment of reference values for endocrine tests. I: Cushing's syndrome. *Netherlands Journal of Medicine* 1998 **53** 153–163.
 - 31 Baas S, Endert E, Fliers E, Prummel MF & Wiersinga WM. Establishment of reference values for endocrine tests. III: primary aldosteronism. *Netherlands Journal of Medicine* 2003 **61** 37–43.
 - 32 Wiersinga WM. The peripheral conversion of thyroxine (T₄) into triiodothyronine (T₃) and reverse triiodothyronine (rT₃). PhD Thesis 1979, Academic Medical Center, Amsterdam.
 - 33 Wiersinga W. (The interpretation of the thyroid stimulating hormone (TSH) assay). *Ned Tijdschr Geneesk* 2003 **147** 1156–1158.
 - 34 Yonkers K & Samson J. Mood Disorder Measures. In *American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorder*, 4th edition. Washington DC: American Psychiatric Association, 2000.
 - 35 Kjellman B, Thorell L, Orhagen T, d'Elia G & Kagedal B. The hypothalamic–pituitary–thyroid axis in depressive patients and healthy subjects in relation to the hypothalamic–pituitary–adrenal axis. *Psychiatry Research* 1993 **47** 7–21.
 - 36 Maes M, Meltzer H, Cosyns P, Suy E & Schotte C. An evaluation of basal hypothalamic–pituitary–thyroid axis function in depression: results of a large-scaled and controlled study. *Psychoneuroendocrinology* 1993 **18** 607–620.
 - 37 Weber B, Lewicka S, Deuschle M, Colla M, Vecsei P & Heuser I. Increased diurnal plasma concentrations of cortisone in depressed patients. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 1133–1136.
 - 38 Baumgartner A, Pietzcker A & Gaebel W. The hypothalamic–pituitary–thyroid axis in patients with schizophrenia. *Schizophrenia Research* 2000 **44** 233–243.
 - 39 Hofmann P, Nutzinger D, Kotter M & Herzog G. The hypothalamic–pituitary–thyroid axis in agoraphobia panic disorder major depression and normal controls. *Journal of Affective Disorders* 2001 **66** 75–77.
 - 40 Lammers C, Garcia-Borreguero D, Schmider J, Gotthardt U, Dettling M, Holsboer F & Heuser I. Combined dexamethasone/corticotropin-releasing hormone test in patients with schizophrenia and in normal controls: II. *Biological Psychiatry* 1995 **38** 803–807.
 - 41 Schmider J, Lammers C, Gotthardt U, Dettling M, Holsboer F & Heuser I. Combined dexamethasone/corticotropin-releasing hormone test in acute and remitted manic patients in acute depression and in normal controls: I. *Biological Psychiatry* 1995 **38** 797–802.
 - 42 Copolov D, Rubin R, Stuart G, Poland R, Mander A, Sashidharan S, Whitehouse A, Blackburn I, Freeman C & Blackwood D. Specificity of the salivary cortisol dexamethasone suppression test across psychiatric diagnoses. *Biological Psychiatry* 1989 **25** 879–893.
 - 43 Posener J, DeBattista C, Williams G, Chmura K, Kalezhan B & Schatzberg A. 24-hour monitoring of cortisol and corticotropin secretion in psychotic and nonpsychotic major depression. *Archives of General Psychiatry* 2000 **57** 755–760.
 - 44 Brown R, Stoll P, Stokes P, Frances A, Sweeney J, Kocsis J & Mann J. Adrenocortical hyperactivity in depression: effects of agitation, delusions, melancholia, and other illness variables. *Psychiatry Research* 1988 **23** 167–178.
 - 45 Anisman H, Ravindran A, Griffiths J & Merali Z. Endocrine and cytokine correlates of major depression and dysthymia with typical or atypical features. *Molecular Psychiatry* 1999 **4** 182–188.
 - 46 Levitan R, Vaccarino F, Brown G & Kennedy S. Low-dose dexamethasone challenge in women with atypical major depression: pilot study. *Journal of Psychiatry and Neuroscience* 2002 **27** 47–51.
 - 47 Gold P & Chrousos G. Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. *Molecular Psychiatry* 2002 **7** 254–275.
 - 48 Adriaanse R, Brabant G, Endert E & Wiersinga W. Pulsatile thyrotropin secretion in patients with Cushing's syndrome. *Metabolism* 1994 **43** 782–786.
 - 49 Maes M, Schotte C, Vandewoude M, Martin M & Blockx P. TSH responses to TRH as a function of basal serum TSH: relevance for unipolar depression in females – a multivariate study. *Pharmacopsychiatry* 1992 **25** 136–144.

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