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Anxiety and Depression Are More Prevalent in Patients with Graves' Disease than in Patients with Nodular Goitre

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Key Words
Graves' disease · Depression · Anxiety · Quality of life · Nodular goitre

Abstract
Background and Objective: Graves' disease has been associated with an increased psychiatric morbidity. It is unclarified whether this relates to Graves' disease or chronic disease per se. The aim of our study was to estimate the prevalence of anxiety and depression symptoms in patients with Graves' disease compared to patients with another chronic thyroid disease, nodular goitre, and to investigate determinants of anxiety and depression in Graves' disease. ***Methods:*** 157 cross-sectionally sampled patients with Graves' disease, 17 newly diagnosed, 140 treated, and 251 controls with nodular goitre completed the Hospital Anxiety and Depression Scale (HADS). The differences in the mean HADS scores between the groups were analysed using multiple linear regression, controlling for socio-demographic variables. HADS scores were also analysed dichotomized: a score >10 indicating probable 'anxiety'/probable 'depression'. Determinants of anxiety and depression symptoms in Graves' disease were examined using multiple linear regression. ***Results:*** In Graves' disease levels of anxiety (p = 0.008) and depression (p = 0.014) were significantly higher than in controls. The prevalence of depression was 10% in Graves' disease versus 4% in nodular goitre (p = 0.038), anxiety was 18 versus 13% (p = 0.131). Symptoms of anxiety (p = 0.04) and depression (p = 0.01) increased with comorbidity. Anxiety symptoms increased with duration of Graves' disease (p = 0.04). Neither thyroid function nor autoantibody levels were associated with anxiety and depression symptoms. ***Conclusions:*** Anxiety and depression symptoms were more severe in Graves' disease than in nodular goitre. Symptoms were positively correlated to comorbidity and duration of Graves' disease but neither to thyroid function nor thyroid autoimmunity.

Introduction

Anxiety and depression are common mental disorders affecting the general population [1]. They are often found in patients with chronic somatic diseases, among these thyroid dysfunction [2]. Hypothyroidism has been linked to depression [2–6] but increased prevalence of anxiety

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and depression is also found in hyperthyroidism [7], particularly in the early phase of Graves' disease [8–11], compared with the general population or compared with patients with other chronic thyroid diseases [2, 12, 13]. It remains unclear to which extent anxiety and depression relate to chronic disease as such, or whether it is uniquely tied to hyperthyroidism. Some studies of hyperthyroid patients found that symptoms of anxiety and depression disappeared within months of starting anti-thyroid drug treatment [2, 14, 15], indicating that increased levels of thyroid hormones may contribute to anxiety and depression [2, 16, 17]. Others found that symptoms persisted despite successful anti-thyroid drug treatment [11, 18–21], indicating that anxiety and depression might be related to other aspects of hyperthyroidism, such as thyroid autoimmunity, rather than thyroid hormone status. Elevated levels of thyroid peroxidase antibodies (TPOAb) have been directly related to anxiety and depression in some [19, 22, 23] but not in all studies [24]. Only one study has investigated the influence of thyroid-stimulating hormone (TSH) receptor antibodies (TRAb) on anxiety and depression, and found a significant association between TRAb and anxiety [25].

A meta-analysis suggested that excess mortality in hyperthyroidism, also when treated, was around 20% [26]. In a recent population-based Danish study this was verified with the finding of 30% excess mortality [27], which to some extent seemed related to an increased pre-existing somatic comorbidity. Recent Danish studies have dissected the extent and type of morbidity before and after the diagnosis of hyperthyroidism [28], but also the differences between Graves' and non-Graves' hyperthyroidism [29]. Psychiatric morbidity, whether pre-existing or as consequence of hyperthyroidism, may well contribute to this increased morbidity and mortality in hyperthyroid patients, but has received less attention [7].

The aim of the present study was to estimate the prevalence of anxiety and depression in patients with Graves' disease and to compare the results with those obtained from patients with another chronic thyroid disease, in this case nodular goitre. Furthermore, we aimed at identifying potential clinical and socio-demographic determinants of anxiety and depression in patients with Graves' disease.

Material and Methods

Patients

The study population consisted of 157 cross-sectionally sampled patients with Graves' disease (defined as elevated thyroid hormone levels, suppressed TSH and presence of TRAb at time of diagnosis) and 257 patients with symptomatic nodular goitre. Patients with clinical Graves' orbitopathy were excluded from this study.

The study population constituted a subgroup of patients from a larger survey from 2007 and the sampling procedure has previously been described in detail [30]. In short, patients were recruited from the endocrine outpatient clinics at two university hospitals in Denmark, Copenhagen University Hospital Rigshospitalet and Odense University Hospital. Patients gave their informed consent to participate in the study. Blood samples were drawn at approximately the same time as completion of a questionnaire, which was either returned by mail or delivered by hand in the laboratory or at the clinic on the day of appointment. Analyses were carried out in patients who had complete and non-missing values for both the depression and anxiety items.

Patient-Reported Outcome

Hospital Anxiety and Depression Scale (HADS) is a self-administered questionnaire consisting of 14 items (each scored 0–3), 7 of which concern depression and 7 anxiety symptoms [31]. One of the main purposes of this instrument was to identify affective symptoms among somatically ill patients [32]. Therefore, the items focused on the non-somatic aspects of depression and anxiety, to avoid that symptoms from the somatic disease, such as fatigue, affected the measurements [31, 33].

Depression and anxiety items are summarized separately in two scales ranging from 0 to 21, where a higher score indicates more symptoms. We analysed HADS scores in two ways: as continuous and as dichotomized variables for depression and anxiety. A score >10 was considered as indicating a 'case' of 'probable depression' or 'probable anxiety', respectively [31]. Following standard recommendations, we used the full distribution of scores for statistical analyses but report the frequencies of 'caseness' for descriptive purposes [34].

Socio-demographic data and information about comorbidity and concomitant medication were self-reported. Information on comorbidity was obtained via a pre-specified list of chronic diseases including asthma, allergy, other chronic disease, diabetes mellitus, cataract, hypertension, ischemic heart disease, stroke, chronic bronchitis/emphysema, arthrosis, osteoporosis, ulcus, cancer, migraine, other psychiatric illness, disease of the spine, incontinence, stranguria, tinnitus, and chronic anxiety/depression.

In Denmark, this type of study protocol does not require approval from ethics committees, but does fulfil the Helsinki III Declaration and has been approved by the Data Protection Agency.

Biochemical Measurements

Serum TSH, total thyroxine (T_4), total triiodothyronine (T_3), free T_4 (fT_4), free T_3 (fT_3), T_3 uptake (only Odense University Hospital), TPOAb, and TRAb were analysed using standard methods at the laboratories of the participating hospitals [35].

Statistical Analysis

All analyses were performed with SAS 9.1. Sample characterization was performed using the procedures SAS PROC FREQ, PROC MEANS, PROC TTEST and PROC NPAR1WAY. Mean levels of depression and anxiety symptoms, as measured by the

Table 1. Characteristics of patients with Graves' disease and nodular goitre

	Patients with Graves' disease (n = 157)	Patients with nodular goitre (controls; n = 251)
Females, n	132 (84)	218 (87)
Mean age ± SD, years	45.1±13	52.7±13***
Duration of education, n		
<10 years	32 (20)	85 (34)**
10–12 years	46 (30)	93 (37)
≥13 years	77 (50)	73 (29)***
Living with partner, n	107 (68)	181 (71)
Non-thyroid comorbidity, n	82 (51)	164 (64)*
Current thyroid function and thyroid antibody levels		
TSH, mU/l	0.7 [0.02–1.8]	1.1 [0.7–2.0]***
fT_4, pmol/l	17.6 [14.3–22.6]	13.8 [12.5–16.9]***
fT_3, pmol/l	5.3 [4.6–6.9]	5.5 [4.9–6.4]***
TPOAb, U/l	276 [38–1,071]	3 [2–6]***
TRAb, U/l	4.1 [1.3–8.3]	0.7 [0.0–0.7]***
Time since diagnosis, months	36.7 [6.0–81.5]	14.4 [2.0–97.7]*
Current thyroid function status, n		
Euthyroid	77 (49)	214 (84)***
Mildly hypothyroid	9 (6)	13 (5)***
Overtly hypothyroid	3 (2)	3 (1)***
Mildly hyperthyroid	27 (17)	22 (22)***
Overtly hyperthyroid	40 (26)	3 (1)***
Thyroid treatment, n		
Never treated (any form)	17 (10)	161 (62)***
Antithyroid medication	83 (52)	0***
Levothyroxine	34 (21)	34 (13)*
Radioiodine	18 (11)	28 (11)
Thyroid surgery	19 (12)	69 (27)**

Data are indicated as numbers with percentages in parentheses or medians with interquartile ranges in brackets.

Mildly hypothyroid: serum TSH above reference range and peripheral thyroid hormones within reference range; overtly hypothyroid: serum TSH above reference range and peripheral thyroid hormones below reference range; mildly hyperthyroid: serum TSH below reference range and thyroid hormones within reference range; overtly hyperthyroid: serum TSH below reference range and peripheral thyroid hormones above reference range. Antithyroid medication: current or earlier anti-thyroid medication. Thyroid surgery: hemi-/total thyroidectomy. Significance level for difference among the two groups: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Frequencies compared by χ^2 tests, means compared by Student's t test and medians compared by Wilcoxon signed rank test.

0–21 scored scales in the two patient groups, were compared using multiple linear regression (SAS PROC GLM). The analyses were also controlled for age, sex, educational level, comorbidity, cohabitation and time since diagnosis (covariates). Clinical and sociodemographic determinants of symptom severity in patients with Graves' disease were evaluated by multiple linear regression (SAS PROC GLM). The covariates were: age, gender, education, comorbidity, cohabitation, time since diagnosis, TRAb, TPOAb, and thyroid function (represented by fT_4) levels. Sensitivity analyses were conducted by entering the covariates fT_3, TSH, current thyroid dysfunction (mild/overt hypo/hyperthyroidism, cf. table 1) and being untreated, both separately and simultaneously in the regression model.

Results

Characteristics of the patients at time of inclusion in this study are given in table 1. Patients with Graves' disease were younger, better educated, and had less comorbidity than patients with nodular goitre. As expected, they also had lower concentrations of TSH, higher levels of total T_4, TPOAb, TRAb, and longer duration of disease, while no differences were found in gender distribution or cohabitation.

HADS anxiety was found in 29 of 157 (18%) patients with Graves' disease and in 32 of 247 (13%) patients with

Table 2. Multiple linear regression showing parameter estimates for HADS anxiety and depression symptoms in Graves' disease compared to nodular goitre (reference value = 0, not shown)

	Estimate	SE	p value
Depression	0.9531	0.421	0.024
Anxiety	1.270	0.465	0.007

Adjusted for age, gender, education, comorbidity, and cohabitation.

Table 3. Covariates significantly influencing anxiety and depression score in patients with Graves' disease: multiple linear regression

	Independent variable	Estimate	SE	p value
Depression	other disease	3.860	1.322	0.007
	duration	0.013	0.007	0.064
Anxiety	other disease	3.407	1.563	0.038
	duration	0.017	0.008	0.035

None of the sensitivity analyses with fT_3, TSH, current thyroid dysfunction, and being untreated, changed these results.

nodular goitre (p = 0.131). HADS depression was found in 15 of 157 (10%) patients with Graves' disease, which was significantly higher than among patients with nodular goitre (11 of 251 (4%) (p = 0.038)).

Employing multiple linear regression (table 2), patients with Graves' disease had significantly higher scores on the anxiety and the depression scales than patients with nodular goitre, even after adjusting for age, gender, education, comorbidity, cohabitation and duration of Graves' disease (depression: p = 0.024; anxiety: p = 0.007).

Multiple linear regression analyses among Graves' patients (table 3) showed higher anxiety score among patients with than without comorbidity (estimated difference 3.41; p = 0.038), and among patients with longer duration of disease (estimated 0.02 points per month; p = 0.035). The anxiety score was not significantly associated with age, gender, education, cohabitation, or levels of TRAb, TPOAb, or fT_4. The depression score was also higher among Graves' patients with than without comorbidity (estimated difference 3.9; p = 0.007), but independent of all other covariates. None of the sensitivity analyses with fT_3, TSH, current thyroid dysfunction, or being untreated, changed these results significantly.

Discussion

We found a significantly higher symptom level of anxiety and depression in patients with Graves' disease compared to patients with nodular goitre. Part of the prevalence of HADS anxiety of 10% in patients with nodular goitre might be attributed to fear of thyroid malignancy, a component less often present in patients with Graves' disease.

Previous studies have demonstrated increased symptoms of depression in untreated [4, 9, 10, 18, 19, 36, 37] as well as in treated hyperthyroid patients [14, 15]. A cross-sectional study by Suwalska et al. [36] investigated the occurrence of depression and depressive symptoms in 47 hyperthyroid patients and 58 healthy controls using the Hamilton Depression Rating Scale and the Beck Depression Inventory. In that study, patients with Graves' disease had a prevalence of depressive symptoms of 40% which is much higher than in our study. However, it was not evident from that study whether patients had recent onset and untreated Graves' disease or whether they were treated and euthyroid.

Hamilton Depression Rating Scale is a questionnaire completed by a medical doctor during a short interview and might be considered more reliable than the self-rated HADS in capturing symptoms of anxiety and depression. However, the validity of HADS is supported by studies of the English version of HADS, which report average sensitivities and specificities of 0.8 or higher [32]. Nevertheless, the gold standard of a clinical diagnosis of anxiety/depression is a thorough psychiatric examination.

In our study, Graves' patients with comorbidity had more symptoms of anxiety and depression than patients without comorbidity. It is well known that anxiety and depression are related to specific chronic diseases including thyroid function disorders and reflect the detrimental effect of chronic physical disease on mental health [2]. However, we compared two groups of patients both with a chronic thyroid disease, and even after controlling for other chronic physical and mental diseases, the symptom levels of anxiety and depression were higher in patients with Graves' disease than in patients with nodular goitre indicating that the increased psychiatric comorbidity was more closely tied to Graves' disease.

Anxiety symptoms increased with duration of Graves' disease. A possible explanation for this finding might be that when the patient realises that the chance of complete and permanent remission is low or even non-existent, anxiety may ensue. Furthermore, it cannot be ruled out that sustained fluctuations of the thyroid hormone con-

centrations over a longer period of time induce mental disturbances through a direct effect on the central nervous system [17]. The variable *duration of disease* only describes duration of known disease, so even if there was a short interval from diagnosis to study participation, the patient may potentially have had undiagnosed disease during a much longer time period. Accordingly, this variable must be interpreted cautiously.

We found no significant correlation between fT_4, TPOAb, TRAb and symptoms of anxiety or depression in patients with Graves' disease in this study. Results diverge regarding the influence of thyroid hormones on anxiety and depression. The study of Trzepacz et al. [38] found no relation between thyroid hormones and anxiety or depression. Others have suggested that excess levels of thyroid hormones may cause psychiatric symptoms by affecting the central nervous system directly or indirectly via adrenergic activity [17, 39]. An association between elevated levels of TPOAb and depression has also been suggested [22, 23, 40]. Patients with depression, although biochemically euthyroid, may have alterations in their thyroid function including slight elevation of T_4, blunted TSH response to thyrotropin-releasing hormone, and loss of the nocturnal TSH rise [13]. While repeated fluctuations of thyroid hormone levels over a long period of time might induce mental disturbances, our design did not allow investigation of such a relationship. We cannot exclude the possibility that the prevalence of the mental symptoms would have been even higher if more patients had been untreated and overtly hyperthyroid, and/or had patients with orbitopathy been included.

The selection of control group in observational studies is critical. One option would be to compare with the general population, but in that case finding increased levels of depression or anxiety symptoms in the hyperthyroid patients could be attributed to having a chronic disease. In order to account for this, and to segregate the influence of Graves' disease per se, we chose a control group with another chronic thyroid disease, but without autoimmunity and with a normal or near-normal thyroid function. The difference in baseline characteristics (age, educational background, duration of thyroid disease, thyroid function) between the two is in this respect a limitation, but adjusting for these baseline characteristics in the multiple regression analyses did not significantly change the results or the conclusions and indicates that the confounding effect of baseline differences is minor.

We excluded patients with Graves' orbitopathy, since this disorder can be very debilitating, and would intuitively be expected to confer a higher prevalence of anxiety and depression. A study of Bunevicius et al. [19] supported this assumption, as the researchers found an increased prevalence of mental disorders in Graves' disease with orbitopathy.

In future research of patients with Graves' disease it would be interesting to evaluate the prevalence of anxiety and depression by means of a clinical diagnosis made by a psychiatrist after a thorough psychiatric interview, and to do this longitudinally. First, it would allow drawing conclusions about cause-and-effect relationships between anxiety and depression and uncover the potential underlying risk factors. Second, it could elucidate the extent to which anxiety and depression are affected by other specific chronic diseases.

In conclusion, anxiety and depression, assessed by HADS, were higher in patients with Graves' disease than in patients with nodular goitre – also after adjusting for covariates – indicating that anxiety and depression are tied closely to Graves' disease and not merely to chronic disease. However, comorbidity did increase anxiety and depression symptoms, and the longer the duration of Graves' disease, the more severe were the symptoms of anxiety.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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