

REVIEW

Psychological aspects of Graves' ophthalmopathy

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Abstract

Purpose: This review aims to discuss the psychological aspects of Graves' ophthalmopathy (GO), estimate the prevalence of depression and anxiety disorders in GO, examine whether these psychiatric disorders are more prevalent in GO than in Graves' disease (GD) without eye disease, and evaluate the main contributors for depression and anxiety in GO.

Methods: A review of the literature.

Results: Both depression and anxiety are associated with GO. The prevalence of depression and anxiety disorders specifically in GO patients was estimated at 18–33% and 26–41%, respectively. The reported prevalence in GD patients ranged from 9% to 70% for depression and from 18% to 88% for anxiety disorders. Significantly higher levels of depression and anxiety were found in GD patients compared with patients with non-autoimmune hyperthyroidism. Conflicting results have been reported regarding the association of antithyroid autoantibodies with depression and anxiety disorders. Serum thyroid hormone levels do not correlate with the severity of depression and anxiety. An improvement of psychiatric symptoms is observed in hyperthyroid patients after treatment of thyrotoxicosis. Moreover, depression and anxiety are significantly related to impaired quality of life (QoL) in GO. Exophthalmos and diplopia were not associated with depression nor anxiety, but orbital decompression and strabismus surgery do seem to improve QoL in GO patients.

Conclusions: The results of this review suggest that altered thyroid hormone levels and autoimmunity are prognostic factors for depression and anxiety in GO. With regard to the visual and disfiguring aspects of GO as contributing factors for depression and anxiety, no decisive conclusions can be made.

Keywords: anxiety disorders; depression; Graves' disease; Graves' ophthalmopathy; thyroid disorders

Introduction

Graves' ophthalmopathy (GO) is an autoimmune disease characterized by the inflammation of the periorbital tissues. Inflammation in GO may result in dry eyes, erythema, periorbital swelling, exophthalmos,

conjunctivitis, upper eyelid retraction, diplopia, and even corneal ulceration and optic neuropathy (1). All these clinical manifestations make GO a vision-threatening and disfiguring illness, heavily affecting the quality of

life (QoL) and mental well-being of patients. GO is six times more prevalent among women than men, with an annual incidence rate of 18 women and three men per 100,000 (1). Due to its pathogenesis, GO is closely related to autoimmunity of the thyroid gland. Eighty-five percent of GO patients have hyperthyroidism, most frequently caused by Graves' disease (GD), 10% of GO patients are hypothyroid, and 5% are euthyroid (2). Among GD patients, 20–50% develop ophthalmopathy, making GO the most prominent extrathyroidal manifestation of GD (3). Besides increased levels of free thyroid hormones and reduced levels of thyroid-stimulating hormone (TSH), GD is characterized by elevated serum thyrotropin receptor antibodies (TRAb) and anti-thyroid peroxidase antibodies (TPOAb).

In the 1990s, multiple studies demonstrated a large negative impact of GO on the QoL of patients (4, 5). These studies, however, utilized general health-related quality of life (HRQL) questionnaires, which contained items of little relevance for GO specifically. To solve this problem, Terwee *et al.* developed a disease-specific QoL questionnaire for GO patients (GO-QoL), consisting of 16 questions pertaining to two aspects: visual functioning and appearance (6). Since then, the GO-QoL questionnaire has turned out to be a valid and reliable assessment tool for patients, even to evaluate the effects of different treatments (7, 8, 9).

Furthermore, many studies have reported the association of thyroid dysfunction and GD with psychiatric disorders, mainly depression and anxiety (10, 11). Although GD and GO are two highly associated diseases, most of these studies do not differentiate between GO and GD without eye disease. Pertaining to GO specifically, numerous studies have been performed on the quality of life of patients (12, 13, 14, 15, 16, 17, 18, 19, 20). Nevertheless, to date, few reports have discussed the prevalence of anxiety and depression in GO patients explicitly (13, 21). Consequently, it is not clear whether the altered thyroid hormone levels, the thyroid autoimmunity, or the visual and disfiguring aspects of GO are the main contributors for psychiatric disorders among GO patients. Previously, Bruscolini *et al.* published a review about neuropsychiatric disorders in GO; however, in this review, no clear distinction was made between studies on GD without eye disease versus GO specifically (22).

The present review aims to discuss the psychological aspects of GO, assess the prevalence of depression and anxiety in GO, and assess whether these psychiatric disorders are more prevalent among GO patients compared with GD patients without eye disease. In this review, we focus on depression and anxiety, because these two psychiatric disorders are the most prevalent among dysthyroid, GD, and GO patients. Additionally, the present review aims to assess the main contributors to depression and anxiety among GO patients.

Materials and methods

A literature search was conducted using the Medline, Embase, and Psycinfo databases. Specific keywords and their synonyms were used, including 'Graves' disease', 'Graves' ophthalmopathy', 'hyperthyroidism', 'thyroid disorder', 'mood disorders', 'anxiety disorders', and 'depression'. The search was conducted without any limitations to the publication date. The publication date of the records found from the search ranged from 1922 to November 2022, when the search was conducted. One author filtered the records first based on the title, then based on the abstract, and finally based on the full text. Every English article with a relation to depression or anxiety disorders among dysthyroid, GD, or GO patients was included. On top of that, references from the retrieved studies that were relevant to the topic were also reviewed. For assessing the prevalence of depression and anxiety in GO, only studies that clearly mentioned that the population only consists of GO patients were used. The prevalence of depression and anxiety in GD without eye disease was assessed from studies that mention using a GD population without specifically mentioning eye disease.

Results

The literature search initially resulted in 776 records. Eventually, 44 articles from the literature search were included and analyzed for this review.

Relation of thyroid disorders and GD with depression and anxiety

The association of thyroid disorders with psychiatric disorders, especially mood disorders, has been described for a long time within the literature. Parry in 1825 and Graves in 1835 reported psychiatric manifestations in patients with thyroid dysfunction (23, 24). Both depression and anxiety are more prevalent in hyperthyroidism compared with hypothyroidism (approximately 50–65% vs 35–45%, respectively) (25, 26) (Table 1). Even though hyper- and hypothyroid patients have significantly higher prevalences of depression and anxiety compared with the healthy population, most psychiatric patients do not have thyroid dysfunction (27, 28). These results indicate a one-directional relation between thyroid dysfunction and psychiatric disorders. Likewise, numerous studies reported a correlation between Graves' hyperthyroidism and depression and anxiety (29, 30, 31, 32, 33) (Table 1). Hamed *et al.* revealed that even GD in children is associated with higher frequencies and severities of depression, anxiety, and inattention (34). The association between thyroid dysfunction and GD with depression and anxiety could be explained through the altered levels

Table 1 Association of clinical features with depression and anxiety in GD patients.

Clinical feature	Correlation with depression	Correlation with anxiety	Key findings
GD (without eye disease)	Correlation with depression	Correlation with anxiety	Significantly higher levels of depression and anxiety in GD patients compared with patients with nodular goiter (non-autoimmune hyperthyroidism) (29, 30, 31, 32, 33)
Thyroid dysfunction	Correlation with depression	Correlation with anxiety	Depression and anxiety more prevalent in hyperthyroidism than hypothyroidism (25, 26)
Serum thyroid hormone levels	No correlation with the severity of depression	No correlation with the severity of anxiety	The severity of hyperthyroidism is not linked to the severity of depression and anxiety (33, 42, 44, 47, 48)
Antithyroid antibodies	Conflicting results	Conflicting results	Some studies show association, others don't (34, 42, 44, 46, 49, 50)
Treatment response	Improvement after treatment	Improvement after treatment	Improvement in psychiatric symptoms in hyperthyroid and GD patients after treatment of thyrotoxicosis (33, 54, 56, 57)

of thyroid hormones that impact the nervous system. In fact, Naicker *et al.* found significant expression of TSH receptors in the limbic regions of healthy adults (35). Comparably, Schreckenberger *et al.* found regional metabolic changes within the limbic and paralimbic structures of hyperthyroid GD patients (36). Multiple recent studies have also reported that GO patients have altered brain connectivity (37, 38, 39, 40, 41).

Prevalence of depression and anxiety in GD

Previous studies have reported various prevalences for depression and anxiety in GD patients, ranging from 9% to 70% for depression and from 18% to 88% for anxiety (11, 32, 33, 42, 43, 44). Placidi *et al.* found no significant difference in depression and anxiety frequencies between GD patients and patients with non-autoimmune hyperthyroidism (11). On the contrary, three larger and more recent studies found significantly higher levels of depression and anxiety in GD patients compared with patients with nodular goiter (42, 45, 46).

Relation of serum thyroid hormone levels and antithyroid antibodies with depression and anxiety

In general, authors reported that serum thyroid hormone levels (TSH, triiodine (T3) and thyroxine (T4)) do not correlate with levels of depression and anxiety, meaning that the severity of hyperthyroidism is not linked to the severity of depression and anxiety in hyperthyroid patients (33, 42, 44, 47, 48) (Table 1). Nonetheless, Krysiak *et al.* studied a population consisting only of females and noted that the severity of depression positively correlated with serum-free thyroid hormone levels and inversely correlated with serum TSH levels (46). In addition, Hamed *et al.* found lower serum TSH levels and higher serum T3 and T4 levels to be significant predictors of emotional and behavioral problems in pediatric GD patients (34). With regards

to the association of antithyroid autoantibodies with depression and anxiety, conflicting results exist. Some studies mentioned that there is no relation between serum TRAb and depression and anxiety (42, 49), while others reported that higher concentrations of TRAb are associated with higher prevalences of depression and anxiety (34, 44, 46). Another study even reported that hyperthyroid GD patients at onset had significantly smaller volumes of amygdalae and hippocampi than healthy controls and that, within these patients, serum TRAb levels negatively correlated with the volumes of these regions (50). Pertaining to TPOAb, Bové *et al.* reported no connection with depression or anxiety. Other authors found that TPOAb-positivity is linked to depression in GD patients (46, 49, 51).

The effect of treatment of hyperthyroidism on depression and anxiety in dysthyroid and GD patients

Previous prospective studies have generally illustrated an improvement in psychiatric symptoms in hyperthyroid patients after treatment of thyrotoxicosis (52, 53, 54, 55). The same thing applies to the treatment of Graves' hyperthyroidism (33, 54, 56, 57) (Table 1). Chattopadhyay *et al.* even reported that there was no significant improvement in psychiatric symptoms in GD patients between only anti-thyroid drug treatment (ATD) and ATD combined with anti-psychotropic medication (43). Yu *et al.* found that patients who became subclinically hypothyroid after treatment had significantly more depression compared to those who were euthyroid (49). This finding is consistent with the literature, as subclinical hypothyroidism has been linked to depression (58). In addition, some studies demonstrated that GD patients with depression were less likely to be cured and more likely to relapse into hyperthyroidism after treatment compared to GD patients without depression (57, 59). On the other hand, a few studies revealed residual psychiatric symptoms after patients

achieved euthyroidism with treatment, indicating that the development of psychiatric manifestations in dysthyroid patients is not necessarily caused by altered thyroid hormone levels alone (60, 61).

The role of stress in the onset of GD

Many studies have been conducted on the influence of psychological stress on the onset of GD. Retrospective studies found that GD patients reported more negative life events and psychological stress within 12 months prior to GD onset compared to healthy controls (62, 63, 64, 65, 66, 67). Despite this, when it comes to prospective studies among euthyroid subjects, experiencing more psychological stress does not precipitate the onset of thyroid autoimmunity (68, 69). Some additional studies illustrated that the incidence of GD and hyperthyroidism did not increase during times of war when the population was exposed to acute and chronic stress (70, 71).

Psychiatric aspects of Graves' ophthalmopathy

Prevalence of depression and anxiety in GO

From the few studies we found, the prevalence of depression and anxiety in GO patients was assessed between 18–33% and 26–41%, respectively (Table 2), compared to 8.2% and 1.1% in the general population (13, 21, 72, 73, 74, 75). One study reported exceptionally high depression and anxiety prevalences in GO patients (60% and 70%, respectively) (76).

Relation of depression and anxiety with QoL in GO patients

Multiple studies have reported a significant relationship between depression and anxiety with impaired quality of life (QoL) in GO patients (13, 73, 74). Some studies also conducted multivariable regression analyses to

determine the unique predictors for QoL in GO patients. Kahaly *et al.* and colleagues found depression and anxiety to be the foremost predictors of HRQL in GO patients (73). Another study used the GO-QoL questionnaire, consisting of two subscales: an appearance-related QoL subscale and a vision-related QoL subscale (77). Two separate multiple regression models were made, one for each GO-QoL subscale. They found that depression, in addition to older age and GO asymmetry, made a significant independent contribution to vision-related QoL (21). Similarly, Wiersinga *et al.* noted that older patients reported significantly lower scores on the vision-related GO-QoL subscale (12). Furthermore, depression, appearance-related social anxiety, and social avoidance (assessed by the Derriford Appearance Scale) were reported as significant unique contributors to appearance-related QoL (21, 78). Another study reported that female GO patients reported more appearance-related problems compared to male patients (12). On the contrary, anxiety (HADS-Anxiety) was not found to be a unique contributor to either of the two GO-QoL subscales (21). The aforementioned tools gauge psychological symptoms from a patient perspective. In contrast, Wang and colleagues investigated QoL impact in GO patients as perceived by physicians. Physicians scored their perceptions on how GO impacted patients' QoL based on a 7-point Likert scale, with 1 being 'not impaired at all' and 7 being 'extremely impaired'. In this study, the proportion of GO patients with depression progressively increased with higher physician-perceived QoL impact scores. The prevalence of anxiety, however, was stable across the spectrum of the physician-perceived QoL impact score (72).

Relation of patient/clinical characteristics with depression and anxiety in GO patients

No significant association was found between depression in GO patients and age or sex (13, 21, 72) (Table 3). One author noted no relation between depression in GO patients and GO or GD duration (13). Also, in multiple studies, GO duration was not associated with QoL, except

Table 2 Prevalences of depression and anxiety in GO patients.

Author (year)	Population size (n)	Female (%)	Mean age +/- s.d. (years)	Prevalence depression (%)	Prevalence anxiety (%)	Questionnaire used to assess depression and anxiety (cut-off score)
Kahaly (2005) (73)	102	78	41, 18–72 (median, range)	23.5	40.2	Hospital Anxiety and Depression Scale (HADS) (≥ 11)
Bunevicius (2005) (76)	30	100	45 \pm 14	60.0	73.0	Standard Mini-International Neuropsychiatric Interview (MINI)
Lee (2010) (13)	49	78	41.4 \pm 13.4	32.7	-	Beck Depression Inventory (BDI) (≥ 16)
Wickwar (2015) (21)	121	72	47.1 \pm 12.3	26.0	37.0	Hospital Anxiety and Depression Scale (HADS) (≥ 11)
Cockerham (2021) (74)	100	47	45.2 \pm 7.6	28.0	34.0	Self reported through an online survey
Wang (2021) (72)	714	65	49.4 \pm 13.6	18.3	26.3	Diagnosis from clinical records

for one study that noted an association between longer GO duration and lower QoL (12, 21, 72, 73). In addition, GO patients with lower QoL had significantly more doctor visits per year compared with patients with high QoL (21).

The role of stress in the onset of GO

Kahaly and colleagues studied 102 GO patients, of whom 86 (84%) reported stressful life events within 6 months prior to GO onset. A positive correlation was described between reported stressful life events and levels of depression and anxiety in GO patients (73) (Table 3). Stressful life events were present significantly more often in optic neuropathy patients compared to GO patients without neuropathy. The main stressful life events reported by GO patients were extreme sleeping problems, changed professional situations, and financial difficulties (73). No association was noted between the occurrence of stressful life events and T3 concentrations, TRAb concentrations, and the presence of exophthalmos.

Relation of GO severity and GO activity with depression and anxiety

Conflicting results have been reported on the association of depression and anxiety with GO severity and GO activity (Table 3). Pertaining to GO severity (European Group on Graves' Orbitopathy (EUGOGO) classification) two authors reported no significant link with depression in GO patients (13, 72, 79). In spite of that, in the study by Farid and colleagues, moderate to severe GO patients scored significantly higher on the depression subscale of the Profile of Mood States (POMS) as opposed to

negligible to mild GO patients (80). However, no significant difference in GO severity was noted regarding the anxiety subscale of the POMS (80). Moreover, Kahaly *et al.* found significantly higher levels of depression and anxiety in severe GO patients versus mild GO patients (73). On the other hand, another study noted the opposite results: a significantly higher anxiety prevalence in patients with moderate GO than in those with severe GO (72). Concerning GO activity (clinical activity score (CAS score)), no significant relation was found with depression in GO patients in two studies (73, 81). In another study, however, depression in the GO patients was associated with a higher CAS score (13). Kahaly *et al.* did find significantly higher levels of anxiety in active GO patients compared with inactive GO patients, but Wang *et al.* reported no significant relation (73, 81).

Relation of GO signs and symptoms with depression and anxiety

Exophthalmos (assessed by Hertel exophthalmometer), one of the most prominent signs of GO, was not associated with depression or anxiety in two studies (13, 73). However, another author linked exophthalmos to higher levels of depression and anxiety (80) (Table 3). Moreover, no relation was found between diplopia (assessed by the Gorman score) and depression or anxiety (13, 80) (Table 3). Other studies found a significant relation between certain GO signs and symptoms on one hand, and QoL on the other hand. Cockerham *et al.* reported a significant relation between diplopia, photophobia, blurred vision, or preorbital pain, and QoL (74). Correspondingly, Wang and colleagues demonstrated that vision-related symptoms (diplopia, decreased

Table 3 Association of demographic/clinical features with depression and anxiety in GO patients.

Clinical feature	Correlation with depression	Correlation with anxiety	Key findings
Age	No correlation	-	Depression not significantly associated with age in GO patients (13, 21, 72)
Sex	No relation	-	Depression not significantly associated with sex in GO patients (13, 21, 72)
GO/GD duration	No relation	-	No significant association between depression and GO/GD duration (13)
Reported stressful life events 6 months prior to GO onset	Positive correlation	Positive correlation	Reported stressful life events correlate with higher depression and anxiety levels in GO patients (73)
GO Severity (EUGOGO)	Conflicting results	Conflicting results	Some studies show association, others do not (13, 72, 73, 80)
GO Activity (CAS score)	Conflicting results	Conflicting results	Some studies show association, others do not (13, 73, 81)
Exophthalmos	Conflicting results	Conflicting results	Mixed findings on the association between exophthalmos and depression/anxiety (13, 73, 80)
Diplopia	No relation	No relation	No significant association between diplopia and depression/anxiety (13, 80)
Orbital decompression surgery	Significantly improved depression	Significantly improved anxiety	Significantly improved depression and anxiety (86)

vision, and color vision changes) and structural GO symptoms (strabismus, soft tissue swelling, conjunctival swelling, eyelid swelling, eyelid redness, conjunctival redness, corneal involvement, eyelid retraction, and eye muscle involvement) are significantly more prevalent in GO patients with lower QoL versus higher QoL (72). Nevertheless, exophthalmos, ocular dryness, and excessive tearing were equally prevalent in GO patients with high and low QoL (72).

Effect of GO-specific treatment on depression, anxiety and GO-QoL

Orbital decompression and strabismus surgery were shown to significantly improve appearance-related GO-QoL and vision-related GO-QoL (17, 18, 20, 82, 83, 84, 85). Additionally, radiotherapy significantly improved the visual functioning aspect of GO-QoL, while eyelid lengthening and blepharoplasty significantly improved the appearance-related aspect of GO-QoL (17, 83). Steroid treatment was also shown to improve GO-QoL (20, 84). Regarding the effects of GO-specific treatment on depression and anxiety in patients, only one study mentions that the levels of depression and anxiety significantly reduced after orbital decompression surgery (86) (Table 3).

Discussion

Depression and anxiety are associated with and highly prevalent in GO (Table 4). Thyroid dysfunction is associated with depression and anxiety, with some studies even showing significant expression of TSH receptors in the limbic regions of healthy adults and regional metabolic changes in the limbic and paralimbic structures of GD patients (35, 36). The severity of hyperthyroidism, however, is not associated with the severities of depression and anxiety (33, 42, 44, 47, 48).

Generally, an improvement in psychiatric symptoms is reported when reaching euthyroidism after treatment (52, 53, 54, 55, 56, 57). Nonetheless, a few studies noted long-term psychological complaints among patients after remission of hyperthyroidism (60, 61). The reported prevalence of depression and anxiety in both GD and GO are particularly discordant. This discordance could be explained due to the use of different psychometric assessment tools and the small population sizes used in these studies. Furthermore, the problem with many of these studies is the lack of distinction between GO and GD without eye disease. In this review, the prevalence of anxiety and depression in GO was assessed by using studies that clearly mentioned that the population only consists of GO patients. The prevalence of depression and anxiety in GD without eye disease, however, was assessed from studies that mention using a GD population without specifically mentioning eye disease. It is possible that these studies also included GD patients with eye disease (i.e. GO patients), without specifically mentioning the eye aspect of the disease. Consequently, it is difficult to decisively estimate, based on the current literature, whether depression and anxiety are more prevalent in GO than in GD without eye disease.

Regardless, it is evident that depression and anxiety are more prevalent in GD than in non-autoimmune hyperthyroidism, indicating that autoimmunity also contributes to psychiatric disorders among GO patients (42, 45, 46). Multiple studies even noted an association between antithyroid antibodies and depression and anxiety (34, 44, 46, 49, 51). This is in agreement with the literature, as autoimmune disease has been linked to psychiatric disorders (87). On the other hand, some studies reported no significant relation between antithyroid antibodies and depression and anxiety (42, 49).

Both depression and anxiety are associated with lower GO-QoL (13, 73, 74). Depression is a significant contributor to impaired QoL in GO, while HADS-anxiety (which focuses primarily on general anxiety disorder

Table 4 Key findings regarding quality of life in GO patients.

Clinical feature	Key findings
Depression	Depression is a significant predictor of impaired QoL in GO patients (13, 21, 73, 74)
Anxiety	Anxiety is not a unique contributor to QoL in GO patients (21)
Age	Older age is associated with lower vision-related QoL (12, 21)
Appearance-related social anxiety and social avoidance	Appearance-related social anxiety and social avoidance contribute to appearance-related QoL (21, 78)
Female gender	Female GO patients report more appearance-related problems compared to male patients (12)
Exophthalmos	Exophthalmos is equally prevalent in patients with high and low QoL (72)
Diplopia	Significant relation between diplopia and QoL (72, 74)
Orbital decompression surgery	Improves appearance-related and vision-related QoL (17, 18, 20, 82, 83, 84, 85)
Strabismus surgery	Improves appearance-related and vision-related QoL (17, 18, 20, 82, 83, 84, 85)
Radiotherapy	Improves vision-related QoL (17, 83)
Eyelid lengthening and blepharoplasty	Improves appearance-related QoL (17, 83)
Steroid treatment	Improves appearance-related and vision-related QoL (20, 84)

symptoms) is not (21, 72). Moreover, older age is a significant contributor to impaired visual-related QoL, while female sex and social anxiety and avoidance (Derriford Appearance Scale) are significant contributors to impaired appearance-related QoL (12, 21).

On top of that, conflicting results exist on the relation between depression and anxiety with GO severity and activity, with some studies reporting an association, while others reporting none (13, 72, 73, 80, 81). These conflicting results could also be explained by the various assessment tools used to assess depression and anxiety and the small population sizes of these studies. Moreover, exophthalmos, the most notable sign of GO, was not associated with depression or anxiety (13, 72). Likewise, no relation was found between diplopia and depression or anxiety (13, 80). Despite that, both exophthalmos and diplopia are associated with impaired GO-QoL, and both orbital decompression and strabismus surgery significantly improve GO-QoL (82, 83). Additionally, orbital decompression has been shown to significantly reduce the levels of depression and anxiety among GO patients (83).

The results we have examined suggest that altered thyroid hormone levels and autoimmunity are prognostic factors for depression and anxiety in GO patients. Regarding the visual and disfiguring aspects of GO as contributors to depression and anxiety, no decisive conclusions can be made.

To conclude, due to a paucity of studies investigating the prevalence of depression and anxiety in GO, the lack of concordance of these results, and the small population sizes of these studies, it is difficult to make general conclusions in this area of research. To solve this problem, we propose that a single, validated assessment tool for psychiatric disorders should be designed specifically for GO patients and used to assess the prevalence and contributors of psychiatric disorders among GO in a large study population.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

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