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ORIGINAL ARTICLE

# The relationship between quality of life, cognition, and thyroid status in Graves' disease

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## Summary

**Purpose** To assess quality of life (QoL) and cognitive function among Graves' disease (GD) patients with different thyroid status, with and without ophthalmopathy.

**Methods** This is a cross-sectional clinic-based study involving 154 patients with GD (81.27% were female, mean age 45.6 ± SD 11.2 years) and 54 (35.06%) had ophthalmopathy. Data were collected after an informed consent from all patients was obtained. All patients completed the 36-Item Short Form Health Survey and Mini-Mental State Examination. Patients with ophthalmopathy also completed the Graves' Orbitopathy Quality of Life Questionnaire.

**Results** Patients with hyperthyroidism presented a greater impairment in QoL when compared to euthyroidism group. A lower score in physical role functioning was found in both subgroups with active disease (hyperthyroidism and euthyroidism using thionamides). A lower score was also seen in visual function, only in patients with hyperthyroidism, without difference in appearance. No difference was found in cognition between patients. Younger ages at diagnosis, male sex, euthyroidism and absence of ophthalmopathy were factors associated with better QoL, as well as a shorter disease duration was associated with better recall, attention and calculation.

**Conclusions** An impairment in QoL among patients with active GD was evidenced, even in those receiving thionamides and in euthyroidism. Ophthalmopathy was a factor associated with a poor QoL and no clear evidence of cognitive impairment was demonstrated.

**Keywords** Graves' disease · Graves' ophthalmopathy · Quality of life · Cognitive function · Hyperthyroidism

## Introduction

Graves' disease (GD) is an autoimmune disorder characterized by glandular hyperfunction and excess of thyroid hormones, associated with loss of the negative feedback between thyroid and hypothalamic-pituitary axis. It is the most common cause of hyperthyroidism, is more commonly found in young and female patients [1, 2].

Thyroid hormones play an essential role in mood regulation and cognition, with a great clinical variability that is directly related to disease duration, thyrotoxicosis severity, individual susceptibility to thyroid hormone excess and patient's age [3, 4]. In the acute phase of GD, patients usually complain of poor concentration and memorization, emotional lability, irritability, insomnia, psychomotor agitation, depression, and anxiety. Some prospective studies have shown that both affective and cognitive symptoms presented at the onset of the condition usually improve after reaching euthyroidism [5], however a Swedish and a Danish prospective study showed that the impairment in quality of life persists even after months and years of euthyroidism [6, 7].

Besides poor quality of life-related to hyperthyroidism, Graves' disease patients with involvement of the eyes have an additional negative impact on psychological, social and work efficiently, which affect the quality of life and is associated with great changes in physical appearance [8]. Previous studies have reported a significantly reduced quality of life and an increased psychosocial morbidity in patients with ophthalmopathy, especially those with severe or active ophthalmopathy [9, 10].

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Most studies that evaluated the quality of life in patients with GD were limited to analyze the subgroup affected by ophthalmopathy, with few studies directed to an overall evaluation of the patient, including cognitive status. Thus, the impact of GD on patient well-being cannot be neglected, regardless of disease state and whether the individual has ocular involvement or not.

Therefore, the objective of this study is to evaluate the quality of life and cognitive function in GD patients according to the status of thyroid function and regarding the different therapeutics options, with and without ocular disease.

## Materials and methods

### Patients recruitment

The study is a cross-sectional clinic-based study involving selected GD patients followed at the Thyroid Disease Unit in a tertiary Endocrinology Department. The diagnosis of GD was based on signs and symptoms of thyrotoxicosis, suppressed level of thyroid stimulating hormone (TSH), high level of free thyroxine (fT4) and presence of TSH receptor antibodies (TRAb). One hundred and fifty-four patients with GD older than 18-year-old were studied (29 men and 125 women, mean age 45.6 ± SD 11.2 years and mean duration of the disease 8.0 ± 6.5 years). To evaluate the influence of thyroid hormones on quality of life and cognition, patients were divided into two groups according to TSH and fT4 levels to determine if the patients were in hyperthyroidism or euthyroidism. To evaluate the repercussion of treatment choice in quality of life and cognition, they were also subdivided into 5 subgroups according to thyroid status and therapeutic option employed during follow up. Groups were respectively: hypothyroidism after radioiodine therapy using levothyroxine with normal thyroid function, hypothyroidism after thyroidectomy using levothyroxine with normal thyroid function, active GD using thionamides with normal thyroid function, active GD using thionamides or not and with hyperthyroidism and disease remission.

Patients were excluded from the study if they showed any acute inflammatory disease, history of recent cardiovascular events (myocardial ischemia, unstable angina or stroke), malignant neoplasia, heart failure (NYHA III or IV), severe hepatic disease, severe kidney disease (CKD stages 4, 5, and hemodialysis), hepatitis B, C and HIV infection, psychiatric disease, cognitive dysfunction or preexistence dementia and functional illiterate. Also, were excluded patients presenting comorbidities that interfere in the quality of life as disabling rheumatoid arthritis, severe obesity or diabetes (type 1 or 2) with inadequate glycemic control.

Data were collected from October 2015 to October 2018, and all participants gave their written informed consent and ethical committee approval for the study was obtained according to Declaration of Helsinki, Human Research Ethics Committee in Lausanne, No 204/14). Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient. CAAE: 47834815.0.0000.5404.

### Clinical assessment

Clinical characteristics, images, and biochemical data were obtained from medical records. Clinical data collected were: age at diagnosis, disease duration, gender, years of schooling, comorbidities (including other autoimmune or chronic disease), smoking habits, use of levothyroxine and methimazole, radioiodine therapy, thyroid ultrasound characteristics, weight, height, body mass index, ophthalmometry (right and left eye), follow-up, and estimated time of thyrotoxicosis and euthyroidism (based on medical appointment). Serum TSH (reference values 0.41–4.5 mUI/L), fT4 (reference values 0.9–1.8 m/dL), thyroglobulin antibodies (reference values < 115 mUI/L), thyroid peroxidase antibodies (reference values < 35 UI/mL) and TRAb (reference values < 1.58 UI/mL) were measured by electrochemiluminescence immunoassay.

Clinical eye evaluation was elaborated to define the degree of ophthalmopathy inflammatory activity and the measure of proptosis. Clinical Activity Score (CAS) assessed the degree of inflammation and was calculated from 7 items, with 1 point assigned to each alteration presented: spontaneous orbital pain, gaze-evoked orbital pain, eyelid swelling, eyelid erythema, conjunctival redness, chemosis and inflammation of caruncle or plica. A CAS of 3 or higher indicates an active inflammatory ophthalmopathy.

Proptosis was evaluated with an ophthalmometer routinely used in our service. It is an instrument composed of a lateral rod with marking in centimeters as a ruler that connects to a front rod, forming an angle of 90°. The lateral rod is adjusted to the temporal region of the patient, and then it is possible to measure the distance between the outer corner of the eye and the cornea.

Health-related quality of life was assessed using a Brazilian version of the 36-Item Short Form Health Survey (SF-36) questionnaire which includes subscales for physical function, limitations due to both health and emotional problems, pain, general health, vitality, social function, and general mental health. These eight domains are summarized in Physical Component Scale and Mental Component Scale. Answers were calculated into scores ranging from 0 (worst) to 100 (best). We did not use a specific questionnaire for quality of life for patients with thyroid disease because there

was no such measure validated for use with Brazilian patients at the time of our study.

Cognition was assessed using the Mini-Mental State Examination (MMSE) which is a 30-point questionnaire used to measure cognitive impairment. The test takes between 5 and 10 min and examines functions including registration, attention and calculation, recall, language, ability to follow simple commands and orientation. Any score higher than or equal to 24 points (out of 30) indicates a normal cognition. Below these 24 points, patients are characterized as having a mild (19–23 points), moderate (10–18 points) and severe cognitive impairment (≤9 points).

Patients with ophthalmopathy were also evaluated with Graves' Orbitopathy Quality of Life Questionnaire (GO-QoL). The GO-QoL contains 8 questions on visual functioning and 8 questions on appearance; answers were calculated into scores ranging from 0 (worst) to 100 (best).

All the subjects were evaluated in a calm and quiet room, with no interference from the outside. They had enough time to answer all the questionnaires. The three instruments were applied at the same day, one followed by the other, by the same physician.

### Statistical analyses

Statistical analyses were performed with the Statistical Analysis System (SAS)—System for Windows, version 9.4. SAS Institute Inc., 2002–2008, Cary, NC, USA. To describe sample profile according to the study variables, frequency tables of categorical variables with absolute ($n$) and percentage (%) values were used, and descriptive statistics of numerical variables, with mean values, standard deviation, minimum and maximum values and median. The Mann–Whitney test was used to compare cognitive function and quality of life. The Kruskal–Wallis test was used to compare cognitive function and quality of life between all groups, followed by Dunn's post-hoc test to identify the differences. The Spearman correlation coefficient was used to correlate fT4 and TSH with cognitive function and quality of life. A linear regression analysis was used to correlate factors with cognitive function and quality of life. The data were transformed into ranks. The significance level was set at $p < 0.05$.

## Results

### Demographic and clinical characteristics

We analyzed 154 GD patients, of which 125 (81.17%) were female and 54 (35.06%) had ophthalmopathy, 41 (26.62%) were smokers. Mean age at diagnosis, age at evaluation, disease duration and years of schooling were respectively: $37.49 \pm 11.45$; $45.6 \pm 11.2$; $8.18 \pm 6.51$; and $8.01 \pm 3.53$. Patients were divided into two groups, according to thyroid status at the evaluation and then subdivided into five subgroups, according to thyroid function and treatment employed. Of these, 128 (83.12%) subjects were in euthyroidism and 26 (16.88%) were in hyperthyroidism at the time of the evaluation. Subgroups were, respectively: 58 (37.66%) at hypothyroidism after radioiodine therapy using levothyroxine with normal thyroid function, 20 (12.99%) at hypothyroidism after thyroidectomy using levothyroxine with normal thyroid function, 27 (17.53%) at active GD using thionamides with normal thyroid function, 26 (16.88%) at active GD using thionamides or not and with hyperthyroidism and 23 (14.94%) at disease remission.

**Table 1** Frequencies of baseline characteristics of patients

| Variables | Frequency $N = 154$ |
|---|---|
| Sex (Female/Male) | 81.17 / 18.83% |
| Smoking | 26.62% |
| Ophthalmopathy | 35.06% (54) |
| CAS 0 | 9.25% (5) |
| CAS 1–2 | 75.92% (41) |
| CAS ≥ 3 | 14.81% (8) |
| *CAS subitem's* | |
| Spontaneous orbital pain | 0 |
| Gaze-evoked orbital pain | 1.85% (1) |
| Eyelid swelling | 14.81% (8) |
| Eyelid erythema | 50% (27) |
| Conjunctival redness | 90.74% (49) |
| Chemosis | 1.85% (1) |
| Inflammation of caruncle or plica | 11.11% (6) |
| Other chronic disease* | 51.30% |
| Other autoimmune disease** | 20.25% |
| TgAb > 115 mUI/L | 46.34% |
| TPOAb > 35 UI/mL | 70.63% |
| *Thyroid status at the evaluation* | |
| Hyperthyroidism | 16.88% |
| Euthyroidism | 83.12% |
| *Subgroups* | |
| Hypothyroidism after radioiodine therapy | 37.66% |
| Hypothyroidism after thyroidectomy | 12.99% |
| Active disease with normal thyroid function under thionamides | 17.53% |
| Active disease with hyperthyroidism | 16.88% |
| Disease remission | 14.94% |

Values are expressed as $n$ (%)

*CAS* Clinical Activity Score, *TbAB* thyroglobulin antibodies, *TPOAb* thyroid peroxidase antibodies, *N* number

*Hypertension, diabetes, dyslipidemia, and obesity

**Type 1 diabetes, vitiligo, psoriatic arthritis, systemic lupus erythematosus, and rheumatoid arthritis

**Table 2** Descriptive analysis of clinical and laboratory characteristics of patients

| Variables | Mean ± SD $N = 154$ |
|---|---|
| Age at diagnosis (years) | 37.49 ± 11.45 |
| Age at the evaluation (years) | 45.67 ± 11.21 |
| Thyroid disease duration (years) | 8.18 ± 6.51 |
| Years of schooling (years) | 8.01 ± 6.51 |
| Body Mass Index (Kg/m$^2$) | 27.69 ± 4.76 |
| Proptosis of the right eye (mm) | 13.50 ± 4.11 |
| Proptosis of the left eye (mm) | 13.67 ± 4.21 |
| Estimated time of thyrotoxicosis (months) | 27.01 ± 19.44 |
| Estimated time of euthyroidism (months) | 59.48 ± 57.39 |
| TSH at the evaluation (mUI/L) | 2.04 ± 1.55 |
| fT4 at the evaluation (m/dL) | 1.61 ± 1.04 |
| Follow-up (months) | 73.34 ± 64.19 |

Values are expressed as mean and SD

*mm* millimeters, *TSH* thyroid stimulating hormone, *fT4* free thyroxine, *SD* standard deviation, *N* number

Clinical and biochemical characteristics are summarized in Tables 1 and 2.

## Quality of life in Graves' disease patients according to the disease status and presence of ophthalmopathy

When comparing patients with hyperthyroidism and euthyroidism, it is possible to state that: hyperthyroidism group showed a greater impairment in quality of life, especially in physical role functioning (59.62 vs. 82.81; $p = 0.006$) and emotional role functioning (61.54 vs. 82.81; $p = 0.009$) (Table 3). Analyzing patients in relation to the current situation of the disease and type of treatment employed, we also found a lower score in physical role functioning, at both subgroups with active disease, in hyperthyroidism and euthyroidism using thionamides ($p = 0.028$) (Table 4).

At evaluation of patients with ophthalmopathy by Graves' Orbitopathy Quality of Life Questionnaire (GO-QoL), a greater impairment of visual function was seen among patients with hyperthyroidism when compared to euthyroidism group (88.93 vs. 95.17; $p = 0.026$), but no difference was found in appearance (53.98 vs. 66.70; $p = 0.177$). No difference in visual function ($p = 0.1637$) and appearance ($p = 0.5714$) was found when they were compared into subgroups of treatment.

At multiple logistic regression analysis of the variables, thyroid status (euthyroidism or hyperthyroidism), age at diagnosis, age at evaluation, disease duration, sex, ophthalmopathy, years of schooling, estimated time of thyrotoxicosis and euthyroidism, showed that factors associated with better quality of life were younger ages at diagnosis (physical functioning, $p = 0.009$; physical role functioning, $p = 0.002$; social role functioning, $p = 0.035$ and emotional role functioning, $p = 0.002$), male sex (pain, $p = 0.0464$ and mental health, $p = 0.0039$) patients in euthyroidism (physical role functioning, $p = 0.005$ and emotional role functioning, $p = 0.001$) and absence of ophthalmopathy (general health perception, $p = 0.0257$; social role functioning, $p = 0.0337$ and mental health, $p = 0.0165$).

**Table 3** 36-Item Short Form Health Survey (SF-36) and Graves' Orbitopathy Quality of Life Questionnaire comparing Graves' disease patients in hyperthyroidism and euthyroidism at the evaluation

| | Hyperthyroidism | Euthyroidism | *p*-value |
|---|---|---|---|
| *36-Item Short Form Healthy Survey (SF-36)* | | | |
| Physical functioning* | 85.38 ± 21.91 | 92.07 ± 12.53 | 0.476 |
| Physical role functioning* | 59.62 ± 47.47 | 82.81 ± 35.87 | **0.006** |
| Bodily pain* | 72.12 ± 30.33 | 70.26 ± 26.24 | 0.692 |
| General health perception* | 66.31 ± 28.62 | 74.13 ± 23.92 | 0.179 |
| Vitality* | 70.58 ± 27.14 | 73.20 ± 22.53 | 0.874 |
| Social role functioning* | 94.17 ± 12.34 | 91.31 ± 18.60 | 0.558 |
| Emotional role functioning* | 61.54 ± 47.79 | 82.81 ± 36.70 | **0.009** |
| Mental health* | 69.23 ± 25.84 | 73.86 ± 25.12 | 0.474 |
| Physical component scale* | 48.82 ± 9.76 | 51.33 ± 6.67 | 0.614 |
| Mental component scale* | 49.10 ± 10.49 | 51.66 ± 11.30 | 0.240 |
| *Graves' Orbitopathy Quality of Life Questionnaire (GO-QoL)* | | | |
| Visual Function | 88.93 ± 9.27 | 95.17 ± 7.11 | **0.026** |
| Appearance | 53.98 ± 25.81 | 66.72 ± 12.5 | 0.177 |

Values are expressed as mean and standard deviation (SD)

The *p*-value indicates if any statistically significant difference was found between groups. Statistically significant *p*-values are in bold

*Mean (SD) based on 2009 US population norms

At evaluation of TSH and fT4 levels with quality of life, we found a direct and positive correlation between TSH level and physical role functioning ($r = 0.1968$, $p = 0.0144$) and emotional role functioning ($r = 0.1613$, $p = 0.0457$).

## Cognitive function in Graves' disease patients according to thyroid hormone status

No significant difference was found in cognitive function, evaluated by MMSE, between patients in euthyroidism and hyperthyroidism (27.8 vs. 28.42, $p = 0.067$) as well as in subgroups ($p = 0.344$). We found a positive correlation between the free T4 level and the MMSE score ($r = 0.1645$, $p = 0.0415$). A shorter disease duration was a factor associated with better recall ($p < 0.0001$), attention and calculation ($p = 0.019$).

**Table 4** 36-Item Short Form Health Survey (SF-36) and Graves' Orbitopathy Quality of Life Questionnaire comparing patient's subgroups according to disease state

| | Hypothyroidism after RIT | Hypothyroidism after thyroidectomy | Active disease with normal thyroid function | Active disease with hyperthyroidism | Disease remission | *p*-value |
|---|---|---|---|---|---|---|
| *36-Item Short Form Healthy Survey (SF-36)* | | | | | | |
| Physical functioning* | 90.43 ± 15.48 | 92.00 ± 10.93 | 92.41 ± 10.04 | 85.38 ± 21.91 | 95.87 ± 6.33 | 0.594 |
| Physical role functioning* | **84.48 ± 35.61** | **85.00 ± 29.69** | **72.22 ± 44.04** | **59.62 ± 47.47** | **89.13 ± 29.99** | **0.028** |
| Bodily pain* | 64.22 ± 27.74 | 77.60 ± 21.27 | 73.67 ± 24.53 | 72.12 ± 30.33 | 75.09 ± 26.40 | 0.246 |
| General health perception* | 71.57 ±26.08 | 74.80 ± 20.88 | 79.74 ± 17.91 | 66.31 ± 28.62 | 73.43 ± 26.98 | 0.508 |
| Vitality* | 70.43 ± 25.59 | 71.75 ± 15.58 | 74.81 ± 24.79 | 70.58 ± 27.14 | 79.57 ± 15.22 | 0.648 |
| Social role functioning* | 91.38 ± 20.31 | 86.25 ± 20.64 | 90.28 ± 18.13 | 94.17 ± 12.34 | 96.74 ± 10.80 | 0.259 |
| Emotional role functioning* | 85.06 ± 35.42 | 83.33 ± 35.05 | 72.84 ± 44.37 | 61.54 ± 47.79 | 88.40 ± 31.16 | 0.051 |
| Mental health* | 71.79 ± 26.07 | 69.80 ± 22.87 | 73.63 ± 28.53 | 69.23 ± 25.84 | 82.87 ± 18.89 | 0.421 |
| Physical component scale* | 50.01 ± 8.08 | 53.02 ± 6.23 | 52.01 ± 5.01 | 48.82 ± 9.76 | 52.35 ± 3.89 | 0.718 |
| Mental component scale* | 51.67 ± 11.80 | 49.44 ± 9.79 | 50.46 ± 13.18 | 49.01 ± 10.49 | 54.98 ± 8.45 | 0.301 |
| *Graves' Orbitopathy Quality of Life Questionnaire* | | | | | | |
| Visual function | 95.71 ± 6.52 | 93.74 ± 7.79 | 95.23 ± 8.68 | 88.93 ± 9.27 | 97.62 ± 5.83 | 0.163 |
| Appearance | 67.08 ± 30.39 | 61.72 ± 26.80 | 72.92 ± 20.41 | 53.98 ± 25.81 | 72.92 ± 28.96 | 0.571 |

Values are expressed as mean and standard deviation (SD)

The *p*-value indicates if any statistically significant difference was found between groups. Statistically significant *p*-values are in bold

*Mean (SD) based on 2009 US population norms

## Discussion

In this study, we found a poor quality of life at both subgroups with active Graves' disease, both in hyperthyroidism and euthyroidism patients using thionamides, particularly in physical and emotional scales. A better quality of life was associated with male sex, younger ages at diagnosis, normal thyroid function and absence of eye disease. No difference was found in cognitive evaluation; however, a shorter disease duration was associated with better memory, attention and calculation.

Our study is in agreement with others presented in literature [11–13], that similarly found a poor quality of life among patients with overt hyperthyroidism, probably due to the physical limitations imposed by the symptoms related to the disease, in association with psychiatric symptoms, also described by Chattopadhyay et al. [14]. in a case-control study in patients with a recent diagnosis of GD. They found significantly higher rates of psychiatric manifestations, including generalized anxiety and mood disorder compared to healthy control group. Some prospective studies also described a persistent impairment in quality of life even after months or years of euthyroidism [6, 7]. Cramon et al. [7]. found a severe disease-specific (evaluated by the thyroid-related patient-reported outcome—ThyPRO) and generic HRQoL (evaluated by SF-36) impairments in Graves' hyperthyroidism and toxic nodular goiter. The same HRQoL deficits were found in both groups after 6 months of treatment. Likewise, Abraham-Nording et al. [6]. found lower scores of vitality, even many years after treatment, when compared GD patients with a large Swedish reference group. At the same time, they did not find a difference in the quality of life scores among the three treatments modalities (antithyroid drugs, radioiodine, and surgery). In contrast, we found a difference between patients using thionamides, apart from thyroid status but still in activity of the autoimmune disease, and other groups of treatment, possibly because of higher levels of FT4 associated partial improvement of hyperthyroidism symptoms, stress and anxiety related to treatment. Male patients presented higher scores on quality of life, in pain and mental health, when compared to women. However, we did not find previous studies that mentioned this difference.

Not only HRQoL questionnaires showed a decrease in quality of life among GD patients, some authors had already evidenced brain changes in imaging tests during overt hyperthyroidism and its association with symptoms reported by patients [15, 16]. Schreckenberger et al. [15]. carried out a cross-sectional study in patients with untreated Graves' disease and healthy controls, correlating the level of anxiety and depression with findings on cerebral glucose metabolism assessed by PET fluorodeoxyglucose. Patients with hyperthyroidism had decreased glucose metabolism in the

limbic system, which was associated with the severity of anxiety and depression. Zhang et al. [16]. compared patients in hyperthyroidism and healthy controls with functional MRI, and found that patients with hyperthyroidism had poor connectivity between anterior cingulate cortex, posterior cingulate cortex, and left hippocampus, and between the right hippocampus and orbitofrontal right medial cortex, brain areas involved with emotional and cognitive control.

Only among patients with ophthalmopathy and hyperthyroidism at evaluation, a greater impairment of visual function was seen, but they did not show a difference in appearance or when they were divided into subgroups. In meantime, most patients reported that they used to avoid photographs and public places, and tried to hide proptosis using sunglasses and make-up. Many others studies, in different countries, showed a worsening quality of life in both visual function and appearance, especially when it is associated with a worse CAS score [8, 17]. Quality of life in GD patients with ophthalmopathy is also a public health concern since can affect psychosocial function, hobbies, and employment, with loss of productivity and increase in coasts at work [18]. Besides the concern about costs with the disease, a Danish study evaluated the incidence of suicide in GD patients and reported an increased suicide rate in GD overall, which is even higher in patients with ophthalmopathy [19].

No difference was found in cognitive function, by MMSE punctuation, between patients in euthyroidism or hyperthyroidism, as well as in their subgroups. However, a shorter disease duration was a factor associated with better recall, attention, and calculation. The MMSE is not the best tool to evaluate cognition in young patients since it is more commonly used in the evaluation of dementia in the elderly, however it is simple, objective and can be applied by any physician and it has been used for a long time. The studies are quite contradictory in relation to the association between hyperthyroidism, overt or subclinical, and cognition, probably because of population variation and the huge diversity of tests for cognition evaluation [20].

Samuels et al. [21, 22]. evaluated young women using suppressive therapy with LT4 and found no difference in cognition, nor when they evaluated older men with no thyroid disease, in relation to cognition and TSH and fT4 levels. Moon et al. [23]. also evaluated older patients with thyroid cancer using suppressive levothyroxine therapy and were compared with healthy controls, they did not find any cognitive impairment. Furthermore, they also describe positive correlations between serum T4 levels and some cognitive domains suggesting a potential beneficial effect of exogenous levothyroxine.

Other studies, from all over the world (Brazil, Italy, Korea), demonstrated the association between dementia and subclinical hyperthyroidism in older adults [24–26]. In contrast, Aubert et al. [27]. found a higher risk of dementia and a larger cognitive decline only among older adults with subclinical hyperthyroidism with a TSH < 0.10mIU/L. Not only TSH levels have been associated with dementia, one recent Australian study has already shown a link between higher fT4 levels and cognitive decline in older man [28].

As for Graves' disease patients, Vogel et al. [5]. compared 31 newly diagnosed patients and in thyrotoxicosis, with 34 healthy individuals. No difference between patients and the control group on neuropsychological tests were found. Lillevang-Johansen et al. [29]. evaluated discordant twin pairs and likewise Vogel et al. they did not demonstrate any clinically relevant negative impact of previous hyperthyroidism on long-term cognitive function.

As a limitation of the study, we can cite the small number of patients in each group and the lack of a prospective evaluation. However, the use of combined tools to assess the quality of life and cognitive function, applied at the same day and by the same physician, is considered as a strong point of our study.

In conclusion, we found a great impairment in quality of life among patients with active GD, especially in physical and emotional areas, even in those with normal thyroid function receiving thionamides. Ophthalmopathy was a factor associated with a poor quality of life and no clear evidence of cognitive impairment was demonstrated. These types of evidence stimulate a discussion about psychological and social well-being among patients with GD, presenting with eye disease or not, and if we are giving the proper attention for them or if we are just worried about TSH and fT4 levels. Physicians must concern about diagnosis and treatment, but they must also be aware of the importance of recognizing, as soon as possible, any sign of psychological suffering.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical standards** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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