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Quality of Life in Patients with Hyperthyroidism: Where do we stand?

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Abstract

Introduction. Increasing interest exists concerning the physical and mental wellbeing of patients with hyperthyroidism.

Aim. This review aims at gathering the most updated literature on the quality of life (QoL) in patients with hyperthyroidism.

Method: We searched PubMed from inception to May 20, 2020 for English language studies using the following entries: “hyperthyroidism AND quality of life”, “Graves’ disease AND quality of life”, “diffuse toxic goiter AND quality of life”, “toxic nodular goiter AND quality of life”, “subclinical hyperthyroidism AND quality of life”. Thirty-nine papers were finally reviewed.

Results: Patients with hyperthyroidism have worse QoL than euthyroid subjects, especially if they have Graves’ disease and Graves’ orbitopathy. Treatment of hyperthyroidism with restoration of euthyroidism may not fully restore QoL even after many years, indicating that such patients have difficulties adapting to and coping with their illness, thus experiencing marked and longstanding limitations in physical, mental and psychosocial functioning.

Conclusion. As differences exist on long-term outcomes between therapeutic options for hyperthyroidism, it is logical to hypothesize related differences in long-term changes in QoL. Future clinical and psychological studies could monitor QoL and its related domains across different stages of disease and deepen patients’ trajectories of illness experience and the use of coping strategies to face their condition.

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1. Introduction

Whereas medicine was predominantly oriented towards etiopathogenic mechanisms of diseases during the last century, during the last decades the physical and mental well-being of patients sparked relevant interest. The term “quality of life” (QoL) was first used in 1966 by Elkinton in an editorial entitled “Medicine and the Quality of Life” (Elkinton, 1966), referring to the Francis Bacon’s “*harmony*” of the “*curious harp of man’s body*”, which was the “*the office of medicine*”. Previously, medicine was “*doing the tuning*” of the harp “*with unprecedented skill*”, but was “*having trouble with the harmony*” (Elkinton, 1966). Thenceforth, medical care outcomes started to take into account also the patient’s point of view (Kahaly et al., 2002; Testa & Simonson, 1996).

It is known that health-related QoL involves the subjective assessment of the impact of disease and treatment across the physical, psychological, social and somatic domains of functioning and well-being (Revicki et al., 2000). Particularly, patients with chronic diseases are not only physically ill, but they also exhibit a variable emotional distress and report a decreased QoL (Bianchi et al., 2004; Martino et al., 2018; Ponto et al., 2013).

Therapeutic interventions for chronic diseases should therefore aim both at maintaining the patient symptom-free as long as possible, and at restoring QoL (Bianchi et al., 2004; Conversano, 2019; Conversano et al., 2020, in press; Kahaly et al., 2002; Lenzo et al., 2020; Martino et al., 2019a; Porcerelli et al., 2017; Vicario & Martino, 2020; Vicario et al., 2020; Zimmerman et al., 2019). Besides, the relevance of QoL can be advocated also in the light of a response shift, regarding the adjustment of expectations and satisfaction about health status beyond functional capacity and role limitation, as shown in several chronic conditions (Caputo, 2014; Cohen & Biesecker, 2010; Graham et al., 2012; Merlo, 2019a, 2019b; Settineri et al., 2019a). This tendency to report good QoL even in serious and persistent disability is known as “disability paradox” (Albrecht & Devlieger, 1999), highlighting that QoL refers to finding a balance between body, mind, and spirit in the self, and more widely, in relation to the external environment (Barberis et al., 2020; Rosa et al., 2019). Furthermore, the increased use and the implications of QoL impact health economics (Donaldson et al., 2011).

Thyroid hormone excess is termed “thyrotoxicosis”, while the term “hyperthyroidism” is restricted to thyrotoxicosis due to inappropriately high synthesis and secretion of thyroid hormones (Ross et al., 2016). However, in the daily practice and in this review, “thyrotoxicosis” and “hyperthyroidism” are used interchangeably.

The prevalence of hyperthyroidism in the United States is approximately 1.2%, with subclinical hyperthyroidism (i.e. low or undetectable serum thyrotropin [TSH] with normal serum free thyroxine [FT4] and triiodothyronine [FT3]) being more frequent than overt hyperthyroidism (i.e. low or undetectable TSH and high FT4 and/or FT3) (Ross et al., 2016). Furthermore, the epidemiology of hyperthyroidism varies based on iodine status, with Graves' disease accounting for 60-80% of cases of hyperthyroidism in iodine sufficient areas (Carlé et al., 2011).

Graves' disease is caused by circulating TSH-receptor stimulating antibodies (TRAb), which induce thyroid hyperfunction and growth, and contribute to the typical ultrasound features of the thyroid (Vita et al., 2019). Toxic multinodular goiter and toxic adenoma are two other common causes of hyperthyroidism and result from multiple or solitary autonomously functioning thyroid nodule(s), respectively (Ross et al., 2016). Below we will refer to toxic multinodular goiter and toxic adenoma as "toxic nodular goiter".

This review focuses on the impact of hyperthyroidism and its treatment on QoL. The relationship between hyperthyroidism and cognitive decline and aging is treated elsewhere (Rieben et al., 2016; Samuels, 2008). We will also disregard exogenous forms of hyperthyroidism, such as iatrogenic hyperthyroidism.

2. Method

We searched PubMed from inception to May 20, 2020 for English language studies using the following entries: "hyperthyroidism AND quality of life", "Graves' disease AND quality of life", "diffuse toxic goiter AND quality of life", "toxic nodular goiter AND quality of life", "subclinical hyperthyroidism AND quality of life". Duplicates were eliminated as well as papers in which non-standardized questionnaires were used. Abstracts were screened to select relevant papers, and subsequently, full texts were assessed. Finally, we also examined references of the included papers. From a total of 747 papers, 39 were ultimately reviewed.

3. Results

Table 1. Thyroid-specific and general questionnaires used to measure quality of life (QoL) in patients with hyperthyroidism.

Questionnaire	Scales/explored domains	N. of Items	Item scoring	Scale scoring	QoL trend with respect to score*	Composite score(s)	Reference
Thyroid-Related Patient-reported Outcome (ThyPRO)	<ul style="list-style-type: none"> 13 multi-item scales: goiter symptoms, hyperthyroid symptoms, hypothyroid symptoms, eye symptoms, tiredness, cognition, anxiety, depressivity, emotional susceptibility, impaired social life, impaired daily life, impaired sex life, cosmetic complaints; 1 single-item scale: overall QoL impact 	85	Likert scale: 0-4	$[\text{Average score in a scale}/4] \times 100 \rightarrow 0-100$	negative	Tiredness, Cognition, Anxiety, Depressivity, Emotional Susceptibility, Impaired Social Life, Impaired Daily Life, and Overall QoL scales	(Watt et al., 2009)
Thyroid-Related Patient-reported Outcome-39 (ThyPRO-39) – ThyPRO short-form	<ul style="list-style-type: none"> 12 multi-item scales: 4 physical symptom scales (2 three-item and 2 four-item scales); 7 three-item scales about physical, 	39	Likert scale: 0-4	$[\text{Average score in a scale}/4] \times 100 \rightarrow 0-100$	negative	7 three-item scales about physical, mental and social well-being and function	(Watt et al., 2015)

	<p>mental and social well-being and function; one three-item scale concerning appearance;</p> <ul style="list-style-type: none"> • 1 single-item scale: overall QoL impact 						
Graves' ophthalmopathy QoL questionnaire (GO-QOL)	<ul style="list-style-type: none"> • 8 questions on visual functioning (e.g. limited in cycling, in driving, in walking indoors, in walking outside, in reading, in watching TV, in hobby and interference with daily life) • 8 questions on changed appearance (e.g. feeling of social isolation, change in appearance, feeling of being watched, unpleasant reactions, influence on self-confidence, influence on friendship, less often on photos, using camouflage) 	16	<p>Likert scale: 0-3. For two questions on the appearance scale (i.e. less often on photos and using camouflage) available options are: no, yes, don't know/not applicable</p>	Sum of 8 questions in each scale and transformation into a 0-100 scale	positive	None	(Terwee et al., 1998)

<p>National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25)</p>	<p>General health (1 item), general vision (1 item), near vision (3 items), distance vision (3 items), driving (2 items), peripheral vision (1 item), color vision (1 item), ocular pain (2 items), role difficulties (2 items), dependency (3 items), social function (2 items), and mental health (4 items).</p>	<p>25</p>	<p>Likert scales</p>	<p>0-100</p>	<p>positive</p>	<p>One overall composite score)</p>	<p>(Bradley et al., 2006)</p>
<p>Short-Form 36 Health Survey (SF-36) or Medical Outcome Study-36 (MOS-36)</p>	<ul style="list-style-type: none"> • 4 multi-item scales on physical aspects: physical functioning (10 items), physical aspects of role functioning (4 items), bodily pain (2 items), general health perceptions (5 items); • 4 multi-item scales on psychosocial aspects: vitality (4 items), social functioning (2 items), emotional aspects of role functioning (3 items) and mental health (5 items) 	<p>36 (35+1 item on change in health during the last year not included in the scoring process)</p>	<p>Likert scales, yes/no options</p>	<p>0-100</p>	<p>positive</p>	<p>Mental composite score on mental health scales Physical composite score on physical health scales</p>	<p>(Jenkinson et al., 1993)</p>

Short-Form 24 Health Survey (SF-24) or Medical Outcome Study-24 (MOS-24)	Physical functioning (6 items), physical aspects of role functioning (2 items), bodily pain (1 item), social functioning (1 item), health perceptions (5 items), energy (4), mental health (5 items)	24	Likert scales, yes/no options	0-100	positive	Mental composite score on mental health scales Physical composite score on physical health scales	(Stewart et al., 1988)
Short-Form 12 Health Survey (SF-12) or Medical Outcome Study-12 (MOS-12)	Physical functioning (2 items), physical aspects of role functioning (2 items), bodily pain (1 item), general health perceptions (1 item); social functioning (1 item), emotional aspects of role functioning (2 items), energy (1 item) and mental health (2 items)	12	Likert scales, yes/no options	0-100	positive	Mental composite score on mental health scales Physical composite score on physical health scales	(Ware et al., 1995)
Nottingham Health Profile (NHP)	Energy, emotional reactions, sleep, social isolation, mobility and pain. Optional: occupation, housework, social life, family life, sexual function, hobbies and holidays	38 (+7 optional)	Yes/no options	0-100	negative	None	(Bertin et al., 1992)
Modified Sickness Impact Profile (SIP) (3 subscales)	3 multi-item scales: social interactions (20 items), household management (10 items),	38	Likert scales	Items are weighted according to standardized weighting scheme	positive	None	(Bergner et al., 1981)

	leisure pastimes and recreation (8 items)						
Psychological General Well-Being Index (PGWI)	6 multi-item scales: anxiety (5 items), depression (3 items), positive well-being (4 items), self-control (3 items), general health (3 items), vitality (4 items)	22	Likert scales (0-4)	0-110	positive	One overall composite score	(Dupuy, 1984)
European QoL (EuroQoL)	<ul style="list-style-type: none"> • 3 three-categories: main activity, social relationships and mood; • 4 three-categories: mobility, self-care, pain. • Visual analogue scale (VAS) from 100 to 0 in which patients indicate how they judge their current health 	6	Likert scale (1-2 or 1-3)	Algorithm from national cost-utility analysis	positive	None	(Carr-Hill, 1992)
Modified Zerssen's complaints scale	One multi-item	38	Likert scale (0-3)	Sum score	negative	None	(Bauer et al., 2001)

* A positive trend of QoL with respect to score means that the higher the score the higher QoL. Conversely, a negative trend of QoL with respect to score means that the higher the score the lower QoL.

3.1 QoL scales

Patients-reported outcome measures (PROMs) are questionnaires developed to capture the impact of diseases and their treatment on QoL from the patient's perspective (Boesen et al., 2018). PROMs can be divided into thyroid-specific and generic questionnaires (Table 1). The main advantage of thyroid-specific PROMs is that they are based on questions on thyroid-related symptoms and aspects. Only two PROMs specific for hyperthyroid diseases have been extensively validated and translated in several languages: the Thyroid-related Patient-Reported Outcome (ThyPRO) and the Graves' Orbitopathy Quality of Life Questionnaire (GO-QOL). A systematic review including 14 standardized QoL questionnaires showed that ThyPRO, GO-QOL and the Thyroid Treatment Satisfaction Questionnaire (ThyTSQ), which received the highest number of positive ratings in overall level of psychometric evidence, were recommended for the assessment of QoL in patients with benign thyroid disease, Graves' orbitopathy (GO) and hypothyroidism, respectively (Wong et al., 2016). In addition, responsiveness is defined as the ability of a PROM to detect relevant clinical changes over time. Importantly, the thyroid-specific PROMs ThyPRO and GO-QOL were shown to be more responsive compared with the general PROM SF-36 (Terwee et al., 2001; Watt et al., 2014; Wiersinga, 2012).

ThyPRO measures a range of aspects of QoL, both thyroid-specific (e.g. goiter) and nonspecific (e.g. fatigue) (Watt et al., 2009, 2014). It consists of 85 items summarized in 13 multi-item scales and one single-item scale (Table 1) (Watt et al., 2009, 2014). Each item is rated on a Likert scale from 0 (no symptoms/problems/impairment) to 4 (severe symptoms/problems/impairment). The average score of items in a scale is divided by four and multiplied by 100, thus ranging from 0 (no symptoms or impairment, i.e. best QoL) to 100 (most symptoms or impairment, i.e. worst QoL). More recently, a short-form of ThyPRO (ThyPRO-39) was developed (Watt et al., 2015). It consists of 39 items, 12 multi-item scales and one single-item scale. Based on factor analysis, a supplemental composite summary score was also developed (Watt et al., 2015).

GO-QOL contains 8 questions on visual functioning and another 8 on changed appearance. Both visual function, which is impaired due to decreased visual acuity and/or diplopia, and eye appearance, are negatively changed in patients with GO (Terwee et al., 1998). GO-QOL scores range from 0 (worst) to 100 (best) (Table 1) (Terwee et al., 1998). GO-QOL correlates positively with another two general QoL questionnaires, namely the Sickness Impact Profile (SIP) and the Short Form 24 Health Survey (SF-24) (Table 1). A GO-QOL change of 6 points on at least one of either subscale is perceived by the patient as beneficial (Terwee et al., 2001; Wiersinga, 2012).

The mostly used generic QoL questionnaire in patients with thyroid diseases is the Short Form 36 Health Survey (SF-36), a 36-item version of the Medical Outcome Study (MOS) (Table 1)

(Jenkinson et al., 1993). SF-36 analyzes both mental and physical aspects of well-being, and it consists of 8 multi-item scales plus one additional item on change in health during the last year. Each scale scores from 0 to 100, with higher scores implying a better health status. In addition, two composite scores are obtained from the mental and physical health scales, Mental Component Summary (MCS) and Physical Component Summary (PCS) respectively (Jenkinson et al., 1993). The 12-item and 24-item short-forms of MOS also exist (Table 1).

Recently, ThyPRO-39 and SF-12 were administered to 308 patients with benign thyroid diseases, and as expected, hyperthyroid symptoms scores or general health scores were significantly higher or lower in patients with Graves' disease (n=13) compared to those without Graves' disease (Wong et al., 2018).

3.2 General aspects and differences in QoL according to etiology of hyperthyroidism

From one-third to two-thirds of patients with hyperthyroidism experience depressive and/or anxiety disorders, although a wide spectrum of neuropsychiatric disturbances may occur, including dysphoria, insomnia, obsessive compulsive disorders, emotional lability, personality disorders, schizophreniform disorders and decreased cognitive function (Bruscolini et al., 2018; Chattopadhyay et al., 2012; Gulseren et al., 2006; Kathol & Delahunt, 1986; Trzepacz et al., 1988). Decreased turnover of catecholamines and changes in serotonergic and noradrenergic receptors in the brain secondary to elevated thyroid hormone levels have been hypothesized. Concerning adrenergic receptors, the number of β -adrenergic or α -adrenergic receptors is increased or decreased, respectively, in patients with hyperthyroidism (Fardella et al., 2000). Indeed, regardless of the hyperthyroidism etiology, antithyroid drugs administered with or without β -adrenergic receptor antagonists can reduce neuropsychiatric symptoms (Kathol & Delahunt, 1986). However, rapid changes in serum thyroid hormones levels and the consequent variations in catecholamine receptor sensitivity and catecholamine metabolism upon antithyroid drugs initiation are capable to trigger acute psychosis in predisposed subjects (Vita et al., 2013). In patients with Graves' disease, brain effects of TRAb have also been hypothesized, as TSH-receptors are expressed in brain areas such as frontal cortex, amygdala, hippocampus and thalamus (Crisanti et al., 2001).

Emotional distress can precede or accompany hyperthyroidism through its course (Vita et al., 2009, 2015). Particularly, physical, psychological or infectious stressful life events may precede the onset of hyperthyroidism in patients with Graves' disease, GO and toxic nodular goiter (Vita et al., 2015; Kahaly et al., 2002, 2005; Topcu et al., 2012). However, the number and the impact of stressful events are higher in patients with Graves' disease compared with those with toxic nodular goiter (Matos-Santos et al., 2001). Genetic predisposition may account for this

difference (Vita et al., 2017). Graves' disease is also associated with higher serum levels of thyroid hormones and more severe thyroid hormone excess-related symptoms, such as palpitations, heat intolerance and emotional lability. All these aspects, together with GO, impact negatively on the well-being of patients with Graves' disease, who report an overall lower QoL compared with patients affected by toxic nodular goiter (Bukvic et al., 2015; Cooper & Biondi, 2012). Two studies compared ThyPRO scores of patients with Graves' disease or toxic nodular goiter, highlighting similarities in three domains (goiter symptoms, hyperthyroid symptoms and tiredness) (Cramon et al., 2016), but differences in other three domains (eye symptoms, anxiety and sex life domains) (Bukvic et al., 2015). Also, differences in three ThyPRO domains (eye symptoms, anxiety and emotional susceptibility) after thyroidectomy were pointed out (Bukvic et al., 2015).

3.3 Subclinical hyperthyroidism

Studies addressing the impact of subclinical hyperthyroidism on QoL are contrasting. Biondi and colleagues compared SF-36 scores of 23 young and middle-aged patients with subclinical hyperthyroidism (15 affected by multinodular goiter and 8 by autonomously functioning thyroid nodule) with those of 23 sex- and age-matched controls (Biondi et al., 2000). MCS and PCS scores were 14 and 13 points lower in patients compared with controls, respectively (36.1 ± 9.5 vs. 50.0 ± 8.5 and 42.6 ± 8.0 vs. 55.6 ± 4.1). Furthermore, MCS and PCS scores correlated inversely with symptoms of hyperthyroidism, but did not correlate with serum levels of TSH, FT3 and FT4 (Biondi et al., 2000). The authors pointed out that young and middle-aged patients with subclinical hyperthyroidism frequently report palpitations, heat intolerance, nervousness, tremor and sweating. Consequently, QoL can be affected in these subjects (Biondi et al., 2000; Cooper & Biondi, 2012).

An Italian case-control study on 368 patients with subclinical or overt thyroid diseases found that all SF-36 domains, except bodily pain, were reduced in patients with overt hypo- or hyperthyroidism (Bianchi et al., 2004). These patients scored lower than controls also at the Nottingham Health Profile (NHP) (Table 1) (Bertin et al., 1992; Bianchi et al., 2004). In contrast, QoL of subjects with subclinical hypo- or hyperthyroidism was in the range of the control population (Bianchi et al., 2004). In a German cross-sectional epidemiological study conducted, in a screened population of about 4,000 subjects free from known thyroid diseases, the rate of overt or subclinical hyperthyroidism was 0.4% or 1.6%, respectively (Grabe et al., 2005). Interestingly, compared to euthyroid subjects, patients with overt hyperthyroidism, but not those with subclinical hyperthyroidism, had lower complaint-score, as measured by the modified 38-item Zerssen Complaint Scale (Table 1) (Grabe et al., 2005). In accordance with these studies (Bianchi et al., 2004; Grabe et al., 2005), in an Australian community-based cross-sectional study,

the authors did not find any difference in the SF-36 composite scores (i.e. MCS and PCS) or in the Psychological General Well-Being Index scores between 52 patients with subclinical hyperthyroidism and 156 age-matched euthyroid controls (Bell et al., 2007). In addition, whether or not QoL scores were adjusted for age, thyroid function was not an independent determinant of well-being (Bell et al., 2007). A Danish study has investigated anxiety and depression in patients with hyperthyroidism through administering the Hospital Anxiety and Depression Scale (HADS) and concluded that symptoms were more severe in Graves' disease than in nodular goiter (Bové et al., 2014). Finally, a Turkish case-control study investigated prospectively the effects of both overt and subclinical hyperthyroidism in terms of depression, anxiety, QoL and disability, using the Hamilton Depression Rating Scale (HAM-D), the Hamilton Anxiety Rating Scales (HAM-A), the SF-36 and the Brief Disability Questionnaire (BDQ), respectively (Gulseren et al., 2006). Compared with 20 euthyroid controls and 13 patients with subclinical hyperthyroidism, 51 patients with overt hyperthyroidism scored higher at BDQ, HAM-D and HAM-A, but lower at PCS and MCS of SF-36, indicating more severe depression, anxiety, disability and QoL impairment. After treatment of hyperthyroidism, all scores improved significantly in the overt group, as opposed to the subclinical group, in which only HAM-D improved (Gulseren et al., 2006). Because of the small sample size and the almost 25% drop-out rate (3 of 13 patients) of the subclinical group, the authors concluded that their results had to be evaluated cautiously (Gulseren et al., 2006).

3.4 Improvement of QoL resulting from treatment of hyperthyroidism

Given that the decreased QoL in patients with hyperthyroidism is assumed to be the consequence of thyroid hormone excess, restoring euthyroidism is expected to restore QoL. To date, three therapeutic options exist for treating hyperthyroidism: antithyroid drugs, radioiodine and thyroidectomy. While antithyroid drugs are effective only in controlling hyperthyroidism, which can relapse over time upon antithyroid withdrawal, radioiodine treatment and thyroidectomy are curative, and therefore, definitive (Ross et al., 2016). European and Asian thyroidologists prefer antithyroid drugs as the first choice of therapy, whereas their American colleagues favor radioiodine, although this choice seems to have declined over the recent years (Burch et al., 2012; Kim et al., 2017). A number of studies have focused on whether these therapeutic options are capable to restore QoL once euthyroidism is achieved (Abraham-Nordling et al., 2005; Bukvic et al., 2015; Conaglen et al., 2018; Cramon et al., 2016; Ljunggren et al., 1998; Tagami et al., 2012; Törning et al., 2019).

A New Zealand cross-sectional study recently compared ThyPRO scores of 123 patients with Graves' disease one year after treatment of their hyperthyroidism with antithyroid drugs, radioiodine or surgery, with those of 18 untreated newly diagnosed Graves' disease patients (Conaglen et al., 2018). QoL improvement was higher in treated patients and did not vary among treatment types. Particularly, the greatest differences were noted for 6 scales, namely hyperthyroid, tiredness, anxiety, emotional susceptibility, impact on social life and impact on daily life scales (Conaglen et al., 2018). However, there is evidence that certain QoL domains may still be variably affected even many years after treatment of hyperthyroidism despite successful restoration of euthyroidism. For instance, a Swedish study (Abraham-Nordling et al., 2005) did not find differences in SF-36 scores in 179 patients with Graves' disease who were randomized to receive antithyroid drugs, surgery or radioiodine treatment. However, compared with a large reference group, all treatment groups showed significantly lower vitality scores 14-21 years after randomization. The authors hypothesized that changes in brain functioning during hyperthyroidism may impact well-being for many years (Abraham-Nordling et al., 2005). Another study with a long-term follow-up showed that patients who had undergone either surgery to preserve thyroid function (n= 38, median follow-up= 18.4 years) or ablative surgery (n= 49, median follow-up= 7.9 years) still had lower SF-36 scores across all subscales compared with the national (British) norms (Al-Adhami et al., 2012). More recently, Cramon et al. (2016) evaluated QoL by ThyPRO and SF-36 in 88 patients with Graves' disease and 68 patients with toxic nodular goiter, and compared their scores with those of two large general population samples. Interestingly, QoL impairments persisted in a wide range of health domains in both groups 6 months after treatment with antithyroid drugs, radioiodine or thyroidectomy. These studies mentioned above (Abraham-Nordling et al., 2005; Al-Adhami et al., 2012; Cramon et al., 2016) are in accordance with a prospective Danish study, in which a considerable proportion of patients had persistent QoL impairments measured with SF-36 one year after initiation of antithyroid drugs (Elberling et al., 2004).

A recent study of a large non-randomized cohort of about 1,000 patients with Graves' disease who had been treated 6-10 years earlier, confirmed that, regardless of treatment modality, they had worse ThyPRO scores compared with the general population (Törring et al., 2019). However, in contrast with a previous study by the same group (Abraham-Nordling et al., 2005), the authors found that radioiodine treatment led to worse thyroid-related QoL (ThyPRO) and generic QoL (SF-36) compared to antithyroid drugs or thyroidectomy (Törring et al., 2019). The authors explain this difference with (i) the larger sample size and the better tools used to measure QoL in the latter study; (ii) the different nationality of the reference population (Swedish in the former study *vs.* Danish in the latter study), (iii) the older age of patients receiving radioiodine

and the consequent excess comorbidity and QoL impairment; (iv) a more prolonged disease course affecting the QoL in the long term in those patients; (vi) the greater exposure to thyroid antigens with prolonged TSH-receptor stimulating antibodies elevation after radioiodine, which might have directly or indirectly, through GO worsening, impacted well-being (Törring et al., 2019).

3.5 Graves' orbitopathy

GO is a debilitating condition resulting from inflammation in the orbital tissue (eye muscles and connective tissue) causing both visual impairment and facial disfigurement (Fallahi et al., 2016; Ferrari et al., 2015). GO occurs because of cross-reactivity between thyroid and orbit antigens. Altered production of preadipocytic fibroblasts and increased adipogenesis along with self-perpetuation of IFN- γ -mediated T-lymphocytes-1 cytokines, such as C-X-C ligand (CXCL)-9, -10 and -11, and the C-X-C chemokine receptor-3 (CXCR-3), have been shown to be involved (Fallahi et al., 2016; Ferrari et al., 2015).

GO can be uni- or bilateral and can range from eye swelling, proptosis and double vision to corneal scarring, optic nerve compression and sight loss. Therefore, in GO an associated psychosocial burden and an additional impairment in QoL, even in the long-term, are present (Egle et al., 1999; Estcourt et al., 2011; Terwee et al., 2002). Patients with GO report lower QoL even compared with patients with diabetes, emphysema, inflammatory bowel disease and heart failure (Gerding et al., 1997; Kahaly et al., 2005; Ponto et al., 2013). Indeed, as much as one third of patients with GO report their eye problems as more troublesome than their hyperthyroidism *per se* (Ljunggren et al., 1998), resulting in feelings of embarrassment, shame, and reduced self-confidence that negatively affect social interactions. Avoiding public places and hiding their proptosis with sunglasses and make-up are some of the coping strategies of patients with GO. Higher somatic and psychiatric morbidity and more frequent sick leaves (Abraham-Nordling et al., 2005; Nexo et al., 2014; Riguetto et al., 2019; Terwee et al., 2002), which eventually result in loss of productivity and increase in costs at work, have been reported (Ponto et al., 2013). A recent Danish registry study on over 28,000 patients with Graves' disease, of whom about 4,000 had GO, showed that patients affected by GO had a 2.7 higher risk of suicides compared to controls (Ferløv-Schwensen et al., 2017). There is also evidence that patients with GO are at higher risk of anxiety, depression and mood disturbance in general, especially those with active or severe disease (Farid et al., 2005; Gerding et al., 1997; Kahaly et al., 2005; Lee et al., 2010; Weng et al., 2019). Clinical activity and severity of GO are measured by the Clinical Activity Scores (a 7-item scale assessing two symptoms and 5 signs of inflammation of the anterior eye soft tissue), and the NOSPECS (a mnemonic composed of the

first character describing classes of the ocular changes in GO: no physical signs or symptoms, only signs, soft tissue involvement, proptosis, extraocular muscle signs, corneal involvement, sight loss), respectively, both being associated with lower GO-QOL scores (Delfino et al., 2017; Kahaly et al., 2005; Park et al., 2004; Terwee et al., 2002).

Two studies showed that patients with GO had lower SF-24 and SIP or SF-36 and HADS scores compared with two large reference groups (Gerding et al., 1997; Kahaly et al., 2002). Interestingly, in both studies duration and severity of GO did not correlate with SF scores (Gerding et al., 1997; Kahaly et al., 2002). However, 9 years later, one of these two groups demonstrated that both the visual functioning and the appearance scales of the GO-specific GO-QOL questionnaire correlate negatively with the severity and the activity of GO (Ponto et al., 2011). Bradley et al. (2006) assessed QoL with the National Eye Institute Visual Function Questionnaire (NEI VFQ-25), a vision questionnaire not specific for GO, in 30 patients with mild to severe GO (Table 1). A moderate impairment of QoL was found, especially in patients with diplopia. However, NEI VFQ-25 was shown to lack important aspects of GO from the patient's perspective, such as altered appearance and ocular discomfort (Bradley et al., 2006). In a recent Brazilian cross-sectional study, 154 patients with Graves' disease, 54 (35%) of whom had GO, completed SF-36 and GO-QOL (Riguetto et al., 2019). Regardless of thyroid status, QoL was reduced in all patients, particularly in those with GO, with the most affected domains being physical role functioning and emotional role functioning of SF-36 (Riguetto et al., 2019). In addition, at multiple logistic regression, euthyroidism and absence of GO predicted a better QoL (Riguetto et al., 2019).

One goal of GO treatment should be improving QoL. For instance, in a Swedish longitudinal study, 5.3±1.2 years after orbital decompression, the visual functioning and the appearance subscales of GO-QOL improved by 28±35 and 26±31 points, respectively (Iacobæus & Sahlin, 2016). GO-QOL was set as a primary outcome in a in a multicenter, double-blinded, randomized, placebo-controlled trial in which 159 patients with GO received selenium or placebo for 6 months; as opposed to placebo, selenium improved GO-QOL (Maccocci et al., 2011). Recently, teprotumumab, a monoclonal antibody directed at the insulin-like growth factor-1 receptor improved the Clinical Activity Score, proptosis and GO-QOL significantly after 24 weeks in two multicenter, double-blinded, randomized, placebo-controlled trials (Douglas et al., 2020; Smith et al., 2017).

Like Graves' hyperthyroidism, also GO should be considered a chronic disease, as even after many years from treatment, QoL may not be fully restored to normality. Interestingly, compared with Graves' disease patients without GO, those who developed GO up to 4 years after antithyroid drugs or radioiodine had decreased SF-36 MCS and PCS regardless of the treatment

modality (Abraham-Nordling et al., 2010). In addition, it took twice as long for them to recover (Abraham-Nordling et al., 2010). Similarly, Villagelin et al., (2019) showed a reduction in GO-QoL scores following treatment for Graves' disease after a 7-year follow-up. QoL could not improve significantly even after GO-specific treatment. Terwee and colleagues (2002) demonstrated that, after 11.7 years (median) from radiotherapy and/or prednisone for GO, SF-36 and GO-QoL scores were higher compared to newly diagnosed Graves' disease patients, but lower compared to healthy subjects, except for the SF-36 scale bodily pain. The same differences were also noticed for the EuroQoL, a general PROM evaluating 6 dimensions: mobility, self-care, main activity, social relationships, pain and mood (**Table 1**) (Terwee et al., 2002).

In 2009, professionals and patient-led organizations signed "the Amsterdam declaration", pledging to enhance the health care of patients with GO in order to improve their QoL (Perros & Wiersinga, 2010). Eight years later one co-author of that declaration wrote that it was "*too early to judge whether progress in these process outcomes will translate to clinically meaningful improvements*" (Perros, 2017).

4. Discussion

Overall, patients with hyperthyroidism have worse QoL than euthyroid subjects, especially if they have Graves' disease and GO. Treatment of hyperthyroidism with antithyroid drugs, radioiodine and thyroidectomy can restore euthyroidism successfully, but may not restore QoL even after many years, maybe because hyperthyroidism induces permanent changes in brain functioning. Similarly, GO affects QoL in the long term, even after treatment with corticosteroids, radiotherapy or orbital surgery. This may indicate that such patients have difficulties adapting to and coping with their illness, thus experiencing marked and longstanding limitations in physical, mental and psychosocial functioning. Indeed, as found in other chronic conditions, such as diabetes (Guicciardi et al., 2019; Marchini et al., 2018; Marchetti et al., 2017; Martino et al., 2019a, 2019b, 2019c, 2020a, 2020c; Settineri et al., 2019b; Verrocchio et al., 2019), cancer (Bălălău et al., 2015; Catalano et al., 2019; Di Giuseppe et al., 2019, 2020; Martino et al., 2020b, 2020d; Motofei et al., 2015; Tomai et al., 2018) or rare diseases (Fabio et al., 2018a, 2018b; Caputo, 2019), processes of personification and protagonization of disease can be enacted over time, progressively leading to ascribe human negative attributes to disease as an external entity.

To date, the use of non-validated PROMs, differences in population sampling (for instance, mild *vs.* moderate to severe GO; subclinical *vs.* overt hyperthyroidism), differences in study

design (longitudinal *vs.* retrospective) and ethnic differences have hindered conclusions based on studies in the literature. In addition, another four methodological issues have emerged.

Firstly, PROM are retrospective in nature, giving rise to concerns about their validity, as memory can be flawed and patients cannot recall past experience properly favoring mental shortcuts to reconstruct it (Stone et al., 2007). Recently, ecological momentary assessment, a real-time measurement method first used for pain and fatigue, was introduced in thyroidology (Boesen et al., 2018a, 2018b). As the ecological momentary assessment investigates experiences by asking repeatedly during the day how patients currently feel, it has three potential advantages: (i) avoiding recall bias; (ii) being ecologically valid (patients answer questions in their everyday lives); (iii) measuring fluctuations of symptoms (Boesen et al., 2018). Boesen et al., (2018a) compared two versions of the same PROM, the traditional, retrospective version of ThyPRO administered on day 28 (as it uses a four-week reference period), and its momentary version administered thrice daily via a smartphone application through 28 days. Eighty-three newly diagnosed hyperthyroid patients (Graves' disease, n= 59, toxic nodular goiter, n= 18; amiodarone-induced hyperthyroidism, n=5, iodine-induced hyperthyroidism, n=1) expected to undergo treatment of hyperthyroidism were enrolled (Boesen et al., 2018a). Although the two versions of ThyPRO correlated each other, the retrospective one provided significantly higher scores, i.e. worse quality of life, on all scales. Also, the head-to-head comparison suggested two types of recall bias: the peak-effect and the end-effect. The peak-effect consisted of the excessive attention paid for tiredness, while the end-effect resulted from the fact that retrospective ratings on emotional susceptibility and anxiety were based on the most recent days (Boesen et al., 2018a). The authors concluded that retrospective and momentary ThyPRO “*should not be used interchangeably*”, and that favoring one over the other “*may depend on the aim of measurement*” (Boesen et al., 2018a). Secondly, questionnaires can be time-consuming, thus reducing the patient's compliance. Thirdly, many QoL questionnaires are administered by an interviewer. It is known that respondents are less willing to disclose their symptoms in interviewer-administered questionnaires than in self-administered questionnaires (Wong et al., 2018), thus explaining, at least in part, the occasionally reported floor and ceiling effects (Al-Adhami et al., 2012; Boesen et al., 2018a; Wong et al., 2018). Floor or ceiling effects occur when there is little variance because of a high floor or a low ceiling of a test, namely most subjects score near the bottom values or near the top values, respectively (Landgraf et al., 1998; Wiersinga, 2012). Using composite scores and a combination of positively and negatively worded items (as in the ThyPRO Tiredness, Depressivity and Emotional Susceptibility scales) may overcome this issue (Watt et al., 2014). Fourthly, most of the studies cited in this review included a clinic-based recruitment. It has been demonstrated that self-awareness of patients' health is heightened when

they have been diagnosed with a medical condition. Consequently, perception of QoL can be biased (Bell et al., 2007; Dayan & Paniker, 2013).

5. Conclusion

Large cross-sectional studies with homogeneous methodology using standardized and validated PROM are needed to evaluate the impact of hyperthyroidism on QoL. Furthermore, large randomized trials with a long-term follow-up will clarify the best care for patients with hyperthyroidism. As differences exist on long-term outcomes between therapeutic options for hyperthyroidism (Sjölin et al., 2019), it is logical to hypothesize related differences in long-term changes in QoL. In this regard, future clinical and psychological studies could monitor QoL and its related domains across different stages of disease and deepen patients' trajectories of illness experience and the use of coping strategies to face their condition. This could allow deeper understandings of patients' perspectives, needs and challenges, which may overall enrich clinical information and contribute to deliver consistent psychological interventions.

Author contributions

R.V. and G.M. made significant contribution to the conception and design of the systematic review, to the acquisition, qualitative analysis and synthesis of data by drafting both the first and revised versions of the manuscript. S.B. and A.C. contributed to the qualitative analysis and synthesis of data by drafting both the first and revised versions of the manuscript. M. C. Q. and P.P. gave significant contribution to draft part of the manuscript. T.W. and U. F-R revised manuscript for intellectual content and gave the final approval of the manuscript to be submitted.

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