

## INVITED REVIEW

# Quality of life in patients with benign thyroid disorders. A review

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## Abstract

The importance of patient-reported outcomes such as health-related quality of life (HRQL) in clinical research is increasingly acknowledged. In order to yield valid results, the measurement properties of HRQL questionnaires must be thoroughly investigated. One aspect of such a validation process is the demonstration of content validity, i.e. that the questionnaire covers all relevant aspects. We review studies reporting on consequences of thyroid disorders and present the frequency of identified aspects, both overall HRQL issues and classical thyroid symptoms, in order to evaluate which issues are relevant for patients with thyroid diseases. Furthermore, existing questionnaires for thyroid patients are reviewed. A systematic search was performed in the Medline, Cinahl and Psycinfo databases and the reference lists of the relevant articles were hand-searched. Seventy-five relevant studies were identified. According to these studies, patients with untreated thyroid disease suffer from a wide range of symptoms and have major impairment in most areas of HRQL. Furthermore, the studies indicate that impairments in HRQL are also frequent in the long term. Six HRQL questionnaires for thyroid patients were identified. Generally, data supporting the validity of these questionnaires were sparse. According to the available literature, the quality of life of thyroid patients is substantially impaired over a wide range of aspects of HRQL in the untreated phase and continues to be so in many patients also in the long term. Studies systematically exploring the relative importance of these various aspects to thyroid patients are lacking, as is a comprehensive, validated thyroid-specific HRQL questionnaire.

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## Background

The evaluation of health-related quality of life (HRQL) implies evaluations of the impact of a disease and its treatment on all relevant dimensions of the patient's life. HRQL measurements usually comprise aspects of physical, mental and social well-being and function. Generally, HRQL is best rated by the patients themselves, usually by means of standardized questionnaires. There are two main types of HRQL measures: disease-specific and generic. Disease-specific questionnaires concern issues of particular relevance for patients with a specific medical condition, whereas generic instruments (e.g. SF-36 or EQ-5D) measure aspects common to most patients. Disease-specific measures often demonstrate greater sensitivity than generic measures, while the latter allow for comparison across diseases and treatments and with scores obtained from the general

population. A combination of disease-specific and generic measures is generally advocated because each provides complementary information (1, 2). The importance of involving HRQL aspects in the evaluation of thyroid patients is increasingly recognized (3–5). Several features of thyroid diseases motivate this. First of all, benign thyroid disorders are rarely life threatening, and thus their treatment mainly deals with optimizing the quality of life of the patients. Furthermore, the diseases are common and occur at all ages. Moreover, since many thyroid diseases can be treated in several ways (e.g. radioiodine, medical treatment or surgery), exact knowledge of the impact of each treatment modality on the HRQL of the patients is important. To date, no trial has compared validly the HRQL outcome of different treatments and there is still a well-documented lack of consensus regarding choice of treatment (6–15). The detrimental impact of acute thyroid disease on HRQL is

obvious and has been documented in several studies (16–18). However, it is the clinical experience of many endocrinologists that some patients have residual complaints despite adequate medical treatment. Application of valid HRQL measurements is crucial for proper clarification of a number of ongoing debates regarding management of thyroid disorders. For example: do patients with subclinical or mild thyroid dysfunction have symptoms and are they fully alleviated by treatment? Is treatment of hypothyroidism with a combination of thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ ) superior to  $T_4$  alone? Does block-replacement therapy as compared with titration therapy of hyperthyroidism result in improved HRQL? Some of the conflicting data regarding these and numerous other questions might be caused by lack of appropriate outcome measures. To ensure valid assessment of a

particular patient population, a number of requirements in relation to HRQL instruments have to be documented (19–23) (Table 1 presents the terminology used). First, HRQL deals with the patients' experience of the disease and its impact on their lives, and is therefore best assessed by the patients themselves. Secondly, the instrument should cover all aspects of HRQL that are relevant to the patients (content validity). Thirdly, empirical tests should evaluate whether the questionnaire measures what is intended (construct validity). For HRQL measures, where no external 'gold standard' exists, several approaches to this subject have been implemented: qualitative, cognitive studies exploring patients' understanding of the items or quantitative studies investigating the underlying measurement model (Table 1). Finally, appropriate measurement

**Table 1** Concepts concerning validation of HRQL questionnaires.

Concept	Meaning	Methods
Multi-item scale	Multiple items measuring the same concept. The responses are combined to a single score to increase reliability and sensitivity.	Usually the responses to individual items are simply summated together, but various other techniques, implying weightings of items or standardizations to general population norms can be applied. The requirements of uni-dimensionality and local independence of individual items are important for multi-item scales and must be evaluated (see below).
Validity	That an instrument measures what it was intended to, i.e. lack of systematic measurement error.	Comprises content validity and construct validity (described below).
Content validity	Evidence supporting that a questionnaire covers all HRQL aspects relevant for the intended purpose.	Literature reviews and interviews or focus groups involving professionals and patients. Qualitative methods are usually applied when evaluating coverage and relevance, e.g. cognitive debriefing techniques.
Construct validity	The extent to which a scale measures the hypothesized construct. Evaluation of construct validity involves the formulation of a theoretical model, a measurement model, and testing hypotheses based on that specified model.	Evaluation of response patterns. It involves testing the dimensionality of the measured scales by studying the response patterns of target populations. Items in a scale should be correlated with the other items in that scale and be less correlated to dissimilar scales, just as scales measuring related constructs should be more closely related than scales measuring dissimilar constructs. More sophisticated models involve the use of latent variable models, such as classical factor analyses or modern psychometric methods including structural equation models and item response theory.
Dimensionality	The number of concepts measured by a set of items. Most of the methods applied to HRQL data rely on the assumption that one scale measures only one concept (or construct), i.e. that it is uni-dimensional.	Statistical analyses, see construct validity.
Sensitivity	The ability of an instrument to differentiate between subjects differing in the measured property.	Evaluate differences between groups assumed to differ in the evaluated scores.
Responsiveness	The ability of an instrument to detect relevant changes in HRQL over time, e.g. as the result of a clinical intervention.	Longitudinal studies of patients undergoing change.
Reliability	The extent to which a measure yields the same score at independent assessments. Formally, it is calculated as a coefficient, which estimates the ratio of true variance to total (i.e. true + error) variance.	Three approaches are used: <ul style="list-style-type: none"> <li>• Test-retest reliability - repeat the measurement and calculate the degree of identity.</li> </ul> For multi-item scales: <ul style="list-style-type: none"> <li>• Split-half reliability - calculate the level of agreement between two halves of the items in a multi-item scale.</li> <li>• Internal consistency reliability (Cronbach's <math>\alpha</math>) - theoretically measures the mean of all possible split-half reliability coefficients for a scale.</li> </ul>

properties, including sensitivity and responsiveness, have to be demonstrated; that is, there must be an acceptable ratio between true variance compared with variance due to random error (reliability), the measure must be sensitive to clinically relevant differences and it must be responsive to relevant changes with time. Our review concerns content validity. We present a systematic literature review the purpose of which is to describe complaints and consequences of thyroid disorders found in previous studies.

## The literature search

A Medline search on the Medline Subheadings (MeSH) thyroid diseases AND (quality of life OR questionnaires OR psychology OR health status OR psychiatric status rating scales OR brief psychiatric rating scale OR severity of illness index OR patient satisfaction OR psychometrics OR depression OR anxiety OR symptoms [title]) NOT carcinoma, identified 1015 references. The search was repeated in the Cinahl and Psycinfo databases, identifying a total of 2033 references. The abstracts were reviewed and possibly relevant articles reviewed in full length. Further references were identified through the reference lists of these articles. Thus, 2094 references were screened. We also consulted leading thyroid textbooks and included issues listed within these. Seventy-five of the reviewed references were selected, based on the following criteria: the study population (index patients) should be thyroid patients, and the paper should report on patient-experienced consequences of the thyroid disease. Consequences should be documented either as a reported frequency or a higher score on an HRQL scale compared with individuals without thyroid disease. This means that technical or 'objective' measures like 'digit span test' and 'ankle reflex relaxation time' without a subjective equivalent, or reported scale-scores without appropriate control groups were not included. In addition, all measures of symptoms and HRQL impact of thyroid disorders used in these studies were identified.

## Identified HRQL aspects and symptoms relevant to thyroid patients

The frequencies of the identified issues in untreated patients are presented in Table 2 whereas results from follow-up studies are presented in Table 3.

From Table 2, it is evident that patients with untreated thyroid disease suffer from a wide range of symptoms and have major impairment in most areas of HRQL. For example, 22–35% of goitre patients, 18–66% of hyperthyroid patients, 7–99% of patients with thyroid associated ophthalmopathy (TAO) and 16–51% of hypothyroid patients experience limitations in usual activities during the untreated phase of their disease. These rather wide ranges are due to different

ways of measuring the concepts in the studies, differences in patient populations as well as our categorization of the issues; e.g. the term 'limitations in usual activities' covers a wide range of different activities and includes scales from various questionnaires. There is evidence of impaired general health perception in all patient groups; for patients with goitre, hyperthyroidism and TAO this is evidenced by lower scores on scales measuring general health perception compared with scores in normal controls, and thus no percentage is available, whereas for hypothyroid patients dichotomous variables document that 53–100% of patients conceive their health as impaired. Thus, a substantial proportion of thyroid patients experience limitations in their usual activities, perceive their general health as impaired and have social and emotional impairment. Cognitive problems are also prevalent, as is fatigue. Cosmetic concern is also common for all thyroid patients. However, no study has reported on cognitive dysfunction in patients with goitre and only one study has reported on fatigue in patients with TAO. Generally, patients with goitre have been the least studied. All the classical symptoms of hyperthyroidism appear to be consistently prevalent in hyperthyroid patients, whereas the classical symptoms of hypothyroidism are more variably present in hypothyroid patients. The latter may, in part, reflect the wide spectrum of clinical presentation of hypothyroidism, with a high frequency of subclinical dysfunction.

From the data presented in Table 3 it appears that persistent HRQL impairment is very frequent among patients with both hyper- and hypothyroidism. About half of the patients have reduced overall quality of life and general health, limitations in usual activities as well as social and emotional problems. Two-thirds are fatigued and about one-third are anxious and have cognitive as well as sexual problems. Furthermore, classical symptoms of hypothyroidism are very frequent among previously hyperthyroid patients and about one-third have persistent hyperthyroid symptoms. However, the association with actual thyroid status has not been addressed in this study. Hypo- or hyperthyroid symptoms have not been examined in long-term follow-up studies of hypothyroid patients and no study has examined the long-term HRQL outcome of goitre treatment. However, there is a general lack of detailed clinical description of the phenotypes of many of the patient populations in these studies and therefore some of the patients classified as hypothyroid may, in fact, be treated goitre patients.

## Available thyroid HRQL questionnaires

We have identified six thyroid HRQL questionnaires (24–29). In addition, various symptom indices (30–43), most of which were physician administered, and one satisfaction-questionnaire (29) have been published. The present review will focus on the six HRQL

**Table 2** Quality of life aspects associated with untreated thyroid disease. Prevalences are given in percent, and where no prevalence is available, the presence of the issue is marked with +.

	Non-toxic goitre	Hyperthyroidism	TAO**	Hypothyroidism*	References
<b>Generic aspects</b>					
Reduced general health perception	+	+	+	53–100	(16–18, 39, 40, 48–53)
Generally unwell		+		57	(27, 54)
Limitations in usual activities	22–35	18–66	7–99	24–53	(16–18, 25–27, 35, 44, 47, 49–51, 55–59)
Social problems	21	33–66	20–52	16–51	(16–18, 25–27, 44, 49–51, 53, 56–60)
Reduced emotional well-being	7	20–80	22–77	14–80	(16–18, 25, 27, 42, 44, 47, 49–51, 53–55, 57–59, 61–78)
Emotional lability		45–99		26	(27, 56, 57, 59, 62, 70, 71, 79–82)
Anxiety/nervousness	13–60	30–100	32–40	13–61	(27, 30, 35, 47, 49–51, 54, 55, 57, 59, 61, 62, 64, 67–72, 74, 77, 78, 80–89)
Lack familiar sense of self		28			(62)
Cognitive complaints		16–54	71–84	15–86	(25, 27, 37, 42–44, 47, 57–59, 63–65, 69–71, 73, 78, 80, 90, 91)
Fatigue	+	24–95	+	18–100	(16–18, 27, 30, 33, 35, 37, 39–43, 47, 51–54, 57, 59, 69–71, 73, 78–86, 88, 89, 92)
Sexual problems	20	17–40		29–47	(16, 27, 57, 59, 70, 80, 86)
Cosmetic complaints	28–36	53	41–90	23–24	(25, 27, 44, 58, 59, 81, 93–95)
Hallucinations/delusions		8		+	(73, 80)
Dizziness				16	(71, 73, 86)
Weight problems	20	0–100		6–67	(27, 30, 33, 37–40, 47, 52, 55, 57, 59, 62, 70, 71, 78, 79, 81–86, 88, 89, 92, 96)
Musculoskeletal problems, including pain	35	18–84	58	8–82	(16, 27, 37, 41–43, 47, 50, 52, 59, 70, 71, 73, 78, 81, 85, 86, 89, 92, 97)
Headache				6–22	(27, 71, 86)
Sleep disturbances	7–57	5–72		5–63	(16, 55–57, 59, 70, 71, 80, 85, 86)
<b>Symptoms in several thyroid disorders</b>					
Bowel disturbances	37	8–33		8–41	(16, 27, 59, 71, 73, 79, 82, 85, 86, 89)
Menstrual disturbances		3–80		17–58	(30, 42, 57, 59, 70, 71, 81, 86, 88)
Eye problems		34–62	***	4–27	(27, 30, 42, 43, 53, 70, 73, 86, 89)
Compression complaints****	17–69	11–16		9–34	(42, 59, 70, 85, 86, 89, 93–95, 98)
Dyspnoea	7–40	3–89		13–52	(27, 30, 33, 57, 59, 70, 73, 78, 79, 81, 85, 86, 89, 93, 94, 96, 98)
Hair, nail and skin changes	22	4–84		2–90	(16, 27, 37–43, 47, 52, 57, 59, 70, 71, 73, 79, 86, 88, 89, 92)
Chest pain		3–38		8	(57, 59, 71, 73, 85, 86, 89)
<b>Classical hyperthyroid symptoms</b>					
Heat intolerance		48–92		4–9	(30, 33, 35, 57, 59, 70, 71, 78, 79, 81–85, 88, 89, 96)
Hyperactivity		31–70			(30, 35, 59, 80, 83, 88)
Increased appetite		10–87		10–33	(30, 33, 35, 40, 59, 70, 71, 78–80, 82–85, 88, 89, 96)
Increased sweating		30–96		10	(30, 33, 35, 59, 78, 79, 81–85, 88, 89, 96)
Diarrhoea		0–83		5	(30, 35, 70, 71, 78, 83–85, 88, 89, 99)
Hand tremor		11–84		8	(30, 33, 35, 57, 59, 70, 78, 82, 84, 85, 88)
Palpitations		30–96			(30, 33, 59, 70, 71, 78, 81–85, 89, 96)
<b>Classical hypothyroid symptoms</b>					
Cold intolerance		2–7		15–95	(27, 33, 37–43, 52, 59, 71, 73, 86, 88, 92)
Diminished sweating		3		11–54	(27, 37, 38, 59, 86, 88)
Change in voice	+	27		2–89	(27, 37–40, 42, 43, 52, 59, 70, 73, 86, 88)
Oedema (puffiness of face, hands or feet)		9–40		30–85	(27, 39, 40, 52, 59, 73, 86, 88, 89)
Decreased appetite		0–46		14–24	(27, 30, 33, 39, 59, 71, 78–80, 82, 84–86, 88, 89)
Nausea/vomiting		28–44		13	(53, 73, 86, 89)
Constipation		4–26		6–56	(30, 37, 38, 41–43, 52, 59, 70, 71, 73, 78, 79, 85, 86, 88, 89, 92, 100)
Hearing problems				3–27	(27, 37, 38, 59, 70, 71, 73, 86)
Disturbances in peripheral nervous system				13–78	(27, 37, 38, 52, 59, 70, 71, 73, 86)
Enlarged tongue				19	(86)
<b>Various uncommon symptoms</b>					
Disturbed sense of smell or taste		+		0.25	(59, 86)
Feverishness		36			(59, 89)
Gynaecomastia		+			(59, 70)

\*Includes all causes of hypothyroidism, also those due to ablative treatment of goitre and/or hyperthyroidism; \*\*both treated and untreated patients; \*\*\*all, by definition; \*\*\*\*difficulty swallowing, sensation of fullness, globulus sensation.

**Table 3** Long-term evaluation of quality of life aspects associated with treated thyroid disease. Prevalences are given in percent, and where no prevalence is available, the presence of the issue is marked with +.

	Non-toxic goitre	Hyperthyroidism	Hypothyroidism	References
<b>Generic aspects</b>				
Impaired overall quality of life			62	(29)
Reduced general health perception		26–69		(40, 52, 101)
Generally unwell			65	(29)
Limitations in usual activities		20–62	49–73	(24, 29)
Social problems		31–50	43–51	(24, 29, 102)
Reduced emotional well-being		29–34	46–87	(24, 28, 29, 62, 102, 103)
Emotional lability		36–46		(24, 101, 102)
Anxiety/nervousness		25–41		(24, 102)
Lack familiar sense of self		40		(24)
Cognitive complaints		35–41	+	(24, 28, 57, 104)
Fatigue		39–58	78–81	(24, 28, 29, 40, 52)
Sexual problems		32	39	(24, 29)
Cosmetic complaints	3–16		62	(29, 93, 94)
Weight problems		6–79	31–75	(24, 28, 29, 40, 52, 62, 101, 105)
Musculoskeletal problems, including pain		15–52	+	(24, 28, 52)
Headache			+	(28)
Sleep disturbances		27–36		(24, 102)
<b>Symptoms in several thyroid disorders</b>				
Compression complaints*	5–32			(93, 94)
Dyspnoea	0–6		40	(93, 94, 106)
Hair, nail and skin changes		23–81		(40, 52)
<b>Classical hyperthyroid symptoms</b>				
Heat intolerance		39		(24)
Hyperactivity		+		(102)
Increased appetite		16		(40)
Increased sweating		33		(24)
Diarrhoea		+		(102)
Hand tremor		15		(24, 102)
Palpitations		32	+	(24, 28)
<b>Classical hypothyroid symptoms</b>				
Cold intolerance		40–70		(28, 40, 52)
Change in voice		18–82		(40, 52)
Oedema (puffiness of face, hands or feet)		26–79		(40, 52)
Constipation		83		(52)
Hearing problems		23		(24)
Disturbance of peripheral nervous system		57	+	(28, 52)

\* Difficulty swallowing, sensation of fullness, globulus sensation.

questionnaires, but results from studies using the symptom indices are presented in Tables 2 and 3. All the identified HRQL questionnaires target particular thyroid conditions and are not applicable across conditions. No questionnaire measuring the symptoms or impact of non-toxic goitre has been identified.

### Hyperthyroidism questionnaires

The Hyperthyroidism Complaint Questionnaire (HCQ) measures residual complaints and psychosocial sequelae in patients treated for hyperthyroidism (24). Thirty-one dichotomous (present/not present) items are summarized in one overall score. Of these, eleven items concern physical symptoms, six are about emotional distress, six evaluate fatigue, and three concern cognitive function whereas existential problems, sleeping problems, anxiety, sexual function and social function are covered by one item each. The development was based on interviews with a small sample of

patients with hyperthyroidism, but no documentation of this has been published. Data from a questionnaire study of 303 formerly hyperthyroid patients were analysed for the purpose of item-reduction (i.e. eliminating items with poor measurement properties or yielding little additional information) yet all items were retained based on an argument that they all contributed to the internal consistency of the scale. Cronbach's  $\alpha$  (cf. Table 1) was 0.93. Correlations between individual items and the overall score were generally low, some as low as 0.21, suggesting problems with uni-dimensionality (i.e. the assumption that all items in a scale measure an underlying construct, and can therefore be summarized into one overall scale). Thus, the appropriateness of collapsing all items, despite the dissimilarity of the covered issues, into one single score is unknown. There was a significant relationship between scores on the HCQ and the degree of self-reported thyroid dysfunction but no further description of the validity of the instrument has been provided. The HCQ

has not been used in any subsequent study and apparently is available in Dutch only.

### **Questionnaires for patients with thyroid-associated ophthalmopathy**

The Graves' Ophthalmopathy Quality of Life Questionnaire (GOQOL) is a disease-specific HRQL instrument for patients with TAO (25, 44, 45). The development was based on a review of existing eye HRQL measures, as well as open-ended questionnaires from 24 patients. It has been pretested in 8 patients. A detailed description of these content validity studies has not been published. The GOQOL consists of 16 items sub-divided into two scales: 'visual functioning' and 'appearance'. Subsequent studies comprising 70–164 well-described patients have shown excellent reliability (25, 44), supported its construct validity (25, 44, 45), and demonstrated good responsiveness (45). According to the developers, the GOQOL is available in six languages (46). However, to our knowledge, the only published validation study regards the Dutch version.

Tehrani and colleagues (26) have also developed a 90-item TAO-specific HRQL instrument in German. Its development was based on contributions from clinicians and was without any patient input. In a study of 104 patients undergoing surgery, the developers found Cronbach's  $\alpha$  as low as 0.63 for the 90-item total score. Given the large number of items, this is a low reliability. No construct validation has been performed, but the low internal consistency reliability suggests lack of uni-dimensionality. In validity analyses, the score did not correlate with clinical variables. Thus, these results do not lend strong support for the reliability and validity of this measure.

### **Hypothyroidism questionnaires**

The Chronic Thyroid Questionnaire (CTQ) is a hypothyroidism and patient-specific HRQL questionnaire. It consists of 104 items, each representing a specific complaint, covering four domains: 'physical complaints', 'mood and emotions', 'energy and general well-being', and 'cognitive complaints' (27, 47). The development of the CTQ was quite thorough. Based on a literature review, a list of symptoms or problems related to hypothyroidism, potentially responsive to treatment and likely to influence the quality of life of the patients was generated (27). This list was expanded through interviews with endocrinologists and patients. The scoring of the CTQ is unusual: of the 104 complaints, each patient identifies applicable items and rates the degree of discomfort represented by these items. Thus, for a patient with two of the 104 complaints, the instrument consists of two items, whereas a patient with 22 complaints rates 22 items. This approach increases the potential sensitivity of the measure to improvements in the individual patient,

but it makes between-patient comparisons and interpretations of what is actually measured difficult and new complaints arising from intervention are ignored in longitudinal studies. We could not identify any studies validating the resulting questionnaire.

The Thyroid Symptom Questionnaire (TSQ) consists of twelve items: six items on cognitive complaints, five items on physical symptoms and one item on fatigue, summarized in one overall score (28). The items were selected on the basis of patient responses to a notice in the British Thyroid Foundation newsletter, inviting patients to tell about persisting complaints despite replacement therapy with L-thyroxine. Moderate correlations with the generic HRQL questionnaire General Health Questionnaire (GHQ-12) were found, but no other evidence of validity has been presented.

Recently, a new hypothyroidism-specific HRQL questionnaire has been developed: the Underactive Thyroid-Dependent Quality of Life Questionnaire (ThyDQoL) (29). ThyDQoL is an 18-item questionnaire measuring the impact of hypothyroidism on various domains of HRQL: overall quality of life (two items), limitations in usual activities (six items), social function (four items), fatigue (two items), emotional well-being (two items), sexual function, cosmetic complaints, weight problems, and bodily discomfort (one item each). Items are scored individually in a two-step procedure: both impact and importance of the items are rated, and the item score is derived by the multiplication of these two ratings. No multi-item scales are constructed. Problems with this approach are the reduced inter-individual comparability of the measure and the sensitivity to a confounding effect of coping. Content validity was ensured by interviews with 38 hypothyroid patients. However, a quarter of the patients had hypothyroidism secondary to treatment of other thyroid disorders. No information regarding the time since diagnosis or the present thyroid status of the interviewees is provided; all patients, except one, were undergoing treatment with L-thyroxine. Measurement properties (dimensionality, reliability, construct validity, sensitivity, and responsiveness) have not yet been evaluated.

### **Comparison of the questionnaires**

The relationship between the identified issues and the thyroid questionnaires is presented in Table 4. The CTQ includes items relating to a wide range of the identified issues. However, since these assessments are based on one single item, the reliability is probably low for each issue. The well-documented GOQOL questionnaire, which is concerned very specifically with the limitations and social/cosmetic consequences of TAO, covers only three of the identified issues, but since each issue is assessed by multiple items, reliability is probably high. Questionnaires like the HCQ and TSQ produce an overall score, but if the set of issues covered are multidimensional, one overall score might not be

**Table 4** Relationship between HRQL aspects and the available thyroid HRQL questionnaires. If the questionnaire has items relating to the issue it is marked by ●.

	Hyperthyroid HCQ	TAO GOQOL	Hypothyroid		
			CTQ	TSQ	ThyDQoL
Generic aspects					
Impaired overall quality of life					●
Reduced general health perception					
Generally unwell			●		●
Limitations in usual activities		●	●		●
Social problems	●	●	●		●
Reduced emotional well-being	●		●		●
Emotional lability	●				
Anxiety/nervousness	●		●		
Lack familiar sense of self	●				
Cognitive complaints	●		●	●	
Fatigue	●		●	●	●
Sexual problems	●		●		●
Cosmetic complaints		●	●		●
Hallucinations/delusions					
Dizziness			●		
Weight problems	●		●	●	●
Musculoskeletal problems, including pain	●		●	●	
Headache			●	●	
Sleep disturbances	●		●		
Symptoms in several thyroid disorders					
Bowel disturbances			●		
Menstrual disturbances	●				
Eye problems			●		
Compression complaints					
Dyspnoea			●		
Hair, nail and skin changes			●		
Chest pain					
Classical hyperthyroid symptoms					
Heat intolerance	●				
Hyperactivity					
Increased appetite					
Increased sweating	●				
Diarrhoea					
Hand tremor	●				
Palpitations	●			●	
Classical hypothyroid symptoms					
Cold intolerance			●	●	
Diminished sweating			●		
Change in voice			●		
Oedema (puffiness of face, hands or feet)			●		
Decreased appetite			●		
Nausea/vomiting					
Constipation			●		
Hearing problems	●		●		
Disturbances in peripheral nervous system			●		

Note: The items from the questionnaire by Tehrani and colleagues (26) are not described in detail. HCQ, Hyperthyroidism Complaint Questionnaire (24); GOQOL, Graves' Ophthalmopathy Quality of Life questionnaire (25); CTQ, Chronic Thyroid Questionnaire (27); TSQ, Thyroid Symptom Questionnaire (28); ThyDQoL, Underactive Thyroid-Dependent Quality of Life Questionnaire (29).

the best way of summarizing results. For example, the HCQ combines existential problems and hand tremor into the overall scale score. Regarding HCQ, the lack of items tapping hypothyroid symptoms renders it less suitable for follow-up studies, considering the high frequency of these symptoms among patients treated for hyperthyroidism, as presented in Table 3. None of the hypothyroidism questionnaires consider hyperthyroid symptoms, which might also (albeit not yet studied)

be present as a result of the treatment of these patients. This is probably especially important if the measure were to be used for evaluation of the presently intensely discussed issue of T<sub>3</sub>-supplementation in hypothyroid patients, in view of the expected higher degree of fluctuations in the serum-concentration of T<sub>3</sub>. The ThyDQoL is concerned with more generic aspects of HRQL but, like the CTQ, it is prone to random error due to the use of only single items.

## Conclusion

According to the available literature, HRQL impairment in patients with benign thyroid disorders is prevalent, both in the untreated phase and in the long term. A wide range of problems has been reported, covering both generic and specific aspects of HRQL. However, many of the studies are small and use unvalidated measures. Most of them lack a thorough clinical description of the patients and include patients covering a wide range of phenotypes and aetiological dissimilarities. No available questionnaire has the potential to cover all aspects relevant to patients in longitudinal studies, where individual patients may shift from one thyroid state to another as a result of natural history or treatment. The available questionnaires lack documented coverage of relevant HRQL issues and, apart from the GOQOL, they all lack a thorough validation. With this review, we have identified the possibly relevant issues reported in the literature. These data are valuable as a basis for the development of HRQL questionnaires possessing content validity. The next step towards valid measures of disease-specific HRQL in thyroid patients would be to test the relevance of the issues presented here among samples of experts as well as properly characterized thyroid patients.

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