

Perceived Health Status of Women with Overt and Subclinical Hypothyroidism

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Key Words

Hypothyroidism · Health status · Quality of life · SF-36

Abstract

Objective: The objective of this study was to investigate the health status of women with overt and subclinical hypothyroidism and relate it to the presence of clinical signs and symptoms of the disease. **Subjects and Methods:** A cross-sectional study was conducted on 232 women divided into 3 groups: overt hypothyroidism (n = 14); subclinical hypothyroidism (n = 152), and controls (n = 66). Health status was evaluated by the questionnaire SF-36, and the clinical signs and symptoms of hypothyroidism were assessed with the Billewicz scale modified by Zulewski. The Kruskal-Wallis test followed by the Mann-Whitney U test with Bonferroni correction was applied to compare continuous variables between the groups. To assess the relationship between SF-36 domains and the clinical score, as well as SF-36 domains and serum thyroid-stimulating hormone levels, the Spearman correlation coefficient was calculated. **Results:** Patients with overt hypothyroidism presented systematically lower scores in all SF-36 domains (p < 0.05), both in relation to subclinical hypothyroidism patients and controls. This indicates a great dissatisfaction with health status in this group. Patients with subclinical hypothyroidism presented statistically lower scores in relation to controls with the exception of the role-emotional and bodily pain domains, where although they were not statistically significant, scores were clinically differ-

ent. Highly negative correlations between SF-36 domains and the clinical score were observed in overt hypothyroidism (physical function r = -0.80, p < 0.01; bodily pain r = -0.74, p < 0.01). **Conclusion:** Overt hypothyroidism seemed to be associated with worse perception of health status, negatively associated with clinical score.

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Introduction

The thyroid hormones T3 and T4 act directly and indirectly upon almost every organ system of the body. In this way, alterations in serum concentrations of these hormones may negatively affect an individual's health status [1].

Overt hypothyroidism and subclinical hypothyroidism are common thyroid disorders, especially in women. Overt hypothyroidism is defined as an elevated serum thyrotropin, also called thyroid-stimulating hormone (TSH), level with decreased concentrations of circulating thyroid hormones [2]. The association of overt hypothyroidism with a broad range of morbidities is well established in the literature. Such morbidities include fatigue, weight gain, abnormalities of lipid metabolism, neuropsychiatric disorders and impaired cardiac-pulmonary function [3, 4]. Subclinical hypothyroidism is also defined as an elevated serum TSH level, while free thyroxine (FT4) remains within the normal range [5]. Concep-

tually, subclinical hypothyroidism is an asymptomatic disease essentially based on biochemical alterations. However, many studies have demonstrated that patients under this condition may have clinical signs and symptoms, besides morbidities, that are suggestive of overt hypothyroidism [6, 7].

The presence of chronic conditions and/or multimorbidities contributes to disability via physical, functional and psychological impairments, and they also place limitations on social relationships, consequently diminishing quality of life, health status and well-being [8]. In this context, the aim of this study was to investigate the health status of women with overt and subclinical hypothyroidism and relate it to the presence of clinical signs and symptoms of the disease.

Subjects and Methods

Study Characteristics and Sample

A cross-sectional study was conducted with ambulatory patients who attended the endocrine clinic of the Clementino Fraga Filho Hospital of the Federal University of Rio de Janeiro (HUCFF/UFRJ), Brazil. The 232 women who voluntarily participated in the study were divided into 3 groups: subclinical hypothyroidism (n = 152); overt hypothyroidism (n = 14), and control (n = 66). Subclinical hypothyroidism was defined when high serum TSH (≥ 4.0 $\mu\text{UI/ml}$) with FT4 within the normal range (0.8–1.9 ng/dl) was detected twice, with a minimum period of 6 weeks between the 2 measurements. Overt hypothyroidism was diagnosed when serum TSH was also above the upper reference limit with decreased serum FT4 (< 0.8 ng/dl). The control group was composed of women without thyroid diseases, with serum TSH and FT4 levels within the normal reference range. The exclusion criteria for participation of the study were the use of medications that could cause thyroid hormone dysfunction, current hospitalization and history of diseases, even if stable, that could affect thyroid hormone secretion. This study was approved by the ethics committee of HUCFF/UFRJ and written informed consent to participate in the investigation was obtained from all the volunteers.

Measures

Hormone Measurements. Hormones levels were assessed by commercial immunocheminescence assays (Immulite 2,000; Diagnostic Products Corp., Los Angeles, Calif., USA) in the clinical pathology laboratory/hormone section of HUCFF/UFRJ.

Clinical Evaluation. Participants were asked about their history of smoking ('yes', 'no' or 'ex-smoker'), menopause and physical activity by an endocrinologist. Individuals were classified as 'active' if, in the past 3 months before the beginning of the study, they were involved in any kind of physical activity program with minimum frequency of 2 times/week and minimum duration of 30 min.

Signs and Symptoms of Hypothyroidism: Clinical Score. Disease-specific morbidity was assessed with the Billewicz scale modified by Zulewski [9], as it has been widely used in studies of hypothyroidism. This scale is composed of 12 items about clinical

signs and symptoms of hypothyroidism: periorbital puffiness, constipation, weight gain, cold skin, paresthesia, hoarseness, dry skin, diminished sweating, impaired hearing, coarse skin, slow movements and delayed ankle reflex. The signs and symptoms were quantified as 1 point when they are present, or 0 when absent. Thus, the maximum score permitted was 12 points. Scores of < 3 points were expected in euthyroid subjects, scores of ≥ 3 to < 5 points in patients with subclinical hypothyroidism and scores of ≥ 5 in patients with overt hypothyroidism. In the present investigation, the sample was classified into 2 categories: normal score (< 3) and abnormal score (≥ 3).

Health Status. The SF-36 (Medical Outcomes Study 36 – Item Short-Form Health Survey) was used to assess the health status of the women in its translated and validated Portuguese version [10]. The SF-36 is a generic health status assessment instrument composed of 36 items, divided into 8 scales or dimensions: physical function, general health, vitality, mental health, social function, role-emotional, role-physical and bodily pain. Answers were presented on a Likert scale. The maximum score permitted on each scale was 100 points (highest level of satisfaction with health status) and the minimum was score 0 (highest level of dissatisfaction with health status).

Statistics

The descriptive analyses were presented as median and interquartile range for numeric variables and as percentages for categorical variables. The distribution of the variables was tested with the Kolmogorov-Smirnov test. Differences in frequencies were tested with the χ^2 test. The Kruskal-Wallis test was applied to compare the subgroups in relation to age, body mass index (BMI), serum hormone levels and the 8 domains of SF-36. For the identification of differences between the groups, the Mann-Whitney U test was applied with Bonferroni correction (values of $p < 0.017$ were considered statistically significant). The internal consistency of the 8 dimensions of SF-36 was assessed with Cronbach's alpha coefficient [11]. To assess the relationship between SF-36 domains and the clinical score, as well as SF-36 domains and serum TSH levels, the Spearman correlation coefficient was calculated [12]. A stratified analysis (TSH and FT4 levels according to the classification of clinical score) was also made in the group of subclinical hypothyroidism. The level of statistical significance adopted was 5% ($p < 0.05$). All analyses were performed using the SPSS 13.0 statistical package, version 13.0.

Results

General Characteristics of the Sample

Clinical and biochemical characteristics of the sample are presented in table 1. The groups seemed to be similar in respect to age, BMI, menopause, smoking and sedentarism ($p > 0.05$).

Signs and Clinical Symptoms of Hypothyroidism:

Clinical Score

The median score of the control group was 2 points (25th percentile = 1 and 75th percentile = 4) and 21 (32%)

Table 1. General characteristics and SF-36 domains scores: median (interquartile range) by subgroup

	Overt hypo- thyroidism (n = 14)	Subclinical hypo- thyroidism (n = 152)	Controls (n = 66)	p value ^a
<i>General characteristics</i>				
Age, years	43.0 (14.0)	47.0 (14.0)	44.0 (15.0)	0.09
BMI, kg/m ²	27.3 (6.4)	27.0 (5.2)	26.5 (6.3)	0.75
TSH, μ UI/ml	44.5 (28.7)	7.0 (34.0)	1.5 (1.0)	<0.05 ^d
FT4, ng/dl	0.5 (0.4)	1.0 (0.3)	1.2 (0.3)	<0.05 ^d
<i>SF-36 domains</i>				
Physical function	62.5 (75.0)	65.0 (35.0)	85.0 (35.0)	<0.05 ^b
Role-physical	25.0 (75.0)	50.0 (75.0)	100.0 (50.0)	<0.05 ^b
Bodily pain	21.0 (20.0)	21.0 (11.0)	21.0 (58.0)	0.20
General health	52.0 (41.0)	62.0 (27.0)	82.0 (30.0)	<0.05 ^b
Vitality	22.0 (43.0)	50.0 (30.0)	60.0 (36.0)	<0.05 ^d
Social functioning	50.0 (37.0)	75.0 (50.0)	75.0 (50.0)	0.01 ^c
Role-emotional	16.0 (50.0)	66.0 (36.0)	100.0 (36.0)	0.03 ^c
Mental health	38.0 (28.0)	58.0 (28.0)	44.0 (32.0)	<0.05 ^d

^a Kruskal-Wallis test; comparison between the 3 subgroups.

^b Mann-Whitney U test with Bonferroni correction. Statistically significant differences ($p < 0.017$) between controls and subclinical hypothyroidism, and controls and overt hypothyroidism.

^c Mann-Whitney U test with Bonferroni correction. Statistically significant differences ($p < 0.017$) between controls and overt hypothyroidism, and subclinical and overt hypothyroidism.

^d Mann-Whitney U test with Bonferroni correction. Statistically significant differences ($p < 0.017$) between all groups.

participants of this group had an abnormal score (≥ 3). Among patients with subclinical hypothyroidism, the median score was 4 points (25th percentile = 3 and 75th percentile = 5), and 114 (75%) patients had scores classified as abnormal. All patients with overt hypothyroidism had scores classified as abnormal, the minimum and maximum scores were 5 and 10 points respectively, and the median was 8 points. The frequency of abnormal scores was statistically different between overt hypothyroidism, subclinical hypothyroidism and control groups ($p < 0.05$).

Considering the whole group of the study, the clinical score was correlated to TSH ($r = 0.33$, $p < 0.01$) and to FT4 ($r = -0.36$, $p < 0.01$), with statistical significance. In the overt hypothyroidism patients, the clinical score was correlated to TSH, but did not reach statistical significance ($r = 0.53$, $p = 0.07$), while in the subclinical hypothyroidism it was correlated with FT4 ($r = -0.24$, $p < 0.05$). Finally, in controls, no correlations were found.

Health Status

All patients completed the SF-36 as requested. The internal consistency of the SF-36 was considered satisfactory ($\alpha = 0.9$), as well as each of its domains with α vary-

ing from 0.7 to 0.9. High internal consistency suggests that the patients of the study reported consistently higher (or lower) levels on questions that correlated well with responses to the other questions of the construct (i.e. health status) or specific domain.

Bodily pain domain, which assessed the frequency of pain and the extent of interference with daily activities due to pain, had the lowest median score (21) in the 3 groups. On the other hand, the groups diverged as for the domain that presented the highest score. Among patients with overt hypothyroidism, the highest median score (62.5) was in the physical function domain, while the patients with subclinical hypothyroidism presented highest median score (75) in the social aspects domain. In the control group, results indicated a higher satisfaction with role-physical and role-emotional domains. At the same time, the group of patients with overt hypothyroidism presented lower scores in the same domains as well as in vitality and bodily pain (table 1).

Comparison of the 8 domains between the 3 groups showed that patients with overt hypothyroidism had tendency to lower scores, indicating great dissatisfaction with health status.

Table 2. Spearman correlation coefficients between SF-36 domains, clinical score and hormone levels, by subgroup

	Physical function	Role-physical	Bodily pain	General health	Vitality	Social functioning	Role-emotional	Mental health
<i>All participants (n = 232)</i>								
Clinical score	-0.35 ^a	-0.30 ^a	-0.30 ^a	-0.40 ^a	-0.43 ^a	-0.25 ^a	-0.25 ^a	-0.40 ^a
TSH	-0.16 ^a	-0.20 ^a	-0.05	-0.27 ^a	-0.19 ^a	-0.07	-0.12	-0.24 ^a
FT4	0.10	0.16 ^a	0.02	0.17 ^a	0.17 ^a	0.15 ^a	0.10	0.23 ^a
<i>Overt hypothyroidism (n = 14)</i>								
Clinical score	-0.80 ^a	-0.33	-0.74 ^a	-0.19	-0.62 ^b	-0.66 ^b	-0.09	-0.48
TSH	-0.33	0.28	-0.12	-0.03	-0.40	-0.08	0.32	-0.10
FT4	0.31	0.20	0.47	0.37	0.32	0.08	-0.04	0.27
<i>Subclinical hypothyroidism (n = 152)</i>								
Clinical score	-0.21 ^a	-0.17	-0.22 ^a	-0.23 ^a	-0.35 ^a	-0.11	-0.14	-0.36 ^a
TSH								
Abnormal	0.20	0.04	0.05	0.04	<0.01	<0.01	-0.02	0.01
Normal	0.18	0.13	0.19	-0.24	0.15	0.19	0.06	0.03
FT4								
Abnormal	-0.13	0.06	-0.04	-0.03	-0.06	-0.02	-0.03	-0.01
Normal	<0.01	-0.15	-0.02	0.12	0.08	<0.01	-0.14	0.04
<i>Controls (n = 66)</i>								
Clinical score	-0.37 ^a	-0.29 ^a	-0.35 ^a	-0.42 ^a	-0.31 ^a	-0.39 ^a	-0.37 ^a	-0.28 ^a
TSH	-0.09	-0.06	0.10	0.09	0.02	-0.11	-0.15	-0.06
FT4	0.05	0.07	-0.12	0.04	0.07	0.22	0.20	0.09

^a Statistically significant correlation ($p < 0.05$).

^b Moderate correlation but not statistically significant.

Health Status versus Clinical Score

Negative correlations between all SF-36 domains and the clinical score punctuation were detected in the 3 groups studied. The highly negative correlations were those present in patients with overt hypothyroidism (physical function $r = -0.80$, $p < 0.01$; bodily pain $r = -0.74$, $p < 0.01$; table 2). In the other groups, we observed weak negative correlations, but with statistical significance.

When SF-36 domains were correlated with the serum TSH level of all participants, we detected weak negative correlations, but which were mostly statistically significant ($p < 0.05$). Similar tendencies were observed when SF-36 domains were correlated with serum FT4 level, but positively. However, on analyzing each subgroup, it was observed that these correlations lost statistical significance, possibly due to the reduction of the number of subjects analyzed, and none of them presented clinical relevance. In the subgroup of subclinical hypothyroidism these correlations were lost, independently of the presence of abnormal clinical score (table 2).

Discussion

In this cross-sectional study, subjects with different grades of hypothyroidism were investigated for their perception of their health status and its relation with the presence of signs and clinical symptoms of the disease. Patients with overt hypothyroidism presented systematically lower scores in the domains evaluated by SF-36, thereby pointing to a greater dissatisfaction with health status among this population. Patients with subclinical hypothyroidism occupied an intermediate position between healthy subjects (control group) and patients with overt hypothyroidism. These results suggest the existence of a gradient of deterioration of health status, according to the gravity of the disease.

The main factors and the mechanisms involved in the process of deterioration of quality of life and health status of patients with thyroid dysfunctions are as yet not established. Part of this inconsistency is due to the fact that quality of life is a subjective construct, influenced by factors of several natures and dynamics in time [13]. More-

over, the use of different methods for diagnosing conditions, measuring quality of life and health status evaluation, besides the lack of comparability between samples, raises difficulties in comparing the studies [14].

Although thyroid-specific instruments such as CTQ and ThyDQoL for evaluating health status are available in the medical literature, we decided to use the SF-36, a generic questionnaire, because both CTQ and ThyDQoL are not yet translated and validated in Portuguese. Equally, the use of a generic questionnaire allows the comparison between healthy and diseased individuals, as well as the identification of the influence on health of comorbidities, which are common in hypothyroidism.

Our findings confirmed previous studies that reported greater dissatisfaction with quality of life in patients with subclinical or overt hypothyroidism compared to controls [15, 16]. Bianchi et al. [16] further pointed out that patients who presented thyroid dysfunctions, even benign ones, had a worse perception of quality of life than the general population, not only because of the clinical diagnosis itself, but also for the 'label' of being diseased. Similar association has been observed in patients suffering from other chronic diseases [17–19]. Strangely, Watt et al. [20] have observed that patients with overt hypothyroidism or hyperthyroidism seemed to maintain the same perception of quality of life even after restoring the euthyroidism state.

The presence of clinical signs of the disease seemed to exert a fundamental role in the decreasing of health status profile. Hypothyroidism is associated with a high prevalence of clinical symptoms, such as neuromuscular dysfunction, paresthesia, fatigue, dry skin and cold intolerance [21]. Furthermore, psychiatric disturbances like anxiety and depression [22] also have been described [16, 23–25]. Bianchi et al. [16] related that the presence of fatigue and psychiatric disturbances was negatively associated with quality of life scores in patients with overt hypothyroidism. Gerding et al. [23] and Ljunggren et al. [24] noted a relation between less favorable health status scores and the presence of clinical signs in patients with hyperthyroidism. Tagay et al. [25] examined the health status in differentiated thyroid cancer patients under short-term hypothyroidism and observed that it was severely impaired in this population (in comparison to the general population). Also, health status was correlated significantly with worse scores in the scale of signs and symptoms.

Our results confirmed the previously reported association between perceived health status and clinical signs of the disease. This association showed more evidence in

overt hypothyroidism, where strong correlations were detected between the domains of SF-36 and the scale of signs and clinical symptoms. This association between clinical signs and health status as noted in our study and previously reported ones have clinical and practical relevance as pointed out by Thompson [26]. However, a study pointed out that women with subclinical hypothyroidism may have the same level of satisfaction with well-being, health status and quality of life as healthy women [27].

To our knowledge, this is the first study to examine the relationship between the presence of clinical signs of the disease and the health status in patients with different degrees of hypothyroidism. The most significant finding of the present study was the association between deteriorations in health status of patients and the degree of the disease severity. This fact is very important in daily clinical practice, and so, evaluation of health status may be one more strategy to be incorporated to the routine of clinical evaluation of patients. Endocrinologists' experience reveals that some patients present residual complaints even after the establishment of euthyroidism state by LT-4 replacement [28, 29]. It is valuable to emphasize that in the subgroup of subclinical hypothyroidism the correlations between hormone levels and the domains of SF-36 were lost, independently of the presence of abnormal clinical score, which reinforces that the deterioration of health status of those patients is associated with the presence of signs and symptoms of the disease, and not to TSH and FT4 levels.

The quality of life and health status assessment may influence the decision to treat the patient and/or stop a previous replacement. Therefore, it reinforces the idea that adding 'life to years' is as important as adding 'years to life' [30].

The limitations of the present study include: (1) its cross-sectional nature that did not allow for investigating the causality of these relationships; (2) data were based on self-report that could be a potential source of bias; (3) the sample size in the 3 groups was not equal, probably due to the higher prevalence of subclinical hypothyroidism in the general population [31]. Nevertheless, independently of the presence of statistical significance, the results obtained are clinically relevant because the groups presented different profiles of perceived health status, emphasizing that overt hypothyroidism patients presented lower scores either in relation to subclinical hypothyroidism or controls.

Conclusion

In the present study, overt hypothyroidism seemed to be associated with worse perception of health status and

negatively associated with clinical score. Additional clinical randomized trials are necessary particularly for decision-making that may improve the quality of life, the well-being and the health status of these subjects.

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