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Health-related quality of life and its association with the symptom score and the thyroid function status of patients with primary hypothyroidism on replacement therapy

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Abstract:

BACKGROUND: A number of patients with primary hypothyroidism have reduced health-related quality of life (HR-QoL), even with optimum thyroid hormone replacement therapy. This study aimed to assess the HR-QoL of patients with hypothyroidism under replacement therapy and identify its relationship with the symptom score and thyroid function status.

MATERIALS AND METHODS: Using a cross-sectional study design, 175 hypothyroid patients under replacement therapy who visited the Endocrinology Outpatient Department of a tertiary care center were selected by convenient sampling technique. Data was collected using a structured data collection tool comprising, HR-QoL Short Form-36 questionnaire, and Zulewski's clinical score. Inferential statistical analyses were performed using Mann-Whitney *U*, Kruskal-Wallis, and Karl-Pearson Correlation tests.

RESULTS: The overall mean quality of life score was 44.22 ± 12.14 , with a substantial decline in role functioning because of physical health. A significant negative correlation ($P < 0.05$) was found between HR-QoL and hypothyroidism symptom score. A significant association was observed between participants' HR-QoL and their dosage of thyroxine supplement ($P < 0.05$), but no association was found with thyroid function status.

CONCLUSION: There was a substantial reduction in the quality of life of the patients despite being on thyroid replacement therapy and achieving euthyroid status. This underlines the importance of symptom reduction and hormone optimization to enhance the quality of life.

Keywords:

Health-related quality of life, hormone replacement therapy, hypothyroidism, thyroxine

Introduction

Primary hypothyroidism is one of the most common thyroid disorders; the prevalence of which is around 11% in India.^[1] It is more common in women of reproductive age, around 2%–4%.^[2] The quality of life includes patient satisfaction, generalized

well-being, and physical and mental factors, which are very important in patients with hypothyroidism on replacement therapy. The clinical manifestations of hypothyroidism are variable, ranging from no signs and symptoms to overt symptoms involving the cardiovascular, neurological, musculoskeletal, renal, and reproductive systems.^[1,3,4] In addition to

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these, hypothyroid patients also suffer from considerable physiological and psychological stress which influences their day-to-day life and ultimately affects their health-related quality of life (HR-QoL)^[2]

Thyroid hormone replacement therapy with levothyroxine (LT4) is the standard of care for hypothyroidism, although there is no permanent cure. The main aims of the treatment of hypothyroidism are to restore the normal levels of thyroid-stimulating hormone (TSH), ameliorate signs and symptoms, and improve the quality of life. LT4 is a monotherapy taken once a day on an empty stomach by which a significant proportion of patients achieve biochemical euthyroidism and symptomatic improvement. However, a subset of patients still complains of the persistence of symptoms which can affect their well-being and activities of daily living.^[3,5] Several studies have revealed that factors like under or over-treatment, weight gain, the presence of comorbidity, age, physical or mental factors, health behavior, and drug interaction influence the HR-QoL. A combination of LT4+ LT3 has also failed to improve the quality of life in those patients.^[6]

In clinical practice, the response to LT4 treatment is often assessed by the treating physician based on clinical symptoms. However, the quality of life is better assessed by HR-QoL structured questionnaire-based instruments. The Medical Outcomes Study Short-Form Health Survey (SF-36) is a generic HR-QoL questionnaire that consists of 36 items in eight domains, namely vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, social role functioning, emotional role functioning, and mental health.^[7]

To understand the extent of the problem, it is essential to study the relationship between the symptoms experienced by the patients and their perceived quality of life. This can help healthcare professionals to effect a change of management and help to modify the lifestyle of patients with hypothyroidism and enhance their HR-QoL. Even modest changes in their physical and mental state could bring about a profound effect on their quality of life. Moreover, since data on HR-QoL of Indian patients with hypothyroidism are scarce, this study was designed to assess the quality of life using the SF-36 questionnaire.

Materials and Methods

This cross-sectional study was conducted to assess the HR-QoL, symptom score, and thyroid function status of the patients with hypothyroidism on replacement therapy attending Endocrinology Outpatient Department (OPD) for follow-up at a tertiary care institution in South India from August 20, 2022 to September 30, 2022. The sample size was estimated as 175, using the

formula for estimating single mean ($n \geq \left[\frac{z_{\alpha/2} \sigma}{D} \right]^2$) with expected mean quality of life of hypothyroidism

patients as 57, standard deviation (σ) 20.2 and absolute precision (D) of 3 at 95% of confidence level.^[8] One hundred and seventy-five patients with known primary hypothyroidism under replacement therapy for a minimum of 6 months, aged 18–60 years were selected by a nonprobability convenient sampling technique. Ethical approval was obtained from the Institutional Ethics Committee vide Letter No. JIP/IEC-OS/2022/152 dated 16/08/2022 and informed written consent was taken from all participants in the study.

Pregnant or lactating women; patients who had undergone thyroidectomy or any major surgery within the past 6 months; those who had major comorbidities considered to have a substantial impact on HR-QoL that would affect the assessment of their HR-QoL such as cancer, chronic renal failure, heart failure, rheumatoid arthritis, cerebrovascular disease, and psychiatric illness; those with thyroid malignancy and on such drugs as lithium or steroids that could interfere with the thyroid function status were excluded from the study. Data were collected using a predesigned subject datasheet and standardized questionnaires to assess HR-QoL and rate symptom scores. The subject data sheet had details on the demographic and clinical characteristics.

The perceived HR-QoL of patients with hypothyroidism was assessed using the SF-36, a standardized widely used validated tool for measuring the HR-QoL available in the public domain and a commonly used tool in the Indian setting. The tool was administered in the Tamil language after obtaining translational validity and a test-retest reliability obtained by administering the translated tool to 10 participants (Karl–Pearson correlation coefficient $r = 0.83$). The SF-36 consists of 36 items on the eight dimensions of health (physical functioning, role limitation due to physical health, role limitation due to emotional problems, energy/fatigue, social functioning, emotional well-being, pain, and general health). Each item in all the domains of SF-36 is scored in a range of 0–100 so that the lowest and highest possible scores are 0 and 100, respectively. Items on the same scale were then averaged together to find the score of each dimension of health.^[9]

A higher score was interpreted as higher quality of life. The hypothyroidism symptom score was rated using Zulewski's score, a validated clinical scoring scale of 12 items (symptoms-7, physical signs-5) for hypothyroidism developed by Zulewski *et al.*, to assess the symptom of hypothyroidism. Each item (symptom) on the scale

was scored as 1 or 0 depending on its presence or absence. A total score of >5 indicates symptomatic hypothyroidism.^[10]

Categorization of Thyroid Function Status was based on TSH level done within a month prior. TSH: 0.4–4.5 $\mu\text{IU}/\text{mL}$ -euthyroidism; TSH: 4.5–10 $\mu\text{IU}/\text{mL}$ – subclinical hypothyroidism; TSH: ≥ 10 $\mu\text{IU}/\text{mL}$ as overt hypothyroidism. TSH level estimation was done by chemiluminescent immunoassay (Advia Centaur XP, Seimens Healthcare Diagnostics Inc, USA). The normal range of TSH in this assay is 0.35–5.5 $\mu\text{IU}/\text{mL}$ and the detection range is 0.01–150 $\mu\text{IU}/\text{mL}$.

Data were analyzed using the Statistical Package for the Social Sciences software (IBM SPSS Statistics for Windows, Version 25, IBM Corporation, Armonk, NY, USA). Descriptive data were reported as the frequency with percentage for all categorical variables (gender, Body mass index [BMI], marital status, education, occupation, duration of diagnosis of hypothyroidism, thyroxine supplementation dosage, history of comorbidity, and thyroid function status) and as mean with standard deviation or median with interquartile range for continuous variables such as age, age at diagnosis, duration of replacement therapy, HR-QoL, symptom score, and TSH based on the normality assumption determined by Kolmogorov–Smirnov test. Based on normality, the relationship between the continuous variables was assessed using the Karl–Pearson correlation coefficient or Spearman rho. Association between a continuous variable (HRQoL, symptom score) concerning the categorical variable was carried out using Mann–Whitney *U*-test, and Kruskal–Wallis test based on the normality of data. All the statistical analyses were carried out at a 5% level of significance.

Results

A total of 175 patients with primary hypothyroidism under replacement attending endocrinology OPD participated in the study. The participants' demographic and clinical characteristics are presented in Table 1. Most, 159 (90.9%) of the study participants were female, with a mean age of 42.81 ± 12.42 years. Most, 86 (49.1%), were overweight, 89 (50.9%) had been diagnosed with hypothyroidism in the last 5 years. The majority, 135 (77.1%), were on thyroxine supplement of between 50 and 100 $\mu\text{g}/\text{day}$. Most participants, 103 (58.9%), on replacement therapy were in euthyroid status and most, 138 (78.9%), had a TSH value of ≤ 10 , and a few, 37 (21.1%) had a TSH value of >10 . In 69 (39.4%) participants diabetes and hypertension were the most common comorbidities, but the remaining 106 (60.6%) participants had no comorbidities.

Table 1: Demographic and clinical characteristics of patients with hypothyroidism (n=175)

Participant's characteristics	N (%)
Age (years), mean \pm SD	42.8 \pm 12.42
Duration of hypothyroidism (years)	
<5	89 (50.9)
5–10	52 (29.7)
>10	34 (19.4)
BMI (kg/m ²)	
<25	67 (38.3)
25–30	86 (49.1)
>30	22 (12.6)
TSH ($\mu\text{IU}/\text{mL}$)	
≤ 10	138 (78.9)
>10	37 (21.1)
Thyroxine dose ($\mu\text{g}/\text{day}$)	
<50	9 (5.1)
50–100	135 (77.1)
>100	31 (17.7)
Gender	
Male	16 (9.1)
Female	159 (90.9)
Marital status	
Married	155 (88.6)
Unmarried	20 (11.4)
Education	
Uneducated	42 (24.0)
Primary/middle school education (1–8 standard)	50 (28.6)
Secondary/higher education (10–12 standard)	59 (33.7)
Graduation and above	24 (13.7)
Occupation	
Employed	62 (35.5)
Unemployed	113 (64.6)
Comorbidity	
Yes	69 (39.4)
No	106 (60.6)

SD=Standard deviation, TSH=Thyroid-stimulating hormone, BMI=Body mass index

The mean HR-QoL (SF-36) of patients with hypothyroidism was 44.22 ± 12.14 . The highest impairment was in role functioning owing to physical health mean of 18.72 ± 33.84 and emotional problems at 25.52 ± 36.91 [Table 2]. Paraesthesia (72%) and increased weight (54.3%) were the most reported symptoms, whereas impairment of hearing was the symptom (15.4%) that was the least experienced by participants. Most, (52%), participants presented with coarse skin, 51.1% had delayed ankle reflex, and 41.1% had cold skin with a mean symptom score of 5.02 ± 1.83 on assessment with Zulewski's clinical score [Table 3].

Age and thyroxine supplementation dosage had a significant relationship with HR-QoL, whereas gender, presence of comorbidity, BMI (calculated from measured weight using a digital weighing machine and height by wall fixed stadiometer), duration of diagnosis of

hypothyroidism, and TSH value had no association with HR-QoL [Table 4].

There was a statistically significant negative correlation between HR-QoL and hypothyroidism symptom score at $P < 0.05$ ($r = -0.486$, Confidence interval $-4.10, -2.36$) [Figure 1]. No significant relationship was noted between participants' HR-QoL and their thyroid function status.

Discussion

The present study evaluated the HR-QoL and its relationship with the hypothyroid symptoms score established by Zulewski's clinical scoring and thyroid function status. The findings of this study showed that the hypothyroidism patients in India under replacement therapy remained with a significant reduction in HR-QoL of seven out of the eight dimensions of SF-36 except the social dimension. In addition, it was also observed

that role limitation owing to physical and emotional problems and fatigue were the most common domains affected in patients with hypothyroidism. This finding is in agreement with the study by Winther *et al.*, which showed a significant reduction in the quality of life in seven of eight domains of SF-36 other than bodily pains in patients with autoimmune hypothyroidism.^[11] Further, the findings of the present study agreed with previous studies conducted by Shivaprasad *et al.*, which revealed that there was significant impairment in the quality of life of the Indian patient in six of the eight domains of SF-36, the severest of which was in physical functioning compared to that of healthy subjects with a statistically significant difference at $P < 0.001$.^[8]

Several previous studies had revealed that the commonest symptoms of hypothyroidism are predominantly tiredness, dry skin, cold intolerance, weight gain, constipation, and hoarseness of voice. The frequently observed clinical signs include delayed ankle reflex relaxation time, coarseness of skin, and hypothyroid face with periorbital puffiness.^[1,12,13] Hypothyroidism symptom scores were established using Zulewski's clinical scoring, a valid effective tool for the identification of hypothyroidism.^[14] Similarly, this study also demonstrated that most of the participants had such symptoms as paresthesia (72%), weight increase (54.3%), and dry skin (53.1%) with such major clinical signs as coarse skin (52%) and delayed ankle reflex (91.1%).

Most (78.9%) of the participants had TSH ≤ 10 following thyroid replacement therapy, although in this study their HR-QoL remained low. The findings of this study demonstrated neither an association between the HR-QoL and thyroid function status nor a correlation with TSH level, which reinforces findings from other studies.^[8,15,16] A possible explanation for the low quality of life even with a normalized TSH value could be

Table 2: Health-related quality of life score for patients with hypothyroidism (n=175)

Short form-36 questionnaire dimensions	Score Mean±SD
Physical functioning	51.37±22.02
Role limitation due to physical health	18.72±33.84
Role limitations due to emotional problems	25.52±36.91
Energy/fatigue	33.57±16.95
Emotional well-being	49.14±12.08
Social functioning	69.66±18.46
Pain	57.74±15.05
General health	38.74±12.13
Overall score	44.22±12.14

SD=Standard deviation

Table 3: Distribution of hypothyroidism symptoms (n=175)

Hypothyroidism symptom score	Hypothyroidism symptoms	
	Present N (%)	Absent N (%)
Symptoms		
Diminished sweating	87 (49.7)	88 (50.3)
Hoarseness	89 (50.9)	86 (49.1)
Paresthesia	126 (72.0)	49 (28.0)
Dry skin	93 (53.1)	82 (46.9)
Constipation	55 (31.4)	120 (68.6)
Impairment of hearing	27 (15.4)	148 (84.6)
Weight increase	95 (54.3)	80 (45.7)
Physical signs		
Slow movements	49 (28.0)	126 (72.0)
Delayed ankle reflex	90 (51.1)	85 (48.9)
Coarse skin	91 (52.0)	84 (48.0)
Periorbital puffiness	12 (6.9)	163 (93.1)
Cold skin	72 (41.1)	103 (58.9)
Hypothyroidism symptom score, mean±SD	5.02±1.83	

n=Number of participants, SD=Standard deviation

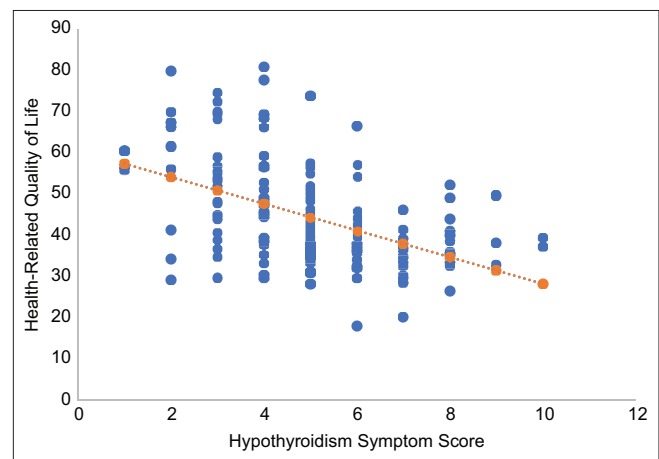


Figure 1: Correlation between health-related quality of life and hypothyroidism symptom score

Table 4: Relationship between health-related quality of life and selected participant's characteristics among patients hypothyroidism (n=175)

Variables	Score Median (IQR)	P-value
Gender ^a		
Male	40 (34–54.50)	0.836
Female	41 (36–51)	
Age (r)	-0.482	0.00*
Comorbidity ^a		
Yes	40 (33.50–48)	0.110
No	41.5 (37–53.25)	
BMI ^b		
<25	44 (37–55)	0.292
25–30	40 (34.75–51)	
>30	40.50 (36.75–45)	
Duration of hypothyroidism (year) ^b		
<5	44 (38–53.5)	0.07
5–10	39 (35–51.7)	
>10	37 (33.7–44.5)	
TSH (μIU/mL) ^a		
≤10	40 (35–51)	0.111
>10	43 (37.50–56)	
Dose of thyroxine ^b (μg/day)		
<50	56 (51.50–69)	0.03*
50–100	40 (35–48)	
>100	41 (36–53)	

*P<0.05, ^aMann–Whitney U-test, ^bKruskal–Wallis test. r=Karl Pearson correlation coefficient, BMI=Body mass index, IQR=Interquartile range, TSH=Thyroid-stimulating hormone

that a normal TSH value could reflect euthyroidism in the hypothalamus without necessarily reflecting euthyroidism in the rest of the body tissues.^[1,16] Congruent to this finding, a study that compared the quality of life of hypothyroidism patients with TSH less than and more than 10 mIU/L did not exhibit any significant difference.^[8,17] However, another study had shown that patients with hypothyroidism who had had replacement therapy reached normalized TSH values and had improved quality of life.^[18]

All the participants in this study were on thyroid hormone replacement therapy. Most on replacement therapy were females (90.9%), with a mean age of 42.81 ± 12.42. This finding is congruent with worldwide reports, especially of middle-aged women of 46–54 years.^[19] The occurrence of hypothyroidism increases with age most probably as a result of the changes in thyroid hormone production in various stages of life and thyroid autoimmunity most notable in perimenopause women.^[1] Similarly, a previous study of Indian patients with hypothyroidism demonstrated that 201 (82.4%) were females, with a mean age of 36.57 years.^[20] In contrast to this, another study reported that hypothyroidism is more common in females of reproductive age. Most participants

were unemployed (64.6%). Similarly, a previous study reported that 83% of hypothyroid patients were unemployed and specifically homemakers. This could be because the study subjects were mostly females.^[21]

The study results revealed a statistically significant association of the HR-QoL with the dosage of the thyroxine supplement. This implies that replacement therapy has an impact on HR-QoL. Furthermore, it remains unclear why the patients exhibited poor HR-QoL despite replacement therapy with thyroxine supplement with a median duration of treatment of 6 months. This might be due to the difference in the sensitivity of the pituitary gland and peripheral tissues to thyroxine supplement. Further, the persistent poor quality of life may be the result of the common symptoms of hypothyroidism found such as weight gain, fatigue, and loss of energy which are not significant in treatment. Another study reported that treated hypothyroid patients had persistent decreased HR-QoL. However, another study revealed that a duration of 6 months since initiating replacement therapy showed significant improvement in the quality of life in role functioning, physical health, social functioning, and mental health on SF-36.^[11,22]

A double-blind randomized cross-over trial by Kelderman-Bolk *et al.*, revealed that the mean BMI of hypothyroid patients was 29.1 ± 5, which belongs to the overweight category.^[3,23] Another prospective case-control study showed similar findings (mean BMI of 25.8 ± 5.1).^[24] The present study revealed that 86 (49.1%) patients with hypothyroidism were overweight but showed no association with the quality of life. Similar to various other studies, the findings of this study demonstrate that HR-QoL remains low despite thyroxine replacement therapy.^[25–28] This study revealed a significant association of HR-QoL with the age of the study participants. This is an expected result as the general and health-specific quality of life gradually declines with advancing age.

In a previous study, it was demonstrated that 64 (46%) hypothyroid patients had comorbidities, i.e., mainly hypertension (42%) and diabetes mellitus (38%).^[21] However, the present study revealed that only 39.4% of hypothyroidism patients presented with co-morbidities such as diabetes and hypertension, whereas 60.6% had no comorbidities since patients with major comorbidities had been excluded because of the substantial impact on the quality of life irrespective of their hypothyroid symptoms. The presence of comorbidities further would have contributed to decreased quality of life and persistence of degrading symptoms.^[18]

The study findings showed that the HR-QoL remains low in hypothyroidism patients still on thyroxine

replacement therapy and experiencing some degree of hypothyroid-related symptoms. Furthermore, this study exhibited a significant correlation between the quality of life and hypothyroidism symptom scores irrespective of thyroid function status. Hence, the study implies that it is essential to routinely assess self-reported hypothyroidism symptoms, quality of life, and hormone level monitoring. This should become an integral part of the medical management of hypothyroidism to enhance the HR-QoL and well-being.

Our study had strengths as well as limitations. The main strength of this study is the association found between hypothyroidism symptom scores and the quality of life in hypothyroid patients with the use of validated questionnaires. However, its limitation is the smallness of the sample size with no group for comparison. Besides, the probability sampling method could not be used for the selection of study participants as the study was undertaken for academic purposes only. There was also the issue of obtaining a sampling frame of patients with hypothyroidism on replacement therapy at short notice.

Conclusion

The study concludes that despite regular thyroid hormone replacement therapy, patients with hypothyroidism still experience many hypothyroid-related symptoms that can adversely affect their perceived quality of life and well-being. It is recommended that a comparison of the quality of life and symptoms between patients with hypothyroidism on replacement therapy for different durations be carried out for a deeper understanding of the lower HR-QoL despite replacement therapy.

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Conflicts of interest

There are no conflicts of interest.

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