Sri Lanka Journal of Medicine **SLJM**

Original Research

Citation: Kumarathunga PADM, Kanchana WGP, Ratnayake P, Antonypillai CN, 2024. Does Thyroidectomy Offer Quality of Life Advantage for Autoimmune Thyroiditis Patients?. Sri Lanka Journal of Medicine, pp 15-24.
DOI: https://doi.org/10.4038/sljm.v33i2.489

Does Thyroidectomy Offer Quality of Life Advantage for Autoimmune Thyroiditis Patients?

PADM Kumarathunga, WGP Kanchana, P Ratnayake, CN Antonypillai

National Hospital Kandy, Sri Lanka.

Correspondence:
PADM Kumarathunga
E mail: dineeshakumarathunga@gmail.com
https://orcid.org/0000-0002-8573-7620

ABSTRACT

Introduction: Significant reduction of subjective health status is frequently reported by many patients with Hashimoto thyroiditis despite adequate thyroxine replacement therapy. Studies have shown that thyroidectomy improves quality of life (QoL) in patients with HT and persistence symptoms, however there are conflicting evidence and we do not have our own data. QoL is an important aspect in management of chronic diseases like hypothyroidism which is less well touched in our population. Our findings highlight the potential of thyroidectomy in enhancing QoL for HT patients, contributing to the ongoing research on optimal management strategies for this condition.

Objectives: To assess the QoL in patients with Hashimoto's thyroiditis (HT) who are biochemically euthyroid on thyroxine replacement therapy and to compare the QoL between patients managed medically and those who have undergone thyroidectomy with histologically confirmed HT.

Methodology: We conducted a case-control study to compare the QoL using the SF-36 questionnaire among two groups of euthyroid Hashimoto's thyroiditis patients: those receiving medical management and those who are post-thyroidectomy, as well as a healthy matched control group. Confounders that could affect QoL were rigorously excluded, and parametric tests were utilized for data analysis.

Results: A significantly lower overall QoL was noted in the medically managed group (n=23) compared to the thyroidectomy group (n=24), with mean scores of 63.72 versus 84.25, respectively (P-value < 0.0001). This trend was consistent across all domains of the SF-36 QoL questionnaire. The QoL scores of patients who underwent surgery were similar to those of the healthy control group. Additionally, no significant correlation was found between thyroperoxidase (TPO) antibody titers and QoL in the regression analysis.

Conclusion: Overall, patients with Hashimoto's thyroiditis on medical management exhibit significantly poorer QoL, despite adequate thyroxine replacement. This may be attributable to a complex interplay of immunological factors associated with an intact thyroid gland. Thyroidectomy could serve as a viable treatment alternative for these individuals. It is essential to develop algorithms to identify patients who would benefit most from thyroidectomy, ensuring they are thoroughly informed about the risks and benefits. Ongoing studies and the establishment of therapeutic guidelines are crucial for improving the management of patients with Hashimoto's thyroiditis.

Keywords: Hypothyroidism, Hashimoto's thyroiditis, Quality of Life, Thyroidectomy, Sri Lanka.

Received: 2023-03-23 **Accepted revised version: 2024-07-24** **Published: 2024-07-30**

INTRODUCTION

Hypothyroidism is a common clinical problem and a significant cause of morbidity. Hashimoto's thyroiditis (HT) is the most common cause of hypothyroidism in iodine-sufficient regions (1). The disease is characterized by elevated circulating antibodies against thyroid antigens, particularly anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) (2), along with distinct histological features (3). It is one of the most frequent autoimmune disorders, affecting 5-10% of the female population of childbearing age (4).

In recent years, a paradigm shift has occurred in the treatment of many chronic diseases. Relieving symptoms and enhancing function are deemed as crucial as restoring physiological balance, particularly as survival rates improve and the burden of chronic disease grows. Consequently, evaluating these outcomes is vital in managing common chronic illnesses like hypothyroidism, which significantly impacts patients' functioning and QoL.

A notable decline in subjective health status is commonly reported by patients with hypothyroidism, despite adequate thyroxine replacement therapy. Population-based studies indicate that 5-30% of patients with treated hypothyroidism continue to exhibit symptoms compared to controls, even when TSH levels are within the normal range (5–7). Patients with euthyroid status often endure general indisposition with various manifestations, including fatigue. Mood disturbances, emotional instability, and excessive anxiety are also frequently noted among hypothyroid patients. Additionally, neck enlargement and goitre development, which are associated with discomfort and cosmetic concerns, can substantially affect health-related QoL (8–10). To date, no studies have assessed the health related QoL in euthyroid HT patients on thyroxine replacement in Sri Lanka, where a significant portion of the population is comorbid with hypothyroidism (11).

Research has demonstrated that euthyroid patients with HT, particularly those with elevated anti-TPO and anti-Tg levels, experience increased symptoms and significantly lower QoL domain scores (9,10,12–14), with a heightened predisposition to major depression and anxiety disorders (15). The pathogenesis of these symptoms remains elusive. As an autoimmune condition, HT may entail systemic autoimmunity triggered by thyroid autoantibodies, with anti-thyroid antibodies potentially altering immune status and contributing to persistent symptoms and decreased QoL (9,10,16,17). Nevertheless, some evidence contradicts this association (14,18). Other factors potentially contributing to poor QoL include selenium deficiency, variable thyroid hormone levels, disease awareness, and comorbidities (7–9). Our population lacks a proper evaluation of the relationship between anti-TPO antibody titres and QoL, which has implications for treatment.

Currently, there is no standardized approach for treating patients with persistent symptoms and poor QoL despite adequate hormone therapy. Thyroidectomy is typically reserved for those with goitre presenting compressive symptoms or cancer suspicions (19). Moreover, studies have indicated a high rate of postoperative complications following thyroidectomy for HT (20,21). Nevertheless, recent trials suggest that thyroidectomy could be a viable treatment for euthyroid patients with low QoL and persistent symptoms with elevated anti-TPO titres (16,19,21–25), despite some conflicting evidence. It is recognized that the complete or near-total removal of the gland leads to the disappearance of major thyroid antigen antibodies (16,23,26). This raises the question: Given the potential role of systemic autoimmunity in symptomatology, can thyroidectomy improve QoL in patients with HT? R. Promberger and colleagues found that thyroidectomy does not improve overall QoL in women with benign euthyroid goitres, including those with elevated TPO antibody titres, concluding that thyroid gland removal should not be recommended for patients with reduced QoL with high TPO-ab levels (27). In light of these varied findings, it is crucial to determine whether thyroidectomy can make a difference in the QoL for HT patients as opposed to medical management alone in our population.

The impact of chronic disease on a patient's daily life is as critical as the survival itself. Health-related QoL broadly reflects the overall effect of a disease and its treatment on an individual's wellbeing,

assessing the physical, social, psychological, and somatic facets of life (8,29). We selected the SF-36 questionnaire, a general rather than thyroid-specific instrument, due to the association of HT with both specific and non-specific thyroid dysfunction symptoms.

The Medical Outcome Study Short-Form Health Survey (SF-36) is a widely utilized tool for measuring health-related QoL, comprising 36 questions that cover eight health dimensions (30):

1. Physical functioning (PF)—the extent of health limiting physical activity;

2. Physical role playing (RP)—the extent of physical health interfering or limiting the usual role activities;

3. Emotional role playing (RE)—the extent of emotional problems interfering or limiting the usual daily role activities;

4. Social functioning (SF)—the extent of physical health or emotional problems interfering with the normal social activities;

5. Bodily pain (BP)—the intensity of pain and effects on normal activities;

6. Mental health (MH)—includes depression and anxiety;

7. Vitality (VT)—including feeling full of pep versus tired and worn-out;

8. General health (GH)—personal evaluation of health.

This instrument has been validated for use in patients with hypothyroidism (30) and within the Sri Lankan population (31). Scores for each dimension are coded, totaled, and transformed on a scale ranging from 0 (representing the worst possible perceived health status) to 100 (representing the best possible perceived health status).

At our institution, we manage a large cohort of hypothyroid patients, including those with intact thyroids and those who are athyreotic. Considering hypothyroidism as a chronic and prevalent condition, the aspect of quality of life in these patients has not been extensively explored in our demographic. This study, therefore, aims to provide new insights into the quality of life of patients undergoing treatment for hypothyroidism, examine how different management strategies impact their well-being, and determine ways to enhance the quality of life among the Sri Lankan population comorbid with hypothyroidism.

METHODOLOGY

This case-control study was conducted at the Endocrinology and Surgical Clinics of the National Hospital Kandy from January to October 2020. The research sample consisted of patients attending the Endocrinology Clinic diagnosed with hypothyroidism and positive TPO antibodies (Group A) and patients attending the Surgical Clinic, post-thyroidectomy for benign goiter with histological confirmation of HT (Group B). An age and sex-matched clinically euthyroid control group (Group C) was randomly selected from the community.

$$k = \frac{n_2}{n_1} = 1$$

$$n_1 = \frac{(\sigma_1^2 + \sigma_2^2/K)(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2}$$

$$n_1 = \frac{(23^2 + 23^2/1)(1.96 + 0.84)^2}{20^2}$$

$$n_1 = 21$$

$$n_2 = K * n_1 = 21$$

$\Delta = |\mu_2 - \mu_1|$ = absolute difference between two means
σ_1, σ_2 = variance of mean #1 and #2
n_1 = sample size for group #1
n_2 = sample size for group #2
α = probability of type I error (usually 0.05)
β = probability of type II error (usually 0.2)
z = critical Z value for a given α or β
k = ratio of sample size for group #2 to group #1

We used expected mean SF36 score of the study group (group 1), expected mean SF36 score of the control group (group 2), expected standard deviation and power of 0.8 as parameters in calculating the sample size.

Mean SF36 score for control group in many studies has shown to range from 80 to 90 while mean SF36

score for study group was found to be 64 from a small pilot study that was conducted. Expected standard deviation in these previous studies was in the range of 20 to 30.

Using these parameters and sample size calculation formula above, a minimum sample of 21 patients per study group was calculated.

All participants provided informed consent and the study protocol was approved by the human research ethics committee at national hospital Kandy, Sri Lanka((NHK/ERC/39/2020).

For Group A, included were patients diagnosed with hypothyroidism for more than six months and who had thyroid function test results from the past six months, confirming biochemical euthyroidism during that time. For Group B, included were patients who had undergone total thyroidectomy more than six months prior, with histology showing chronic lymphocytic thyroiditis and who were biochemically euthyroid for the past six months. For Group C, included were age and sex-matched individuals without significant comorbidities, who were clinically euthyroid, selected randomly from the community in the Kandy suburb.

Exclusion criteria encompassed patients under 15 or over 80 years of age, with major socio-economic issues, secondary hypothyroidism, other autoimmune diseases, significant comorbidities such as diabetes mellitus (DM), chronic kidney disease (CKD), cardiovascular disease (CVD), extrathyroidal malignancy, thyroid malignancy diagnosed prior to surgery, pregnancy, dementia, other psychiatric disorders, history of brain injury, and surgically managed patients who experienced post-operative permanent hypoparathyroidism, significant voice changes due to recurrent laryngeal nerve injury, and subjectively disfiguring surgical scars.

Participants received a brief overview of the study's objectives and completed the SF-36 Questionnaire. Sociodemographic data, medical history, anti-TPO antibody titers, recent thyroid function tests, thyroxine dosage, and histological findings were additionally collected. Trained staff ensured the completeness of the questionnaires.

Data were catalogued and analysed using an Excel spreadsheet. Descriptive statistics were expressed as mean ± standard deviation. Further statistical analyses were performed using the MS Excel statistical package.

Demographic data were categorized as shown in table 1 and difference of mean between the groups were assessed using the Chi-square test for all non-parametric data. The only parametric data in the demographic analysis was BMI and the difference of mean was calculated using single factor ANOVA.

As many of the previous studies published in world literature had used parametric tests such as ANOVA to analyse SF36 data (8,19), we have used one-way ANOVA test to assess the difference of mean between the three groups.

Differences with a P-value of less than 0.05 were deemed statistically significant for all statistical tests.

RESULTS

A total of 23 hypothyroid patients on medical management with elevated TPO titers (referred to as 'medical patients') and 24 patients who had undergone total thyroidectomy with histology confirming chronic lymphocytic thyroiditis (referred to as 'surgical patients'), along with 24 controls, were eligible for analysis after screening for inclusion and exclusion criteria.

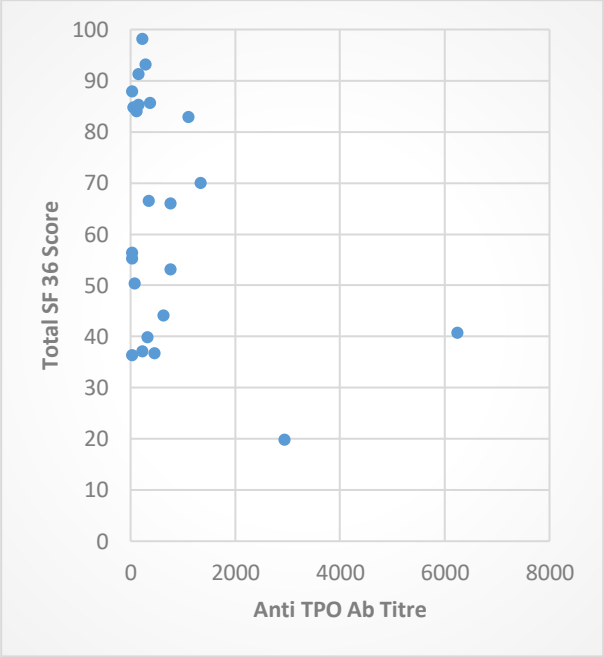
Comparative analysis between the medical patients (n=23) and the surgical patients (n=24) revealed no statistically significant differences in demographic and patient characteristics as observed in Table 1.

Graph 1 shows the regression plot between Anti-TPO antibody titre and the total SF-36 score for each patient in medical group. This regression analysis did not show any relationship between the Anti TPO antibody titre and the SF-36 scores.

Table 1: Comparative analysis between demographics of medical and surgical patients.

	Surgical	Medical	
Median Age	47.5	50	P=0.77
Male	2	2	
Female	22	21	
Male: Female	0.09	0.10	
Median BMI	25.31	24.98	p=0.78
Ethnicity			p=0.32
Sinhalese	21	22	
Other	3	1	
Education level			p=0.44
1ry / 2ry	13	15	
A/L and above	11	8	
Occupation			p=0.30
No Occupation	18	14	
Any occupation	6	9	
Social Class			p=0.88
Upper Middle	12	12	
Lower Middle	12	11	

The average SF-36 scores across the eight domains, as well as the aggregate scores for each group and the control group, were analysed and are presented in Table 2. Compared to the healthy controls, euthyroid patients in the medical arm displayed significantly lower scores in all dimensions, indicating a reduced quality of life.



Graph 1: Regression plot between Anti-TPO antibody titre and the total SF-36 score for each patient in medical group.

Table 2: Comparison of median SF 36 scores for all the domains between medical, surgical and control groups. (The differences of means were analysed using single factor ANOVA test).

	Medical (ANTI TPO ab +VE)	Surgical (HISTOLOGY PROVEN THYROIDIST)	Healthy Control Group	P Value
General health	54.13	68.33	74.83	0.000115
Physical functioning	77.17	90.41	86.90	0.018378
Role limitation due to physical features	57.61	82.29	93.97	0.001123
Role limitation due to emotional problems	57.97	100	91.95	0.000001
Energy fatigue	64.56	76.25	76.90	0.014910
Emotional wellbeing	66.26	86.5	85.52	0.000008
Social functioning	77.17	89.58	90.09	0.014901
Pain	54.89	80.62	79.14	0.000065
Total Score	63.72	84.25	84.91	0.000025

In contrast, euthyroid patients who underwent thyroidectomy, with histological confirmation of HT, showed scores comparable to healthy controls across all seven domains assessed. The average total SF-36 score was 63.7 for the medical patients and 84.25 for the surgical patients (P-value = 0.000025), with similar trends observed across all individual SF-36 domains.

DISCUSSION

Our study reveals that Sri Lankan patients with Hashimoto's thyroiditis (HT) on medical management suffer from significantly lower health-related quality of life across all eight domains of the SF-36, despite being euthyroid. Interestingly, patients with histologically confirmed HT showed quality of life scores comparable to those of age- and sex-matched healthy controls following thyroidectomy.

The primary management of HT involves medical management with thyroxine hormone supplementation. However, many euthyroid patients continue to experience persistent symptoms and a poor quality of life, including profound fatigue, musculoskeletal symptoms, anxiety, other mental health issues, and impaired well-being. Numerous studies have reported significant impairments in physical, psychological, and social well-being in euthyroid patients with HT compared to similar-age and sex-matched controls (9,10,12,13,18,32). Consistent with the available evidence, our findings indicate that the medically managed cohort had significantly lower scores across all SF-36 domains.

The underlying pathogenesis of these symptoms is not fully understood, but several hypotheses have been proposed. Systemic autoimmunity induced by elevated anti-thyroid antibodies is considered a primary factor. Evidence suggests that TPO antibodies may cross-react with various tissues and are associated with higher levels of T-lymphocyte-derived pro-inflammatory cytokines, such as interferons and TNF (33). Research has identified brain perfusion abnormalities and a higher prevalence of antibodies against central nervous system tissue and gangliosides in patients with HT compared to controls (34,35), implicating CNS involvement in symptomatology. Additionally, electron microscopic studies of skeletal muscle biopsies from euthyroid HT patients have revealed capillary alterations and mononuclear cell infiltrates, suggesting a link between thyroid autoimmunity and muscle symptoms (32). A study on rheumatological manifestations in autoimmune thyroid disease has found anti-thyroid antibodies in synovial fluid, sometimes before serum antibodies are detectable (36). These findings imply that the clinical course of HT is more complex than previously thought and that systemic autoimmunity triggered by thyroid autoantibodies plays a significant role.

Given the pathogenic role of systemic inflammation by anti-thyroid antibodies, their depletion should mitigate the inflammatory response. Studies have indicated that the complete removal of antigenic thyroid tissue results in the disappearance of major anti-thyroid antibodies (16,23,26) and the concurrent clearance of other immunological mediators (33). Recent trials have demonstrated that thyroidectomy improves the quality of life in patients with HT suffering from persistent symptoms and impaired well-being (16,19,20,22–24).

Tatipamula et al. conducted a retrospective study assessing QoL with the SF-36 among euthyroid patients with Hashimoto's thyroiditis diagnosed with TPO antibodies or histology, who underwent thyroidectomy for refractory symptoms. The study compared their post-operative QoL with that of matched healthy controls and found no significant difference between the two groups on all SF-36 sub-scores (19). Our study's findings among post-surgical patients align with these results. Guldvog et al. conducted the first randomized control trial among euthyroid HT patients with TPO titres >1000 IU/L, having persistent symptoms despite being euthyroid, randomizing them to medical management or total thyroidectomy. The outcomes, measured by SF-36 scores at 18 months, showed that thyroidectomy improved general health scores and normalized TPO antibody titres, whereas medical therapy did not (16). This confirms the benefit of thyroidectomy, corroborated by several other studies, including patients with a range of elevated antibody titres, similar to those in our study. An extension of

Guldvog's study published by Hoff et al. indicated that the positive effects of surgical treatment on health scores persisted during a 5-year follow-up (21). The study by Promberger et al. indicated no quality-of-life benefits from thyroidectomy in TPO positive patients; however, a subgroup with histological evidence of HT showed improved outcomes. The average TPO level in this cohort was 8 IU/ml, suggesting that the most significant benefits may be seen in patients with high antibody titres. They also noted a substantial negative impact from transient post-operative complications on post-operative quality of life.

All surgical procedures are associated with the potential for postoperative complications. It is essential to balance the risks of surgery against the benefits when selecting patients for thyroidectomy. In the follow-up study by Hoff et al., it was found that 14% of patients experienced long-term complications, while 18% experienced short-term complications, such as recurrent laryngeal nerve (RLN) palsy, hypoparathyroidism, postoperative hematoma, or infection. They concluded that while total thyroidectomy can improve the symptom burden in euthyroid patients with Hashimoto's thyroiditis (HT), it carries a high risk of complications. Some studies have shown that thyroidectomy in HT is associated with a high complication rate (20), whereas other research suggests it is a safe procedure with a low risk of permanent surgical complications when performed by experienced surgeons (10,22,37). However, given the totality of evidence, careful consideration and informed consent are imperative before proceeding with thyroidectomy in patients with HT.

T3/T4 combination therapy has been explored as another treatment option to improve symptoms in euthyroid patients with low quality of life (QoL), due to the purported lack of efficacy of levothyroxine (LT4) alone in restoring tissue-level euthyroidism. However, combination therapy has not shown a clear advantage over LT4 monotherapy in clinical trials. While some evidence suggests that selenium supplementation can reduce TPO antibody titers, there is insufficient data to confirm an improvement in QoL with selenium, warranting further research.

Although thyroidectomy has traditionally been reserved for patients with compressive symptoms or suspected malignancy, there is substantial evidence to support its role in improving health related QoL in patients with persistent symptoms and impaired well-being due to HT. Our study corroborates that thyroidectomy can improve QoL in euthyroid HT patients with impaired well-being. This information is vital for addressing the management challenges of HT within the Sri Lankan population, especially considering the significant impact of chronic illness on health related QoL and life expectancy. Moreover, there is evidence to suggest that total thyroidectomy may be more cost-effective than hormone therapy alone in managing euthyroid HT patients with persistent symptoms.

Nevertheless, there is no definitive algorithm to determine the exact criteria for qualifying euthyroid HT patients with low QoL for thyroidectomy. With the high prevalence of HT, it is not cost-effective to offer thyroidectomy to all euthyroid patients with any level of well-being impairment, and it is uncertain whether all symptoms would improve, especially since most supporting evidence favours patients with high antibody titres and severe symptoms. Therefore, it is crucial to develop a local or international algorithm to identify patients who are suitable candidates for surgery and to maintain a low threshold for offering thyroidectomy as a therapeutic intervention to this selected group of patients.

The study underscores the significance of routine evaluation of the impact of the disease on the QoL, particularly with the availability of potential therapeutic options. Such assessments can positively influence patient satisfaction and foster a favourable experience with healthcare professionals, which in turn may indirectly improve QoL.

As noted, thyroidectomy could alleviate symptoms by reducing antigenicity and, consequently, systemic autoimmunity in HT. In the current climate of advancing immunomodulatory medications, additional research is imperative to evaluate the role of immunomodulatory treatments alongside thyroidectomy, especially given the theory of systemic autoimmunity underlying persistent symptoms.

This research is the first study to evaluate the QoL in HT patients who are biochemically euthyroid on hormone therapy within the Sri Lankan population. A strength of this study is the comparison of euthyroid HT patients under both medical management and surgical management with a matched control group, providing robust data.

However, the study does have limitations, including a small sample size and the fact that the criteria for thyroidectomy in the surgical cohort did not consider the symptomatology of thyroiditis. Also, the study having a single centre cross sectional design will affect its generalizability to other different populations across the country. The absence of preoperative QoL assessments in surgical patients is a limitation; nonetheless, we postulate that their QoL would be analogous to that of the medically managed cohort. Therefore, we infer that the postoperative normalization of QoL scores in our population denotes an improvement from the preoperative state. Absence of biochemical confirmation of the control group with serum TSH levels is a limitation of the study, however the clinical assessment of euthyroid status in the control group is still valid and widely accepted approach in this type of research (9). Further despite histological confirmation of Hashimoto thyroiditis in surgical group, absence of TPO titre may be a limitation. However, we could not demonstrate any association between TPO titre and symptomatology in medical group, thus we assume it would not have significant impact on study findings.

Despite these constraints, our study contributes valuable evidence in support of thyroidectomy as a management strategy for this particular group of euthyroid patients with HT.

CONCLUSIONS

Health-related QoL is a crucial aspect of managing patients with chronic diseases. Managing refractory symptoms alongside reduced QoL presents a challenge in patients with euthyroid Hashimoto's thyroiditis (HT). Our study has demonstrated that euthyroid HT patients under medical management exhibit significantly poorer QoL compared to matched controls, whereas those who have undergone thyroidectomy exhibit QoL comparable to the controls. These findings endorse thyroidectomy as a potential therapeutic option for euthyroid HT patients experiencing persistent symptoms and diminished QoL. There is a need to develop algorithms to identify patients who would benefit most from thyroidectomy, ensuring they are comprehensively informed about the associated risks and benefits. Further research is also needed on non-surgical therapeutic options such as selenium and targeted immunotherapy treatments.

Author declaration

Acknowledgements:
The authors acknowledge staff in Endocrine and Surgical Clinic National Hospital Kandy.

Authors' contributions:
Study concept and design: P.A.D.M.K., P.K., P.R., and C.A.N.; Acquisition of data, analysis, and interpretation of data: P.A.D.M.K., P.K and P.R.; Drafting of the manuscript: P.A.D.M.K and P.K. Study supervision: C.A.N.

Conflicts of interest:
The authors declare that there are no conflicts of interests.

Funding statement:
Self-funded

Ethics statement:
All participants provided informed consent and the study protocol was approved by the human research ethics committee at national hospital Kandy, Sri Lanka((NHK/ERC/39/2020).

Statement on data availability:
Data generated or analysed during this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Hypothyroidism: Practice Essentials, Background, Pathophysiology [Internet]. [cited 2024 Mar 1]. Available from: https://emedicine.medscape.com/article/122393-overview
2. Akamizu T, Amino N. Hashimoto's Thyroiditis. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2024 Mar 1]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK285557/
3. Caturegli P, De Remigis A, Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. Autoimmun Rev. 2014;13(4–5):391–7. DOI: 10.1016/j.autrev.2014.01.007
4. Peterson CM. THYROID DISEASE AND FERTILITY. Immunol Allergy Clin North Am. 1994 Nov 1;14(4):725–38. DOI:10.1016/S0889-8561(22)00338-1
5. Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R, Dayan CM. Psychological well-being in patients on 'adequate' doses of l-thyroxine: results of a large, controlled community-based questionnaire study. Clin Endocrinol (Oxf). 2002 Nov;57(5):577–85. DOI:10.1046/j.1365-2265.2002.01654.x
6. Wekking EM, Appelhof BC, Fliers E, Schene AH, Huyser J, Tijssen JGP, et al. Cognitive functioning and well-being in euthyroid patients on thyroxine replacement therapy for primary hypothyroidism. Eur J Endocrinol. 2005 Dec;153(6):747–53. DOI:10.1530/eje.1.02025
7. Mitchell AL, Hegedüs L, Žarković M, Hickey JL, Perros P. Patient satisfaction and quality of life in hypothyroidism: An online survey by the british thyroid foundation. Clin Endocrinol (Oxf). 2021 Mar;94(3):513–20. DOI:10.1111/cen.14340
8. Shivaprasad C, Rakesh B, Anish K, Annie P, Amit G, Dwarakanath CS. Impairment of Health-related Quality of Life among Indian Patients with Hypothyroidism. Indian J Endocrinol Metab. 2018;22(3):335–8. DOI:10.4103/ijem.IJEM_702_17
9. Bektas Uysal H, Ayhan M. Autoimmunity affects health-related quality of life in patients with Hashimoto's thyroiditis. Kaohsiung J Med Sci. 2016 Aug;32(8):427–33. DOI: 10.1016/j.kjms.2016.05.005
10. Ott J, Promberger R, Kober F, Neuhold N, Tea M, Huber JC, et al. Hashimoto's thyroiditis affects symptom load and quality of life unrelated to hypothyroidism: a prospective case-control study in women undergoing thyroidectomy for benign goiter. Thyroid Off J Am Thyroid Assoc. 2011 Feb;21(2):161–7. DOI:10.1089/thy.2010.0191
11. The clinical epidemiology of thyroid disease in Sri Lanka - PDF Free Download [Internet]. [cited 2024 Mar 1]. Available from: https://docplayer.net/38716690-The-clinical-epidemiology-of-thyroid-disease-in-sri-lanka.html
12. Müssig K, Künle A, Säuberlich AL, Weinert C, Ethofer T, Saur R, et al. Thyroid peroxidase antibody positivity is associated with symptomatic distress in patients with Hashimoto's thyroiditis. Brain Behav Immun. 2012 May;26(4):559–63. DOI:10.1016/j.bbi.2011.11.017
13. Watt T, Hegedüs L, Bjorner JB, Groenvold M, Bonnema SJ, Rasmussen AK, et al. Is Thyroid Autoimmunity per se a Determinant of Quality of Life in Patients with Autoimmune Hypothyroidism? Eur Thyroid J. 2012 Oct;1(3):186–92. DOI:10.1159/000342778
14. Delitala AP, Terracciano A, Fiorillo E, Orrù V, Schlessinger D, Cucca F. Depressive symptoms, thyroid hormone and autoimmunity in a population-based cohort from Sardinia. J Affect Disord. 2016 Feb;191:82–7. DOI:10.1016/j.jad.2015.11.032
15. Giynas Ayhan M, Uguz F, Askin R, Gonen MS. The prevalence of depression and anxiety disorders in patients with euthyroid Hashimoto's thyroiditis: a comparative study. Gen Hosp Psychiatry. 2014;36(1):95–8. DOI:10.1016/j.genhosppsych.2013.10.008
16. Guldvog I, Reitsma LC, Johnsen L, Lauzike A, Gibbs C, Carlsen E, et al. Thyroidectomy Versus Medical Management for Euthyroid Patients With Hashimoto Disease and Persisting Symptoms: A Randomized Trial. Ann Intern Med. 2019 Apr 2;170(7):453–64. DOI:10.7326/M18-2658
17. Boelaert K, Newby PR, Simmonds MJ, Holder RL, Carr-Smith JD, Heward JM, et al. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. Am J Med. 2010 Feb;123(2):183.e1-9. DOI:10.1016/j.amjmed.2009.06.030
18. Patti M, Christian R, Palokas M. Association between anti-thyroid antibodies and quality of life in patients with Hashimoto thyroiditis: a systematic review and meta-analysis. JBI Evid Synth. 2021 Sep;19(9):2307–38. DOI:10.11124/JBIES-20-00147
19. Thatipamala P, Noel JE, Orloff L. Quality of Life After Thyroidectomy for Hashimoto Disease in Patients With Persistent Symptoms. Ear Nose Throat J. 2022 Aug;101(7):NP299–304. DOI:10.1177/0145561322101007252
20. McManus C, Luo J, Sippel R, Chen H. Is thyroidectomy in patients with Hashimoto thyroiditis more risky? J Surg Res. 2012 Dec;178(2):529–32. DOI: 10.1016/j.jss.2012.04.043
21. Hoff G, Bernklev T, Johnsen L, Reitsma L, Sina D, Lauzike A, et al. Thyroidectomy for Euthyroid Patients With Hashimoto Disease and Persisting Symptoms. Ann Intern Med. 2023 Nov 28;177. DOI:10.7326/M23-0658
22. Zivaljevic VR, Bukvic Bacotic BR, Sipetic SB, Stanisavljevic DM, Maksimovic JM, Diklic AD, et al. Quality of life improvement in patients with Hashimoto thyroiditis and other goiters after surgery: A prospective cohort study. Int J Surg Lond Engl. 2015 Sep;21:150–5.
23. Surgical Treatment of Hashimoto's Thyroiditis – Pros and Cons from the Perspective of Clinical Results. Lett Appl NanoBioScience. 2020 Jun 15;9(3):1208–16. [Available from: https://nanobioletters.com/wp-content/uploads/2020/06/2284680893.12081216.pdf]

24. Latif SA, Robbins SE, MacDonald C, Connor N, Sippel RS. Can Thyroidectomy Improve Quality of Life in Patients With Hashimoto's Thyroiditis? J Endocr Soc. 2021 May 1;5(Supplement_1):A825–6. DOI: 10.1210/jendso/bvab048
25. McManus C, Luo J, Sippel R, Chen H. Should patients with symptomatic Hashimoto's thyroiditis pursue surgery? J Surg Res. 2011 Sep;170(1):52–5. DOI: 10.1016/j.jss.2011.03.065
26. Chiovato L, Latrofa F, Braverman LE, Pacini F, Capezzone M, Masserini L, et al. Disappearance of humoral thyroid autoimmunity after complete removal of thyroid antigens. Ann Intern Med. 2003 Sep 2;139(5 Pt 1):346–51. DOI: 10.7326/0003-4819-139-5_Part_1-200309020-00010
27. Promberger R, Hermann M, Pallikunnel SJ, Seemann R, Meusel M, Ott J. Quality of Life After Thyroid Surgery in Women with Benign Euthyroid Goiter: Influencing Factors Including Hashimoto's Thyroiditis. Am J Surg. 2014 Jun;207(6):974–9. DOI: 10.1016/j.amjsurg.2013.08.045
28. Guidance for Industry. 2009 [Internet] Available from: https://www.fda.gov/media/77832/download. Accessed: [7/4/2024].
29. Speech and Survival — Tradeoffs between Quality and Quantity of Life in Laryngeal Cancer | NEJM [Internet]. [cited 2024 Mar 7]. Available from: https://www.nejm.org/doi/full/10.1056/NEJM198110223051704
30. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992 Jun;30(6):473–83. DOI:10.1097/00005650-199206000-00002
31. Suraweera C, Hanwella R, Sivayokan S, Silva V de. Rating Scales validated for Sri Lankan populations. 2013 Dec 30;4(2):16. DOI:10.4038/sljpsyc.v4i2.6320
32. Dardano A, Bazzzichi L, Bombardieri S, Monzani F. Symptoms in euthyroid Hashimoto's thyroiditis: is there a role for autoimmunity itself? Thyroid Off J Am Thyroid Assoc. 2012 Mar;22(3):334–5. DOI:10.1089/thy.2011.0100
33. Karanikas G, Schuetz M, Wahl K, Paul M, Kontur S, Pietschmann P, et al. Relation of anti-TPO autoantibody titre and T-lymphocyte cytokine production patterns in Hashimoto's thyroiditis. Clin Endocrinol (Oxf). 2005 Aug;63(2):191–6. DOI:10.1111/j.1365-2265.2005.02324.x
34. Piga M, Serra A, Deiana L, Loi GL, Satta L, Di Liberto M, et al. Brain perfusion abnormalities in patients with euthyroid autoimmune thyroiditis. Eur J Nucl Med Mol Imaging. 2004 Dec;31(12):1639–44. DOI:10.1007/s00259-004-1625-7
35. Zettinig G, Asenbaum S, Fueger BJ, Hofmann A, Diemling M, Mittlboeck M, et al. Increased prevalence of sublinical brain perfusion abnormalities in patients with autoimmune thyroiditis: evidence of Hashimoto's encephalitis? Clin Endocrinol (Oxf). 2003 Nov;59(5):637–43. DOI:10.1046/j.1365-2265.2003.01901.x
36. Punzi L, Betterle C. Chronic autoimmune thyroiditis and rheumatic manifestations. Joint Bone Spine. 2004 Jul 1;71(4):275–83. DOI:PMID: 15245705
37. Shih ML, Lee JA, Hsieh CB, Yu JC, Liu HD, Kebebew E, et al. Thyroidectomy for Hashimoto's thyroiditis: complications and associated cancers. Thyroid Off J Am Thyroid Assoc. 2008 Jul;18(7):729–34. DOI:10.1089/thy.2007.0384
38. Peterson SJ, Cappola AR, Castro MR, Dayan CM, Farwell AP, Hennessey JV, et al. An Online Survey of Hypothyroid Patients Demonstrates Prominent Dissatisfaction. Thyroid Off J Am Thyroid Assoc. 2018 Jun;28(6):707–21. DOI:10.1089/thy.2017.0681
39. Toloza FJK, Espinoza Suarez NR, El Kawkgi O, Golembiewski EH, Ponce OJ, Yao L, et al. Patient Experiences and Perceptions Associated with the Use of Desiccated Thyroid Extract. Med Kaunas Lith. 2020 Apr 3;56(4):161. DOI:10.3390/medicina56040161
40. Hu Y, Feng W, Chen H, Shi H, Jiang L, Zheng X, et al. Effect of selenium on thyroid autoimmunity and regulatory T cells in patients with Hashimoto's thyroiditis: A prospective randomized-controlled trial. Clin Transl Sci. 2021 Jul;14(4):1390–402. DOI:10.1111/cts.12993
41. Mazokopakis EE, Papadakis JA, Papadomanolaki MG, Batistakis AG, Giannakopoulos TG, Protopapadakis EE, et al. Effects of 12 months treatment with L-selenomethionine on serum anti-TPO Levels in Patients with Hashimoto's thyroiditis. Thyroid Off J Am Thyroid Assoc. 2007 Jul;17(7):609–12. DOI:10.1089/thy.2007.0040.
42. Toulis KA, Anastasilakis AD, Tzellos TG, Goulis DG, Kouvelas D. Selenium supplementation in the treatment of Hashimoto's thyroiditis: a systematic review and a meta-analysis. Thyroid Off J Am Thyroid Assoc. 2010 Oct;20(10):1163–73. DOI:10.1089/thy.2009.0351.
43. Memeh K, Ruhle B, Vaghaiwalla T, Kaplan E, Keutgen X, Angelos P. Thyroidectomy for euthyroid patients with Hashimoto thyroiditis and persisting symptoms: A cost-effectiveness analysis. Surgery. 2021 Jan;169(1):7–13. DOI: 10.1016/j.surg.2020.03.028