

Assessment of Levothyroxine Therapy, Medication Adherence and Treatment Outcomes in Patients with Hypothyroidism: A Cross-Sectional Observational Study

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Abstract - Levothyroxine (LT4) is the standard treatment for hypothyroidism, yet real-world adherence, administration technique and treatment outcomes are seldom assessed together in clinical practice. This cross-sectional, questionnaire-based observational study assessed LT4 therapy, medication adherence and treatment outcomes among 200 patients with hypothyroidism attending a tertiary care outpatient department over 6 months. Participants were predominantly female (60.5%) and relatively young (64.0% aged ≤ 40 years). Simple dose-taking adherence was high (85.5% "always/usually" compliant), but administration technique was markedly weaker: only 52.5% always took LT4 on an empty stomach, only 29.0% always waited the recommended 30–60 minutes before eating, and 31.0% co-administered calcium, iron or an antacid within four hours of dosing. Hypothyroid symptoms persisted in a substantial minority despite therapy, and only 48.0% perceived clear symptomatic improvement. Of five pre-specified Chi-square comparisons, only missed-dose frequency was significantly associated with symptom persistence ($\chi^2=7.235$, $p=0.007$). These findings indicate that while dose-taking adherence to levothyroxine was good, correct administration technique is a specific and largely unaddressed gap, and pharmacist-led counselling targeting administration technique, not adherence alone, is likely to improve treatment outcomes in hypothyroid patients.

Key Words: Hypothyroidism, Levothyroxine, Medication adherence, Administration technique, Thyroid-stimulating hormone, Treatment outcome, Pharmacy practice

1. INTRODUCTION

Hypothyroidism is one of the most common endocrine disorders worldwide, arising from inadequate production or action of thyroid hormones, and is more prevalent in women and with advancing age [1, 38]. In India, community-based screening across eight cities has estimated a prevalence of overt hypothyroidism of around 3.9% in the general population, with a marked female preponderance [2]. Levothyroxine (LT4), a synthetic form of thyroxine, remains the cornerstone of treatment, recommended as first-line therapy by both the American Thyroid Association and the American Association of Clinical Endocrinologists on account of its predictable pharmacokinetics, long half-life and low cost [14, 15].

Despite its apparent simplicity, achieving stable biochemical control with LT4 is highly sensitive to how the drug is taken rather than merely whether it is taken. Its narrow therapeutic index and dependence on consistent gastrointestinal absorption mean that co-administration with calcium or iron supplements, or with acid-suppressing agents such as proton pump inhibitors, can substantially reduce bioavailability and destabilise thyroid-stimulating hormone (TSH) control [6, 7, 9]. Composite adherence scales used in most prior surveys typically capture only whether a dose was taken, not whether it was taken correctly with respect to food and interacting substances [3, 4, 5, 22, 23, 24].

Pharmacists are well placed to identify and correct these specific, modifiable behaviours through targeted counselling [26, 27]. This study was undertaken to assess LT4 therapy, medication adherence, administration technique and treatment outcomes among patients with hypothyroidism attending a tertiary care outpatient department in Tamil Nadu, India, and to examine associations between adherence/technique variables and reported treatment outcomes.

2. MATERIALS AND METHODS

2.1 Study Design, Site and Duration

This was a prospective, observational, cross-sectional, questionnaire-based study conducted over 6 months in the Outpatient Department of Medicine, Ranjitham Hospital and General Medicine Department, Mathur City, Krishnagiri District, Tamil Nadu, India, after obtaining necessary institutional permissions.

2.2 Study Population

Two hundred patients aged 18 years or above with a confirmed diagnosis of hypothyroidism, currently receiving levothyroxine therapy, were enrolled by convenience sampling after providing informed consent. Patients unable to give consent, pregnant patients, and those with central (secondary) hypothyroidism were excluded.

2.3 Study Tool and Data Collection

Data were collected using a structured, pre-validated, self-administered questionnaire covering six domains: demographics; disease/therapy profile; medication adherence and administration technique; persistence of hypothyroid symptoms; monitoring practice and treatment history; and overall treatment satisfaction. The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants.

2.4 Statistical Analysis

Data were entered in Microsoft Excel and analysed using SPSS. Categorical variables were summarised as frequencies and percentages. Associations between adherence/administration-technique variables and treatment outcomes were tested using the Chi-square test, with $p < 0.05$ considered statistically significant.

3. RESULTS

A total of 200 patients with hypothyroidism receiving levothyroxine therapy completed the study questionnaire.

3.1 Demographic and Clinical Profile

Participants were predominantly female (60.5%), with the largest age band being 18–30 years (37.5%). Most participants (43.5%) had been diagnosed 1–3 years previously, and the most commonly prescribed LT4 dose was 75 µg/day (26.0%). The majority (61.5%) had been on LT4 for under one year (Table -1).

Table -1: Demographic and clinical profile of study participants (n = 200)

Parameter	Category	n	%
Age (years)	18–30	75	37.5
Age (years)	31–40	53	26.5
Age (years)	41–50	41	20.5
Age (years)	51–60	22	11.0
Age (years)	>60	9	4.5
Gender	Male	79	39.5
Gender	Female	121	60.5
Duration since diagnosis	<1 year	68	34.0
Duration since diagnosis	1–3 years	87	43.5
Duration since diagnosis	4–6 years	39	19.5
Duration since diagnosis	>6 years	6	3.0

Current LT4 dose	25 µg	49	24.5
Current LT4 dose	50 µg	45	22.5
Current LT4 dose	75 µg	52	26.0
Current LT4 dose	100 µg	45	22.5
Current LT4 dose	>100 µg	9	4.5
Duration of LT4 use	<6 months	46	23.0
Duration of LT4 use	6 months–1 year	77	38.5
Duration of LT4 use	1–3 years	58	29.0
Duration of LT4 use	>3 years	19	9.5

3.2 Medication Adherence and Administration Technique

Simple dose-taking adherence was high (85.5% “always/usually”). However, correct administration technique was considerably weaker: only 52.5% always took LT4 on an empty stomach and only 29.0% always waited the recommended interval before eating. Co-administration of calcium, iron or an antacid within four hours of LT4 was reported by 31.0% of participants, with a further 19.5% unsure (Table -2).

Table -2: Medication adherence and administration technique (n = 200)

Variable	Response	n	%
Take LT4 every day as prescribed	Always	141	70.5
Take LT4 every day as prescribed	Usually	30	15.0
Take LT4 every day as prescribed	Sometimes	21	10.5
Take LT4 every day as prescribed	Never	8	4.0
Take LT4 on empty stomach	Always	105	52.5
Take LT4 on empty stomach	Usually	34	17.0
Take LT4 on empty stomach	Sometimes	14	7.0
Take LT4 on empty stomach	Never	47	23.5
Wait 30–60 min before eating	Always	58	29.0
Wait 30–60 min before eating	Usually	72	36.0
Wait 30–60 min before eating	Sometimes	55	27.5
Wait 30–60 min before eating	Never	15	7.5
Frequency of missed doses	Never	51	25.5
Frequency of missed doses	Rarely	89	44.5
Frequency of missed doses	Sometimes	53	26.5
Frequency of missed doses	Often	7	3.5
Co-administration of Ca/Fe/antacid within 4 h	Yes	62	31.0
Co-administration of Ca/Fe/antacid within 4 h	No	99	49.5
Co-administration of Ca/Fe/antacid within 4 h	Don't know	39	19.5

3.3 Persistence of Hypothyroid Symptoms

Despite ongoing therapy, symptoms were reported at least “sometimes” by 30.5% of participants for fatigue, 36.0% for weight gain, 43.5% for constipation and 42.5% for cold intolerance (Table -3). Only 48.0% agreed that symptoms had improved since starting levothyroxine.

Table -3: Persistence of individual hypothyroid symptoms despite therapy (n = 200)

Symptom	Never n(%)	Rarely n(%)	Sometimes n(%)	Often n(%)
Fatigue	76 (38.0)	63 (31.5)	47 (23.5)	14 (7.0)
Weight gain	69 (34.5)	59 (29.5)	65 (32.5)	7 (3.5)
Constipation	60 (30.0)	53 (26.5)	78 (39.0)	9 (4.5)
Cold intolerance	62 (31.0)	53 (26.5)	65 (32.5)	20 (10.0)

3.4 Monitoring Practice and Treatment Outcomes

Most participants (79.5%) underwent thyroid function testing at least every six months, and 67.0% reported a physician-directed dose adjustment. Only 40.0% recalled a normal recent TSH result (Table -4).

Table -4: Monitoring practice, treatment history and overall treatment outcomes (n = 200)

Variable	Response	n	%
Frequency of thyroid function testing	Every 3 months	71	35.5
Frequency of thyroid function testing	Every 6 months	88	44.0
Frequency of thyroid function testing	Once a year	17	8.5
Frequency of thyroid function testing	Only when advised	24	12.0
Dose adjusted by physician	Yes	134	67.0
Dose adjusted by physician	No	66	33.0
Any side effects experienced	Yes	91	45.5
Any side effects experienced	No	109	54.5
Most recent TSH (patient-recalled)	Normal	80	40.0
Most recent TSH (patient-recalled)	High	44	22.0
Most recent TSH (patient-recalled)	Low	47	23.5
Most recent TSH (patient-recalled)	Don't remember	29	14.5
Symptomatic improvement since LT4	Agree	96	48.0
Symptomatic improvement since LT4	Neutral	87	43.5
Symptomatic improvement since LT4	Disagree	17	8.5
Overall satisfaction with therapy	Agree	95	47.5

Overall satisfaction with therapy	Neutral	91	45.5
Overall satisfaction with therapy	Disagree	14	7.0

3.5 Association between Adherence/Technique Variables and Outcomes

Of five pre-specified Chi-square comparisons, only missed-dose frequency was significantly associated with symptom persistence ($\chi^2=7.235$, $p=0.007$); administration-technique variables were not significantly associated with TSH result at this sample size, though the empty-stomach-versus-TSH comparison showed the largest effect size among non-significant tests ($\chi^2=2.466$, $p=0.116$) (Table -5).

Table -5: Chi-square tests of association between adherence/technique variables and treatment outcomes

Variable 1	Variable 2	n	χ^2	p-value	Inference
Dose-taking consistency (Always/Usually vs Sometimes/Never)	Symptomatic improvement (Agree vs Neutral/Disagree)	200	0.326	0.568	NS
Empty-stomach administration (Always/Usually vs Sometimes/Never)	Most recent TSH (Normal vs High/Low)	171	2.466	0.116	NS
Ca/Fe/antacid co-administration (Yes vs No)	Most recent TSH (Normal vs High/Low)	141	0.255	0.613	NS
Missed-dose frequency (Never/Rarely vs Sometimes/Often)	Symptom persistence composite	200	7.235	0.007	S ($p<0.05$)
Duration of LT4 use (<1 year vs ≥ 1 year)	Most recent TSH (Normal vs High/Low)	171	1.702	0.192	NS

NS = not significant; S = significant.

4. DISCUSSION

The predominance of female participants (60.5%) in this study is consistent with the female preponderance reported in India's largest community-based thyroid screening study [2]. Overall dose-taking adherence in this study (85.5%) was considerably higher than the 32.2% high-adherence rate reported by Kumar and Shaukat [3], and closer to the 87% figure reported by Cappelli et al. [22]. However, this favourable simple-adherence figure did not extend to administration technique: only 52.5% always took LT4 on an empty stomach and 31.0% co-administered calcium, iron or an antacid within four hours of dosing. This is clinically important given well-established evidence that calcium, iron and acid-suppressing agents can substantially impair levothyroxine absorption [6, 7, 9].

A substantial minority continued to report hypothyroid symptoms despite therapy, and only 48.0% perceived clear symptomatic improvement. The single statistically significant association identified between missed-dose frequency and symptom persistence ($\chi^2=7.235$, $p=0.007$) is consistent with the principle that inconsistent dosing undermines the steady-state pharmacokinetics on which levothyroxine's symptomatic benefit depends [18]. This pattern supports the case for targeted, technique-specific pharmacist counselling [26, 27], rather than counselling focused solely on simple dose-taking adherence.

5. CONCLUSIONS

In this cross-sectional study of 200 hypothyroid patients on levothyroxine therapy, simple dose-taking adherence was good (85.5%), but correct administration technique empty-stomach dosing, an adequate pre-food waiting interval, and avoidance of calcium/iron/antacid co-administration was a clear and specific gap. Missed-dose frequency was significantly

associated with persistent symptoms. Pharmacist-led counselling at the point of dispensing should specifically target administration technique and interacting-substance avoidance, in addition to simple adherence, to improve both symptomatic and biochemical outcomes in patients with hypothyroidism.

ACKNOWLEDGEMENT

The authors thank the Department of Pharmacy Practice, Sri Vijay Vidyalaya College of Pharmacy, Nallampalli, Dharmapuri, for institutional support, and all patients who participated in this study.

REFERENCES

- [1] L. Chaker, A. C. Bianco, J. Jonklaas, and R. P. Peeters, "Hypothyroidism," *Lancet*, vol. 390, no. 10101, pp. 1550-62, 2017.
- [2] A. G. Unnikrishnan, S. Kalra, R. K. Sahay, G. Bantwal, M. John, and N. Tewari, "Prevalence of hypothyroidism in adults: an epidemiological study in eight cities of India," *Indian J Endocrinol Metab*, vol. 17, no. 4, pp. 647-52, 2013.
- [3] R. Kumar and F. Shaukat, "Adherence to Levothyroxine Tablet in Patients with Hypothyroidism," *Cureus*, vol. 11, no. 5, pp. e4624, 2019.
- [4] R. M. Alofi, L. S. Alrohaily, R. A. Jan, S. L. Alsaedi, F. A. Mahrous, and M. M. Alreefi, "Adherence to Levothyroxine Treatment Among Patients with Hypothyroidism in Madinah, Saudi Arabia: A Cross-Sectional Study," *Cureus*, vol. 15, no. 6, pp. e40686, 2023.
- [5] M. I. Al et al., "Adherence to levothyroxine treatment among patients with hypothyroidism in Oman: a national cross-sectional study," *Curr Med Res Opin*, vol. 39, no. 10, pp. 1313-9, 2023.
- [6] N. Singh, P. N. Singh, and J. M. Hershman, "Effect of calcium carbonate on the absorption of levothyroxine," *JAMA*, vol. 283, no. 21, pp. 2822-5, 2000.
- [7] I. Sachmechi, D. M. Reich, M. Aninyei, F. Wibowo, G. Gupta, and P. J. Kim, "Effect of proton pump inhibitors on serum thyroid-stimulating hormone level in euthyroid patients treated with levothyroxine for hypothyroidism," *Endocr Pract*, vol. 13, no. 4, pp. 345-9, 2007.
- [8] R. Vita, G. Saraceno, F. Trimarchi, and S. Benvenga, "Switching levothyroxine from the tablet to the oral solution formulation corrects the impaired absorption of levothyroxine induced by proton-pump inhibitors," *J Clin Endocrinol Metab*, vol. 99, no. 12, pp. 4481-6, 2014.
- [9] R. C. Abi-Abib and M. Vaisman, "Is it necessary to increase the dose of levothyroxine in patients with hypothyroidism who use omeprazole?," *Arq Bras Endocrinol Metabol*, vol. 58, no. 7, pp. 731-6, 2014.
- [10] P. Trimboli and S. Mouly, "Pharmacokinetics and Clinical Implications of Two Non-Tablet Oral Formulations of L-Thyroxine in Patients with Hypothyroidism," *J Clin Med*, vol. 11, no. 12, pp. 3479, 2022.
- [11] I. Sachmechi, K. J. Lucas, L. D. Stonesifer, J. F. Ansley, P. Sack, F. S. Celi, C. Scarsi, G. Lanzi, L. Wartofsky, and K. D. Burman, "Efficacy of Levothyroxine Sodium Soft Gelatin Capsules in Thyroidectomized Patients Taking Proton Pump Inhibitors: An Open-Label Study," *Thyroid*, vol. 33, no. 12, pp. 1414-22, 2023.
- [12] D. E. Morisky, L. W. Green, and D. M. Levine, "Concurrent and predictive validity of a self-reported measure of medication adherence," *Med Care*, vol. 24, no. 1, pp. 67-74, 1986.
- [13] S. J. Moon, W. Y. Lee, J. S. Hwang, Y. P. Hong, and D. E. Morisky, "Accuracy of a screening tool for medication adherence: a systematic review and meta-analysis of the Morisky Medication Adherence Scale-8," *PLoS One*, vol. 12, no. 11, pp. e0187139, 2017.
- [14] J. Jonklaas, A. C. Bianco, and A. J. Bauer et al., "Guidelines for the Treatment of Hypothyroidism: Prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement," *Thyroid*, vol. 24, no. 12, pp. 1670-751, 2014.
- [15] J. R. Garber, R. H. Cobin, and H. Gharib et al., "Clinical Practice Guidelines for Hypothyroidism in Adults: Cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association," *Endocr Pract*, vol. 18, no. 6, pp. 988-1028, 2012.
- [16] World Health Organization, *Adherence to Long-Term Therapies: Evidence for Action*. Geneva: World Health Organization, 2003.

- [17] Patil N, Rehman A, Jialal I, Hypothyroidism. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2023.
- [18] K. D. Tripathi, Essentials of Medical Pharmacology, 8th ed. New Delhi: Jaypee Brothers Medical Publishers, 2019.
- [19] J. E. Hall, Guyton and Hall Textbook of Medical Physiology, 14th ed. Philadelphia: Elsevier, 2020.
- [20] S. Melmed, R. J. Auchus, A. B. Goldfine, R. J. Koenig, and C. J. Rosen, Eds., Williams Textbook of Endocrinology, 14th ed. Philadelphia: Elsevier, 2020.
- [21] O. R. G. A. N. I. Z. A. T. I. O. N. World, UNICEF, and ICCIDD, Assessment of Iodine Deficiency Disorders and Monitoring their Elimination, 3rd ed. Geneva: World Health Organization, 2007.
- [22] Cappelli C, Castello R, Marini F, Paoletta A, Marchetti M, Saullo M, Cristiano A, Pirola I, Gandossi E, Ferlin A, Castellano M. Adherence to Levothyroxine Treatment Among Patients with Hypothyroidism: A Northeastern Italian Survey. *Front Endocrinol (Lausanne)*. 2018;9:699.
- [23] H. Patel and J. Vaghasiya, "A Medication Adherence and Effect of Patient Counselling in Hypothyroidism Patients: A Randomized Control Study," *J Popul Ther Clin Pharmacol*, vol. 30, no. 4, pp. 693-9, 2023.
- [24] K. Annavarapu, H. L. Borra, and R. S. Chakka et al., "Assessment of medication adherence and risk factors for hypothyroidism in South Indian tertiary care hospital: a cross-sectional study," *J Diabetes Metab Disord Control*, vol. 6, no. 3, pp. 60-79, 2019.
- [25] S. Shakya, K. Risal, R. Shrestha, and R. D. Bhatta, "Medication Adherence to Levothyroxine Therapy among Hypothyroid Patients and their Clinical Outcomes with Special Reference to Thyroid Function Parameters," *Kathmandu Univ Med J*, vol. 16, no. 62, pp. 129-37, 2018.
- [26] Y. E. Ayhan, M. Y. Bektay, D. Gogas, and M. Sancar, "Evaluation of the clinical pharmacist's effect on achieving treatment goals in patients with hypothyroidism: a randomized controlled trial," *BMC Endocr Disord*, vol. 25, no. 1, pp. 94, 2025.
- [27] R. M. Kamil, V. A. W. Esmail, and D. S. Hamid, "The impact of pharmaceutical care intervention on the depressive symptoms of patients diagnosed with hypothyroidism," *Iraqi J Pharm Sci*, vol. 32, no. 2, pp. 139-49, 2023.
- [28] S. L. Thorat and S. S. Patil, "A Cross-Sectional Study on Knowledge, Attitude and Practices among Patients Suffering from Primary Hypothyroidism," *Sch J App Med Sci*, vol. 6, no. 9, pp. 3395-9, 2018.
- [29] Arora R, Mittal P, Verma A, Trivedi J. Evaluation of Knowledge, Attitude and Practice towards Hypothyroidism among Population in Moradabad District: A Pilot Study. *Int J Pharm Investig*. 2023;13(2).
- [30] Berta E, Lengyel I, Halmi S, Zrínyi M, Erdei A, Harangi M, et al. Hypertension in Thyroid Disorders. *Front Endocrinol (Lausanne)*. 2019;10:482.
- [31] D. Liu, F. Jiang, Z. Shan, B. Wang, J. Wang, and Y. Lai et al., "A cross-sectional survey of relationship between serum TSH level and blood pressure," *J Hum Hypertens*, vol. 24, no. 2, pp. 134-8, 2010.
- [32] B. Romero-Gómez, P. Guerrero-Alonso, J. M. Carmona-Torres, D. P. Pozuelo-Carrascosa, J. A. Laredo-Aguilera, and A. I. Cobo-Cuenca, "Health-Related Quality of Life in Levothyroxine-Treated Hypothyroid Women and Women without Hypothyroidism: A Case-Control Study," *J Clin Med*, vol. 9, no. 12, pp. 3864, 2020.
- [33] J. P. Brito, Y. Deng, J. S. Ross, N. H. Choi, D. J. Graham, Y. Qiang, E. Rantou, Z. Wang, L. Zhao, N. D. Shah, and K. J. Lipska, "Association Between Generic-to-Generic Levothyroxine Switching and Thyrotropin Levels Among US Adults," *JAMA Intern Med*, vol. 182, no. 4, pp. 418-25, 2022.
- [34] Kalra S, Khandelwal SK. Why are our hypothyroid patients unhappy? Is tissue hypothyroidism the answer? *Indian J Endocrinol Metab*. 2011;15(Suppl 2):S95-8.
- [35] S. Kalra, N. Agarwal, R. Aggarwal, S. Agarwal, S. Bajaj, and G. Bantwal et al., "Patient-centered management of hypothyroidism," *Indian J Endocrinol Metab*, vol. 21, no. 3, pp. 475-7, 2017.
- [36] C. G. Roberts and P. W. Ladenson, "Hypothyroidism," *Lancet*, vol. 363, no. 9411, pp. 793-803, 2004.
- [37] R. P. Peeters, "Subclinical Hypothyroidism," *N Engl J Med*, vol. 376, no. 26, pp. 2556-65, 2017.
- [38] P. N. Taylor, D. Albrecht, A. Scholz, G. Gutierrez-Buey, J. H. Lazarus, C. M. Dayan, and O. E. Okosieme, "Global epidemiology of hyperthyroidism and hypothyroidism," *Nat Rev Endocrinol*, vol. 14, no. 5, pp. 301-16, 2018.
- [39] B. Biondi and D. S. Cooper, "The clinical significance of subclinical hypothyroidism," *Endocr Rev*, vol. 29, no. 1, pp. 76-131, 2008.

- [40] B. Vaidya and S. H. Pearce, "Management of hypothyroidism in adults," *BMJ*, vol. 337, pp. a801, 2008.
- [41] A. R. Cappola, A. S. Desai, and M. Medici et al., "Thyroid and Cardiovascular Disease: Research Agenda for Enhancing Knowledge, Prevention, and Treatment," *Circulation*, vol. 139, no. 25, pp. 2892-909, 2019.
- [42] S. Razvi, A. Jabbar, A. Pingitore, S. Danzi, B. Biondi, I. Klein, R. Peeters, A. Zaman, and G. Iervasi, "Thyroid Hormones and Cardiovascular Function and Diseases," *J Am Coll Cardiol*, vol. 71, no. 16, pp. 1781-96, 2018.
- [43] M. P. Vanderpump, "The epidemiology of thyroid disease," *Br Med Bull*, vol. 99, pp. 39-51, 2011.
- [44] L. Persani, "Clinical review: Central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges," *J Clin Endocrinol Metab*, vol. 97, no. 9, pp. 3068-78, 2012.
- [45] M. H. Samuels, "Psychiatric and cognitive manifestations of hypothyroidism," *Curr Opin Endocrinol Diabetes Obes*, vol. 21, no. 5, pp. 377-83, 2014.
- [46] E. K. Alexander, E. N. Pearce, G. A. Brent, R. S. Brown, H. Chen, and C. Dosiou et al., "2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum," *Thyroid*, vol. 27, no. 3, pp. 315-89, 2017.
- [47] E. A. McAninch and A. C. Bianco, "Thyroid Hormone Signaling in Energy Homeostasis and Energy Metabolism," *Ann N Y Acad Sci*, vol. 1311, pp. 77-87, 2014.
- [48] J. Ott, R. Promberger, F. Kober, N. Neuhold, M. Tea, J. C. Huber, and M. Hermann, "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*, vol. 21, no. 2, pp. 161-7, 2011.
- [49] K. Müssig, A. Künle, A. L. Säuberlich, C. Weinert, T. Ethofer, and R. Saur et al., "Thyroid peroxidase antibody positivity is associated with symptomatic distress in patients with Hashimoto's thyroiditis," *Brain Behav Immun*, vol. 26, no. 4, pp. 559-63, 2012.
- [50] W. M. Wiersinga, "Paradigm shifts in treatment of hypothyroidism: are patients paying the price?," *Nat Rev Endocrinol*, vol. 10, no. 3, pp. 164-74, 2014.