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ORIGINAL ARTICLE

Weekly Versus Daily Levothyroxine Tablet Replacement in Adults with Hypothyroidism: A Meta-Analysis

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Abstract

Objectives. Daily levothyroxine is the treatment of choice and standard of care in hypothyroidism, sufficient to restore thyroid stimulating hormone (TSH) to normal range. For many patients, daily lifelong therapy is required, making adherence a major issue. In such cases, weekly replacement may be a suitable alternative to improve adherence. In this study, we aimed to determine the efficacy and safety of weekly levothyroxine replacement among adults with hypothyroidism.

Methodology. Electronic databases were searched. Two reviewers (HCC and RBL) independently screened the abstracts, reviewed full-text papers, critically appraised the quality of included studies using PRISMA guidelines. Meta-analysis was performed using the random-effects model. The primary outcome is the difference in serum TSH levels between weekly and daily administration, while secondary outcomes included adverse events and symptoms of hypothyroidism.

Results. The primary outcome is the difference in serum TSH levels between weekly and daily administration. Secondary outcomes included adverse events and clinical symptoms. The study included two randomized trials (n=109) in the primary analysis. The difference in TSH levels was 1.78 mIU/mL higher [(95% confidence interval (CI): 1.28 to 2.28, p<0.00001] at 6 weeks and 1.22 mIU/mL higher (95% CI: 0.76 to 1.67, p<0.00001) at 12 weeks for the weekly regimen. There was no significant heterogeneity between the two groups. There was no significant difference in hypothyroid symptoms and adverse events before and after levothyroxine treatment within each group.

Conclusions. Weekly levothyroxine resulted in less suppression and higher mean serum TSH levels, while still remaining within the normal reference range. It may be a suitable alternative for non-adherent patients. However, larger randomized trials with longer duration of follow-up are needed to firmly establish its role.

Key words: hypothyroidism, levothyroxine, thyroid hormone, adherence, weekly replacement

INTRODUCTION

Hypothyroidism is a common hormone deficiency with a prevalence ranging from 4 to 5% worldwide.[1] It presents with classic signs and symptoms as a result of low thyroxine levels. Treatment in the form of thyroid hormone replacement carries an overall excellent prognosis if patients are adherent to regular treatment.[1] Daily levothyroxine (LT4) at a dose of 1.6 to 1.8 μg/kg of body weight per day is the treatment of choice and standard of care, sufficient to restore the thyroid stimulating hormone (TSH) to normal range.[2] However, for many patients with primary hypothyroidism and post-procedural hypothyroidism, lifelong therapy is needed, and adherence then becomes a major issue. When higher than usual doses are needed to maintain TSH in the normal range, clinicians must determine the reason for high dose requirements.[2-4] One of the most commonly cited reasons is non-adherence brought about by the following reasons: (1) the need to take the medication while fasting, (2) the need to wait for 30 to 60 minutes before the next meal, (3) the need to take the medication on a daily basis, and (4) the need to avoid various medications that may interfere with absorption, as many drugs have the potential to interfere with LT4 metabolism.[3,5,6]

To overcome these issues leading to non-adherence, various strategies have been employed including once-weekly therapy, twice-weekly therapy, alternate-day therapy, liquid formulations, use of patient education manuals, intramuscular and parenteral administration.[2-4,7-18] Since LT4 has an elimination half-life of approximately 7 days and an even longer biological effect, giving it once weekly may be a logical alternative.[2-4] Normalization of serum TSH in patients suspected of being non-adherent to their therapy was achieved with weekly or twice weekly oral therapy.[2-4,7-13]

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Ingested LT4 is further converted in the peripheral tissues to the more metabolically active triiodothyronine (T3) by deiodinase enzymes. Given its long elimination half-life and metabolic conversion *in vivo*, the available depot of LT4 suggests the possibility of using LT4 at a longer dosing interval.[3] In addition, the weekly dosing regimen may also be advantageous to caregivers taking care of patients who are unable to or have physical difficulty taking daily doses.

A few published studies consisting mostly of case reports and prospective studies have reported on weekly administration of LT4.[7-11] The first trial comparing daily and weekly administration of levothyroxine was done by Grebe and colleagues in 1997, who found that weekly LT4 replacement was well-tolerated with no evidence of cardiac toxicity.[4] Since then, only two additional trials have been completed over the past two decades.[3,4] Currently, only three relevant randomized cross-over trials have been performed comparing the effect of weekly and daily LT4 replacement on serum TSH, clinical symptoms and adverse events.[2-4] However, all trials were as short-term, limited to 12 weeks in duration, and none were conducted in truly non-adherent patients.[2-4] Results of the three studies have demonstrated no statistically significant differences between daily and weekly dosing in terms of both clinical and biochemical parameters.

In this study, we aimed to determine the efficacy and safety of daily versus weekly levothyroxine tablet replacement in adults with hypothyroidism with the effect on serum TSH as our primary outcomes, and clinical symptoms using the hypothyroidism symptom scale (HSS) and adverse events as our secondary outcomes.

METHODOLOGY

Our study was approved by the Institutional Review Board and Research Ethics Board of the University of the Philippines Manila (UPM-REB Code 2020-399-EX, RGAO Registration No. 2020-0328) prior to commencement.

The study included only randomized controlled trials that determined the effect of weekly versus the daily administration of levothyroxine on thyroid function tests as a standard of care for replacement therapy. Trial settings were restricted to participants ≥19 years of age, and with hypothyroidism of any etiology. All studies were required to have measured thyroid function in study participants using thyroid stimulating hormone.

We performed a comprehensive search strategy from inception to February 2021 in the following databases: PubMed/MEDLINE, Ovid MEDLINE, Google Scholar, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Web of Science and ClinicalTrials.gov. The search was limited to adults (age ≥19 years), randomized controlled trials, systematic reviews and meta-analyses. There was no language restriction on the searches performed. To identify all the relevant studies, the following descriptors were used to build the search strategies: levothyroxine, L-thyroxine, L-T4, hypothyroidism, daily replacement and weekly replacement, among others. Terms were combined with the Boolean operators AND and OR using the following strategy: "weekly"[All Fields] AND ((((("levothyroxine"[All Fields] OR "thyroxine"[MeSH Terms]) OR "thyroxine"[All Fields]) OR "levothyroxine"[All Fields]) OR "levothyroxine"[All Fields]), Filters: Clinical Trial.

The eligibility criteria were as follows: (1) the study was a randomized controlled trial; (2) the study compared daily levothyroxine administration to weekly levothyroxine administration in patients on replacement therapy; (3) the formulation must be in tablet, not in soft gel capsule or liquid form; (4) the reported outcome included serum TSH levels; and (5) the study was published as full text with complete outcomes. The studies that did not fulfill the eligibility criteria were excluded. We supplemented our electronic search with manual searches and by cross-referencing included papers, relevant sections of clinical practice guidelines, and relevant systematic and narrative reviews.

Two investigators (HCC and RBL) independently screened citations from the electronic search, reviewed full text papers for inclusion, critically appraised the quality of the included studies using PRISMA guidelines and abstracted the data. Consensus was achieved for inclusion of papers by discussion between reviewers. A third reviewer/clinical content expert (ABU/CAJ) was consulted in the event of any discrepancies that could not be resolved by reviewer discussion. Each study was evaluated for their risk of bias of using the Risk of Bias evaluation tool developed by the Cochrane Collaboration. All outcomes were reported according to PRISMA standards. Continuous data for thyroid functions tests (TSH) and clinical symptoms using the hypothyroidism symptom scale were reported as means with corresponding standard deviations. Adverse events were presented as narratives. A random-effects model meta-analyses was performed estimating the levels of thyroid function tests and HSS scores with 95% confidence intervals using the Review Manager Software (Revman) Version 5.3.

RESULTS

Search strategy

A total of 354 articles were retrieved after a comprehensive search of databases. Forty three duplicate studies were eliminated, 303 were excluded based on title and abstract, and six articles were excluded after full text assessment (four case reports, one prospective study and one unable to fully extract data). Eventually, two articles were included in this meta-analysis. The study selection schematic diagram is shown in Figure 1.

Study characteristics

The baseline characteristics of the studies included in this meta-analysis are summarized in Table 1. The studies were carried out in two countries, India and Brazil.[2,3] These were published in 2017 and 2012, respectively. Overall, there were 114 participants in both studies. Both trials included patients with primary hypothyroidism who were maintained on hormone replacement and were euthyroid for at least three months at the time of recruitment. The mean age of the subjects ranged from 35.4 to 42.5 years old. The duration of the interventions for both trials was 12 weeks. A summary of the risk of bias of included trials is shown in Figure 2.

Table 1. Characteristics of the included studies

Author	Design	N	Mean Age (y)	Intervention	Comparison	Outcome	Duration
Bornschein (2012)	Randomized cross-over study	14	Group 1: 41.2 ± 8.41 Group 2: 42.5 ± 7.48	Weekly dose of LT4[a] (seven times higher than usual dose) for 6 weeks then switched to daily dosing	Usual daily dose of LT4[a] for 6 weeks then switched to weekly dosing	TSH,[b] Total T4,[c] Total T3[d]	12 weeks
Raiput (2017)	Randomized cross-over study	100	Group 1: 36.1 ± 10.7 Group 2: 35.4 ± 8.4	Weekly dose of LT4[a] (seven times higher than usual dose) then switched to therapeutic regimen after 6 weeks	Usual daily dose of LT4[a] for 6 weeks then switched to weekly dosing; switched to therapeutic regimen after 6 weeks	TSH,[b] free T4,[c] Total T3[d]	12 weeks

[a]LT4, levothyroxine; [b]TSH, thyroid stimulating hormone; [c]T4, thyroxine; [d]T3, triiodothyronine

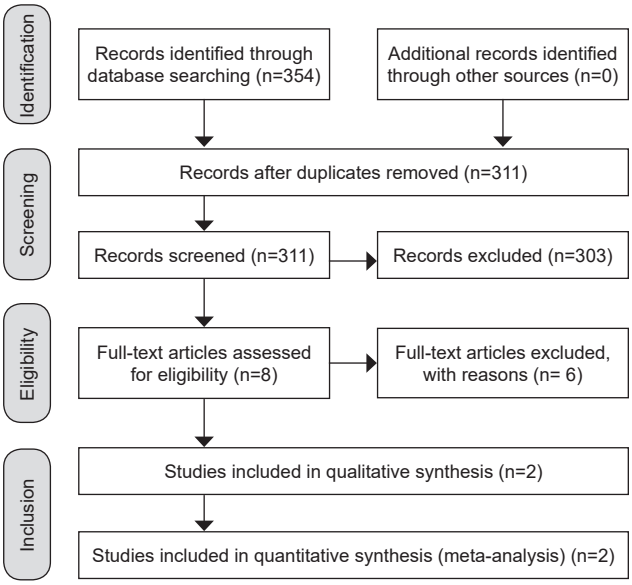
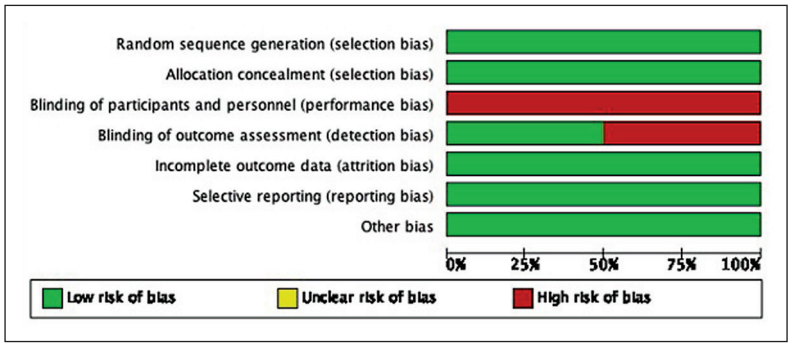


Figure 1. Schematic diagram of the literature search and study selection.

Effect of weekly administration on TSH

The pooled estimate from the random-effects model performed on the two studies showed that weekly administration of levothyroxine had significantly higher serum TSH levels at 6 weeks [standard mean difference (SMD) = 1.78, 95% confidence interval (CI): 1.28 to 2.28, $p<0.00001$). There was no significant heterogeneity between the two groups ($P = 0.71$, $I^2 = 0$) (Figure 3).

Similarly, the pooled estimate from the random-effects model performed on the two studies showed that weekly administration of levothyroxine still had significantly higher serum TSH levels at 12 weeks (SMD = 1.22, 95% CI: 0.76 to 1.67, $p<0.00001$). There was no significant heterogeneity between the two groups ($P = 0.75$, $I^2 = 0$) (Figure 4).



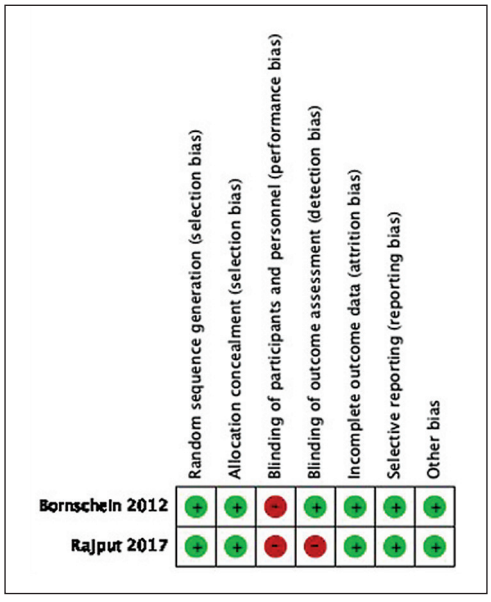


Figure 2. Quality assessment of the included randomized controlled trials.

Clinical symptoms and adverse events

Both studies measured hypothyroid symptoms using the HSS scale. In the Rajput study, there was no significant difference in HSS scores between weekly and daily administration of LT4 (6.4 ± 2.8 after daily therapy and 6.4 ± 2.3 after weekly therapy, $p=0.771$).[2] Similarly, Bornscheiner and colleagues noted that the HSS scores were similar in both groups at all times: group 1, daily regimen (5.5 to 6.00 afterwards, $p>0.05$) followed by weekly regimen (5.75 to 5.75, $p>0.05$); and group 2, weekly regimen (5.33 to 5.50, $p>0.05$) followed by daily regimen (5.5 to 5.33, $p>0.05$).[3]

Bornscheiner and colleagues also assessed cardiac adverse events by measuring echocardiographic parameters during systole, specifically pre-ejection period (PEP), aortic ejection time (ET), isovolumetric contraction time (ICT) and heart rate (HR).[3] There were no significant differences in all echocardiographic parameters before and after LT4 within each group. The study done by Rajput did not assess cardiac adverse events.[2]

DISCUSSION

This is the first meta-analysis that compared the effects of weekly versus daily LT4 administration on thyroid function of adult patients with hypothyroidism. There is an overall low risk of bias for both studies except for the blinding of participants which was difficult to achieve given the stark difference in terms of the method of administration being obvious to the participants (weekly versus daily

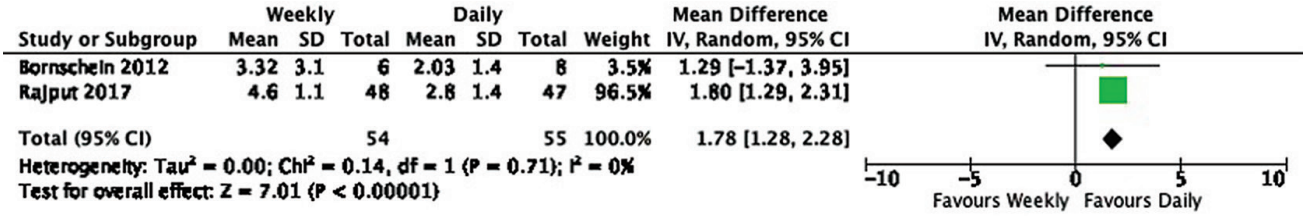


Figure 3. Forest plot showing the effect of weekly levothyroxine administration on TSH at 6 weeks.

TSH, thyroid stimulating hormone; SD, standard deviation; CI, confidence interval.

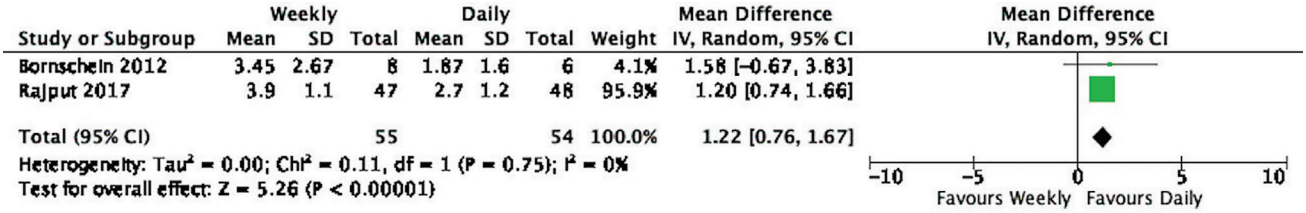


Figure 4. Forest plot showing the effect of weekly levothyroxine administration on TSH at 12 weeks.

TSH, thyroid stimulating hormone; SD, standard deviation; CI, confidence interval.

regimen). The lack of participant blinding has no effect on serum TSH levels, since these are objectively quantified using either radioimmunoassay or chemiluminescence methods. However, it can affect subjective parameters such as hypothyroid symptoms as measured using the hypothyroidism symptom scale. There was no significant heterogeneity between the studies. However, the analysis is limited by the very few numbers of studies available in literature, as well as the overall small sample size in both studies. We still believe that despite these limitations, this meta-analysis is still a crucial contributor to new scientific knowledge, as it highlights novel and practical insights and approaches in terms of the use and administration of levothyroxine among our patients with hypothyroidism.

Overall, we observed a significant difference in the levels of TSH when weekly LT4 was compared to daily administration. The weekly replacement regimen showed a statistically higher level of mean serum TSH at both 6 and 12 weeks, respectively. From a clinical and biochemical standpoint, this meant less TSH suppression. Despite the observed higher mean TSH in the weekly regimen, levels remained within the reference range of normal at all times. This is consistent with the treatment target of maintaining the TSH level within the normal range as recommended by the American Thyroid Association (ATA) in the treatment of hypothyroidism.[1] In addition, patients did not experience cardiac adverse events, symptoms of overtreatment, as well as symptoms of hypothyroidism during weekly administration of LT4. Our limited data suggests that weekly LT4 is safe from a cardiac point of view; however, due to the small number of patients and short follow-up period, firm safety data for weekly therapy has not yet been established definitively.

There are only very few studies worldwide that compared weekly and daily administration of LT4 in hypothyroid patients. Three clinical trials and one prospective study have shown that weekly LT4 is as effective as daily treatment for non-adherent patients and have concluded that once weekly LT4 is a safe regimen.[2-4,19] However, Grebe and colleagues showed that while weekly therapy was well tolerated, the thyroid function tests are biochemically consistent with mild hypothyroidism with an overall increase in mean serum TSH levels and a decrease in thyroxine before the next weekly dose.[2] It can be hypothesized that the type 2 deiodinase enzyme might be responsible for sufficient peripheral conversion of LT4 to T3 which would have resulted in maintenance of euthyroidism despite the rise in TSH level from less negative feedback observed in the weekly group. This mechanism may be responsible for the maintenance of euthyroidism while on the weekly regimen.[4,13]

Patient adherence is a significant factor in the achievement of treatment goals.[20] Non-adherence to medications remains a major challenge in the management of hypothyroidism, particularly the requirement of daily drug intake after prolonged fasting.[1-16] This is often elicited by physicians during patient consults as persistently elevated TSH, despite the patient being given very high LT4 doses. However, it must be noted that there have been many concerns regarding the potential toxicity of high doses being administered in the weekly regimen (as high as seven times the daily dose). Serious complications have been reported in toxicologic and overdose investigations. Those taking levothyroxine ranging from 3 to 4 mg can develop cardiac complications, and these patients should be closely monitored.[20-22] The dose of the weekly regimen is far below this potentially toxic dose range of 3 to 4 mg of LT4 daily. However, cardiac safety cannot be generalized for the entire population, especially for the elderly, since both studies have utilized relatively younger patients. Furthermore, the short period of follow-up in both studies makes it difficult to predict long-term differences between the two regimens.

Given our results showing that serum TSH levels remain within reference ranges with weekly administration of LT4, changing the drug administration to a weekly regimen may increase adherence among non-adherent patients. However, it must be highlighted that the weekly regimen is not suitable for patients who are planning to conceive in view of more stringent TSH targets in that group.

Assay difference is also another limitation in our study. Fortunately, both third generation assays using the immunoradiometric (IRMA) and chemiluminescence immunoassay (CLIA) methods are precise up to 0.1 mIU/mL.[2,3] Furthermore, the reference range of these assays are almost identical and utilize the same unit of measurement for TSH in mIU/mL.

To summarize, the current meta-analysis is mainly limited by the few numbers of trials and participants, differences in TSH assays (IRMA versus CLIA), generalizability of cardiac safety especially in the elderly, short period of follow-up, as well as the lack of measurement of treatment adherence as an outcome among participants in both trials. Given the paucity of data on efficacy and safety, future randomized trials with larger sample sizes and a longer duration of follow-up are needed to firmly establish the definite role of weekly LT4 in the management of hypothyroidism.

CONCLUSION

In summary, weekly LT4 administration has less suppression and higher overall serum TSH levels, while remaining within the normal reference range as recommended in international treatment guidelines. It may be a feasible alternative for patients with hypothyroidism, especially when adherence is a concern. However, more randomized trials with larger sample sizes and longer duration of follow-up are needed to firmly establish the role of weekly LT4 in the management of hypothyroidism.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
Dr. Chiu, Dr. Larrazabal and Dr. Uy have declared no conflict of interest. Dr. Jimeno is the Vice Editor-in-Chief of JAFES.

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References

1. Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on thyroid hormone replacement. Thyroid. 2014;24(12):1670-751. PMID: 25266247. PMCID: PMC4267409. https://doi.org/10.1089/thy.2014.0028.
2. Rajput R, Pathak V. The effect of daily versus weekly levothyroxine replacement on thyroid function test in hypothyroid patients at a tertiary care center in Haryana. Eur Thyroid J. 2017;6(5):250-4. PMID: 29071237. PMCID: PMC5649268. https://doi.org/10.1159/000477348.
3. Bornschein A, Paz-Filho G, Graf H, de Carvalho GA. Treating primary hypothyroidism with weekly doses of levothyroxine: A randomized, single-blind, crossover study. Arq Bras Endocrinol Metabol. 2012;56(4):250-8. PMID: 22790470. https://doi.org/10.1590/s0004-27302012000400006.
4. Grebe SK, Cooke RR, Ford HC, et al. Treatment of hypothyroidism with once weekly thyroxine. J Clin Endocrinol Metab. 1997;82(3):870-5. PMID: 9062499. https://doi.org/10.1210/jcem.82.3.3830.
5. John-Kalarickal J, Pearlman G, Carlson HE. New medications which decrease levothyroxine absorption. Thyroid. 2007;17(8):763-5. PMID: 17725434. https://doi.org/10.1089/thy.2007.0060.
6. Wiersinga WM. Thyroid hormone replacement therapy. Horm Res. 2001;56(Suppl 1):74-81. PMID: 11786691. https://doi.org/10.1159/000048140.
7. Bernstein RS, Robbins J. Intermittent therapy with L-thyroxine. N Engl J Med. 1969; 281(26):1444-8. PMID: 4187605. https://doi.org/10.1056/NEJM196912252812603.
8. Sekadde CB, Slaunwhite WR Jr, Aceto T Jr, Murray K. Administration of thyroxin once a week. J Clin Endocrinol Metab. 1974;39(4):759-64. PMID: 4411877. https://doi.org/10.1210/jcem-39-4-759.
9. Rangan S, Tahrani AA, Macleod AF, Moulik PK. Once weekly thyroxine treatment as a strategy to treat non-compliance. Postgrad Med J. 2007; 83(984):e3. PMID:17916865. PMCID:PMC2600132. https://doi.org/10.1136/pgmj.2007.060244.
10. Oliver C, Grino M, Moatti-Vacher Coponat P, Morange I, Retornaz F. Prise hebdomadaire de L-thyroxine dans un cas de non-observance du traitement substitutif [Once weekly L-thyroxine treatment in non-compliance: A case report]. La Revue de Médecine Interne. 2017; 38(11):766-8. https://doi.org/10.1016/j.revmed.2017.06.005.
11. Walker JN, Shillo P, Ibbotson V, et al. A thyroxine absorption test followed by weekly thyroxine administration: A method to assess non-adherence to treatment. Eur J Endocrinol. 2013;168(6):913-7. PMID: 23554450. https://doi.org/10.1530/EJE-12-1035.
12. Taylor J, Williams BO, Frater J, Stott DJ, Connell J. Twice-weekly dosing for thyroxine replacement in elderly patients with primary hypothyroidism. J Int Med Res. 1994;22(5):273-7. PMID: 7867872. https://doi.org/10.1177/030006059402200504.
13. Altuntaş F, Uysal AR, Çorapçıoğlu D, Erol Ç. Twice weekly L-T4 for the treatment of primary hypothyroidism. Turk J Endocrinol Metab. 2004;1:25-34. http://www.turkjem.org/uploads/pdf/8-1-0_25-34.pdf.
14. Dayal D, Saini L, Attri SV, Singh B, Bhalla AK. Daily versus alternate day thyroxine therapy to maintain euthyroidism in children with congenital hypothyroidism. Int J Endocrinol Metab. 2013;11(4):e9499. PMID: 24719634. PMCID: PMC3968978. https://doi.org/10.5812/ijem.9499.
15. Negro R, Valcavi R, Agrimi D, Toulis KA. Levothyroxine liquid solution versus tablet for replacement treatment in hypothyroid patients. Endocr Pract. 2014; 20(9):901-6. PMID: 24793916. https://doi.org/10.4158/EP13378.OR.
16. Crilly M, Esmail A. Randomised controlled trial of a hypothyroid educational booklet to improve thyroxine adherence. Br J Gen Pract. 2005;55(514):362-8. PMID: 15904555. PMCID: PMC1463159.
17. Laycock K, Beale C, Peters C, Anderson J. Intramuscular levothyroxine: A solution to a mental health related thyroid crisis. BMJ Case Rep. 2019;12(8):e228147. PMID: 31434663. PMCID: PMC6706664. https://doi.org/10.1136/bcr-2018-228147.
18. Hays MT. Parenteral thyroxine administration. Thyroid. 2007; 17(12):127-9. PMID: 17316114. https://doi.org/10.1089/thy.2006.0283.
19. Jayakumari C, Nair A, Khadar JP, et al. Efficacy and safety of once-weekly thyroxine for thyroxine-resistant hypothyroidism. J Endocr Soc. 2019;3(12):2184-93. PMID: 31723717. PMCID: PMC6834071. https://doi.org/10.1210/js.2019-00212.
20. Centanni M, Benvenga S, Sachmechi I. Diagnosis and management of treatment-refractory hypothyroidism: an expert consensus report. J Endocrinol Invest. 2017; 40(12):1289-301. PMID: 28695483. PMCID: PMC5680379. https://doi.org/10.1007/s40618-017-0706-y.
21. Shilo L, Kovatz S, Hadari R, Weiss E, Nabriski D, Shenkman L. Massive thyroid hormone overdose: Kinetics, clinical manifestations and management. Isr Med Assoc J. 2002;4(4):298-9. PMID: 12001709.
22. Savran Y, Mengi T, Keskinkilic M. A severe case of levothyroxine intoxication successfully treated in intensive care unit. J Acute Dis. 2018;7(4):175-7. https://doi.org/10.4103/2221-6189.241029.