Heliyon 9 (2023) e12797

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

In silico dose adjustment of levothyroxine after total thyroidectomy using fuzzy logic methodology: A proof-of-concept study

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ARTICLE INFO

Keywords:
Thyroid
Levothyroxine
Personalized dose adjustment
Fuzzy logic system
Total thyroidectomy

ABSTRACT

Thyroid hormone replacement therapy is used to raise undesirably low concentrations of natural thyroid hormones, commonly by administrating levothyroxine (LT4). Finding the appropriate LT4 dose regime, particularly for patients undergone thyroidectomy, is still demanding more effort, and much research has been conducted. Providing a new fuzzy logic system, a useful control algorithm, we aim to introduce a proper LT4 dosing regimen for every thyroidectomized patient in a computerized environment. Consequently, we contrast the differences between our proposed dose regime and conventional monotherapy methods using THYROSIM, a thyroid simulation application. Considering our nine defined comparative criteria, results reveal that the FLS dose regime is dominant in terms of six indexes, while the discrepancies are not noticeable in the other three indexes. A great superiority of FLS dose regime is its ability to reduce the time to reach desirable thyrotropin (Thyroid Stimulating Hormone, TSH) serum concentration to 6 days post-thyroidectomy, and keep the T4, T3, and TSH values in the normal window afterward. The proposed FLS could be an applicable decision support system for physicians as they can define their intended Individual Target Value of TSH for each patient to optimize LT4 dose adjustment.

1. Introduction

Thyroid hormone replacement therapy (THRT) is a therapeutic strategy for various thyroid diseases such as hypothyroidism, subtotal thyroidectomy, total thyroidectomy, etc. [1]. In general, the goal of hormone replacement therapy is to ensure that the lacking hormone is adequately supplied in a way that results in physiological effects [2,3]. Nowadays, the tendency to replace subtotal thyroidectomy with total or slightly total thyroidectomy to heal benignant thyroid disease has dramatically increased [4,5]. Although total thyroidectomy is now more preferred, it is challenging while almost all of the thyroid gland has been removed and only a small portion, about 1–2%, remains [6].

As more and more centers in favor of total thyroidectomy, finding an optimal way of replacing thyroid function after total thyroidectomy to avoid hypothyroidism becomes imperative [7,8]. In 1950, synthetic levothyroxine (LT4) commercially became

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https://doi.org/10.1016/j.heliyon.2023.e12797
Received 30 August 2022; Received in revised form 27 December 2022; Accepted 2 January 2023
Available online 5 January 2023

available and its oral administration has been shown to be rapidly and constantly effective [9]. The main purpose of administering LT4 after total thyroidectomy is to restore the physiological function of the thyroid, i.e. bringing TSH level within the normal reference range [10,11]. Mak and DiStefano applied an optimal-control-system methodology for calculating appropriate oral medication doses of synthesized thyroid hormones (T3 & T4) to be used in hypothyroidism [12,13]. Although a proper replacement pattern for thyroid hormones is crucially important, it is yet a challenging issue. On the one hand, long-term uncontrolled suppressive LT4 doses could enhance the risks of arrhythmias, fractures, left ventricular malfunction and accelerated bone loss [14,15,16]. On the other hand, weight gain, unpleasant and disruptive symptoms, and poor quality of life could arise as a consequence of under-dosing of LT4 [10,17]. In order to understand the importance of proposing a proper modified therapeutic strategy and optimal LT4 dose after total thyroidectomy, we can mention the reduction of time to achieve normal physiological status, less need for subsequent visits and follow-ups, enhance patient's amelioration, as well as reduction of care costs [18,19,20].

Much clinical research have been conducted on LT4 dose regimes and finally evaluated numerous parameters impacting LT4 demands such as patient's gender, age, weight, body surface area (BSA) and body mass index (BMI). Meanwhile, there is still challenges in prescribing LT4 dose regime with an appropriate procedure for each individual patient [21]. An individualized dosing approach for each patient must be provided if a method claims to present the optimal results [1,22]. Nevertheless, clinical studies are not only associated with concerns about volunteer patients' health but also consume a lot of time and costs; however, some clinical research has been performed on animal samples or human, especially on elderly, a major issue in thyroid field [23,24,25,26,27].

Recently, the interest in artificial intelligence (AI) has extended in different healthcare systems, and it could be considered as an applicable solution to address the aforementioned challenges in THRT [28,29,30]. AI techniques comprise fuzzy logic systems (FLS), artificial neural networks, colony optimization, particle swarm optimization, evolutionary computing, simulated annealing, genetic algorithm, etc. [31,32]. Although AI is regarded to be one of the very promising technological advancements and is regarded to make an impressive improvement on the overall healthcare system, its application in THRT is still not specifically explored. Fuzzy Logic is a technique used widely in Artificial Intelligence applications [33,34,35].

The use of fuzzy logic in medical applications, especially in dose adjustment, has been more noticed in recent years [36,37,38,39]. In this study, we employed FLS in order to propose a new levothyroxine dosing regimen to be used by a thyroidectomized virtual patient. The FLS dose regime is then compared with several conventional LT4 monotherapy methods considering the serum levels of TSH, T3 and T4 for a period of 30 days using a well-established web application for thyroid simulation. Eventually, the pros and cons of conventional LT4 dose regimens are juxtaposed with the proposed FLS dose regime based on our defined indexes including time to reach normal reference range of TSH, T3, and T4, as well as their discrepancies with individual target values.

2. Methods

2.1. Simulation method

THYROSIM 3.0©, a free web application developed by UCLA Biocybernetics Laboratory, was utilized as a model of feedback control of hypothalamus-pituitary-thyroid axis. THYROSIM[1] is also able to track responses to exogenous LT4 and LT3 dosages via either oral, IV, or infusion routs. In this web application, euthyroid condition, as a default mode, is defined by 100% secretion of T3 and T4 along with 88% absorption of T3 and T4. Reference hormone ranges are considered as 0.5–5 mU/L, 45–105 μg/L and 0.6–1.8 μg/L for TSH, T4, and T3 respectively. Simulation of pathological conditions is then accomplished by adjusting the percentages of thyroid hormones secretion (0–125%) while the simulation of THRT could be tuned by T4 and T3 gut absorption rates (0–100%). Hypothyroidism can be shown by setting the secretion percentages from 10% to 80% and thyroidectomy is considered as 1% hormone secretion [40,41].

2.2. Virtual patient

In the current study, THYROSIM was employed to simulate thyroid hormones courses of a virtual thyroidectomized patient. The potential practical use of THYROSIM here was to adjust LT4 dose that induces the serum TSH level into the normal window. We set the absorption rate to 88% assuming that the patient is not using any other medication. Also, for a better simulation, we adjusted the post-thyroidectomy remained thyroid function into 1% and applied an altering pattern of everyday oral thyroid supplement and then, monitored his thyroid hormones level. The characteristics of our virtual patient is presumed as described in Table 1.

Furthermore, THYROSIM allows single or multiple exogenous inputs at user-specified dosages and times. In the current work, these inputs calculated from our self-designed lab-developed fuzzy rule-based control system. This FLS designed in a way to enable tracking of TSH responses via negative feedback while minimizing its deviation from a predefined "set point". Here, the desirable euthyroid ITV-TSH is supposed 1.93 mU/l which is indeed considered as the controller set point. We used TSH concentration (and its deviation from the assumed individual target value, ITV) only as a controlling element and the input of our Fuzzy Logic System. Ultimately, the FLS output, an appropriate LT4 dose for each day, would increase the concentration of T3 and T4 hormones and reduce the concentration of TSH as well. We want "all three hormones" to reach their normal reference range, and TSH is only a means to attain this.

[1] Available at http://biocyb1.cs.ucla.edu/thyrosim/cgi-bin/Thyrosim.cgi/.

Table 1
The characteristics of our thyroidectomized virtual patient.

Characteristic	Value	Reference
Gender	Male	[42]
Age (years)	37	[42]
Weight (kg)	72	[42]
BMI (kg/m^2)	25.4	[43]
Height (m)	1.7	[42]
BSA (body surface area, m^2)	1.9	[44]
LBM (lean body mass, kg)	51.7	[45]
Postoperative assumed TSH (after total thyroidectomy) (mU/L)	51.7	[40]
Assumed ITV-TSH (mU/L)	1.93	[a]
Postoperative assumed T3 (μg/L)	0.57	[40]
Assumed ITV-T3 (μg/L)	1.35	[a]
Postoperative assumed T4 (μg/L)	18.76	[40]
Assumed ITV-T4 (μg/L)	78.21	[a]
T4 secretion	1%	[40]
T4 Absorption	88%	[40]
T3 Secretion	1%	[40]
T3 Absorption	88%	[40]

[a] Assumed in this work.

2.3. Proposed fuzzy-logic system

Fuzzy logic-based controller was designed by MATLAB software ver. 2019 (The Mathworks Inc., USA). The discrepancies of TSH value at day "n" and one-step time back TSH value (at day "n-1") in regard with the TSH set point (ITV-TSH) were assumed as the controlled variables while LT4 daily dosage was regarded as the manipulated variable. In Fig. 1, a schematic block diagram of our fuzzy control loop is demonstrated.

Our FLS comprises nine membership functions. The rules use the input membership values as weighting factors to determine their influence on the fuzzy output sets of the final output conclusion [46]. Negative, moderately positive, and highly positive errors are three inputs membership functions that we used for both TSH errors (namely TSH of day n and TSH of day n-1). In addition, low dose, median dose, and high dose were included for LT4 output membership functions. After the definition of fuzzy membership functions, we developed 27 IF-THEN rules in order to mimic the decision procedures of a physician. These 27 rules covers all possibilities of LT4 dose adjustments. After an almost 100 iterations of fuzzy controller, the rules that used less frequently, were excluded from the rule table in order to reduce the time and cost of simulation procedure; and therefore, fuzzy rules were reduced to nine. The developed FLS rule interface in MATLAB software is shown in Fig. 2.

Mapping of "recent TSH error" and "one-step time back TSH error'' to LT4 dose administration was created by 3D Surface Viewer as represented in Fig. 3.

As it can be seen in Fig. 3, a high value of LT4 dose administration for large recent TSH error and one-step time back TSH error is obvious. However, a large flat area in the middle corresponding to the median LT4 dose administration versus median TSH errors is noticeable.

In MATLAB rule viewer, where each column shows a set of membership functions for a particular variable, three membership functions for TSH error (n), as input 1, three membership functions for TSH error (n-1), as input 2, and three membership functions for LT4, as an output variable, are defined. The number of the rows corresponds to the number of rules, here defined as 9 rules which are shown in Fig. 4.

In Fig. 4, the plot in the output column shows how the rules are applied on the output variable. The plot indicated by the arrow in Fig. 4, demonstrates how the output of each rule is combined to make an aggregated output and a defuzzified value while the red line provides the defuzzified value for LT4 dose.

The simulation through the control loop starts with calculating the amount of error with the predicted amount of the TSH by THYROSIM on the first day after thyroidectomy considering the TSH set point value. In the controller, these errors are used as inputs.

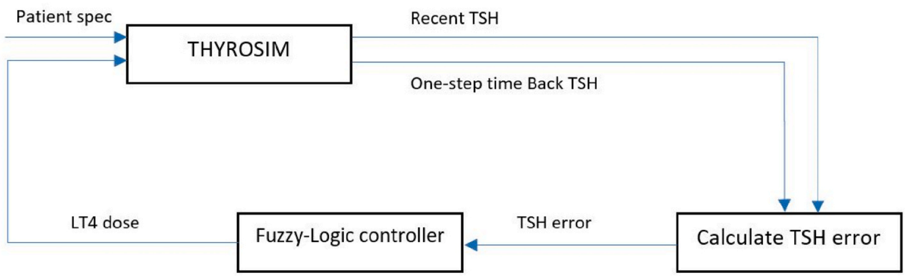


Fig. 1. Schematic block diagram of FLS control loop.

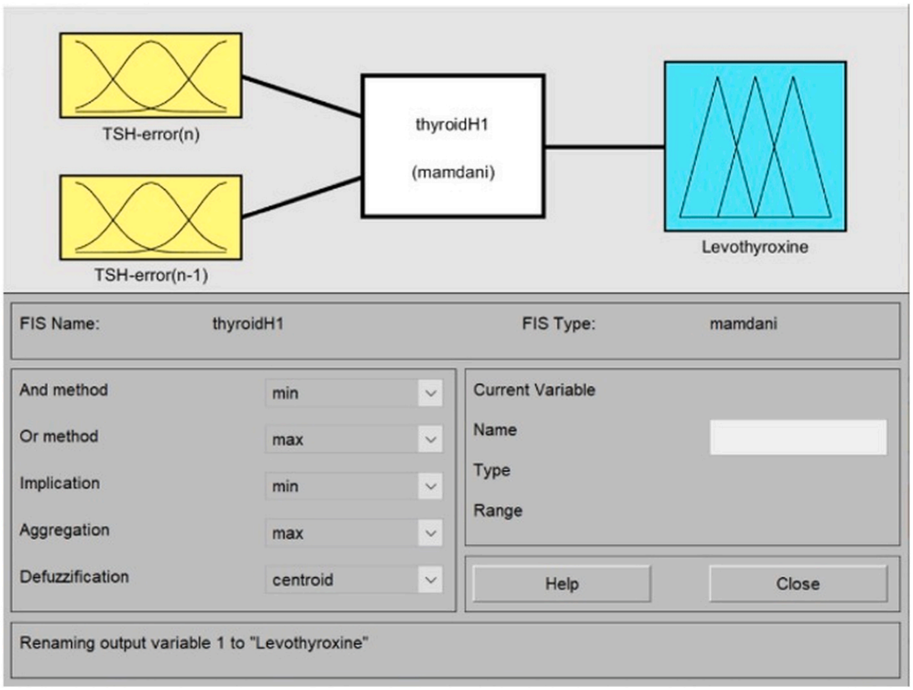


Fig. 2. Fuzzy logic-based control algorithm user interface in MATLAB software.

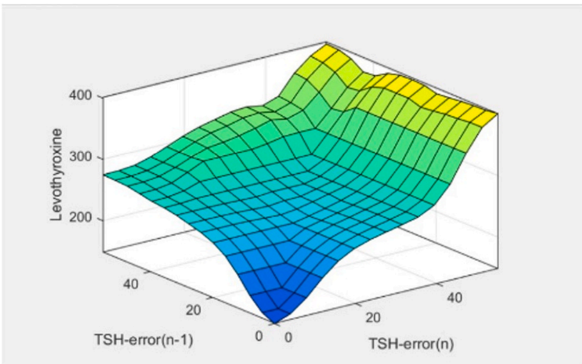


Fig. 3. Surface display of mapping TSH errors and levothyroxine.

The fuzzy controller operates the specified 9 rules to predict oral LT4 dosage for day one. At this time, we indicate the oral LT4 dosage on day one in THYROSIM and repeat this loop for the next day. These predictions should continue until TSH errors tend to zero.

2.4. Conventional dosing regimens

The proposed FLS is capable of receiving any reasonable amount of TSH concentration as its set-point and offers an appropriate LT4 dose regime. Therefore, the suggested dose regime for each set-point is different, and it can simply be individualized for each patient with their age and other physiological conditions. In this research, we aim to illustrate the ability of our FLS to predict appropriate LT4 doses for patients after total thyroidectomy and compare our results with the previous investigations. To meet a fair and rational comparison, we used a virtual patient (THYROSIM app) with characteristics reported in Table 1 for all dosing methods and assumed a TSH target value of 1.93 mU/L, which indeed can be changed.

Based on our literature review, we singled out eight monotherapy schemes proposed to calculate the proper LT4 dose after total thyroidectomy. We considered the most recent publications investigating LT4 treatment in adult thyroidectomized patients. The heterogeneity of these schemes implies the contribution of several parameters for accurately LT4 dose calculation. The selected monotherapy LT4 dosing regimens are classified in Table 2.

Comparisons between different methods of LT4 dose prediction, indicated in Table 2, with our developed fuzzy logic dose regime

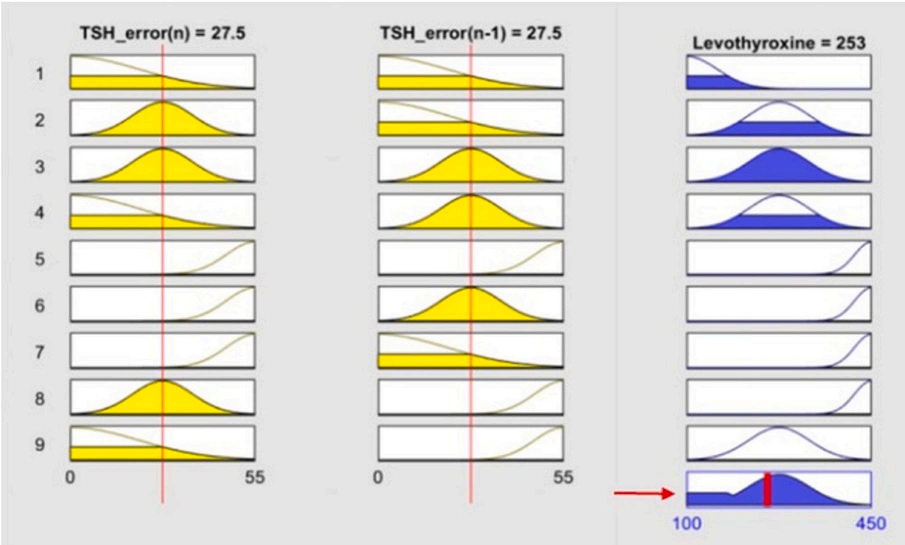


Fig. 4. Rule viewer of the nine membership functions used in the FLS.

were provided by implementing each regime in THYROSIM application. The resulted courses of serum T3 and T4 in addition to TSH were then compared for fuzzy logic dose regime and each conventional regime in pairs.

This article aims to help patients in the first 30 days after total thyroidectomy to quickly and properly reduce the TSH concentration and keep it within the normal window.

2.5. Comparison of LT4 dose regimes

We sought to evaluate and compare our FLS dose regime with recently proposed methods. Therefore, we implemented our virtual patient characteristics (refer to Table 1) into conventional methods, which are fundamentally based on variables e.g., patient age, sex, BMI, weight, and BSA (refer to Table 2). Also, we compared our FLS dose regime with a decision tree method recently presented by Chen S.S. et al. [50]. We applied the Relative Standard Error (RSE) term in order to demonstrate the closeness of the results to the intended values. RSE is defined as the discrepancy between intended and calculated values divided by the calculated value. According to the statistical references, if the RES is less than 25%, the desired and calculated values are significantly close together [51].

3. Results

3.1. Simulation of euthyroidism and total thyroidectomy

The simulation of serum level of thyroid hormones with 100% and 1% secretion for both T3 and T4 using the THYROSIM is demonstrated in Fig. 5. In this figure, the blue lines indicate the conditions of a normal thyroid (100% secretion) and the green lines are for total thyroidectomy (1% secretion) without administering any medication. Obviously, the purpose of prescribing LT4 for thyroidectomized patients is to bring the serum levels of hormones TSH, T4, and T3 close to the 100% secretion in the normal window.

3.2. FLS LT4 dose regime for total thyroidectomy

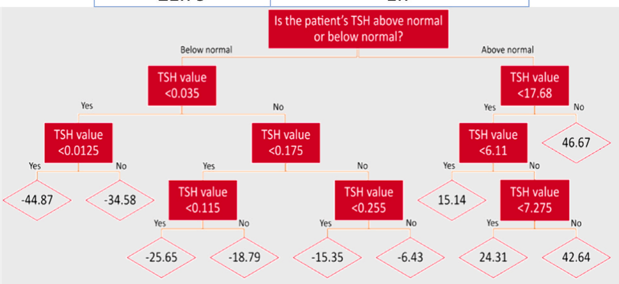
According to the algorithm shown in Fig. 1, our developed FLS proposes a LT4 monotherapy dose regime for the assumed total thyroidectomized virtual patient (refer to Table 1) on a daily basis as presented in Table 3. For a period of 30 days, the recommended doses provided by FLS are indicated as “Precise FLS LT4 dose” in Table 3. Nevertheless, available doses are also presented by rounding the precise dose considering 12.5 and 25 μg intervals in respect with the smallest increment between LT4 dosing strengths.

It can be revealed from Table 3 that the FLS dose regime changes 6 times in the first 9 days of treatment considering 12.5 μg intervals while it changes 5 times in the first 7 days of treatment. Subsequently, the LT4 dose would be stable for the rest of treatment at 150 μg. The TSH error (mU/L) computed by FLS in respect with the assumed TSH set point (ITV-TSH) and the T3 error is calculated in respect with the euthyroidism.

The illustration of thyroid hormones’ variations of our total thyroidectomized patient administrated LT4 based on our FLS dose regime is depicted in Fig. 6.

To confirm that our FLS method is applicable to recommend appropriate LT4 doses for each patient with different physiological characteristics, we supposed another virtual patient (patient 2) with an assumed ITV-TSH of 3.50 mU/L and used FLS for these two patients. The results are shown in Table 4.

Table 2
Conventional LT4 monotherapy dosing regimens for thyroidectomy.

<table>
<tr><th>Reference</th><th>Formula</th><th>Years</th></tr>
<tr><td>Olubowale and Chadwick [4]</td><td><table><tr><th>Patient weight (kg)</th><th>LT4 dose (μg)</th></tr><tr><td><54</td><td>100</td></tr><tr><td>54-86</td><td>125</td></tr><tr><td>87-108</td><td>150</td></tr><tr><td>>108</td><td>175</td></tr></table></td><td>2006</td></tr>
<tr><td>Sukumar et al. [7]</td><td>LT4 dose (μg) = 75.2 μg/m^2 BSA per day</td><td>2010</td></tr>
<tr><td>Mistry et al. [47]</td><td>LT4 dose (μg) = (0.943 × bodyweight) + (-1.165 × age) + 125.8</td><td>2011</td></tr>
<tr><td>Ojomo et al. [14]</td><td>LT4 dose (μg) = (-0.018 × BMI + 2.13) × weight</td><td>2013</td></tr>
<tr><td>Jin et al. [48]</td><td>LT4 dose (μg) = 1.5 × weight</td><td>2013</td></tr>
<tr><td>Di Donna et al. [18]</td><td><table><tr><th>BMI (kg/m^2)</th><th>≤23</th><th>23-28</th><th>>28</th></tr><tr><th>Age</th><th colspan="3">LT4 dose (μg/kg)</th></tr><tr><td>≤40</td><td>1.8</td><td>1.7</td><td>1.6</td></tr><tr><td>> 40-55</td><td>1.7</td><td>1.6</td><td>1.5</td></tr><tr><td>>55</td><td>1.6</td><td>1.5</td><td>1.4</td></tr></table></td><td>2014</td></tr>
<tr><td>Elfenbein et al. [10]</td><td><table><tr><th>BMI (kg/m^2)</th><th>Male (μg/kg)</th><th>Female (μg/kg)</th></tr><tr><td>< 21</td><td>2.1</td><td>1.8</td></tr><tr><td>22-26</td><td>1.9</td><td>1.7</td></tr><tr><td>27-32</td><td>1.7</td><td>1.6</td></tr><tr><td>33-40</td><td>1.5</td><td>1.4</td></tr><tr><td>> 40</td><td>1.3</td><td>1.2</td></tr></table></td><td>2016</td></tr>
<tr><td>Al-Dhahri et al. [49]</td><td><table><tr><th>BSA (m^2)</th><th>LT4 dose estimation (μg/kg)</th></tr><tr><td>>1.79</td><td>1.4</td></tr><tr><td>≤1.79</td><td>1.7</td></tr></table></td><td>2019</td></tr>
<tr><td>Chen et al. [50]</td><td>
</td><td>2019</td></tr>
</table>

3.3. Comparison of FLS LT4 monotherapy dose regime with conventional ones

The evaluations of FLS dose regime and conventional ones, using the THYROSIM application, are presented in pairs considering the serum levels of T3, T4, and TSH. The results presented here are based on chronological order of the conventional methods.

Firstly, the method proposed by Olubowale and Chadwick [4], which calculates the predicted LT4 dose based on patient weight, results a LT4 dose of 125 μg/day for our virtual patient. Fig. 7a demonstrates the results of FLS dose regime in comparison with this method.

As we can see in Fig. 7a, the method of Olubowale and Chadwick fails to reach normal TSH window in the period of 30 days.

Sukumar et al. [7] presented a dose regime based on BSA in 2010. The recommended dose for our virtual patient based on this method would be 138.72 μg/day. In Fig. 7b, we can see the comparison of the FLS and Sukumar LT4 dosing regimens.

In a study conducted by Mistry D. et al. [47], the dose recommended for our virtual patient, based on weight and age, would be 154.53 μg/day. Fig. 8a depicts the simulations of this dose regime along with FLS one.

Jin et al. [48] proposed a simple equation based on weight of patient, which predicts 105 μg/day of LT4 for our virtual patient. Fig. 8b shows the simulation of this dose regime and FLS using THYROSIM application.

In 2013, a study had been organized by Ojomo K. A. et al. [14] in order to evaluate a dose regime based on weight and BMI. By applying the characteristic of our patient in their equation, the predicted LT4 dose was 120.3 μg/day. In Fig. 9a, we can see the comparison of Ojomo K. A. and fuzzy logic system dose regimes.

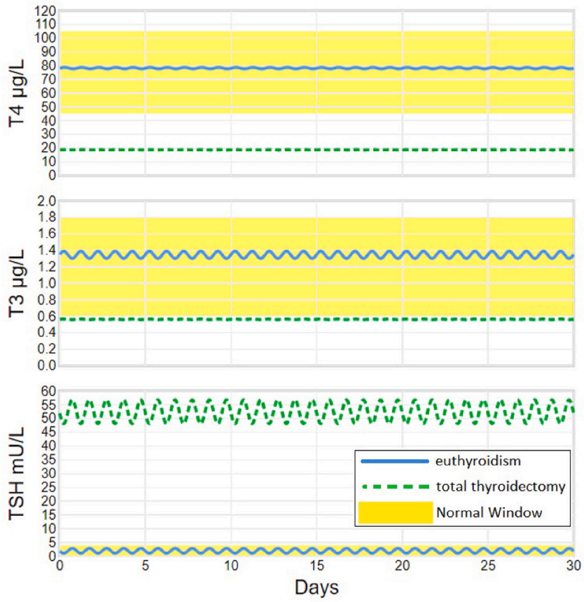


Fig. 5. Simulation of euthyroidism (100% secretion) and total thyroidectomy (1% secretion) with THYROSIM application.

Table 3
The proposed FLS dose regime for the thyroidectomized patient.

Day	Precise FLS LT4 dose (µg)	Available LT4 dose (at 12.5 µg intervals)	Available LT4 dose (at 25 µg intervals)	Serum TSH (mU/L)	TSH error (mU/L) (calculated by FLS)	Serum T3 (µg/L)	T3 error (µg/L)
1	377.87	375	375	51.98	50.05	0.57	−0.78
2	307.86	312.50	300	22.75	20.82	0.63	−0.72
3	241.83	237.50	250	14.28	12.35	0.68	−0.67
4	207.31	212.50	200	10.22	8.29	0.73	−0.62
5	180.45	175	175	7.74	5.81	0.76	−0.59
6	166.31	162.50	175	6.23	4.30	0.79	−0.56
7	159.66	162.50	150	5.31	3.38	0.81	−0.54
8	156.40	162.50	150	4.59	2.66	0.83	−0.52
9	154.22	150	150	4.13	2.20	0.84	−0.51
10	153.00	150	150	3.81	1.88	0.84	−0.51
11	152.24	150	150	3.45	1.52	0.85	−0.50
12	151.43	150	150	3.33	1.40	0.86	−0.49
13	151.18	150	150	3.18	1.25	0.86	−0.49
14	150.88	150	150	2.95	1.02	0.87	−0.48
15	150.43	150	150	2.87	0.94	0.87	−0.48
16	150.28	150	150	2.72	0.79	0.87	−0.48
17	150.02	150	150	2.69	0.76	0.88	−0.47
18	150.01	150	150	2.57	0.64	0.88	−0.47
19	149.75	150	150	2.54	0.61	0.88	−0.47
20	149.70	150	150	2.48	0.55	0.88	−0.47
21	149.60	150	150	2.40	0.47	0.89	−0.46
22	149.47	150	150	2.38	0.45	0.89	−0.46
23	149.46	150	150	2.36	0.43	0.89	−0.46
24	149.40	150	150	2.34	0.41	0.89	−0.46
25	149.37	150	150	2.27	0.34	0.89	−0.46
26	149.26	150	150	2.25	0.32	0.89	−0.46
27	149.23	150	150	2.23	0.30	0.89	−0.46
28	149.19	150	150	2.22	0.29	0.89	−0.46
29	149.20	150	150	2.23	0.30	0.89	−0.46
30	149.19	150	150	2.20	0.27	0.89	−0.46

Di Donna V. et al. [18] presented a dose regime based on BMI and age. The predicted LT4 dose based on this method is 126 µg/day, which can find its simulation graph in Fig. 9b in comparison with FLS method.

In 2016, a study by Elfenbein D. M. et al. [10], the dose required for a thyroidectomized patient was calculated based on gender and

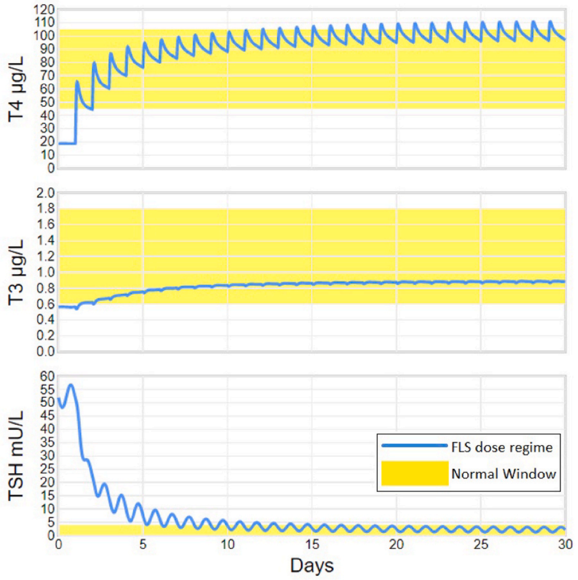


Fig. 6. Thyroid hormones courses for the total thyroidectomized virtual patient threated by FLS LT4 dose regime using THYROSIM application.

Table 4
FLS LT4 dose regime for two different virtual patients with their own ITV-TSH.

days	FLS recommended LT4 dosing for patient 1 (ITV-TSH: 1.93 mU/L)		FLS recommended LT4 dosing for patient 2 (ITV-TSH: 3.50 mU/L)	
	Precise doses (μg)	Available doses (μg)	Precise doses (μg)	Available doses (μg)
1	377.87	375	365.39	375
2	307.86	300	303.72	300
3	241.83	250	237.98	250
4	207.31	200	198.91	200
5	180.45	175	171.57	175
6	166.31	175	159.77	150
7–30	From 149.19 to 159.66	150	From 148.95 to 154.94	150

BMI. Using this equation, the required dose of LT4 for the virtual patient would be 133 μg/day. In Fig. 10a, we can see the difference between this dose regime and the fuzzy logic-based one.

In a recent study conducted by Al-Dhahri S.F. et al. [49], a dose regime based on the BSA has been proposed. The suggested LT4 dose of this article for our virtual patient is 98 μg/day. Fig. 10b shows the simulation of this dose regime along with the fuzzy logic system method.

In 2019, Chen S.S. et al. [50] presented a decision tree for prescribing LT4 after thyroidectomy. With the help of THYROSIM, we monitored the patient's TSH hormone level each day after taking the recommended LT4 dose and then prescribed the next day dose based on the decision tree. The LT4 doses for our virtual patient according to the proposed decision tree are demonstrated in Table 5 in a daily basis.

4. Discussion

Figs. 7–11 demonstrate the performance of FLS dose regime in comparison to conventional LT4 monotherapy methods for our virtual thyroidectomized patient. To scrutinize the discrepancies between these methods, we highlighted the following issues. As we can see in Fig. 7a, TSH course in the dose regime proposed by Olubowale and Chadwick can reach the normal range much later than fuzzy logic method, and also it fails to stay totally in the normal window. It is obvious from Fig. 7b that TSH serum level would reach to normal window faster by FLS method compared with Sukumar dose regime. It can be revealed from Fig. 8a that the patient would experience a higher TSH value for the first 20 days of therapy under Mistry et al. method in comparison with the FLS dose regime.

Interestingly the TSH value resulted from Jin et al. method (refer to Fig. 8b) would stay out of the normal range for the whole 30 days of therapy. Based on Fig. 9a, there is no doubt that Ojomo dose regime is not able to bring TSH value to the normal window. In the last days of study period, Di Donna dose regime (shown in Fig. 9b) is able to reach the normal range to some extent, which is not an acceptable performance compared to the FLS dose regime.

As it is obvious in Fig. 10a, although the Elfenbein dose regime is able to catch the normal TSH window up at the end of the study period (around day 30), it takes much longer time than fuzzy logic system to enter the normal TSH window. The Al-Dhahri dose regime

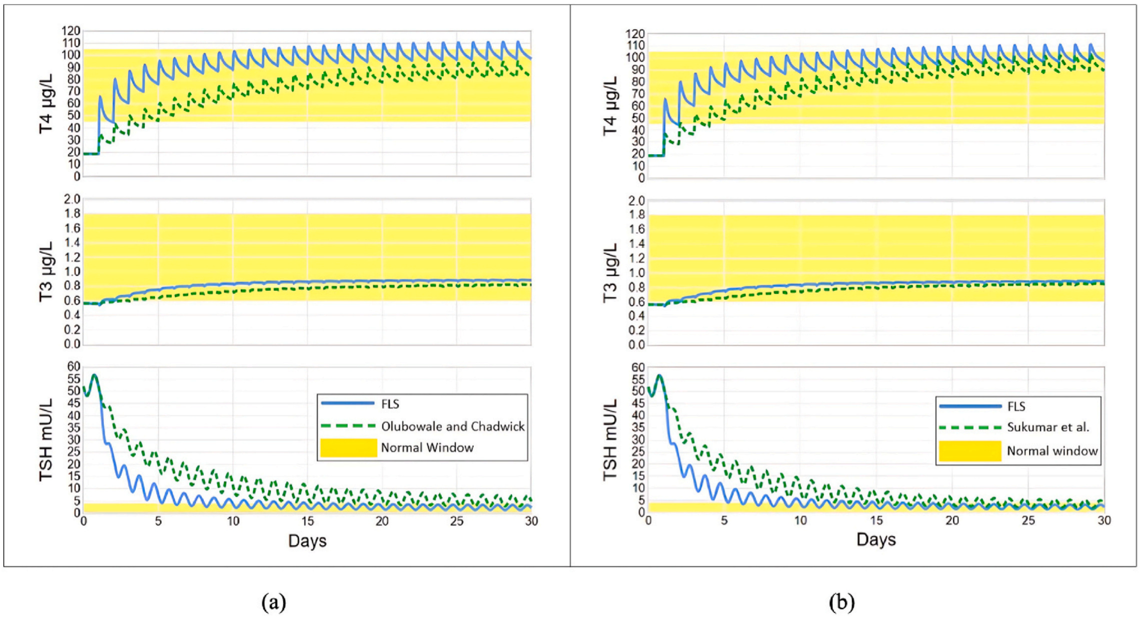


Fig. 7. Comparison of *Olubowale and Chadwick* vs. FLS (7a) and *Sukumar* vs. FLS (7b) LT4 dose regimes.

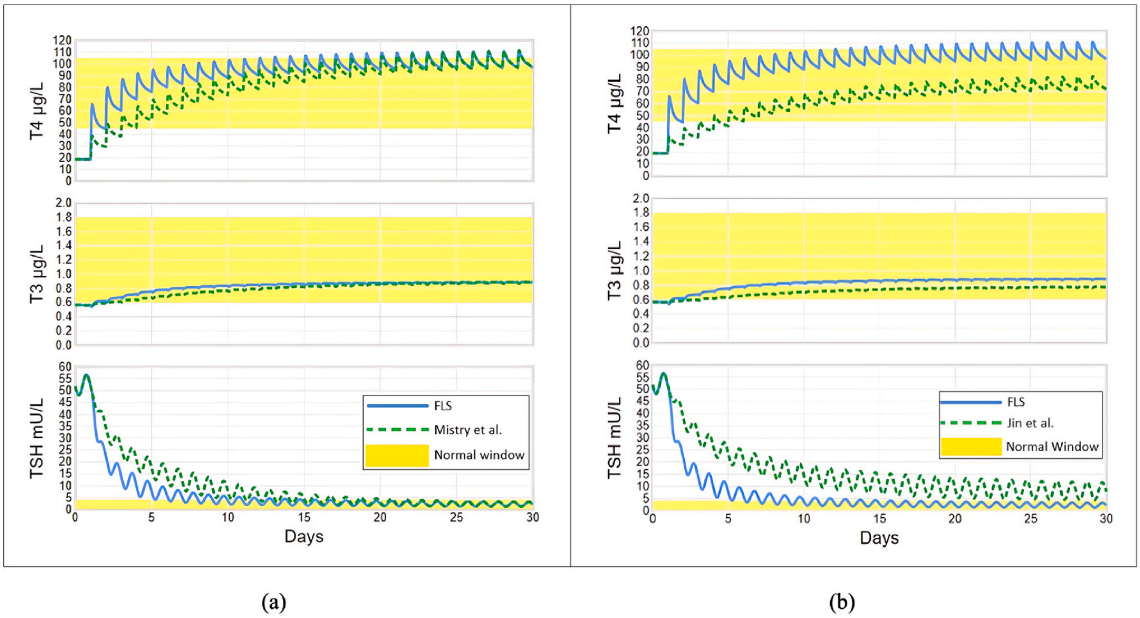
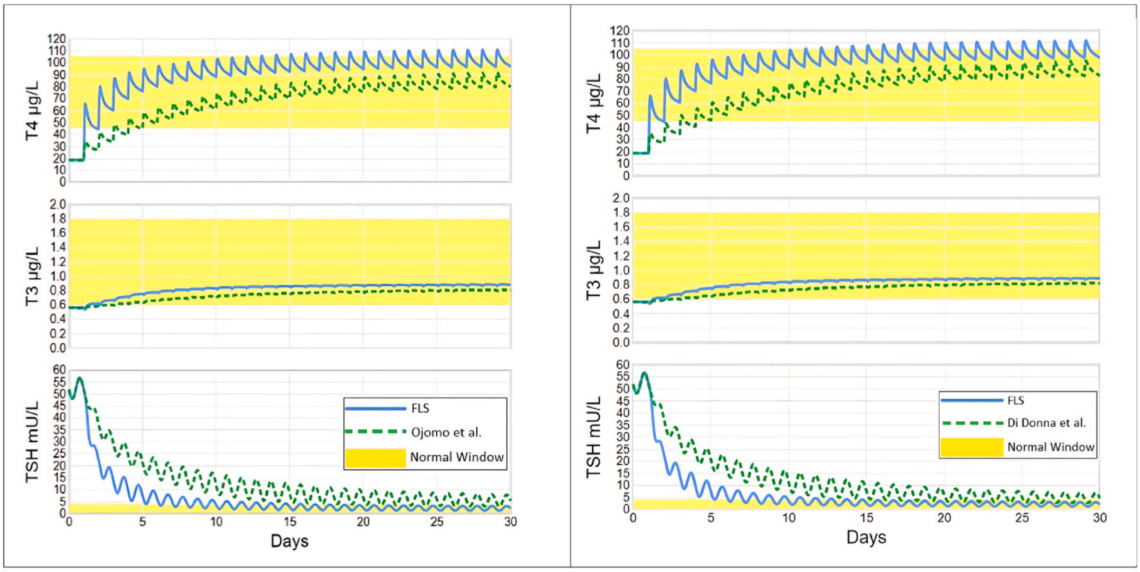


Fig. 8. Comparison of *Mistry* vs. FLS (8a) and *Jin* vs. FLS (8b) LT4 dose regimes.

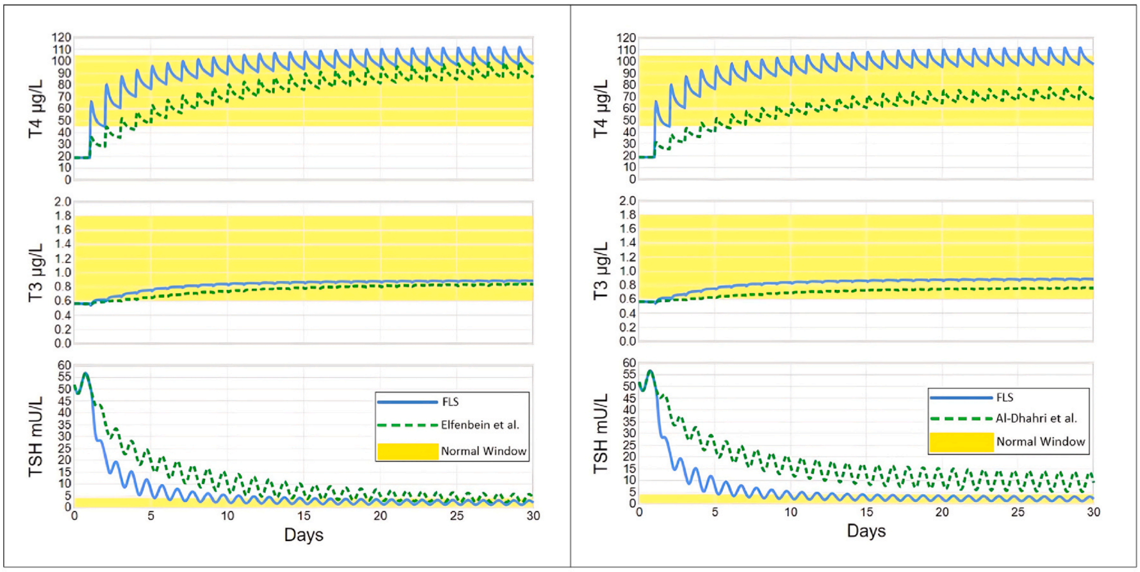
(refer to Fig. 10b) not only fails to enter into the normal TSH window, but also cannot bring the TSH value down to the normal range during the 30 days of therapy. Therefore, this dose regime is not appropriate for total thyroidectomized patients compared to other dose regimens. Although Chen dose regime (shown in Fig. 11) is able to rapidly bring the TSH value to the normal range, the same way as the FLS dose regime, but it is obvious that this method, after day 6 of therapy, raises the amount of T4 above its normal window while at the same time brings the TSH concentration lower than the Individual target value which would have some negative effects on the patient's quality of life.

Considering the alteration of TSH of virtual thyroidectomized patient, although TSH values based on the methods of Di Donna et al. and Sukumar et al. demonstrated in Figs. 9b and 7b respectively, could follow the normal range over a longer period of time than the FLS dose regime, they ultimately match the FLS TSH goal. However, methods such as Mistry et al. (Fig. 8a), Jin et al. (Fig. 8b), Ojomo et al. (Fig. 9a), Elfenbein et al. (Fig. 10a), and Al-Dhahri et al. (Fig. 10b) are not successful to bring the TSH value to the normal range



(a) (b)

Fig. 9. Comparison of *Ojomo* vs. FLS (9a) and *Di Donna* vs. FLS (9b) LT4 dose regimes.



(a) (b)

Fig. 10. Comparison of *Elfenbein* vs. FLS (10a) and *Al-Dhahri* vs. FLS (10b) LT4 dose regimes.

although during the study period, T4 and T3 values stay in their normal windows.

As far as we investigated publications, no specific criterion was proposed to compare the performance of two different dose regimens in LT4 monotherapy of total thyroidectomized patients. To decide on the appropriate dose regime, we have defined nine criteria including the time to reach TSH normal window, time to reach T3 normal window, time to reach T4 normal window, discrepancy between TSH at day 30 and ITV-TSH, discrepancy between T3 at day 30 and ITV-T3, discrepancy between T4 at day 30 and ITV-T4, and the number of days that TSH, T4 and T3 are out of normal ranges. Based on the results of THYROSIM simulations demonstrated in Figs. 7 to 15, the comparison of the conventional dosing regimens besides FLS, in respect with the nine aforementioned criteria, is presented in Table 6.

Criteria defined in Table 6 compare the performances of LT4 dosing regimen, in a way that, lower value of each parameter indicates better performance. As presented in Table 5, FLS shows superiority compared to other methods in six criteria, among which an

Table 5
Chen et al. LT4 dose regime recommended for our virtual patient.

Days	TSH value (mU/L)	Recommended LT4 dose (μg)
1	35.09	196.67
2	24.53	243.34
3	17.24	285.98
4	11.51	328.62
5	7.14	352.93
6	4.13	346.50
7	2.42	340.07
8	1.47	333.64
9	0.92	327.21
10	0.60	320.78
11	0.43	314.35
12	0.31	307.92
13	0.24	292.57
14	0.19	277.22
15	0.17	258.43
16	0.15	239.64
17	0.20	224.29
18	0.15	205.50
19	0.16	186.71
20	0.17	167.92
21	0.19	152.57
22	0.22	137.22
23	0.27	130.79
24	0.34	124.36
25	0.41	117.93
26	0.51	111.50
27	0.62	105.07
28	0.77	93.64
29	0.96	92.21
30	1.20	85.78

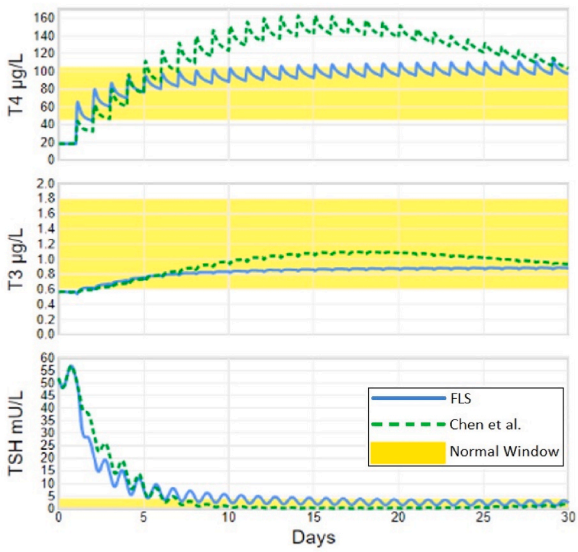


Fig. 11. Chen et al. vs. FLS LT4 dosing regimens for the virtual thyroidectomized patient.

important index would be the "time to reach TSH normal window". FLS is behind Mistry et al. in terms of "discrepancy between TSH at day 30 and ITV-TSH"; however, the difference is only 0.03 which could be ignored and both methods have an RSE less than 25%. The same behavior is recognized in criterion "discrepancy between T3 at day 30 and ITV-T3"; however, due to using monotherapy methods, none of the proposed algorithms could result a T3 at day 30 and ITV-T3 discrepancy RSE less than 25%

Considering the proposed items in Table 6, although Chen T3 discrepancy is less than FLS one, which is 0.05, the FLS performance is better in other aspects, turning this difference into an insignificant issue. Regarding the "discrepancy between T4 at day 30 and ITV-T4", although FLS T4 value is above ITV-T4, it is not exert a great influence on the patient's health. Ojomo et al. dose regime performs

Table 6
Pros and cons of FLS and conventional LT4 dosing regimens for the total thyroidectomized virtual patient.

LT4 monotherapy method	Time to reach TSH normal window (days)	Time to reach T3 normal window (days)	Time to reach T4 normal window (days)	TSH out of normal window (days)	T3 out of normal window (days)	T4 out of normal window (days)	Discrepancy between TSH at day 30 and ITV-TSH (1.93)	Discrepancy between T3 at day 30 and ITV-T3 (1.35)	Discrepancy between T4 at day 30 and ITV-T4 (78.21)
FLS	**6**	**2**	**2**	**5**	**1**	**1**	0.24[a]	−0.47	18.7[a]
Olubowale and Chadwick	16	3	4	17	2	3	2.83	−0.53	4.24[a]
Sukumar et al.	14	3	4	13	2	3	1.38	−0.5	11.27[a]
Mistry et al.	11	**2**	3	10	**1**	2	**0.21**[a]	−0.47	19.2[a]
Jin et al.	30	**2**	5	30	**1**	4	5.8	−0.57	−6.23[a]
Ojomo et al.	17	4	4	16	2	3	3.44	−0.54	**1.8**[a]
Di Donna et al.	16	4	4	15	3	3	2.71	−0.53	4.75[a]
Elfenbein et al.	15	3	4	14	2	3	1.93	−0.51	8.35[a]
Al-Dhahri et al.	30	4	5	30	3	4	7.11	−0.59	−9.95[a]
Chen et al.	**6**	3	3	19	2	24	−0.7	**−0.42**	24.82

Numbers in **Bold** indicates the minimum value of each column.
[a] Indicates the RSE less than 25% (in the last three columns).

very well in this item but we must keep in mind that this method reaches the ITV-TSH much later than FLS and is not comparable with FLS in other aspects as well.

Setting aside FLS method, overall review of Table 6 indicates that methods presented by Mistry et al. and Chen et al. could be considered appropriate for our thyroidectomized virtual patient. At long last, although FLS is superior to other methods in most criteria, it is the physician who makes the final decision for the patient's ITVs, based on the priority of criteria as well as the patient pathophysiological conditions.

5. Conclusion

Our comparative study reveal that the proposed FLS-based LT4 dose regime is quite able to bring and keep the T4, T3, and TSH values in their normal window as well as remarkably reduce the time to reach this normal level for all thyroid hormones in comparison with conventional monotherapy dosing regimens. The FLS method would also be beneficial in terms of declining the number of days in which our total thyroidectomized virtual patient experiences thyroid hormones levels out of the normal windows. Although this appropriate dose regime was optimized for virtual thyroidectomized patient, this method could be utilized for dose adjustment in therapeutic procedure of any arbitrary patient too. Although the results presented by FLS in this study has not yet clinically validated, it introduces FLS as a potential means to predict appropriate LT4 dosing regimens for thyroidectomy and hypothyroidism.

There are some limitations in this study which can be addressed in future works. The underlying diseases and supplements taken in the dietary did not considered for our virtual patient. This approach is patient specific and should be further modified for any particular age and gender. We also have not discussed the pregnancy and breastfeeding conditions which may significantly affect the thyroid hormone replacement therapy. Moreover, in the future works, this method should be applied on real patients and the results could corroborate our proposed LT4 dose regime.

Nowadays, due to the Covid-19 pandemic, there is a great challenge for patients to see a doctor in person. It is no longer time to write conventional prescriptions for patients; and as a matter of fact, patients should learn to cope with their diseases on their own. Indeed, predicting the optimal dose is like a concert in which the patient and Al are the main leaders. Besides, physicians could review the outcome and modify the dose proposed by the employed AI methodology.

Acknowledgments

The authors would like to thank all researchers around the globe concerned with thyroid diseases for their tireless endure to enhance the patients' quality of life.

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