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Patient-Tailored Levothyroxine Dosage with Pharmacokinetic/Pharmacodynamic Modeling: A Novel Approach After Total Thyroidectomy

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Background: After seven decades of levothyroxine (LT4) replacement therapy, dosage adjustment still takes several months. We have developed a decision aid tool (DAT) that models LT4 pharmacometrics and enables patient-tailored dosage. The aim of this was to speed up dosage adjustments for patients after total thyroidectomy.
Methods: The DAT computer program was developed with a group of 46 patients post-thyroidectomy, and it was then applied in a prospective randomized multicenter validation trial in 145 unselected patients admitted for total thyroidectomy for goiter, differentiated thyroid cancer, or thyrotoxicosis. The LT4 dosage was adjusted after only two weeks, with or without application of the DAT, which calculated individual free thyroxine (fT4) targets based on four repeated measurements of fT4 and thyrotropin (TSH) levels. The individual TSH target was either <0.1, 0.1–0.5, or 0.5–2.0 mIU/L, depending on the diagnosis. Initial postoperative LT4 dosage was determined according to clinical routine without using algorithms. A simplified DAT with a population-based fT4 target was used for thyrotoxic patients who often went into surgery after prolonged TSH suppression. Subsequent LT4 adjustments were carried out every six weeks until target TSH was achieved.
Results: When clinicians were guided by the DAT, 40% of patients with goiter and 59% of patients with cancer satisfied the narrow TSH targets eight weeks after surgery, as compared with only 0% and 19% of the controls, respectively. The TSH was within the normal range in 80% of DAT/goiter patients eight weeks after surgery as compared with 19% of controls. The DAT shortened the average dosage adjustment period by 58 days in the goiter group and 40 days in the cancer group. For thyrotoxic patients, application of the simplified DAT did not improve the dosage adjustment.
Conclusions: Application of the DAT in combination with early postoperative TSH and fT4 monitoring offers a fast approach to LT4 dosage after total thyroidectomy for patients with goiter or differentiated thyroid cancer. Estimation of individual TSH-fT4 dynamics was crucial for the model to work, as removal of this feature in the applied model for thyrotoxic patients also removed the benefit of the DAT.

Keywords: decision aid tool, levothyroxine dosage, patient tailored, pharmacokinetic modeling, thyroidectomy

Introduction

An estimated 5% of the population require thyroxine replacement therapy due to thyroid dysfunction or surgery (1,2). In the United States, levothyroxine (LT4) has been among the three most prescribed medications for years (3). Surprisingly, dosage adjustment remains a significant clinical problem even though LT4 has been on the market for almost seven decades and was first synthesized in 1927 (4). The time to achieve euthyroidism after thyroidectomy is often more than a year (5,6). The long interval could be due to the long half-life of LT4 (about one week), the narrow therapeutic window, variations in bioavailability and pharmacodynamics, and nonadherence. Long-term hypothyroidism and

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iatrogenic thyrotoxicosis have implications for cardiovascular disease, osteoporosis, quality of life, neurological disease, dementia, cancer treatment, and even mortality (7–16). Shorter periods with suboptimal dosage are more likely to affect quality of life, work capacity and have social consequences (17,18).

Several attempts have been made to predict the required LT4 dosage after thyroidectomy or in treatment of hypothyroidism (5,6,19–23). The published dosage schemes are variations of weighted relationships between LT4 dosage and person weight, height, sex, age, and drug interactions. At best, they *retrospectively* predict the correct dosage for 60–65% of the patients (1,23). However, *prospective* testing of the formulas is limited and often provides inferior results. Leaving *a priori* dosage estimates behind, we decided to use a patient-tailored approach that estimates the free thyroxine (fT4) pharmacokinetics and the thyrotropin (TSH)/fT4 relationship for each individual patient based on repeated blood samples. We hypothesized that rather than waiting six to eight weeks for hormone levels to stabilize, dosage adjustments after only two weeks would be feasible if the clinician was assisted by a computerized decision aid tool (DAT) predicting the future fT4 and TSH responses. We further assumed that the best prediction could be done by combining population data and the results of individual blood samples drawn during the first two weeks after thyroidectomy. The objective of the study was to test whether application of the DAT led to more efficient dosage adjustments for patients starting LT4 therapy after total thyroidectomy, as compared with randomized controls.

Methods

Participants

Patients >18 years old admitted for total thyroidectomy or completion thyroidectomy after previous hemithyroidectomy were recruited consecutively, after obtaining informed consent. Their diagnosis was nontoxic goiter, thyroid malignancy Graves' disease, or toxic multinodular goiter. Exclusion criteria were pregnancy, use of liothyronine, or inability to cooperate on later follow-up by telephone. First, 46 patients were recruited for collection of pilot data that were used to develop the DAT algorithms. Second, a validation group of 145 new patients (103 female) were consecutively recruited in a randomized controlled trial (RCT): 84 from the University Hospital of North Norway, 28 from Haukeland University Hospital, Norway, and 33 from Västervik Hospital, Sweden. Ten patients were excluded after enrolment in the RCT, because they did not take the blood samples required by the study design ($n=7$), because of technical problems with the DAT (server crash, $n=2$), or because of other health emergencies ($n=1$). The excluded patients were evenly distributed between the DAT and control groups (Table 1). This left 135 participants for data analysis. Of these, all completed the 8 weeks postoperative checkpoint and 122 successfully completed dosage adjustment according to the TSH goals in the study. The thyrotoxicosis/DAT group consisted of 21 patients with Graves' disease and 5 patients with toxic nodular goiter, while the thyrotoxicosis/control group contained 20 patients with Graves' disease and 5 patients with toxic nodular goiter.

DAT development and validation study design

The DAT was developed on pilot data as described in Supplemental Data. Briefly, the model parameters were derived from four blood draws analyzed for TSH and fT4 obtained during the first two weeks of LT4 therapy. We assumed a log-linear relationship between TSH and fT4 (24), and we modeled individual TSH-fT4 response and fT4 pharmacokinetics informed by population data. Individual TSH-fT4 responses are illustrated in Figure 1. We tested the DAT in a prospective multicenter trial where participants were randomized to either application of the DAT or not (controls). We used an automated stratified randomization based on diagnosis and participating hospital. After surgery, and before randomization, all participants were prescribed an LT4 starting dosage, usually between 100 and 150 μg/day depending on diagnosis, body weight, age, and comorbidity. They were then asked to give pre-LT4 ingestion blood samples twice per week for two weeks postoperatively (Fig. 2). To reduce variation in the measurements and model, patients were

Table 1. Patient Characteristics for Validation Randomized Controlled Trial

	Goiter		*Cancer*		*Thyrotoxicosis*		
Variable	*DAT*	*Control*	*DAT*	*Control*	*DAT*	*Control*	*All*
No. total	16	18	29	28	28	26	145
No. exclusions	1	2	2	2	2	1	10
No. analyzed	15	16	27	26	26	25	135
Age (years)	55 ± 4.6	55.9 ± 4.1	57.5 ± 2.3	55.7 ± 2.6	51.5 ± 2.8	53.8 ± 2.9	54.8 ± 1.2
Height (cm)	167 ± 2	165 ± 2	169 ± 1	173 ± 2	171 ± 2	168 ± 2	169 ± 1
Weight (kg)	76.7 ± 5.7	77.5 ± 5	79.7 ± 2.8	83.6 ± 3.2	78.5 ± 3.3	80.2 ± 3.7	79.7 ± 1.5
BMI (kg/cm^2)	27.1 ± 1.6	28.2 ± 1.6	27.6 ± 0.7	28 ± 1.1	26.6 ± 0.8	28.4 ± 1.2	27.6 ± 0.5
% Female	80	88	70	54	73	72	71
Initial LT4 dose (μg/day)	112 ± 3	109 ± 4	131 ± 4	137 ± 3	113 ± 3	117 ± 4	121 ± 2
Final LT4 dose (μg/day)	117 ± 9	118 ± 12	144 ± 7	150 ± 7	119 ± 5	114 ± 7	129 ± 3
TSH target <0.1 mIU/L	0	0	21	17	1	0	39
TSH target 0.1–0.5 mIU/L	0	0	5	8	4	4	21
TSH target 0.5–2.0 mIU/L	15	16	1	1	21	21	75

Baseline characteristics and dosage data for participants in the study. There was no statistical difference between the DAT groups and control groups within each diagnosis group (all p-values <0.15). The lower three rows show the number of patients assigned to each possible TSH target within each group.

BMI, body mass index; DAT, decision aid tool; LT4, levothyroxine; TSH, thyrotropin.

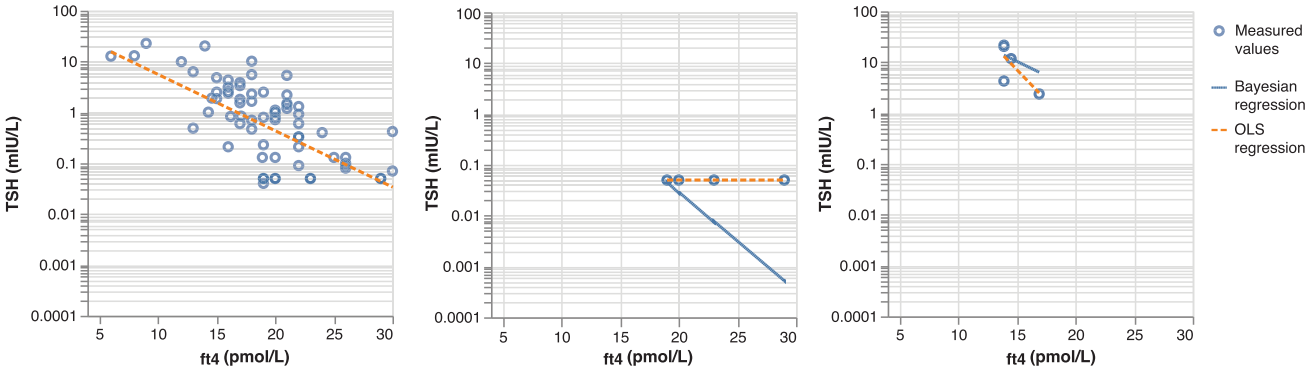

FIG. 1. Measurements of TSH and fT4 from a subset of the RCT population (left) and two example patients (center and right) during the first two weeks after thyroidectomy. Hyper parameters of the Bayesian regression lines estimated from the pilot population used to develop our model. For estimation of individual TSH/fT4 relationships a Bayesian regression model was used instead of OLS to compensate for the low number of samples and for censoring. Center: A patient without detectable TSH, naive OLS would give flat/no response. The Bayesian model gives more plausible estimate with response extending below censoring limit, slope is informed by population data. Right: Bayesian slope is less steep than naive patient specific OLS as informed by population data. fT4, free thyroxine; OLS, ordinary least squares; RCT, randomized controlled trial; TSH, thyrotropin.

instructed to take the medicine and give all blood samples in the morning. On days of blood samples, patients were instructed to delay intake of LT4 until the blood was drawn. Two to three weeks after surgery, the participants received a follow-up call advising them to either keep the current dosage or change it. In the DAT group, the responsible surgeon was assisted by the DAT with a graphical plot of the predicted fT4 and TSH given a suggested dosage change (Fig. 3). The DAT was disabled in the control group, but the same blood samples were available to the clinician. We collected preoperative data about diagnosis, TSH-target, height, weight, age, sex, surgery date, creatinine, albumin, TSH, fT4, and free triiodothyronine. Postoperative data were collected about LT4 dosage, TSH, and fT4.

Eight weeks after surgery (i.e., 5–6 weeks after the first follow-up), blood tests were again evaluated. If the TSH target was reached, they left the study and continued follow-ups by surgeons, endocrinologists, or general practitioners, according to local routines. If the TSH target was not reached, the participants entered loops of follow-up every six weeks until the TSH target was reached (Fig. 2). On each follow-up, the DAT was applied only to the DAT group.

Outcome measures

The primary endpoint in the study was the number of patients who reached their clinically determined TSH target eight weeks after thyroidectomy. Before discharge, the surgeon assigned each patient to either substitution treatment (TSH 0.5–2.0 mIU/L), mild suppression (TSH 0.1–0.5 mIU/L), or full suppression (TSH <0.1 mIU/L and fT4 < 30 pmol/L), depending on a clinical evaluation. Usually, patients with goiter and thyrotoxicosis received substitution therapy, while patients with cancer received suppression therapy (Table 1). The secondary endpoint was the number of days from surgery to the completion of LT4 dosage adjustment.

Ethical considerations and patient consent

The study was approved by the Norwegian Regional Ethics Committee (2016/1782) and by the Swedish Ethical Review Authority (443-17). All participants, including the ones contributing to pilot data, signed a written consent form. Very few (<5%) declined the invitation to participate. Patients reported no perceived ethical dilemma participating in the study and did not receive any financial compensation.

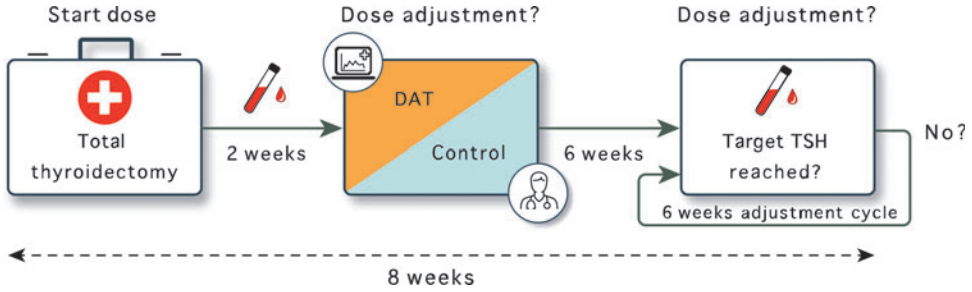

FIG. 2. Study design for randomized controlled validation trial. After total thyroidectomy, the surgeon chose an LT4 starting dosage based on diagnose and clinical routine. TSH and fT4 was measured four times the next two weeks to allow early dosage adjustment. The patients were randomized to the application of a DAT or not (control) for dosage adjustments that were supervised by an experienced endocrine surgeon in either case. Eight weeks after surgery, successful dosage adjustment was evaluated based on TSH measurements. If the TSH target was not achieved, the patient continued six-week dosage adjustment cycles. DAT, decision aid tool.

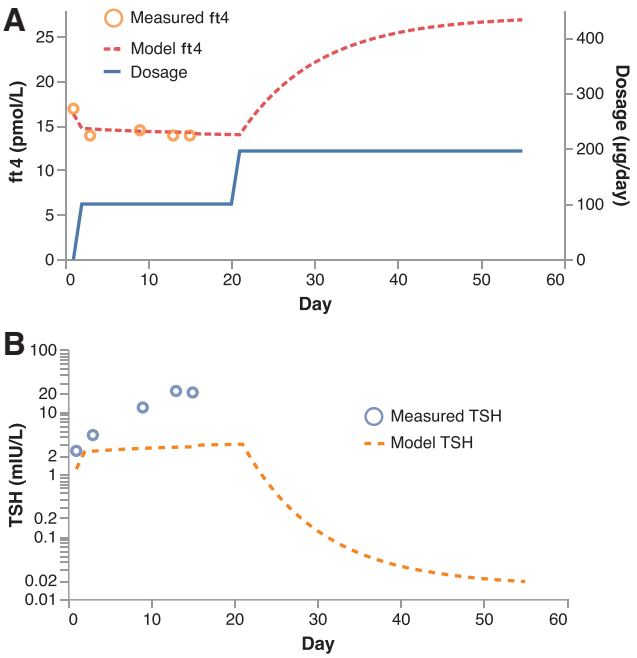

FIG. 3. Output from the DAT guided the clinician to increase LT4 dosage 20 days after thyroidectomy, when the DAT was applied in this example patient (same as in Fig. 1, right). A near twofold increase in dosage is suggested to reach the target of TSH <0.10 mIU/L. The plots show the actual measurements of fT4 (**A**) and TSH (**B**) alongside the model estimates. The suggested dosages and the projected responses are also shown to facilitate evaluation from the clinician before deciding on the final dosage.

Statistical methods and data analysis

All values are reported mean ± standard error of the mean. We used two-tailed Student's *t*-tests, univariate analysis of variance, and Pearson Chi-square tests for all statistics. The Markov Chain Monte Carlo model (25) is written in JAGS (26), with pre- and postprocessing in Julia (https://julialang.org). Data were collected by using Microsoft Access for the pilot study, and using REDCap for the multicenter study. Final results were exported for statistical analysis in Microsoft Excel, SPSS, and Julia. The dosage optimization was calculated by using JuMP (27) and Couenne (https://github.com/coin-or/Couenne).

Results

The DAT was tested in a validation RCT on patients diagnosed with goiter and differentiated thyroid cancer, and the simplified DAT was tested on patients with thyrotoxicosis. There was no statistical difference between the DAT and control groups in the basic characteristics of the groups, nor in the initial and final dosages of LT4 (Table 1, multiple *t*-tests, uncorrected *p*-values >0.15 for all variables). Most patients with cancer received TSH suppression, while all patients with goiter and most patients with thyrotoxicosis received replacement therapy. There was no difference in clinically decided TSH targets between DAT and controls (all patients with goiter had the same TSH target, Pearson Chi-square $p = 0.58$ for cancer and $p = 0.61$ for thyrotoxicosis).

Faster dosage adjustment with DAT in patients with goiter and cancer

For all RCT-groups together, 24 of 68 patients (35%) had reached their narrow TSH targets eight weeks after surgery if the dosage adjustment was assisted by the DAT, in contrast to 10 of 67 patients (15%) in the control group (Chi-square = 7.43, $p = 0.006$). As the applied DAT for thyrotoxic patients used a simplified population based fT4 target, in contrast to the individually estimated fT4 targets for patients with goiter and cancer, all further analysis was done on subgroups. Forty percent of patients with goiter and 59% of patients with cancer in DAT groups were within the TSH target after 8 weeks compared with 0% and 19% in control groups, respectively (Fig. 4A, Chi-squares 7.94, $p = 0.005$ and 8.87, $p = 0.003$). To make our results more comparable with other published dosage schemes, we also calculated the proportion of patients with goiter with TSH within the normal reference range rather than within the narrower TSH goal (0.5–2.0 mIU/L) used in the study. The reference range was 0.2–4.3, 0.3–3.7 or 0.4–4.5 mIU/L depending on the recruiting hospital. After 8 weeks, 80% of patients with DAT had TSH values within the normal range, which was significantly higher than 19% of controls (Chi-square 9.31, $p = 0.002$).

To evaluate how the DAT impacted the clinician's decision after two to three weeks, we classified the early adjustments as either in the ''right direction'' (toward what later became the final dosage) or in the opposite ''wrong direction,'' or as ''no change'' (Table 2). For all control groups, ''no change'' was the preferred choice, while adjustments in the right direction was far more common than wrong direction adjustments for all groups. For statistical analysis, the difference between LT4 dosage at any timepoint and the final dosage was calculated for the first 20 weeks (Fig. 4B). After 2 weeks, clinicians made significant adjustments toward the ''correct'' final dosage for patients with DAT [$t(65) = 3.31$, $p = 0.002$], but not for controls [$t(65) = 1.00$, $p = 0.32$]. Subgroup analysis revealed that the effect of DAT was present in both goiter [$t(15) = 3.16$, $p = 0.006$] and cancer [$t(27) = 3.52$, $p = 0.002$] groups. The results from control groups indicate that the experienced clinicians were not able to make significant dose adjustments based on the TSH and fT4 values from the first two weeks without assistance of the DAT. The effect of the DAT in goiter and cancer groups was reflected in the total time to reach TSH targets (Fig. 4C). The average time to reach the TSH targets in the DAT/goiter group was 105 ± 13 days compared with 162 ± 17 days in the control/goiter group [$t = t(25) = 2.59$, $p = 0.016$]. The DAT/cancer group reached TSH targets on average 87 ± 10 days after surgery, significantly shorter than 127 ± 13 days in controls [$t(49) = 2{,}48$, $p = 0.017$].

No effect of population-based DAT version for thyrotoxic patients

In the thyrotoxicosis group, we could not reliably estimate individual fT4 targets due to frequent TSH suppression. Instead, we applied a simplified DAT version with a population-based fT4 target. The number of patients who reached their TSH target after 8 weeks was not different between the DAT and control groups (Fig. 5A; Chi-square 1.63, $p = 0.20$).

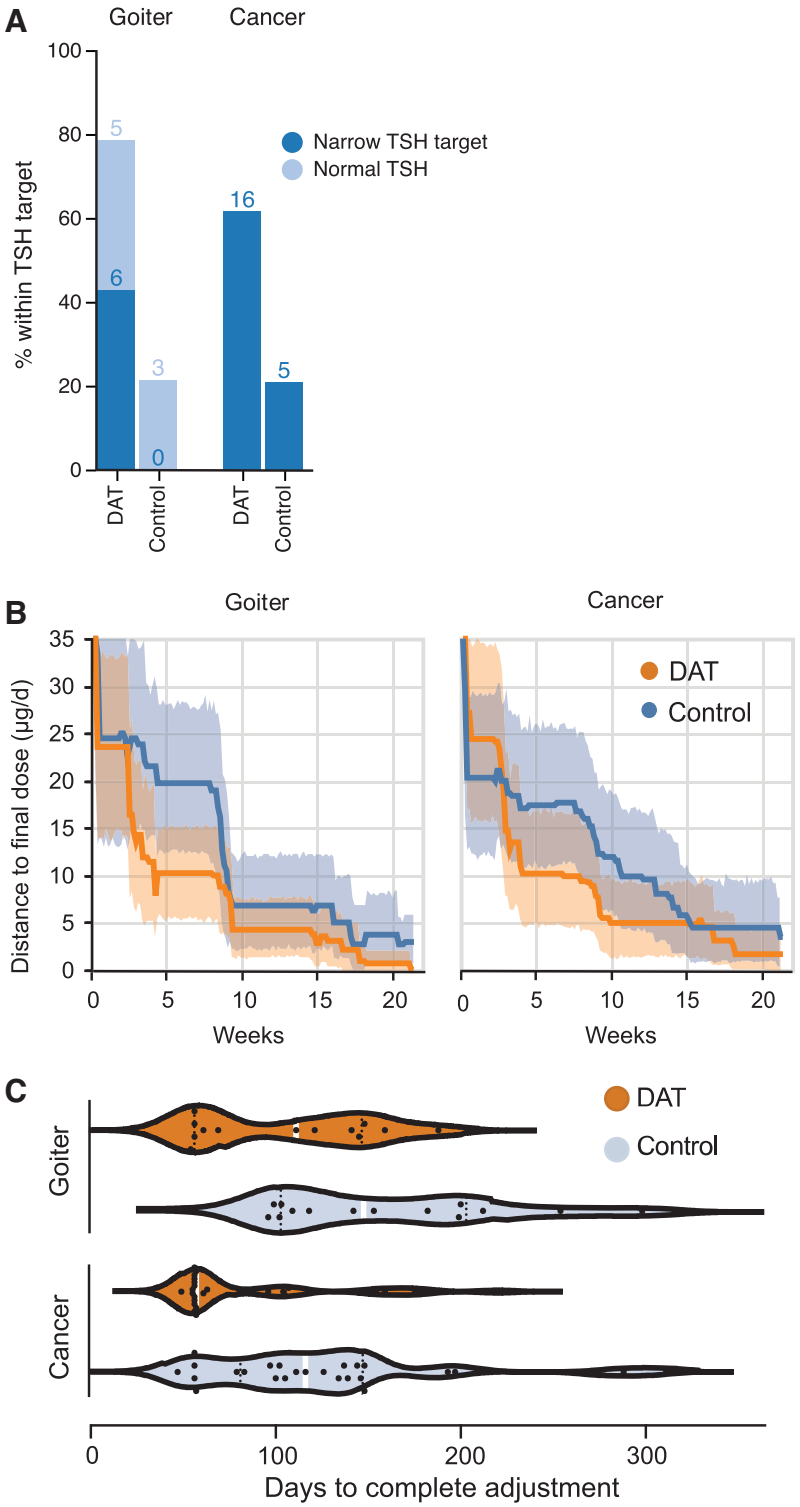

FIG. 4. Number of patients (above bars) who achieved their TSH goals eight weeks after thyroidectomy and initiation of LT4 replacement therapy. (**A**) When the DAT was applied, more patients reached their narrow TSH goal after 8 weeks in patients treated for goiter ($p=0.005$) and cancer ($p=0.003$). For goiter patients, light color illustrates the proportion of patients with TSH within the normal reference range as compared with the narrower TSH target in the study (0.5–2.0 mIU/L, dark colors). (**B**) Dynamics of LT4 dosage adjustments and total distance to reach TSH goals. Distance to final LT4 dosage during the first 20 weeks of follow-up for patients with goiter and cancer. Light colors indicate CIs. The distance to the final dosage dropped significantly after 2 weeks in DAT groups [goiter $t(15)=3.16$, $p=0.003$, cancer $t(27)=3.52$, $p=0.001$], but not in controls (n.s.). (**C**) Violin plots showing time to achieve TSH targets (black dots for individual patients). Median is indicated in white lines, and quartiles are indicated in black dotted lines. The TSH targets were reached earlier in the goiter ($p=0.016$) and cancer ($p=0.017$) groups that used the DAT. CI, confidence interval.

TABLE 2. CLASSIFICATION OF EARLY DOSAGE ADJUSTMENTS

	Goiter		*Cancer*		*Thyrotoxicosis*	
Variable	*DAT*	*Control*	*DAT*	*Control*	*DAT*	*Control*
No adjustment	3	7	5	13	6	16
Right direction	11	6	20	8	12	8
Wrong direction	1	2	2	4	5	1

The dosage adjustments that were performed after two to three weeks, based on early blood samples after thyroidectomy, showed that less adjustments were made in control groups compared with DAT groups. Most adjustments were made in the direction of the final dosage for each patient, termed ''right direction,'' while a few were made in the opposite ''wrong direction.''

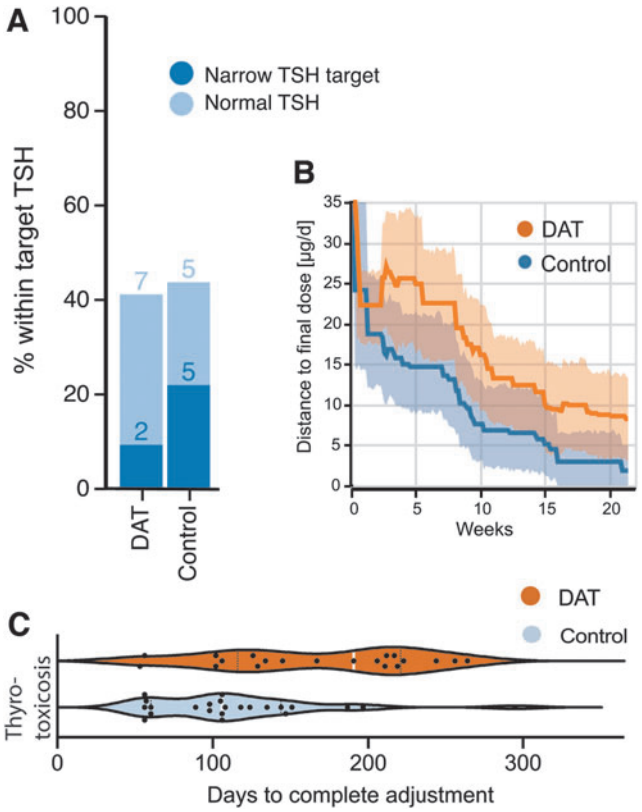

FIG. 5. Number of thyrotoxic patients (above bars) who achieved their TSH goals eight weeks after thyroidectomy and initiation of LT4 replacement therapy. (**A**) Application of a simplified DAT, which only used population-based fT4 targets, had no effect on the number of patients who reached their TSH target after eight weeks ($p = 0.20$). (**B**) Distance to final LT4 dosage during the first 20 weeks of follow-up for patients with thyrotoxicosis. Light colors indicate CI. Distance to final dosage was not significantly reduced in the DAT group after 2 weeks [$t(21) = 0.99$, $p = 0.34$]. (**C**) Violin plots for time to achieve TSH targets with black dots for individual patients. Median is indicated in white lines, and quartiles are indicated in black dotted lines. It took longer to reach the TSH targets when the simplified DAT was used, as compared with controls [$t(42) = -2{,}96$, $p = 0.005$].

The DAT group spent longer than controls to finalize dosage adjustment [182 ± 20 days vs. 115 ± 12 days, $t(42) = -2.96$, $p = 0.005$], indicating that clinicians were misinformed by the DAT for this group (Fig. 5B). Undetectable TSH levels was a significant problem in this group, as 16 out of 26 patients had TSH below the laboratory's detection level (0.01–0.05 mIU/L depending on hospital) preoperatively, of whom 10 remained with undetectable TSH values during blood samples the first 2 weeks. Excluding these 10 DAT patients from analysis eliminated the group difference regarding time to finalize dosage adjustment [$t(34) = 1.76$, $p = 0.09$].

To check whether the surgeons responsible for dosage adjustment followed the suggestions of the DAT, we calculated the difference between DAT suggestion and the actual prescribed dosage at the two-week follow-up. The deviation was 16.4 ± 4.6 µg/day in the thyrotoxicosis group, in contrast to 4.9 ± 2.3 µg/day in the goiter group and 7.7 ± 2.4 µg/day in the cancer group. There was a significant effect of group [one-way analysis of variance $F(2,64) = 4.19$, $p = 0.019$], and subsequent orthogonal testing revealed that the surgeons deviated significantly more from the suggested dosage in the thyrotoxicosis group compared with the two other groups [$t(64) = 2.47$, $p = 0.016$]. There was no significant difference between the goiter and cancer groups [$t(64) = 1.18$, $p = 0.24$].

Cost versus benefit

The average follow-up period in the study was 127 ± 6.4 days, or ~18 weeks, ranging from 47 to 468 days. The average number of postoperative blood draws in this period was 6.6 ± 0.15, and the average number of follow-up visits was 3.6 ± 0.14 (Table 3). For goiter and cancer groups, the application of the DAT reduced the number of blood draws needed [$t(25) = 2.47$, $p = 0.02$ and $t(50) = 3.14$, $p = 0.003$ respectively] and the number of follow-up visits [$t(25) = 2.16$, $p = 0.04$ and $t(50) = 3.15$, $p = 0.003$] as compared with their respective controls. As our RCT did not have a control arm with an ordinary standard of care, we made a comparison with retrospective data from a similar population operated three years before the DAT study (Supplementary Table S1). Lab records from these patients showed that the average number of blood draws before the TSH targets were reached was 8.6, which is higher than for patients in the current RCT (Supplemental Data).

TABLE 3. BIOCHEMICAL DATA

	Goiter		*Cancer*		*Thyrotoxicosis*		
Variable	*DAT*	*Control*	*DAT*	*Control*	*DAT*	*Control*	*All*
TSH preoperative (mIU/L)	1.23 ± 0.2	1.13 ± 0.2	2.88 ± 0.5	2.74 ± 0.42	0.78 ± 0.31	1.37 ± 0.57	1.77 ± 0.19
TSH 8 weeks (mIU/L)	2.03 ± 0.50	4.88 ± 2.35	0.42 ± 0.24	0.50 ± 0.15	5.75 ± 1.83	1.49 ± 0.44	2.36 ± 0.49
TSH final (mIU/L)	1.16 ± 0.18	1.15 ± 0.13	0.15 ± 0.06	0.14 ± 0.03	1.17 ± 0.23	0.95 ± 0.11	0.71 ± 0.07
fT4 preoperative (pmol/L)	16.3 ± 0.6	15.1 ± 0.5	15.8 ± 0.6	16.8 ± 0.7	22.1 ± 3.4	17.8 ± 1.4	17.6 ± 0.8
fT4 8 weeks (pmol/L)	19.0 ± 1.0	20.2 ± 1.1	24.6 ± 1.0	24.3 ± 1.3	19.3 ± 1.2	19.1 ± 0.7	21.3 ± 0.5
fT4 final (pmol/L)	19.3 ± 1.0	18.0 ± 0.9	24.3 ± 0.8	22.6 ± 0.7	20.1 ± 0.9	18.3 ± 0.4	20.8 ± 0.4
No. of postoperative blood draws	5.8 ± 0.38	7.1 ± 0.40	5.8 ± 0.17	6.9 ± 0.30	7.8 ± 0.52	6.2 ± 0.27	6.6 ± 0.15
No. of postoperative visits	3.1 ± 0.31	4.1 ± 0.34	2.8 ± 0.17	3.8 ± 0.30	4.67 ± 0.48	3.3 ± 0.25	3.6 ± 0.14

Biochemical data preoperatively, after eight weeks and at the end of the study period (final), and the total number of blood draws and follow-up visits for the validation RCT (average ± SEM). The TSH reference range for TSH was 0.2–4.3, 0.3–3.7, and 0.4–4.5 mIU/L in the three recruiting hospitals. fT4 reference range was 9–22, 12–22, and 9.5–22 pmol/L.

fT4, free thyroxine; LT4, levothyroxine; SEM, standard error of the mean.

Discussion

This is the first study to suggest LT4 dosage adjustment based on repeated fT4 and TSH measurements during the first two weeks after thyroidectomy. Application of the DAT enabled the clinician to make appropriate dosage adjustments after only two weeks. It is hard to compare the performance of our model directly against other published dosage schemes, because they all use the entire TSH reference range as goal achievement (5,6), while we used a narrower TSH target also for replacement therapy. The reason we did not include TSH range >2.0 mIU/L in our targets was that high normal TSH values are associated with comorbidity (12,28–31), and to make our TSH targets more applicable to all diagnoses in the study, including cancer. The study was thus not designed to evaluate our model against other published dosage schemes, but to evaluate whether computerized modeling would allow meaningful early LT4 dose adjustments, before a steady state is reached. When recalculating our eight-week data for patients with goiter using the entire TSH reference range as goal achievement, we found, however, that our model outperforms other published dosage schemes. Care must be taken when interpreting these data, as the number of patients is low both in our study groups and in comparable studies.

The consequences of efficient dosage adjustments after thyroidectomy in terms of work capacity, sick leave, quality of life, or other patient-reported outcomes have to be determined before we know whether a minimum of five postoperative blood draws is acceptable. The number is comparable with routine follow-up in the first author's clinic before development of the DAT (Supplemental Data). There is, however large variation in the reported number of necessary dosage adjustments after thyroidectomy (32–34), probably reflecting that optimal care is yet to be established. We believe that the advantages of the DAT outweigh the extra cost of early blood samples, for example by reducing the number of follow-up visits and shortening the dosage adjustment period. In addition, further refinement of our model could lower the number of needed samples.

The failure of the simplified DAT to improve dosage for thyrotoxic patients suggests that individual fT4-TSH estimations are necessary to achieve successful dosage with our model. The majority of the patients in the thyrotoxicosis group had a totally suppressed TSH before surgery and were still on anti-thyroid hormone drugs. Slow recovery of normal TSH dynamics after prolonged suppression made our model vulnerable to mistakes, as it relied heavily on initial blood samples. In addition, our assumption that a log-linear relationship exists between TSH and fT4 (32–34) may not be valid for this group. The overall altered metabolism in patients with Graves' disease could also be changing during the course of follow-up, making initial estimations invalid later on.

In conclusion, application of the DAT for LT4 dosage was superior to clinician dosage adjustment in patients who were euthyroid before total thyroidectomy. Further studies should include patient-reported outcome measures and investigate whether faster dosage adjustment has direct implications for health or quality of life.

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Authors' Contributions

V.H.B. and L.H. conceived the idea, developed the study design, and raised funding. L.H. and M.K. developed computational models and software. A.H.E., R.S., K.J., B.D., and R.V. collected data, and they followed up patients. A.H.E., V.H.B., and L.H. analyzed the data. V.H.B. wrote the article.

Author Disclosure Statement

No competing financial interests exist.

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Supplementary Material

Supplementary Data
Supplementary Table S1

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