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RESEARCH ARTICLE

Shift from Levothyroxine Tablets to Liquid Formulation at Breakfast Improves Quality of Life of Hypothyroid Patients

Rinaldo Guglielmi[1], Franco Grimaldi[2], Roberto Negro[3], Andrea Frasoldati[4], Irene Misischi[1], Filomena Graziano[1], Claudia Ciprì[2], Edoardo Guastamacchia[5], Vincenzo Triggiani[5,*] and Enrico Papini[1]

[1]*Department of Endocrinology and Metabolic Diseases, Ospedale Regina Apostolorum, Albano (Rome), Italy;* [2]*Endocrinology and Metabolic Disease Unit, Azienda Ospedaliero-Universitaria "S. Maria della Misericordia", Udine, Italy;* [3]*Division of Endocrinology, "V. Fazzi" Hospital, Lecce, Italy;* [4]*Endocrine Unit, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy;* [5]*Interdisciplinary Department of Medicine, Section of Internal Medicine, Geriatrics, Endocrinology and Rare Diseases. University of Bari "A. Moro", Bari, Italy*

Abstract: ***Background:*** Until recently, treatment of hypothyroidism has been accomplished using monotherapy of synthetic L-thyroxine (L-T4) sodium tablets that should be taken 30-60 minutes before breakfast. Nowadays, a liquid preparation of levothyroxine is available and can effectively replace tablets without the need of waiting before having breakfast. Evidence of Quality of life (QoL) improvement when shifting from the former to the latter preparation, however, is still lacking.

Objective: The study aimed to assess changes in QoL of hypothyroid patients dissatisfied with their therapy with L-T4 sodium tablets who were switched from tablets taken 30-60 minutes *before breakfast* to liquid L-T4 *at breakfast*.

Methods: A total of 418 consecutive hypothyroid subjects treated by means of L-T4 tablets were asked about their satisfaction/dissatisfaction in order to take the medication 30-60 minutes before having breakfast. Overall, 110 patients (26.3%) complained of the timing of their L-T4 therapy (30-60 minutes *before breakfast*). A dedicated QoL questionnaire (ThyTSQ), taking just a few minutes to be filled in was then administered to these dissatisfied patients. They were therefore switched to L-T4 to be taken *at breakfast*. Aiming to avoid TSH elevation due to L-T4 tablets malabsorption caused by meal interference and gastric pH changes, patients were invited to take L-T4 liquid form, as this is claimed to be scarcely affected by the non-fasting state. The questionnaire (ThyTSQ) was administered again at the control visit 3 months later. TSH, FT4, FT3 serum concentrations and metabolic parameters were also recorded.

Results: An improved QoL, mainly due to an easier adherence to treatment, was reported by 66.6% of 102 patients who completed the study after shifting from taking medication 30-60 minutes *before breakfast* to *at breakfast* ingestion ($P<0.01$). An overall 10.7% of patients found the liquid formulation distasteful. Mean values of TSH, FT4, FT3, and of metabolic parameters did not significantly change but in eight patients (7.7%) who showed a TSH increase > 2mIU/L

Conclusion: In hypothyroid subjects dissatisfied with L-T4 tablets ingested 30-60 minutes *before breakfast*, the shift to the same dose of L-T4 in liquid form taken *at breakfast* improved QoL in the majority of patients, without affecting thyroid function.

Keywords: Hypothyroidism, Quality of Life, Levothyroxine, replacement therapy, TSH, monotherapy, .

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1. INTRODUCTION

Hypothyroidism is a chronic disease that may adversely affect the quality of life (QoL) which is significantly improved in most but not in all patients treated with levothyroxine monotherapy (L-T4) [1-4]. Replacement therapy consists of once-a-day oral administration of L-T4 and measurement of serum TSH provides a reliable assessment of the treatment adequacy [5, 6].

Despite the simple monitoring and the easy adjustment of replacement therapy, thyroid hormone under- or over-replacement is frequent in hypothyroid subjects [7-9] with possible adverse events [10-13]. Besides the intra-individual variability of TSH levels [14, 15], changes in serum TSH are mainly due to the alteration of the intestinal absorption of L-T4 tablets that may be induced by gastro

*Address correspondence to this author at the Interdisciplinary Department of Medicine. Section of Internal Medicine, Geriatrics, Endocrinology and Rare Diseases. University of Bari "A. Moro", Bari, Italy;
Tel: 00390805478814; E-mail vincenzo.triggiani@uniba.it

enteric disorders, drugs or food ingestion [16-22]. For these reasons, L-T4 tablets should be ingested with empty stomach, 30-60 minutes before breakfast and in the absence of interfering drugs [5, 6]. Due to interference with usual morning activities, the protracted waiting time required before breakfast is a potential obstacle to the adherence to treatment. This factor may in part explain why some hypothyroid patients receiving L-T4 treatment have been reported to be dissatisfied either with their well-being and/or their treatment schedule [9, 23-26].

A liquid L-T4 form has been made commercially available in Europe in the last few years and its absorption was demonstrated to be more rapid than that of solid formulation, with a shorter time to maximum plasma concentration (Tmax, 1.94 vs. 2.42 hours) [27, 28]. This pharmacokinetics could modify the rate and extent of L-T4 absorption and might decrease the interference due to a non-fasting state [27, 29-31]. Several case-reports and clinical studies suggested that the ingestion of liquid L-T4 at breakfast or with beverages does not result in changes of serum thyroid profile [32-35] and is also associated with a decreased variability of TSH levels [35].

The aim of the present study was to evaluate any changes in QoL of patients, who, dissatisfied with taking L-T4 tablets 30-60 minutes *before breakfast*, were switched to take LT4 *at breakfast*. As it is known that the non-fasting state adversely affects L-T4 tablets' absorption resulting in elevated TSH, patients were invited to take L-T4 liquid form.

Currently, no data evaluating the impact on the QoL and the adherence to treatment with this different schedule of therapy are available.

2. METHODS

2.1. Subjects and Study Protocol

A total of 418 consecutive hypothyroid patients without interfering drug treatments, pregnancy, or known comorbidities potentially affecting L-T4 absorption, and with stable TSH levels on L-T4 replacement therapy (Eutirox® Bracco, Italy or Tirosint®, IBSA, Italy) were recruited at two Italian thyroid referral centers ("Regina Apostolorum", Albano, and "S. Maria della Misericordia", Udine) since January 2015 to January 2016. Serum TSH was considered as stable when its change in two consecutive controls during a 6-month period was lower than 0.75 mIU/L (according to the previously reported threshold of spontaneous intra-individual variability both in normal subjects and in patients with subclinical hypothyroidism) [13, 14]. During the visit, patients were asked about their satisfaction with the current treatment for underactive thyroid. Those who declared to be unsatisfied with the current treatment were proposed to switch from L-T4 30-60' *before breakfast* (tablets) to L-T4 *at breakfast* (liquid form; Tirosint® oral solution, IBSA, Italy; 25-50-75-100 mg/1-mL vials). Breakfast was defined as the first meal (that is any solid or liquid food, including tea or coffee) taken in the early morning.

A validated QoL questionnaire (ThyTSQ questionnaire) [1] was filled by the patients at baseline and 3 months after the treatment shift. ThyTSQ is a condition-specific questionnaire, taking just a few minutes to be filled in, aimed to evaluate patients' treatment experience for underactive thyroid. Patients responded to seven items by circling a number on a scale from 6 to 0 (from very satisfied to very dissatisfied), indicating their degree of satisfaction with different aspects of treatment.

Serum TSH, FT4 and FT3 measurements were obtained in a fasting state from 8:00 to 9:00 AM and L-T4 intake was delayed until after blood sampling.

TSH, FT4 and FT3 were measured using a chemiluminescence immunometric assay (Immulite 2000, Siemens Medical Solutions Diagnostics, Los Angeles, CA) with the following reference range: TSH = 0.20 to 4.0 mIU/L, analytical sensitivity = 0.004 mIU/L, inter-assay coefficient of variation = 6.0%; FT4 = 8.8 to 17.8 pg/ml, analytical sensitivity = 1.0 pg/ml, inter-assay coefficient of variation = 4.6%; FT3 = 2.3 to 4.2 pg/ml, analytical sensitivity = 0.2 pg/ml, inter-assay coefficient of variation 4.1%.

Total Cholesterol and HDL were measured with commercial kits while LDL-cholesterol level was obtained with the Friedewald formula.

3. STATISTICAL ANALYSIS

Quantitative variables are presented as mean ± SD while qualitative variables were presented as percentage of the analyzed group. Quantitative variables were analyzed using Student *t test for* paired data whereas for qualitative variables we used either chi^2 or exact Fisher tests.

As statistical software, we used SPSS version 11 (SPSS Inc).

4. RESULTS

A total of 102/110 patients who accepted to switch from *before breakfast* to *at breakfast* completed the study (5 patients missed the control visit and 3 refused the taste of the liquid LT4 formulation and returned to the previous therapy).

Modifications in the Quality of life. After changing from *before breakfast* to *at breakfast* the majority of patients (68/102, 66.6%) reported an improvement in their quality of life, whereas 23/102 (22.5%) did not report substantial change, and only 11/102 (10.7%) complained of a worsening.

Specifically, significant changes were observed in three questions (Table **1**): # 1 "How satisfied are you with the current treatment for your underactive thyroid?" (from 0.0% (0/102) at baseline to 66.6% (68/102) three months after the shift; $p< 0.01$); # 3 "How convenient have you found your treatment to be during the last three months (that is remembering to take the medication)?" (from 38.2% (39/102) to 93.0% (96/102); $p<0.01$); and # 7 "How satisfied would you be to continue with your present treatment and dose?" (from 32.3% (33/102) to 85.0% (87/102); $p< 0.01$). The other four questions did not show significant changes. Most patients decided to continue with the liquid treatment, while 11/102 (10.7%) of them found distasteful or undeserving the L-T4 solution and asked to return to tablets.

Table 1. ThyTSQ questionnaire.

Questions	Baseline	3 Months Later	P
How satisfied are you with the current treatment for your underactive thyroid?	0.0% (0/102)	66.6% (68/102)	*<0,01*
How well do you feel the treatment is working?	72,3% (73/102)	81,4% (83/102)	*0,13*
How convenient have you found your treatment to be recently (e.g. remembering to take the medication, getting prescriptions)?	38.2%(39/102)	93%(96/102)	<0.01
How satisfied are you with your understanding of your underactive thyroid?	69,8% (71/102)	78,5%(80/102)	*0,20*
Would you encourage someone else with underactive thyroid to have your kind of treatment?	72,5% (73/102)	83,4% (85/102)	*0,06*
How well do you feel that the treatment is controlling symptoms of underactive thyroid?	69,8% (71/102)	72%(76/102)	*0,53*
How satisfied would you be to continue with your present treatment and dose?	32.3% (33/102)	85% (87/102)	*0,03*

Changes in serum thyroid hormone and metabolic profile. Three months after the shift from *before breakfast* (tablet) to *at breakfast* (liquid), mean TSH, FT3, FT4 total cholesterol, LDL cholesterol, and BMI remained unchanged (Table **2**). Three months after the therapeutic shift, 12 of 102 patients (11.7%) showed an increase in their TSH level that was greater than 0.75 mIU/L. Six of these patients (5.8% of the total) had TSH increased more than 2.0 mIU/L) and 2 (1.9%) showed an increase of TSH level above the normal limits (5.2 and 4.8 mIU/L, respectively). Conversely, serum TSH decreased more than 0.75 mIU/L but remained within the normal limits in 5 subjects (4.9%). These changes were independent of baseline TSH or etiology of hypothyroidism but all patients who showed an increase in TSH reported the liquid form as distasteful and subsequently asked to return to the solid L-T4 formulation.

5. DISCUSSION

Quality of life. Hypothyroidism is characterized by signs and symptoms that may adversely affect the quality of life if inadequately treated [1-4, 9]. Few data concerning the prevalence of dissatisfaction with the traditional treatment schedule are available [23-26]. The results of our study showed that a relevant proportion (over 20%) of hypothyroid patients were dissatisfied with their replacement therapy, in particular because of the need of waiting 30-60 minutes after the ingestion of tablets for having breakfast. As for other chronic diseases, in fact, the adherence to treatment may reveal itself difficult in the long-term and the waiting time between L-T4 ingestion and breakfast may unfavorably condition the usual morning activities, thus contributing to patients' dissatisfaction. The shift to a liquid formulation at breakfast resulted in the majority (over 60%) of these dissatisfied subjects in a significant improvement of the adherence to therapy and in the perception of a greater ease of treatment as has been clearly shown comparing the answers to the questionnaire for the assessment of well being in hypothyroidism at the baseline and after 3 months from the shift. Two out of the seven questions pertain to the patient's satisfaction about treatment and its convenience. A significant proportion of patients was more satisfied and found it more convenient to take L-T4 at breakfast. They also declared that given this advantage, would like to continue the same treatment. A nearly significant proportion of patients would also encourage someone else to shift L-T4 at breakfast. However, shifting L-T4 at breakfast and exchanging tablets with liquid form did not change the sensitivity of the disease. Notably, a minority of patients found the liquid formulation distasteful, showing an increase in TSH level and asked to return to tablets.

Thyroid function test. In hypothyroid patients, the shift from solid L-T4 30 minutes before breakfast to the same dose of liquid L-T4 at breakfast resulted in no significant change in the mean values of serum TSH and FT4. This finding is in agreement with the previous studies which did not show any significant difference in thyroid hormone levels in patients either taking liquid L-T4 at breakfast or 30 minutes before breakfast, in a fasting state [32-35]. Accordingly, stability of liquid L-T4 formulation in different beverages (e.g. milk, tea, coffee) has been demonstrated [31]. Furthermore, evidence obtained from *in vivo* studies indicate that liquid L-T4 formulation may overcome different factors known to interfere with the absorption of traditional L-T4 tablets [16-20]. In our study, at variance with previous reports [32-35], an increase in serum TSH level was recorded in nearly 12% of patients after three months of liquid L-T4 treatment and in about 8% of cases, changes in TSH were greater than 2 mIU/L. Also, a minority of hypothyroid subjects (about 8%) showed a less relevant TSH decrease. These changes were apparently not associated with a history of gastro enteric disorders, peculiar breakfast habits or a poor adherence to treatment but were strongly correlated with a reported unpleasant taste of the liquid form. These data suggest that some hypothyroid subjects may have exhibited a relevant variation in TSH, probably due to poor adherence to treatment, when shifted to the liquid form. Interestingly, these data do not confirm the reduced variability in TSH levels that has been described in hypothyroid patients with the use of LT4 liquid formulation as compared to tablets [34]. Due to the potential consequences of subclinical thyroid dysfunction [36], especially in the elderly, the change from tablet to liquid formulations at breakfast [33] should be monitored.

A limitation of our study is that it does not provide any information about long-term TSH variability either in patients treated with traditional L-T4 tablets or in patients un-

Table 2. Characteristics of patients.

	Baseline	3 months later	*p*
No. of cases	102		-
Gender (F/M)	91/11		-
Age (years)	49.1±15.3		-
BMI (kg/m^2)	25,7±4,6	26,02±6	NS
Dose LT4μg (mean)	88±34,7		-
Etiology of hypothyroidism (postsurgical/autoimmune)	23/79		-
Mean TSH value (IU/mL)	2,23±1,46	2,37±1,4	NS
Mean FT4 value (pg/mL)	11,59±0,84	11,2±5,4	NS
Mean FT3 value (pg/mL)	3,1±0,55	2,99±0,69	NS
Mean total Cholesterol (mg/dL)	204,9±23	209,31±31	NS
Mean LDL cholesterol (mg/dL)	147±29	150±28	NS

der treatment with liquid L-T4 form. Thus, the reliability of our findings needs to be confirmed by further studies based on repeated TSH measurements both at baseline and after changing L-T4 form. Moreover, the clinical relevance of TSH fluctuations may be challenged; in our study, based on short follow-up period, no significant change was registered in serum metabolic parameters and in patients' BMI. Long-term longitudinal studies may help to clarify this issue. In the meanwhile, we would recommend monitoring TSH levels after the switch from L-T4 tablet to liquid L-T4 at breakfast.

Another limitation derives from the chance that the better QoL may be due to the shift from tablet to liquid form in itself. This is because there are two variables included in the study: 1) change of L-T4 timetable; 2) change from tablet to liquid form. It seems unrealistic that the better QoL is due to the liquid form in itself, as about 10% found the L-T4 solution distasteful and asked to return to the solid L-T4 formulation. So, the improvement was mostly due to the easier timetable offered by the liquid formulation.

Furthermore, well-designed studies comparing the two different formulations of L-T4, with control-groups, longer period of observation, and more adequate questionnaires exploring different aspects of QoL as well as compliance and acceptance by the patients by means of questions aiming at evaluating differences in terms of preparation, ingestion, taste, side-effects, *etc*, can further shed some light on these issues.

CONCLUSION

In summary, in our series of overt hypothyroid subjects, a non-negligible number of patients on the traditional treatment schedule with L-T4 tablets complained of unsatisfactory quality of life.

Notably, the recommended time period between the ingestion of the tablets and breakfast can be very burdensome for a relevant fraction of hypothyroid patients.

In the majority of these patients, the shift to a liquid formulation to be ingested at breakfast resulted in the perception of a greater convenience of the treatment. The change from solid L-T4 ingested in a fasting state to the same amount of liquid L-T4 at breakfast resulted in no significant change in serum thyroid profile or metabolic parameters. A minority of cases presented either an increase or, less frequently, a decrease in their TSH levels that, in general, indicate a TSH monitoring when shifting from tablet to liquid form.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was an observational study therefore, it did not require approval from ethics committee.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are bases of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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