Thyroid hormonal profile in elderly patients treated with two different levothyroxine formulations: a single institute survey

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Abstract:

Purpose: Recent evidences suggest that, despite the large use of levothyroxine (L-T4), up to 40% of patients are over-treated developing sub-clinical hyperthyroidism. We compared TSH, fT4 and fT3 serum levels of elderly patients in treatment with liquid and tablet L-T4 formulations over a period of time of five years.

Subjects: Patients were recruited by searching the database of those treated and followed at the Thyroid Unit of the University of Brescia.

Results: 299 patients (251 female, 48 male) were treated with L-T4 in tablet form (Group T) and 118 subjects (107 female, 11 male) with liquid LT4 (Group L). The two groups were super-imposable by age, median L-T4 dosage, TSH, fT4 and fT3 values. A slightly but not significantly higher BMI value was observed among patients of Group L over those of Group T (26.9±2.9 vs. 26.4±2.1, Kg/cm^2, respectively). During five years of LT-4 treatment, sub-clinical or over-hypothyroidism was found in 13 (4.3%) and 3 (2.5%) patients of Group T and Group L (p=0.335), whereas, subclinical or clinical hyperthyroidism was significantly more frequent among patients of Group T than those of Group L [69 (23%) vs. 5 (4.2%) patients, (p=0.0001)]. Logistic regression analysis showed that only the Tablets were associated with the risk of developing subclinical or hyperthyroidism [OR 2·354 (1·136–4·827), p=0.021].

Conclusions: We show a greater stability in the thyroid profile of hypothyroid elderly patients in treatment with liquid thyroxine as opposed to those being treated by tablet formulation over 5 years of follow-up.

Introduction

Thyroid hormones are crucial in controlling metabolism and have an impact on a wide array of tissues including brain, heart, muscle and bone. Thyroid dysfunction is common, with a higher frequency in women and older individuals. In the Chianti survey dysthyroidism was found in 12.9% of people aged 65 years and older, and it was independently associated with mortality [1]. Levothyroxine (L-T4) replacement therapy is having worldwide growth and in the United States it has doubled in the last ten years [2]. A similar increase has been seen in Europe, in particular in England and Wales, for elderly people [3]. Despite its widespread use, cross sectional surveys of patients taking levothyroxine have shown that between 40% and 48% are either over-treated or under-treated [4,5].

Traditionally, thyroxine is used worldwide in tablet form but new formulations in soft gel capsules or liquid formulation are now available.

The aim of this study was to compare thyroid hormonal profiles (TSH, fT4 and fT3) of elderly patients in treatment with liquid and tablet L-T4 formulations over a period of time of five years.

Materials and methods:

Patients were recruited by searching the database of those treated and followed at the Thyroid Unit of the Department of Clinical and Experimental Sciences, University of Brescia. Searching criteria was as follows: a) Age ≥ 65 years old; b) hypothyroidism in treatment with L-T4; c) euthyroidism at the time of enrolment (baseline visit); d) annual thyroid hormonal profile evaluation for the last 5 years at least; e) declared compliance to the therapy at each evaluation; f) complete personal medical history.

All patients satisfying the above criteria were enrolled in this study, and written informed consent was obtained from all subjects recruited.

Serum concentrations of free thyroxine (fT4; normal range: 8.0-19.0 pg/mL, analytical sensitivity 1 pg/mL; intra and inter-assay coefficient of variation, 2.4% and 6.8%, respectively), free triiodothyronine (fT3; normal range: 2.4-4.7; analytical sensitivity 0.35 pg/mL; intra and inter-assay coefficient of variation, 4.6% and 6.5%, respectively), and TSH (normal range: 0.4-4.5 mIU/L, analytical sensitivity 0.004 mlU/L; intra and inter-assay coefficient of variation, 2.5% and 5.7%, respectively) were measured by means of immunochemoluminiscent assays using an automated analyser (Immulite 2000, DPC Cirrus, Los Angeles, CA, USA) employing commercial kits (Diagnostic Products Corporation, Los Angeles, CA, USA).

Statistics:

Statistical analysis was performed using SPSS software (SPSS, Inc., Evanston, IL).
Comparisons between groups and differences between proportions were calculated using the ANOVA test for quantitative variables, as appropriate. A logistic analysis was performed to examine the influence of confounders (age, sex, BMI, thyroid disorder, drug therapy and levothyroxine treatment) on the developing of hyperthyroidism. Data was expressed as mean ± standard deviation.

Results:

Among patients in treatment with L-T4, 417 subjects (358 female, 59 male) satisfied the inclusion criteria and were recruited into this study; 299 patients (251 female, 48 male) were treated with L-T4 in tablet form (Group T) and 118 subjects (107 female, 11 male) were in replacement therapy with liquid LT4 (Group L) (IBSA Farmaceutici Italia srl, Italy). Patients in the two Groups were on the respective treatment from when they were diagnosed as hypothyroid, and were never switched from one treatment to the other one. Table 1 showed clinical and biochemical parameters of patients on recruitment.

The two groups were super-imposable by age, median L-T4 dosage, TSH, fT4 and fT3 values. A slightly but not significantly higher BMI value was observed among patients of Group L over those of Group T (26.9±2.9 vs. 26.4±2.1, Kg/cm^2, respectively).

Hashimoto's thyroiditis was the cause of hypothyroidism in 258 subjects (86.2%) of Group T and in 100 (84.7%) of Group L, whereas thyroidectomy was the cause of benign multinodular goitre in 41 (13.8%) and 18 (15.3%) patients of Group T and L, respectively.

The median dosage of levothyroxine was super-imposable between the two groups of patients [89.8±11.5 µg/day (Group T) vs 90.4±10.6 µg/day (Group L), p=0.888, respectively]. No significant change in BMI was observed among the patients in each group from baseline to the end of the study [Group T: 26.4±2.1 vs 26.5±2.4 (Kg/cm^2), p=0.620; Group L: 26.9±2.9 vs 26.7±2.6 (Kg/cm^2), p=0.578], and the two groups at the end of the study [26.5±2.4 Kg/cm^2 (Group T) vs. 26.7±2.6 Kg/cm^2 (Group L) p=0.468]. During five years of LT-4 treatment, 90/417 (21.6%) patients (82 and 8 subjects of Group T and Group L, respectively) showed an abnormal thyroid hormonal profile.

In detail, sub-clinical or over-hypothyroidism was found in 13 (4.3%) and 3 (2.5%) patients of Group T and Group L (p=0.335). On the other hand, sub-clinical or clinical hyperthyroidism was significantly more frequent among patients of Group T than those of Group L [69 (23%) vs. 5 (4.2%) patients, p<0.001] **(figure 1). Treatment with Tablet formulation increased in fact the risk to develop TSH suppression (relative risk 4.6, 95 percent confidence interval, 1.9 to 7.7,**

p<0.001). When analyzing the above outcomes on the basis of the thyroid disorder (Hashimoto's thyroiditis and thyroidectomy), the findings were not statistically significant.

A logistic regression analysis, taking into account age, gender, BMI, thyroid disorder, concomitant drugs therapy and levothyroxine treatment, showed that only the Tablets were associated with the risk of developing subclinical or hyperthyroidism [OR 2·354 (1·136–4·827), p=0.021] (Table2).

Discussion:

The present study confirms and extends the data of Negro et al [6], showing a greater stability of thyroid hormonal profile among hypothyroid elderly patients taking liquid L-T4 than those taking tablets over a period of time of five years. In particular, subclinical or hyperthyroidism is significantly lower among our patients treated with liquid L-T4 over five years of replacement therapy. This is of particular interest in old patients (≥ 65 years old) for the well documented increase risk to developing heart disease, osteoporosis, bone fracture and cognitive impairment [7-10].

Thyroid disorders are common in the elderly and are associated with significant morbidity if untreated [8]. Despite the large use of levothyroxine, it has been shown that up to 40% of patients are over-treated developing sub-clinical hyperthyroidism [4,5]. This condition is well known to be associated with an increased risk of developing many other disorders. In a recent review, Biondi recommended treating subclinical hyperthyroidism in elderly patients for the increased risk of atrial fibrillation, osteoporosis and bone fractures and for the higher risk of progression to overt disease [8]. Moreover, Collet and colleagues, have clearly demonstrated from 52,674 participants that subclinical hyperthyroidism is also associated with an increased risk of total coronary heart disease mortality [9].

Also cognitive aspects do not seem to be immune to low values of serum thyreotropin. Moon JH et al. have in fact recently shown that low TSH levels are associated with the development or progression of cognitive impairment including dementia in elderly [10]. For all these reasons prolonged TSH stability in patients in substitutive L-T4 treatment is mandatory.

Traditionally, thyroxine is used worldwide in tablet (also generic) form but new formulations in soft gel capsule or liquid formulation are now available. We have no experience with generic L-T4, but a few reports have concluded that generic and branded thyroxine do not seem bioequivalent [11,12]. Prospective double blind studies are needed to clarify this important issue.

On the other hand, many reports have shown an increased absorption rate with liquid L-T4 formulation as opposed to tablet form both in adults and in children [13-16].

Also our Group has recently shown that oral liquid L-T4 could diminish the problem of L-T4 malabsorption caused by coffee when using traditional tablet formulations [17]. In agreement with our data, Bernareggi et al. demonstrated that liquid L-T4 is stable in many beverages for at least after 20 min incubation [18].

In theory, a better absorption could mean the possibility of developing subclinical or overt hyperthyroidism more frequently. Cassio et al. have recently observed, in a small number of infants with congenital hypothyroidism, a more frequent suppression of TSH among patients treated with liquid formulation, suggesting that liquid form is more efficacious than tablet form which has to be crushed and thereby undergoing a process that might cause some loss of the drug [15]. On the contrary, our study shows greater TSH stability among hypothyroid elderly patients treated with liquid rather than tablet formulations over five years of follow-up (93.2% vs 75.9 %, respectively), particularly in the development of subclinical or over hyperthyroidism (4.2% vs 23%, $p<0.001$, respectively). The fact that median dosage of L-T4 was super-imposable between the two groups ($p=0.888$) and moreover that no change in BMI was observed among the patients of each group and between the groups strengthens our results. Moreover, multi-variation analysis demonstrated that only patients in replacement therapy with tablet formulation are at risk of developing TSH suppression ($p=0.021$). Differently from the study of Cassio and colleagues [15], in which thyroid function tests were performed at 15 and 30 days and at 3 and 6 months after the beginning of therapy, our data has been collected on an annual basis. Even if we have no data on TSH, fT4 and fT3 in the short period (6 months), our results clearly show a greater TSH profile (with significantly lower prevalence of iatrogenic hyperthyroidism) in older people in long term liquid L-T4 treatment.

Unfortunately, the small number of patients of Group L who developed sub-or hyperthyroidism [5 (4.2%) patients] do not permit us to reach any conclusion about the development of atrial fibrillation or coronary heart disease or other disorders related to this condition. Ongoing speculation about this possibility would make it easy to think that good stability in thyroidal replacement therapy with

a low incidence of hyperthyroidism could be related to lower prevalence of adverse effects associated with such formulation. This is particularly relevant if you consider the large number of elderly patients taking levothyroxine worldwide, and the fact that half of them show altered TSH values during a lifetime treatment with L-T4. Further studies are needed to clarify this important issue.

In conclusion, we show a greater stability in the thyroid profile of hypothyroid elderly patients in treatment with liquid thyroxine as opposed to those being treated by tablet formulation over a period of time of five years.

Key words: TSH, levothyroxine, euthyroidism, hormonal profile, liquid formulation

Refererences:

1. Ceresini G[1], Ceda GP, Lauretani F, Maggio M, Usberti E, Marina M, et al. Thyroid status and 6-year mortality in elderly people living in a mildly iodine-deficient area: the aging in the Chianti Area Study. J Am Geriatr Soc *2013;* 61, 868-74.

2. IMS Institute for Healthcare Informatics. The use of medicines in the United States: review of 2010. April 2011: report by the IMS Institute for Healthcare Informatics. http://www.imshealth.com/imshealth/Global/Content/IMS%20Institute/Documents/IHII_UseOfMed_report%20.

3. Mitchell AL, Hickey B, Hickey JL, Pearce SH. Trends in thyroid hormone prescribing and consumption in the UK. BMC Public Health 2009; 9**,** 132.

4. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado Thyroid Disease Prevalence Study. Arch Intern Med 2000; 160, 526-34.

5. Parle JV, Franklyn JA, Cross KW, Jones SR, Sheppard MC. Thyroxine prescription in the community: serum thyroid stimulating hormone level assays as an indicator of undertreatment or overtreatment. Br J Gen Pract 1993; 43, 107-9.

6. Negro R, Valcavi R, Agrimi D, Toulis KA. Levothyroxine liquid solution versus tablet for replacement treatment in hypothyroid patients. Endocr Pract. 2014; 1, 1-20.

7. Rehman SU, **Cope** DW, Senseney AD, Brzezinski W. Thyroid disorders in elderly patients. SouthMed J 2005; 98, 543-49.

8. Biondi B. Natural history, diagnosis and management of subclinical thyroid dysfunction. Best Pract Res Clin Endocrinol Metab 2012; 26, 431-46.

9. Collet TH, Gussekloo J, Bauer DC, den Elzen WP, Cappola AR, Balmer P, et al. Thyroid Studies Collaboration. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. Arch Intern Med 2012; 172, 799-809.

10. Moon JH[1], Park YJ, Kim TH, Han JW, Choi SH, Lim S, et al. Lower-but-normal serum TSH level is associated with the development or progression of cognitive impairment including mild cognitive impairment and dementia in elderly: A result from Korean Longitudinal Study on Health and Aging (KLoSHA). J Clin Endocrinol Metab 2014; 99, 424-32.

11. Carswell JM, Gordon JH, Popovsky E, Hale A, Brown RS. Generic and brand-name L-thyroxine are not bioequivalent for children with severe congenital hypothyroidism. J Clin Endocrinol Metab 2013; 98, 610-17.

12. Bolton S. Bioequivalence studies for levothyroxine. *AAPS J* 2005; 7, E47-53.

13. Brancato D, Scorsone A, Saura G, Ferrara L, Di Noto A, Aiello V, et al. Comparison of TSH Levels with Liquid Formulation Versus Tablet Formulations of Levothyroxine in the Treatment of Adult Hypothyroidism. Endocr Pract 2014; 21, 1-17.

14. Peroni E, Vigone MC, Mora S, Bassi LA, Pozzi C, Passoni A, et al. Congenital Hypothyroidism Treatment in Infants: A Comparative Study between Liquid and Tablet Formulations of Levothyroxine. Horm Res Paediatr 2014; 81, 50-4.

15. Cassio A, Monti S, Rizzello A, Bettocchi I, Baronio F, D'Addabbo G, et al. Comparison between liquid and tablet formulations of levothyroxine in the initial treatment of congenital hypothyroidism. J Pediatr 2013;**162,** 1264-9.

16. Pirola I, Daffini L, Gandossi E, Lombardi D, Formenti A, Castellano M, et al. Comparison between liquid and tablet levothyroxine formulations in patients treated through enteral feeding tube. J Endocrinol Invest 2014; [Epub ahead of print]

17. Cappelli C, Pirola I, Gandossi E, Formenti A, Castellano M. Oral liquid levothyroxine treatment at breakfast: a mistake? Eur J Endocrinol 2013; 170, 95-9.

18. Bernareggi A, Grata E, Pinorini MT, Conti A. Oral liquid formulation of levothyroxine is stable in breakfast beverages and may improve thyroid patient compliance. *Pharmaceutics*, 2013;**5,** 621-33.

Table 1. Clinical and biochemical parameters of patients at recruitment

	Group T (299 patients)	**Group L (118 patients)**	**P value**
Age (yrs)	71±6.8	72.1±6.1	0.127
BMI (Kg/cm^2)	26.4±2.1	26.9±2.9	0.051
L-T4 dosage (mcg/Kg/day)	1.9±0.4	1.8±0.9	0.117
TSH (mUI/L)	3.0±1.1	2.9±1.7	0.479
fT4 (pg/mL)	10.8±1.9	11.0±2.8	0.402
fT3 (pg/mL)	3.2±0.5	3.3±0.7	0.103

Table 2. Logistic regression analysis of developing subclinical or hyperthyroidism in the study population.

	Odds ratio (95% CI)	**P value**
Age (yrs)	1·00 (0·96–1·05)	NS
Gender (female)	1·51 (0·76–3·01)	NS
BMI (Kg/cm^2)	0·54 (0·25–1·10) NS	NS
Thyroid disorder (Hashimoto thyroiditis)	0·72 (0·36–1·56) NS	NS
Concomitant Drugs therapy	0·56 (0·25–1·10)	NS
Levothyroxine (tablets)	2·35 (1·14–4·83)	0.021

Figure 1. Schematic diagram of the study design and data collection