

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

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1 **Abstract:**

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

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

8 **Results:** 299 patients (251 female, 48 male) were treated with L-T4 in tablet form (Group T) and
9 118 subjects (107 female, 11 male) with liquid LT4 (Group L). The two groups were super-
10 imposable by age, median L-T4 dosage, TSH, fT4 and fT3 values. A slightly but not significantly
11 higher BMI value was observed among patients of Group L over those of Group T (26.9 ± 2.9 vs.
12 26.4 ± 2.1 , Kg/cm², respectively). During five years of LT-4 treatment, sub-clinical or over-
13 hypothyroidism was found in 13 (4.3%) and 3 (2.5%) patients of Group T and Group L ($p=0.335$),
14 whereas, subclinical or clinical hyperthyroidism was significantly more frequent among patients of
15 Group T than those of Group L [69 (23%) vs. 5 (4.2%) patients, ($p=0.0001$)]. Logistic regression
16 analysis showed that only the Tablets were associated with the risk of developing subclinical or
17 hyperthyroidism [OR 2.354 (1.136–4.827), $p=0.021$].

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

1 **Introduction**

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

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

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

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1 **Materials and methods:**

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

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

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

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19 **Statistics:**

20 Statistical analysis was performed using SPSS software (SPSS, Inc., Evanston, IL).

21 Comparisons between groups and differences between proportions were calculated using the
22 ANOVA test for quantitative variables, as appropriate. A logistic analysis was performed to
23 examine the influence of confounders (age, sex, BMI, thyroid disorder, drug therapy and
24 levothyroxine treatment) on the developing of hyperthyroidism. Data was expressed as mean \pm
25 standard deviation.

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1 **Results:**

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

9 The two groups were super-imposable by age, median L-T4 dosage, TSH, fT4 and fT3 values. A
10 slightly but not significantly higher BMI value was observed among patients of Group L over those
11 of Group T (26.9±2.9 vs. 26.4±2.1, Kg/cm², respectively).

12 Hashimoto's thyroiditis was the cause of hypothyroidism in 258 subjects (86.2%) of Group T and in
13 100 (84.7%) of Group L, whereas thyroidectomy was the cause of benign multinodular goitre in 41
14 (13.8%) and 18 (15.3%) patients of Group T and L, respectively.

15 The median dosage of levothyroxine was super-imposable between the two groups of patients
16 [89.8±11.5 µg/day (Group T) vs 90.4±10.6 µg/day (Group L), p=0.888, respectively]. No significant
17 change in BMI was observed among the patients in each group from baseline to the end of the
18 study [Group T: 26.4±2.1 vs 26.5±2.4 (Kg/cm²), p=0.620; Group L: 26.9±2.9 vs 26.7±2.6 (Kg/cm²),
19 p=0.578], and the two groups at the end of the study [26.5±2.4 Kg/cm² (Group T) vs. 26.7±2.6
20 Kg/cm² (Group L) p=0.468]. During five years of LT-4 treatment, 90/417 (21.6%) patients (82 and 8
21 subjects of Group T and Group L, respectively) showed an abnormal thyroid hormonal profile.

22 In detail, sub-clinical or over-hypothyroidism was found in 13 (4.3%) and 3 (2.5%) patients of
23 Group T and Group L (p=0.335). On the other hand, sub-clinical or clinical hyperthyroidism was
24 significantly more frequent among patients of Group T than those of Group L [69 (23%) vs. 5
25 (4.2%) patients, p<0.001] (**figure 1**). **Treatment with Tablet formulation increased in fact the**
26 **risk to develop TSH suppression (relative risk 4.6, 95 percent confidence interval, 1.9 to 7.7,**

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

3 A logistic regression analysis, taking into account age, gender, BMI, thyroid disorder, concomitant
4 drugs therapy and levothyroxine treatment, showed that only the Tablets were associated with the
5 risk of developing subclinical or hyperthyroidism [OR 2.354 (1.136–4.827), p=0.021] (Table2).

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1 **Discussion:**

2 The present study confirms and extends the data of Negro et al [6], showing a greater stability of
3 thyroid hormonal profile among hypothyroid elderly patients taking liquid L-T4 than those taking
4 tablets over a period of time of five years. In particular, subclinical or hyperthyroidism is
5 significantly lower among our patients treated with liquid L-T4 over five years of replacement
6 therapy. This is of particular interest in old patients (≥ 65 years old) for the well documented
7 increase risk to developing heart disease, osteoporosis, bone fracture and cognitive impairment [7-
8 10].

9 Thyroid disorders are common in the elderly and are associated with significant morbidity if
10 untreated [8]. Despite the large use of levothyroxine, it has been shown that up to 40% of patients
11 are over-treated developing sub-clinical hyperthyroidism [4,5]. This condition is well known to be
12 associated with an increased risk of developing many other disorders. In a recent review, Biondi
13 recommended treating subclinical hyperthyroidism in elderly patients for the increased risk of atrial
14 fibrillation, osteoporosis and bone fractures and for the higher risk of progression to overt disease
15 [8]. Moreover, Collet and colleagues, have clearly demonstrated from 52,674 participants that
16 subclinical hyperthyroidism is also associated with an increased risk of total coronary heart disease
17 mortality [9].

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

22 Traditionally, thyroxine is used worldwide in tablet (also generic) form but new formulations in soft
23 gel capsule or liquid formulation are now available. We have no experience with generic L-T4, but
24 a few reports have concluded that generic and branded thyroxine do not seem bioequivalent
25 [11,12]. Prospective double blind studies are needed to clarify this important issue.

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

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

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

24 Unfortunately, the small number of patients of Group L who developed sub-or hyperthyroidism [5
25 (4.2%) patients] do not permit us to reach any conclusion about the development of atrial fibrillation
26 or coronary heart disease or other disorders related to this condition. Ongoing speculation about
27 this possibility would make it easy to think that good stability in thyroidal replacement therapy with

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

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

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

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1 **Table 1.** Clinical and biochemical parameters of patients at recruitment

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	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

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

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

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