FoRiSIE Winter School in Clinical Endocrinology
8-11 gennaio 2020 - Roma

LA TERAPIA SOSTITUTIVA E SOPPRESSIVA CON L-TIROXINA: QUANDO E QUALE

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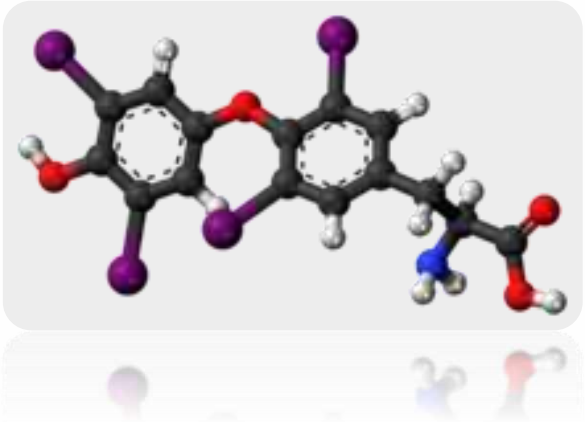
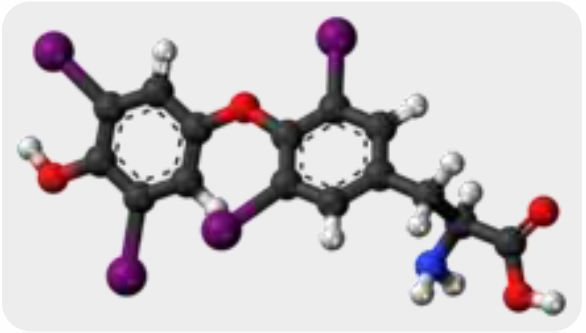
Definition

LT4 as a pharmacological compound is synthesized to be identical to the natural hormone, and, for that reason, is generally well tolerated when used correctly



History of levo-thyroxine



1914 → 1927 → 1949

*Thyroxine was first isolated in pure form in **1914** at the Mayo Clinic by Edward Calvin Kendall from extracts of hog thyroid glands*

*The hormone was synthesized in **1927** by British chemists Charles Robert Harington and George Barger*

*In **1949**, a commercial product containing synthesized sodium thyroxine was launched in the USA and some years later in Europe*

List of the most prescribe drugs

1 **Lisinopril** *ACEi* **Antihypertensive** **PO** ADR: CV, CNS ***BB: Pregnancy***	2 **Levothyroxine** *Hypothyroidism* **PO** ADR: CV, CNS ***BB: Weight Loss***	3 **Atorvastatin** *HMG-CoA Reductase Inhibitor* **Antihyperlipidemic** **PO** ADR: GI, Neuromuscular	4 **Metformin** *Biguanide* **Antidiabetic** **PO** ADR: GI, Diarrhea ***BB: Lactic Acidosis***	5 **Simvastatin** *HMG-CoA Reductase Inhibitor* **Antihyperlipidemic** **PO** ADR: CV, CNS	6 **Omeprazole** *PPI* **Anti-GERD** **PO** ADR: Carcinoma, CDAD	7 **Amlodipine Besylate** *CCB* **Antihypertensive** **PO** ADR: CV, Respiratory	8 **Metoprolol** *Beta Blocker* **Antihypertensive** **PO** ADR: CV, Dermatologic ***BB: CI***	9 **Acetaminophen; Hydrocodone** *Opioid* **Analgesic** **PO** ADR: CV, CNS ***BB: Respiratory Depression***	10 **Albuterol** *Beta-2 Agonist* **Bronchodilator** **Inh.** ADR: Respiratory, CNS
11 **Hydrochlorothiazide** *Diuretic* **Antihypertensive** **PO** ADR: CV, Endocrine	12 **Losartan** *ARB* **Antihypertensive** **PO** ADR: Respiratory ***BB: Fetal Toxicity***	13 **Gabapentin** *Anticonvulsant* **PO** ADR: CNS, Viral infection	14 **Sertraline** *SSRI* *Antidepressant* **PO** ADR: CNS, GI ***BB: Suicidal Thoughts***	15 **Furosemide** *Loop Diuretic* **Antihypertensive** **PO** ADR: CV, Endocrine ***BB: Electrolyte Loss***	16 **Acetaminophen** **Analgesic** **PO** ADR: Endocrine, Renal ***BB: Hepatotoxicity***	17 **Atenolol** *Beta Blocker* **Antihypertensive** **PO** ADR: CV, CNS ***BB: Abrupt Withdrawal***	18 **Pravastatin** *HMG-CoA Reductase Inhibitor* **Antihyperlipidemic** **PO** ADR: CV, CNS	19 **Amoxicillin** *Antibiotic* **PO** ADR: CV, GI	20 **Fluoxetine** *SSRI* *Antidepressant* **PO** ADR: CNS, GI ***BB: Suicidal Thoughts***
21 **Citalopram** *SSRI* *Antidepressant* **PO** ADR: CNS, GI ***BB: Suicidal Thoughts***	22 **Trazodone** *SSRI* *Antidepressant* **PO** ADR: CNS, GI ***BB: Suicidal Thoughts***	23 **Alprazolam** *Benzodiazepine* *Antianxiety* **PO** ADR: CNS ***BB: Concomitant with Opioids***	24 **Fluticasone** *Corticosteroid* **Nasal** ADR: CNS	25 **Bupropion** *Dopamine/Norepinephrine Reuptake Inhibitor* *Antidepressant* **PO** ADR: CV, CNS ***BB: Suicidal Thoughts***	26 **Carvedilol** *Beta Blocker* **Antihypertensive** **PO** ADR: CV, CNS	27 **Potassium Chloride** **Electrolyte Supplement** **PO** ADR: Dermatologic, Endocrine	28 **Tramadol** **Opioid** **Analgesic** **PO** ADR: CNS, GI ***BB: Respiratory Depression***	29 **Pantoprazole** *PPI* *Anti-GERD* **PO** ADR: CNS	30 **Montelukast** *Leukotriene Receptor Antagonist* **Anti-asthmatic** **PO** ADR: CNS, Dermatologic
31 **Escitalopram** *SSRI* *Antidepressant* **PO** ADR: CNS, GI ***BB: Suicidal Thoughts***	32 **Prednisone** *Corticosteroid* **Anti-inflammatory** **PO** ADR: CV, Endocrine	33 **Rosuvastatin** *HMG-CoA Reductase Inhibitor* **Antihyperlipidemic** **PO** ADR: Neuromuscular	34 **Ibuprofen** *NSAID* **Analgesic** **PO** ADR: CV, GI ***BB: Thrombotic events***	35 **Meloxicam** *NSAID* **Analgesic** **PO** ADR: CNS, GI ***BB: Thrombotic Events***	36 **Insulin Glargine** **Antidiabetic** **Inj.** ADR: Primarily Hypoglycemia	37 **Hydrochlorothiazide & Lisinopril** *ACEi/Diuretic* **Antihypertensive** **PO** ADR: CV, CNS ***BB: Fetal Toxicity***	38 **Clonazepam** *Benzodiazepine* *Anticonvulsant* **PO** ADR: CNS ***BB: Concomitant with Opioids***	39 **Aspirin** *Salicylate* **Antiplatelet** **PO** ADR: CV, CNS	40 **Clopidogrel** **Antiplatelet** **PO** ADR: Hematologic, Dermatologic ***BB: CYP2C9 Poor Metabolizer***
41 **Glipizide** *Sulfonylurea* **Antidiabetic** **PO** ADR: CNS, Dermatologic	42 **Warfarin** **Anticoagulant** **PO** ADR: Hematologic, CV ***BB: Bleed Risk***	43 **Cyclobenzaprine** *Muscle Relaxant* **Analgesic** **PO** ADR: CNS, GI	44 **Insulin Human** **Antidiabetic** **Inj.** ADR: CV, Endocrine	45 **Tamsulosin** *Alpha-1-Antagonist* **Urinary Retention** **PO** ADR: CV, CNS	46 **Zolpidem** **Hypnotic** **PO** ADR: CNS	47 **Ethinyl Estradiol; Norgestimate** **Contraceptive** **PO** ADR: CV, CNS ***BB: Cigarette Smoking***	48 **Duloxetine** *SNRI* *Antidepressant* **PO** ADR: CNS, GI ***BB: Suicidal Thoughts***	49 **Ranitidine** *Histamine H2 Antagonist* **Antiulcerant** **PO** ADR: CV, CNS	50 **Venlafaxine** *SNRI* *Antidepressant* **PO** ADR: CNS, Dermatologic ***BB: Suicidal Thoughts***

Pharmacy **2018**, 6, 43;

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LA TERAPIA SOSTITUTIVA E SOPPRESSIVA CON L-TIROXINA: QUANDO E QUALE

When is administration of levothyroxine necessary?

- ✓ Hypothyroidism is a chronic disease associated with deficiency in the thyroid hormones, thyroxine (T4) and triiodothyronine (T3).
- ✓ In Europe, the estimated prevalence of overt (i.e. symptomatic) hypothyroidism in the general population is 0.2–5.3%
- ✓ Primary hypothyroidism is up to 8–9 times more common in women than in men, and the prevalence increases with age, with a peak incidence between the ages of 30 and 50 years

Luca Chiovato et al, *Adv Ther (2019)* 36:S47–S58

AETIOLOGY OF HYPOTHYROIDISM

In over 99% of cases, hypothyroidism is caused by a failure of the thyroid gland to produce thyroid hormones (primary hypothyroidism). Central hypothyroidism, account for less than 1% of cases

Subtypes of primary hypothyroidism:

- ***Autoimmune hypothyroidism (84.4%)***
- *Post-partum (4.7%)*
- *Amiodarone-induced hypothyroidism (4.0%)*
- *Subacute thyroiditis (1.8%)*
- *Previous radiation or surgery (1.8%)*
- *Congenital hypothyroidism (1.6%)*
- *Lithium-associated (1.6%)*
- ***Nowadays, iatrogenic causes have become more frequent due to various immunotherapies***

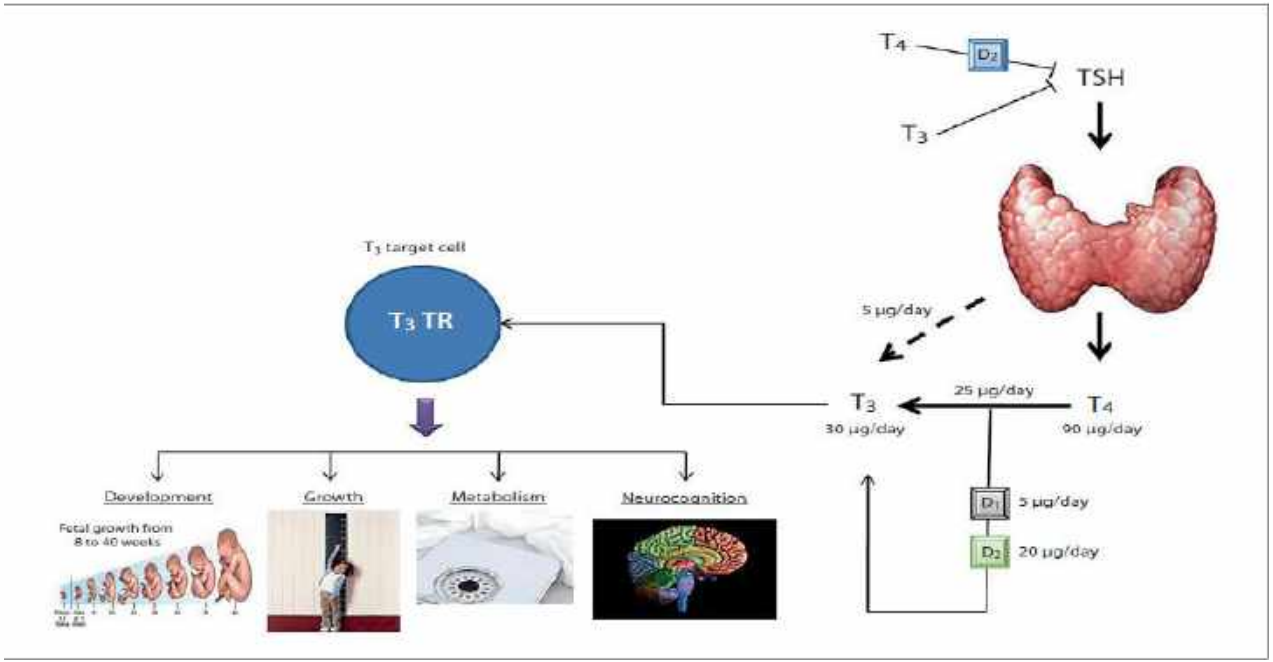
Luca Chiovato et al*, Adv Ther (2019)* 36:S47–S58

Standard Treatment of hypothyroidism

Guidelines/ Position steatment	*Indications*
AACE/ATA guidelines 2012[1]	LT4 is recommended
ETA guidelines 2012 [2]	LT4 is recommended
ATA Guidelines 2014[3]	LT4 is recommended
British steatment 2016[4]	LT4 is recommended
Italian steatment 2016[5]	LT4 is recommended

[1]Garber Jr et al, Thyroid 2012, [2]Wiersinga WM et al, Eur Thyroid J 2012, [3]Joanklaas J et al, Thyroid 2014, [4]Okosieme aet al Clinical Endocrinology 2016, [5]Biondi et al, J Edocrinol Invest 2016

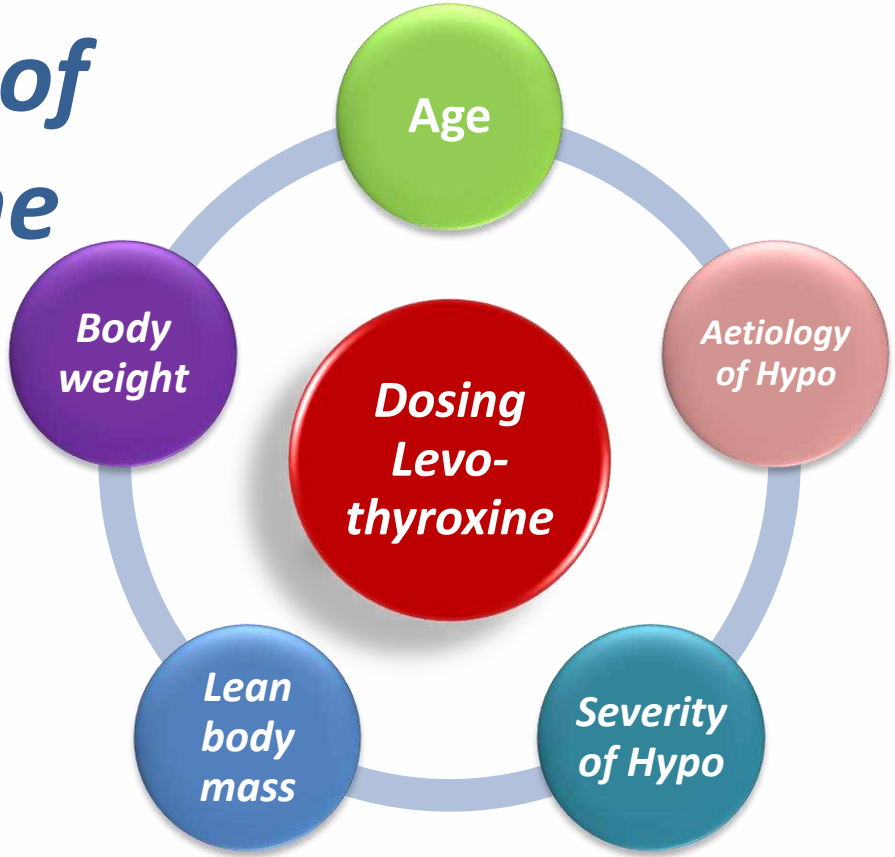
Why is L-T4 monotherapy considered to be the standard of care for hypothyroidism?



Antonio C. Bianco and Sabina Casula, Eur Thyroid J 2012;1:88–98

Initial dosing of levo-thyroxine

Dose required by a patient depends primarily on several factors:



Jonklaas J et al Thyroid. 2014;24(12):1670–751.

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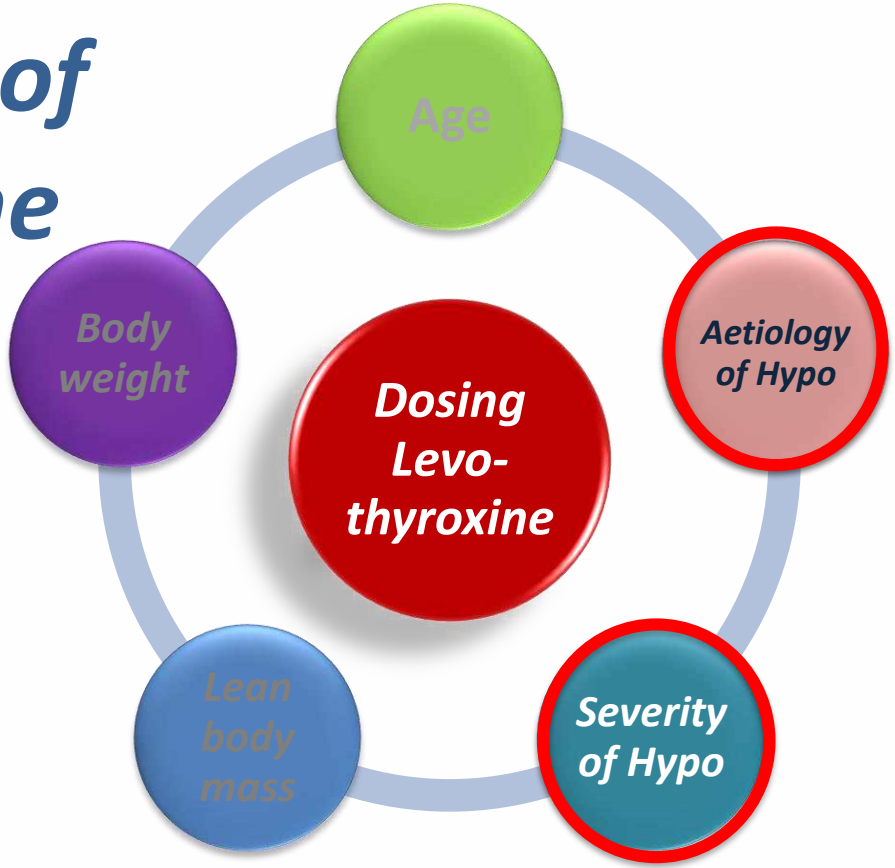

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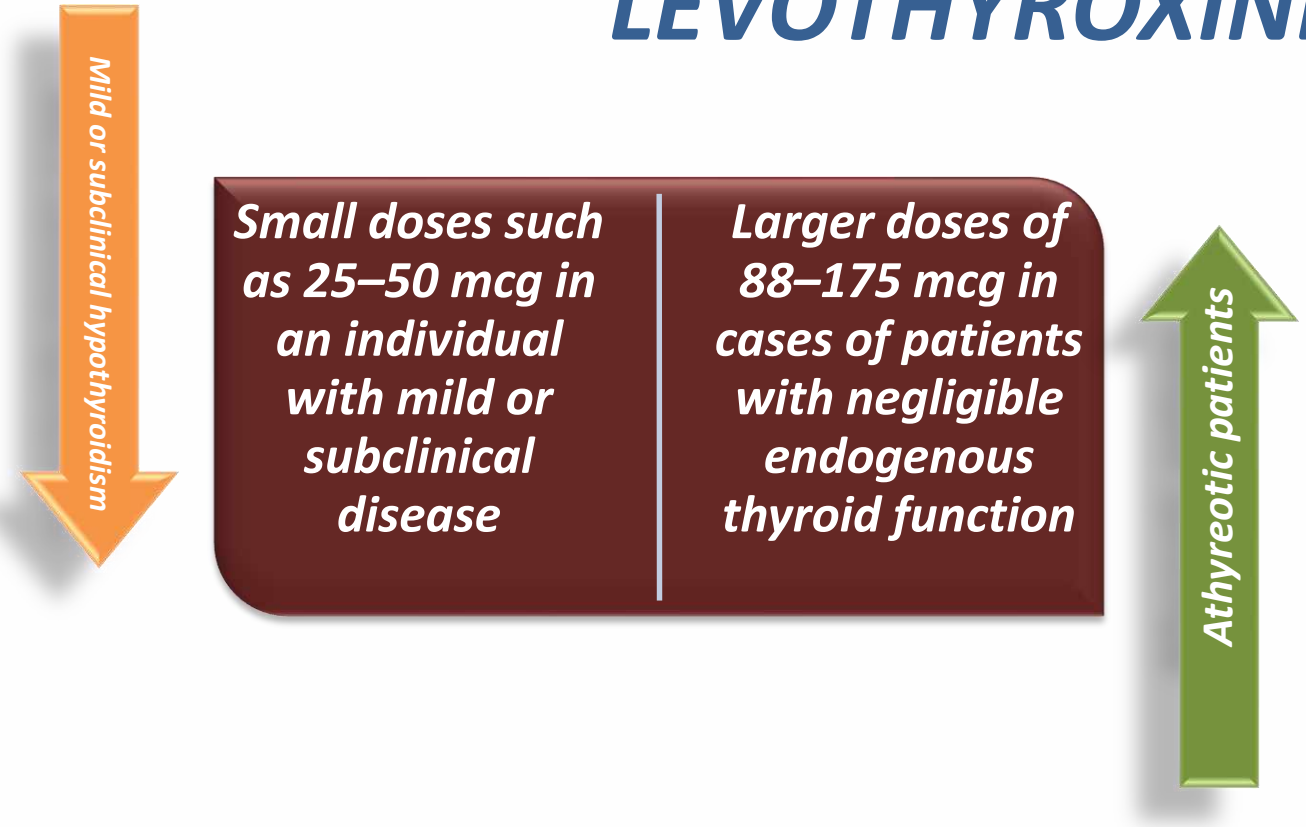
INITIAL DOSING OF LEVOTHYROXINE



Leonidas H. Duntas . Jacqueline Jonklaas, Adv Ther (2019) 36:S30–S46

Initial dosing of levo-thyroxine

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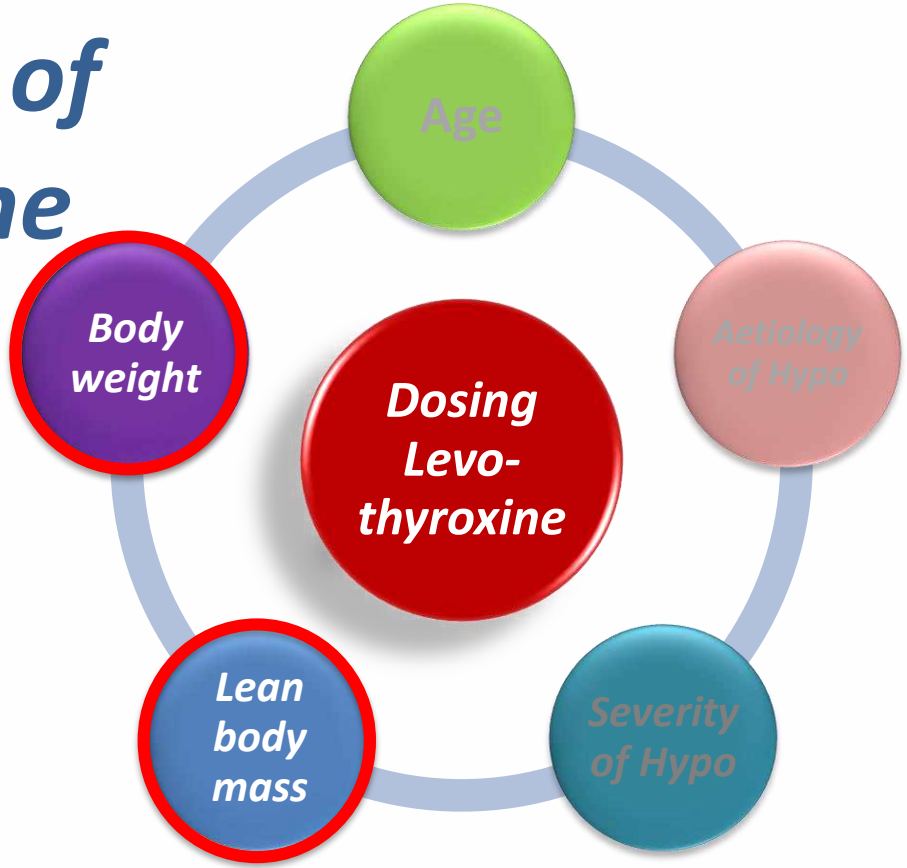
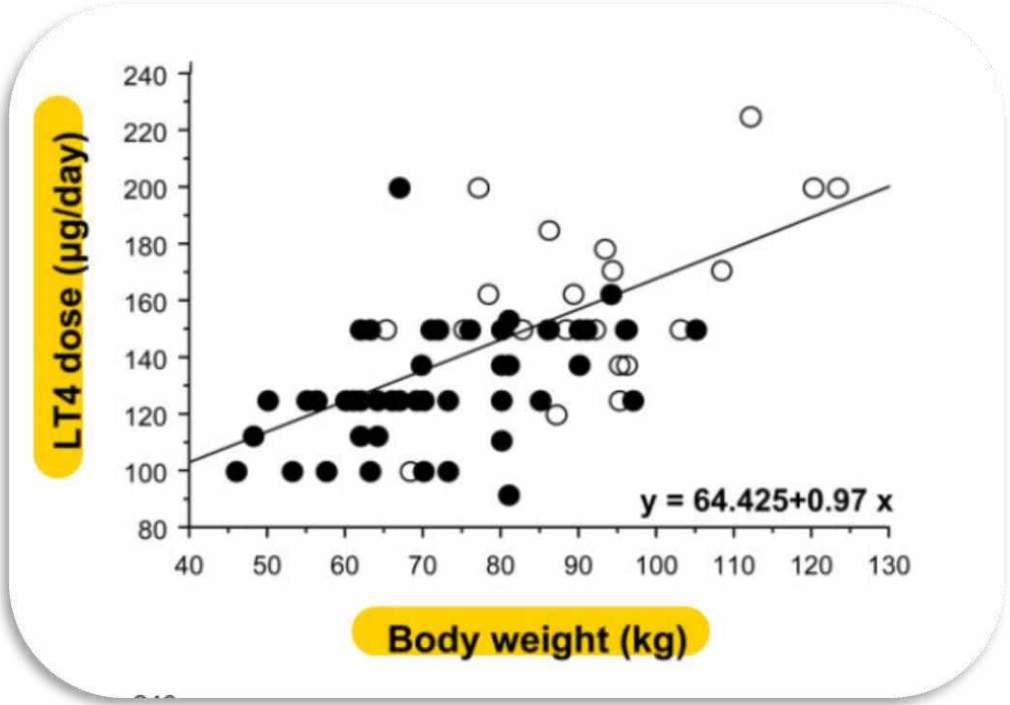


Jonklaas J et al Thyroid. 2014;24(12):1670–751.

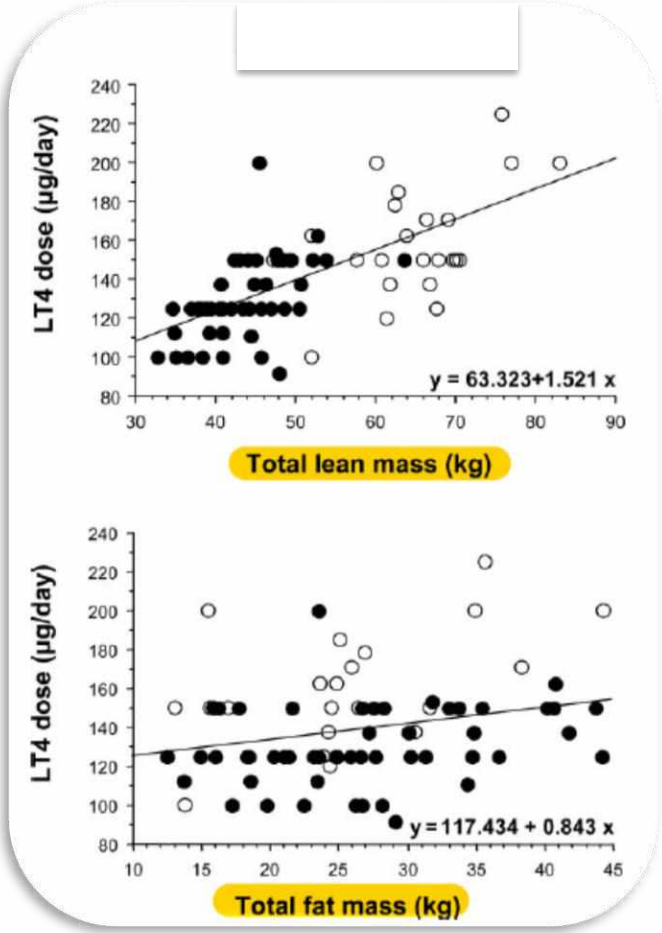
Correlations between the daily dose of L-T4 and total body weight in 75 thyroidectomized patients on L-T4 therapy at TSH-suppressive doses.



Open circles, Males; *filled circles*, females.

Santini et al J Clin Endocrinol Metab 90: 124–127, 2005

Correlations between the daily dose of L-T4 and total lean mass (middle panel), or total fat mass (lower panel) in 75 thyroidectomized patients on L-T4 therapy at TSH-suppressive doses.

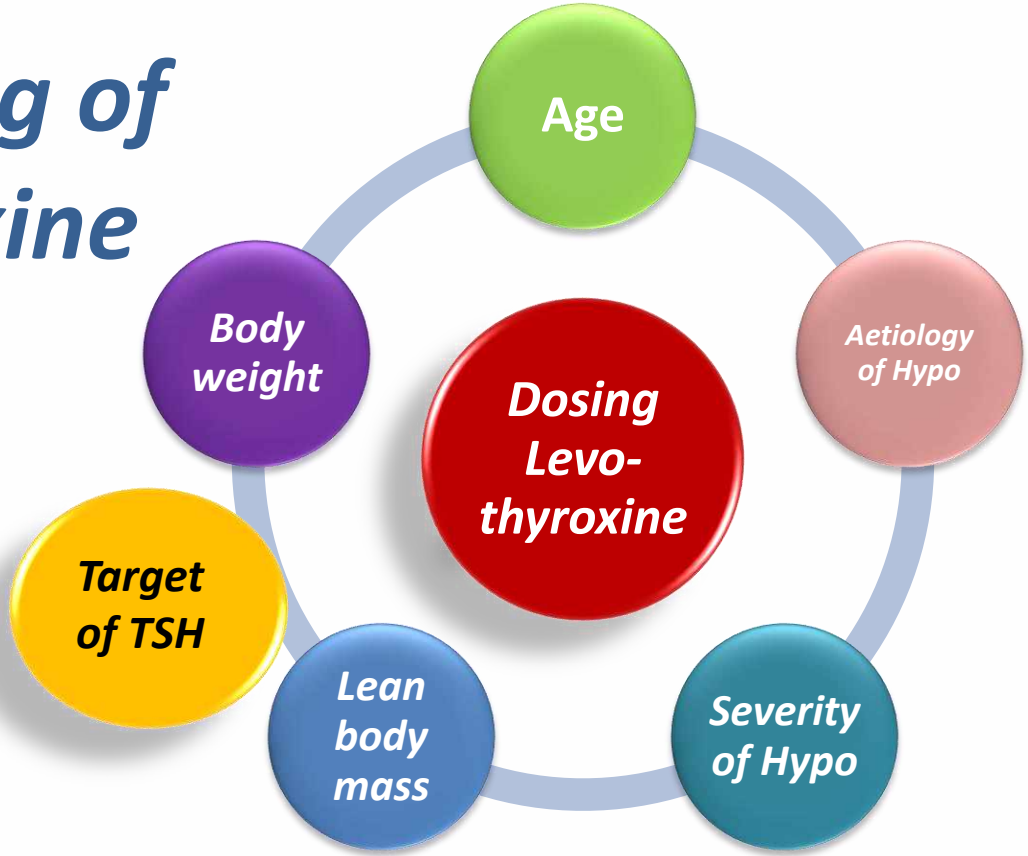


Santini et al J Clin Endocrinol Metab 90: 124–127, 2005

Open circles, Males; *filled circles*, females.

Initial dosing of levo-thyroxine

Dose initially required by a patient depends primarily on several factors:



Jonklaas J et al Thyroid. 2014;24(12):1670–751.

Initial dosing of levo-thyroxine

Target of TSH

Replacement therapy	Suppressive therapy
TSH: 0.4-4.0 mUI/l	TSH <0.1 mUI/l
Hypothyroidism	Differentiated thyroid cancer

*Daily **L-T4 doses of 1.6 to 1.8 mcg/kg** are required to achieve a normal TSH level in athyreotic individuals,*

*Daily L-T4 **doses of 2.0 to 2.2 mg/kg** are needed to suppress the serum TSH*

Thyroid Hormone Suppression Therapy

Thyroid hormone suppression therapy is a strategy ***to lower serum thyroid-stimulating hormone (TSH) levels*** *in patients with differentiated thyroid cancer in the hope that it will improve outcomes*

Biondi & Cooper, Endocrinol Metab Clin N Am (2018)

Current ATA recommended targets for serum TSH levels during the initial follow-up of DTC

Patient groups	Target range for serum TSH
High-risk	<0.1 mU/L
Intermediate-risk	0.1–0.5 mU/L
Low-risk, RAI remnant-ablated with undetectable Tg levels	0.5–2 mU/L
Low-risk, RAI remnant-ablated with low Tg levels	0.1–0.5 mU/L
Low-risk, no RAI remnant ablation	0.1–0.5 mU/L
Lobectomy	0.5–2 mU/L

Grani et al, Endocrine (2019) 66:43–50

Current ATA recommended targets for serum TSH levels during the long term follow-up of DTC

Excellent response	• *TSH 0.4-2.0 mU/l*
Indeterminate response	• *TSH 0.1-0.5 mU/l*
Biochemical incomplete response	• *TSH <0.1 mU/l*
Structural incomplete response	• *TSH <0.1 mU/l*

ATA 2015 guidelines

Adverse effects of subclinical exogenous hyperthyroidism

The exogenous subclinic thyreotossicosis is associated:

- ✓ Increased risk of atrial fibrillation
- ✓ Increased risk of cardiovascular mortality
- ✓ Increased risk of osteoporosis in post- menopausal females
- ✓ Increased risk of vertebral fractures in post-menopausal females

….adverse effects increased with:

Older age

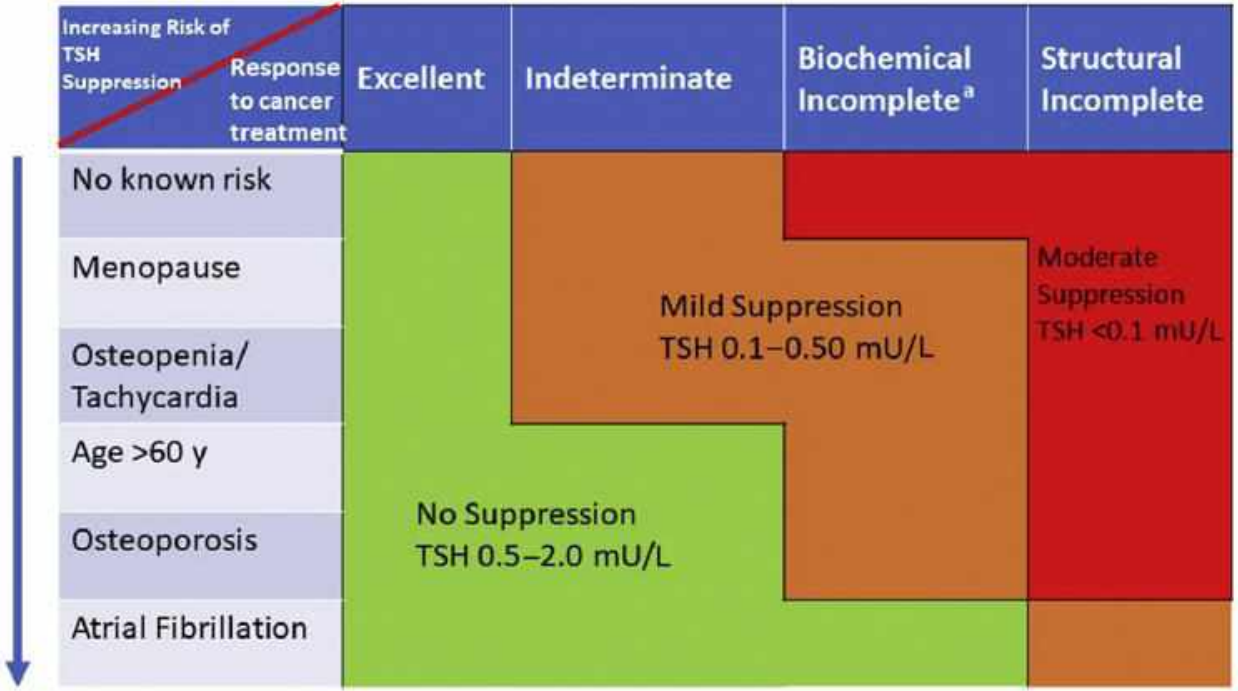
Lower TSH levels

Duration of suppressive therapy

Grani et al, Endocrine (2019) 66:43–50

Benefits of Thyrotropin Suppression Versus the Risks of Adverse Effects in Differentiated Thyroid Cancer

RECOMMENDATIONS FOR THYROID HORMONE THERAPY IN THYROID CANCER



ATA 2015 Guidelines

Dose adjustment of levothyroxine

- ✓ *Given the half-life of levothyroxine (approximately 1 week), reassessment of thyroid status by serum TSH levels, and free thyroxine levels if desired, is indicated after 6 weeks of therapy when the pharmacokinetic steady state is reached.*

- ✓ *If the TSH is not at the desired goal, the levothyroxine dose can be adjusted up or down. TSH values that are slightly out of range may be corrected by a single dose increment or decrement, such as increasing from 100 to 112 mcg or decreasing from 175 to 162 mcg.*

- ✓ *TSH values that are considerably out of range may require larger percentage changes.*

Leonidas H. Duntas . Jacqueline Jonklaas, Adv Ther (2019) 36:S30–S46

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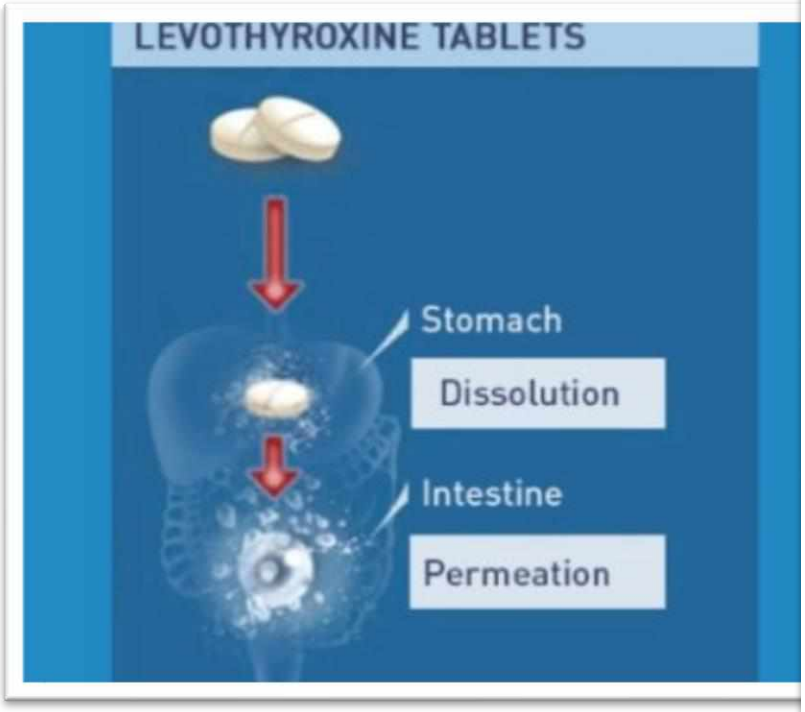
Levo-thyroxine formulations

1. *LT4 sodium tablet preparations (branded/generic)*
2. *Soft gel LT4 fomulaion (branded)*
3. *Liquid LT4 fomulation (branded)*

TABLET FORMULATIONS



About 70% of tablet L-T4 is absorbed

- ✓ *Food and beverages can interfere with L-T4 tablets absorption. L-T4 is normally taken before breakfast.*
- ✓ *Many gastric (gastritis) or intestinal disorders (CD, LI) can influence the L-T4 tablet absorption*
- ✓ *The PPI may reduce absorption of L-T4*
- ✓ *Restrictive/malabsorptive bariatric surgery*

Expert Opinion on Drug Delivery, 2017, 14:5, 647-655

Novel oral L-T4 formulations

The ***soft gel capsule*** contains, in an outer gelatine shell, L-T4 dissolved in glycerin. This structure warrants a rapid dissolution in the acid gastric environment and prevents binding with other substances in the jeunal lumen (e.g., coffee, calcium, or iron salts).

The ***liquid formulation*** is composed of L-T4, glycerin, and ethanol. The most important advantage of the oral solution, compared to the tablets, is that it does not need a gastric phase of dissolution.

Expert Opinion on Drug Delivery, 2017, 14:5, 647-655

Conclusions

The comparisons performed herein suggest that the solution formulation is associated with a similar rate and overall extent of exposure/bioavailability as the Tirosint ® soft gel capsules and the US Synthroid ® tablets, but reaches its maximum concentration (Cmax) quicker by an average of 30 min.

This makes sense as the tablet and soft gel capsule formulations need to dissolve and exist in a solution before they can be absorbed

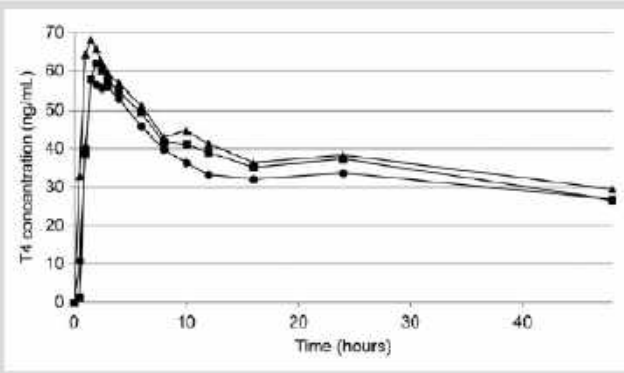


Fig. 1 Mean Levothyroxine Profiles by Formulation for 48 h Post-Dose. Triangles, squares and circles represent mean concentrations for solution, capsules and tablets respectively.

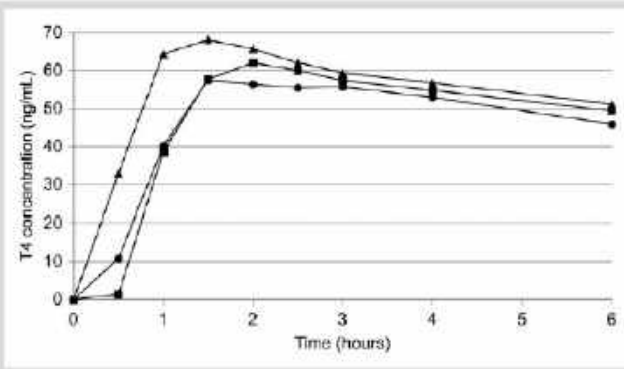
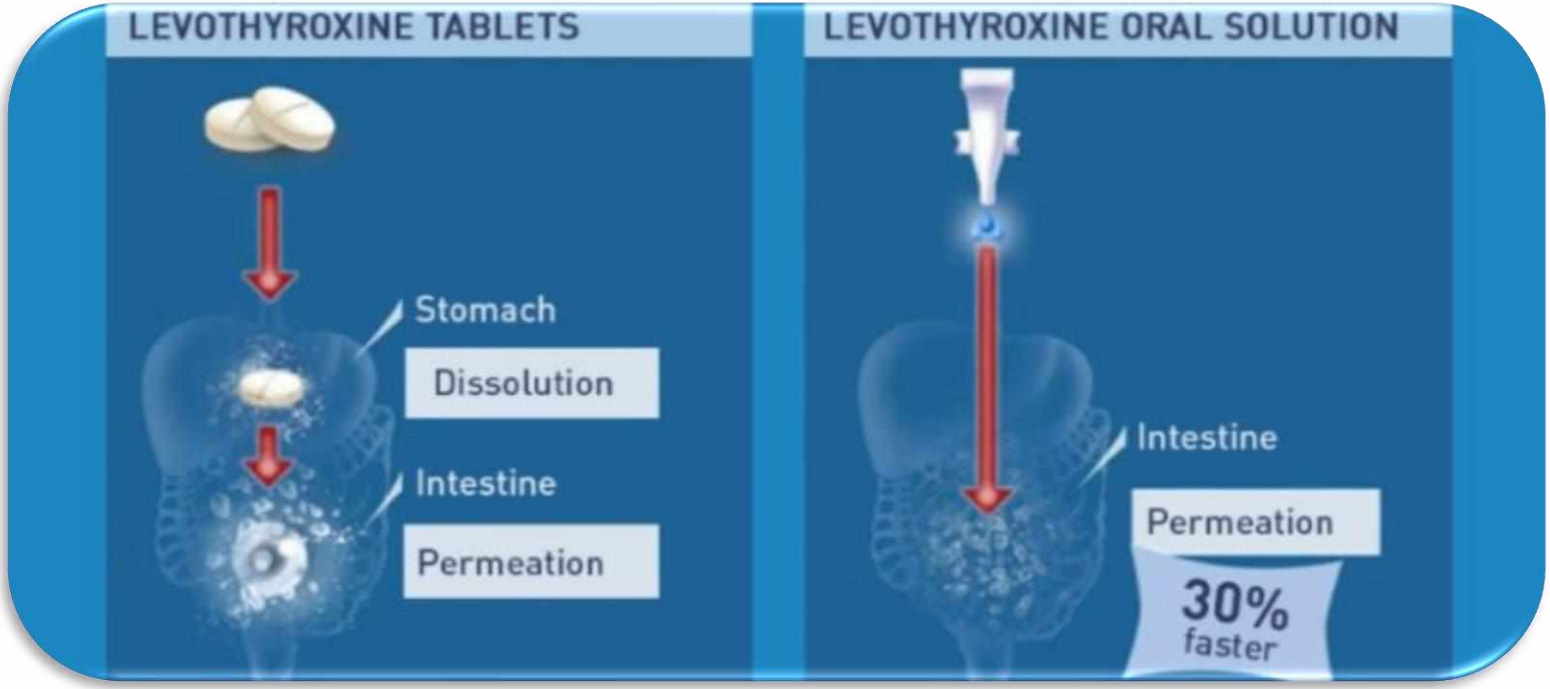


Fig. 2 Mean Levothyroxine Profiles by Formulation for 6 h Immediately Post-Dose. Triangles, squares and circles represent mean concentrations for solution, capsules and tablets respectively.

Arzneimittelforschung 2012; 62: 631–636

TABLET AND LIQUID FORMULATIONS



Possible Advantages of liquid LT4 formulation

- ✓ *Liquid L-T4 and interaction with food*
- ✓ *Liquid L-T4 in malabsorption*
- ✓ *In adult hypothyroidism*

Expert Opinion on Drug Delivery, 14:5, 647-655

Possible Advantages of liquid LT4 formulation

- ✓ ***Liquid L-T4 and interaction with food***
- ✓ *Liquid L-T4 in malabsorption*
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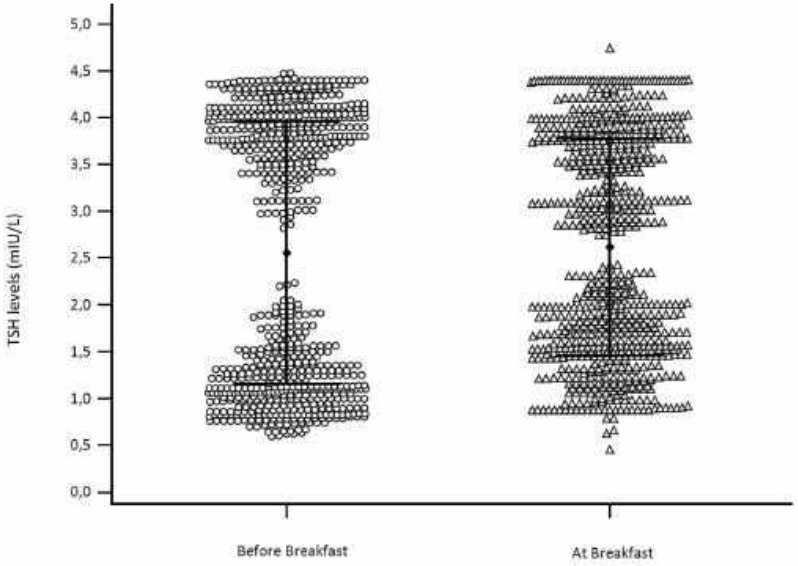
Expert Opinion on Drug Delivery, 14:5, 647-655

Liquid L-T4 and interaction with food



761 patients

Same dose of oral liquid LT4 either at breakfast or in a fasting state, 30 min before breakfast

No significant differences in serum TSH level were observed whether LT4 was ingested
at breakfast or 30 min prior in a fasting state: 2.61 ± 1.79 vs. 2.54 ± 1.86 mIU/L, $p = 0.455$).

Conclusions This study confirms in a large set of patients that a liquid LT4 formulation can be taken directly at breakfast and potentially improve therapeutic compliance.

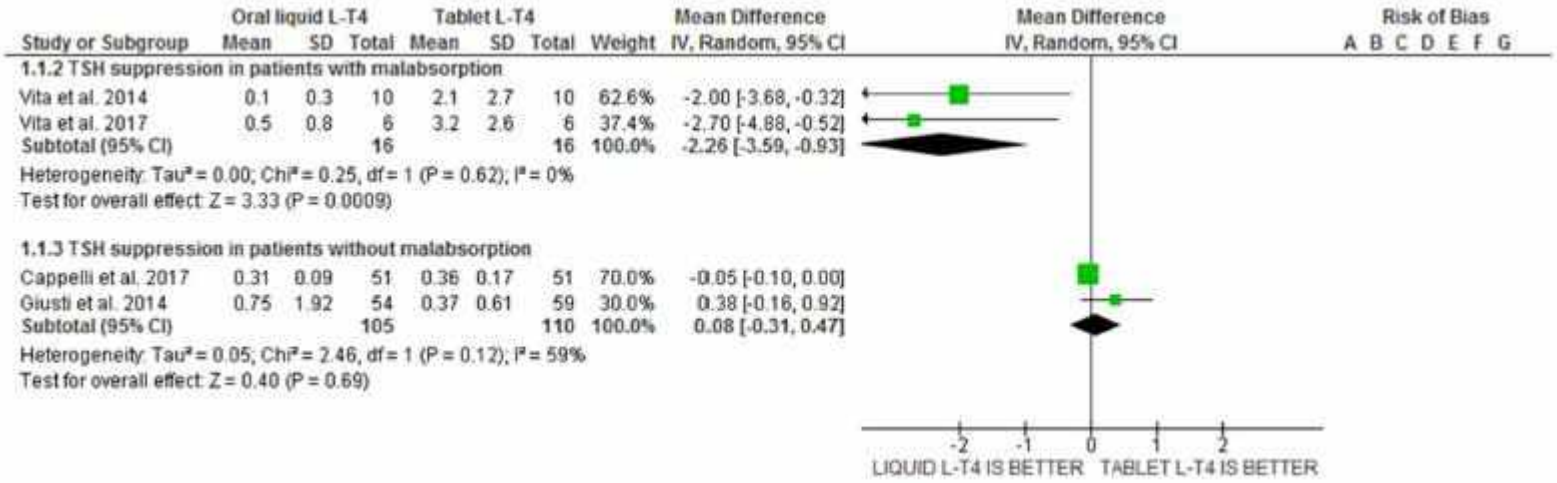
Pitoia et al, Journal of Endocrinological Investigation, 2018

Possible Advantages of liquid LT4 formulation

- ✓ *Liquid L-T4 and interaction with food*
- ✓ ***Liquid L-T4 in malabsorption***
- ✓ *In adult hypothyroidism*

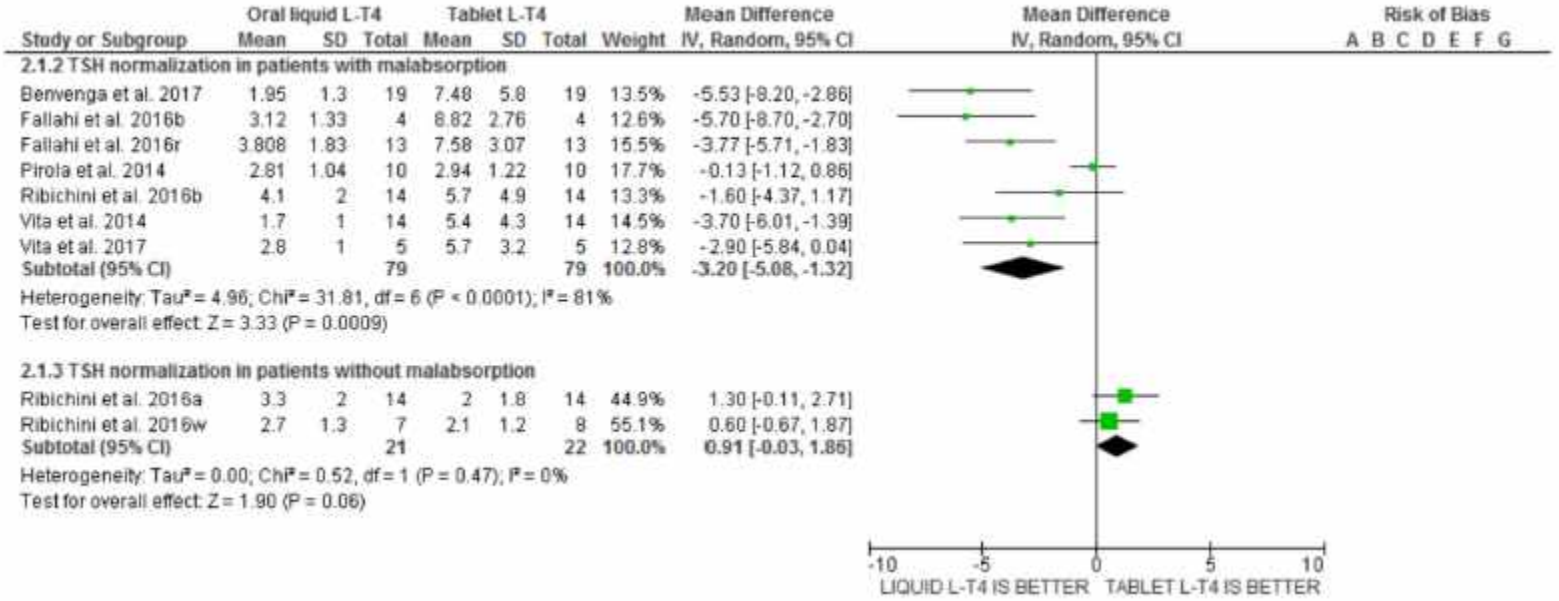
Expert Opinion on Drug Delivery, 14:5, 647-655

TSH suppression, when comparing liquid L-T4 and tablet L-T4 in patients on L-T4 suppressive therapy with or without malabsorption



Laurent et al, Endocrine 2018

TSH suppression, when comparing liquid L-T4 and tablet L-T4 in patients on L-T4 replacement therapy with or without malabsorption



Laurent et al, Endocrine 2018

TSH levels, when comparing liquid L-T4 and tablet L-T4 in patients on L-T4 therapy with or without malabsorption

Conclusion

This is the first meta-analysis comparing liquid L-T4 and tablet L-T4 in patients on L-T4 replacement or suppressive therapy. Our findings proved again that liquid L-T4 is significantly more efficient than tablet L-T4 in patients on LT4 replacement or suppressive therapy with malabsorption.

No significant differences were found in patients without malabsorption.

Further large–sized studies or RCTs should be conducted to verify these findings.

Laurent et al, Endocrine 2018

Possible Advantages of liquid LT4 formulation

- ✓ *Liquid L-T4 and interaction with food*
- ✓ *Liquid L-T4 in malabsorption*
- ✓ ***In adult hypothyroidism***

Expert Opinion on Drug Delivery, 14:5, 647-655

Comparison of liquid formulation versus tablets in adult hypothyroidism

Table 1
Descriptive Characteristics of the Study Population[a]

	Tablet Group	Liquid Group	*P*
Baseline			
n (female)	100 (81)	100 (81)	NS
Time since diagnosis (yrs)	5.17 ± 1.07	5.15 ± 1.07	NS
Age (yrs)	53.0 (13.4)	52.9 (12.1)	NS
Weight (kg)	66.7 (12.0)	65.8 (11.7)	NS
Thyroidectomy/autoimmunity	29/71	29/71	NS
TSH (mIU/L) (at baseline)	1.71 (0.95)	1.65 (0.89)	NS
Follow-up visit			
Weight (kg)	66.8 (11.7)	66.0 (12.0)	NS
LT4/week	664 (149)	613 (130)	.016[b]
LT4/kg/day	1.44 (0.31)	1.33 (0.21)	.006[c]
TSH (mIU/L)	1.76 (1.17)	1.69 (0.88)	NS
Subclinical hypothyroidism	10	5	NS
Subclinical hyperthyroidism	9	3	NS
Absolute difference in TSH	0.70 (1.05)	0 (0.58)	NS
% Difference in TSH	17.8 (84.6)	5.5 (38.2)	NS

Endocr Pract. 2014;20:901-906

Comparison of liquid formulation versus tablets in adult hypothyroidism ***with*** **TSH change from baseline to follow-up**

Table 2
TSH Levels at Follow-up by Subgroup[a,b,c]

	Subgroup A			Subgroup B		
	Tablet group	Liquid group	*P*	Tablet group	Liquid group	*P*
n	47	56		53	44	
TSH (mIU/L)	2.40 (1.15)	1.83 (0.94)	.016	1.20 (0.86)	1.51 (0.78)	.052
TSH change*	+0.96 (0.65)	+0.31 (0.51)	.0001	–0.72 (0.59)	–0.40 (0.36)	.001

TSH = thyroid-stimulating hormone
[a] Follow-up visit conducted 12 months after baseline
[b] Subgroup A = increased TSH from baseline to follow-up; Subgroup B = decreased TSH from baseline to follow-up
[a] Data are presented as mean ± SD, *P* values calculated with Mann-Whitney *U* tests

Conclusion: The use of LT4 liquid formulation compared to tablet resulted in a significantly higher number of hypothyroid patients who maintained the euthyroid state in a 12-month follow-up period and a reduced variability in TSH values.

Endocr Pract. 2014;20:901-906

LA TERAPIA SOSTITUTIVA E SOPPRESSIVA CON L-TIROXINA: QUANDO:

- ✓ ***Thyroid hormone replacement therapy*** *with oral levothyroxine is the standard treatment for patients with hypothyroidism. The goals of treatment include resolution of symptoms and signs of hypothyroidism and normalization of circulating TSH levels.*

- ✓ ***Thyroid hormone suppression therapy*** *is a strategy to lower serum thyroid-stimulating hormone (TSH) levels in patients with differentiated thyroid cancer in the hope that it will improve outcomes. The use of thyroid hormone suppression should be based on initial risk of disease and ongoing risk assessment of disease status. The lowest amount of thyroid hormone should be used whenever possible*

Take Home Messages

LA TERAPIA SOSTITUTIVA E SOPPRESSIVA CON L-TIROXINA: QUALE

Tablets *Capsules* *Solution*

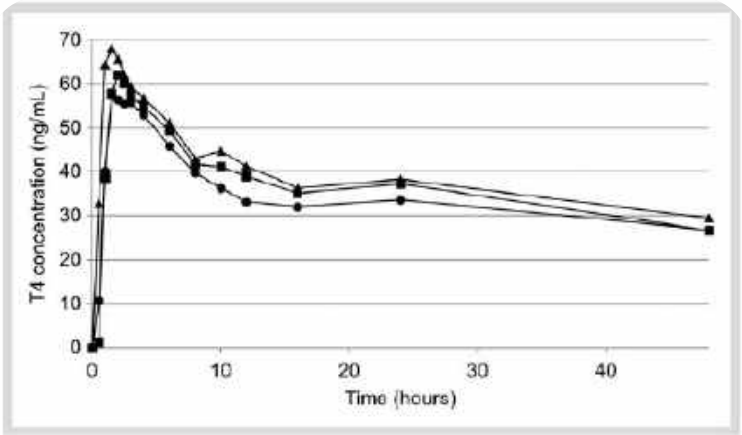


Fig. 1 Mean Levothyroxine Profiles by Formulation for 48 h Post-Dose. Triangles, squares and circles represent mean concentrations for solution, capsules and tablets respectively.

Recommendations

Patients should be maintained on the same formulation/brand name of levothyroxine. If a change is necessary, a blood test after 6 weeks is recommended to determine, if any adjustment to dosage is required

Eur Thyroid J 2018;7:238–242

Take Home Messages

LA TERAPIA SOSTITUTIVA E SOPPRESSIVA CON L-TIROXINA: QUALE

The most important advantage of the liquid L-T4 solution:

1) The possibility of administration in patients who are not able to swallow tablets or capsules

2) To overcome the food and beverages intereference with L-T4 tablets absorption, potentially improving therapeutic compliance

3) L-T4 oral liquid formulation could circumvent malabsorption induced by the increased gastric pH (atrophic gastritis, PPI therapy) or by bariatric surgery

4) L-T4 is more effective than L-T4 tablets in maintaining TSH values under control in hypothyroid patients without malabsorption

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UOC Endocrinologia-Siena

Grazie!

Con il talento si vincono le partite ma è con il lavoro di squadra e l'intelligenza che si vincono i campionati!

M. Jordan