La patologia tiroidea nell'anziano

Implicazioni per la terapia e il monitoraggio

Carlo Cappelli, MD

Department of Clinical and Experimental Sciences, Endocrine and Metabolic Unit, University of Brescia.

Struttura per età della popolazione

ITALIA - Dati ISTAT al 1° gennaio di ogni anno - Elaborazione TUTTITALIA.IT

http://www.agenziafarmaco.gov.it

Comunicato Stampa 313, 31/07/2013

Studio AIFA fotografa correttezza cure nella popolazione anziana/fragile

Un anziano su due oltre i 65 anni nel nostro Paese assume dai 5 ai 9 farmaci al giorno.

I pazienti fragili aumentano il numero di farmaci assunti giornalmente di 3 principi attivi nel primo anno.

Quasi il 60% della popolazione ultra-65enne e il 50% dei pazienti fragili manifestano scarsa aderenza alle terapie.

Dispensed prescriptions Mn		2009	2010	2011	2012	2013
Total U.S. market		**3,953**	**3,995**	**4,022**	**4,139**	**4,208**
1	acetaminophen/hydrocodone	129.4	132.1	136.7	136.4	129.2
2	levothyroxine	100.2	103.2	104.7	112.2	115.2
3	lisinopril	83.0	87.6	88.8	99.1	101.5
4	metoprolol	76.9	76.6	76.3	82.6	83.9
5	simvastatin	84.1	94.4	96.8	89.3	79.1
6	amlodipine	52.1	57.8	62.5	69.1	74.0
7	metformin	53.8	57.0	59.1	67.8	72.8
8	omeprazole	45.6	53.5	59.4	66.6	70.7
9	atorvastatin	51.7	45.3	43.3	55.5	68.4
10	albuterol	54.5	55.1	56.9	61.2	63.5
11	amoxicillin	52.8	52.4	53.8	52.8	54.2
12	hydrochlorothiazide	47.9	47.8	48.1	51.2	50.2
13	alprazolam	45.3	47.7	49.1	49.5	49.6
14	azithromycin	54.7	53.6	56.2	54.6	48.6
15	fluticasone	30.1	34.8	38.4	42.1	45.3
16	furosemide	43.8	43.6	42.3	44.1	45.0
17	gabapentin	25.7	29.6	33.4	38.6	43.9
18	sertraline	34.8	36.2	37.6	39.7	41.7
19	zolpidem	42.7	43.7	44.6	44.0	41.5
20	tramadol	25.5	28.0	33.9	39.3	41.5
21	citalopram	27.3	32.2	37.8	41.6	39.5
22	prednisone	27.8	28.7	33.7	35.2	36.5
23	acetaminophen/oxycodone	36.7	37.9	38.8	38.0	35.9
24	ibuprofen	30.3	31.1	32.6	34.2	35.1
25	pravastatin	17.2	20.2	23.9	33.3	34.7

Source: IMS Health, National Prescription Audit, Dec 2013

Management of hypothyroidism in adults

Bijay Vaidya,[1] Simon H S Pearce[2]

[1]Department of Endocrinology, Royal Devon and Exeter Hospital, Exeter EX2 5DW, and Peninsula Medical School, Exeter

[2]Endocrine Unit, Royal Victoria Infirmary and Newcastle University, Newcastle upon Tyne

Correspondence to: B Vaidya bijay.vaidya@pms.ac.uk

Cite this as: *BMJ* 2008;337:a801
doi:10.1136/bmj.a801

Hypothyroidism is one of the commonest chronic disorders in Western populations. In the United Kingdom, the annual incidence of primary hypothyroidism in women is 3.5 per 1000 and in men 0.6 per 1000.[1] During 2006 12 million prescriptions for levothyroxine (50 µg or 100 µg tablets) were dispensed in England, equivalent to about 1.6 million people taking long term thyroid replacement therapy, about 3% of the population.[2] The management of hypothyroidism is generally considered straightforward and is mostly carried out in primary care in the UK. Cross sectional surveys of patients taking levothyroxine have, however, shown that between 40% and 48% are either over-treated or under-treated.[3 4] Furthermore, a to a severe impairment of consciousness, termed "myxoedema coma" (box 2). Advanced presentations of hypothyroidism are rarely seen nowadays in developed countries.

How to diagnose hypothyroidism?

The diagnosis of primary hypothyroidism is confirmed by an increase in the serum thyroid stimulating hormone concentration above the upper limit of the reference range. Adults presenting with symptomatic hypothyroidism often have a thyroid stimulating hormone level in excess of 10 mU/l, coupled with a reduction in the serum free or total thyroxine concentration below the reference range. Some adults

BMJ. 28:337-348, 2008

http://www.agenziafarmaco.gov.it

Comunicato Stampa 313, 31/07/2013

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Quasi il 60% della popolazione ultra-65enne e il 50% dei pazienti fragili manifestano scarsa aderenza alle terapie.

Best Practice & Research Clinical Endocrinology & Metabolism 23 (2009) 781–792

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journal homepage: www.elsevier.com/locate/beem

8

Conditions and drugs interfering with thyroxine absorption

Llanyee Liwanpo, MD, Doctor *, Jerome M. Hershman, MD, Professor

Department of Endocrinology, VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA

Compliance

Politerapia

Conditions and medications that may affect absorption of levothyroxine.

Foods	Medical conditions	Drugs
Food intake	Jejunoileal bypass or other bowel resection	Cholestyramine
Dietary fiber	Inflammatory bowel disease	Colesevelam
Espresso coffee	Celiac disease	Ferrous sulfate
	Lactose intolerance	Sucralfate
	H. pylori infection	Calcium carbonate
	Chronic gastritis of the stomach body	Aluminum hydroxide
		Sevelamer hydrochloride
		Lanthanum carbonate
		Raloxifene
		Proton pump inhibitors
		Orlistat

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Hot topics

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La non-compliance alla terapia farmacologica: strategie diagnostico-terapeutiche

Antonino Cartabellotta[1*]

[1] Presidente Fondazione GIMBE

La mancata aderenza (non-compliance) di un paziente alle prescrizioni farmacologiche è oggi universalmente riconosciuta come un problema frequente che aumenta i costi dell'assistenza[1]. Negli USA, ad esempio, il 30-50% degli adulti non segue adeguatamente le prescrizioni di farmaci a lungo termine, con un costo evitabile stimato in circa 100 mld di dollari/anno. Nonostante l'ampia prevalenza del fenomeno e i costi correlati, la mancata aderenza alle prescrizioni farmacologiche non viene riconosciuta e adeguatamente trattata in una significativa percentuale di pazienti adulti in vari setting assistenziali. Secondo l'OMS "massimizzare l'efficacia degli interventi finalizzati ad aumentare la compliance può avere un impatto di gran lunga maggiore sulla salute delle popolazioni di qualunque altro progresso terapeutico".

Box. I sei fenotipi di non-compliance alla terapia farmacologica

1. Il paziente non è consapevole dell'importanza di seguire le prescrizioni farmacologiche per la sua salute e il suo benessere a lungo termine.
2. Il paziente è convinto che i benefici legati all'assunzione dei farmaci non siano superiori all'impegno richiesto per seguire la terapia.
3. La gestione della terapia farmacologica è troppo complessa per il paziente.
4. Il paziente non è sufficientemente vigile.
5. Il paziente ha convinzioni personali sui farmaci errate, irrazionali o conflittuali.
6. Il paziente non è convinto dell'efficacia del farmaco.

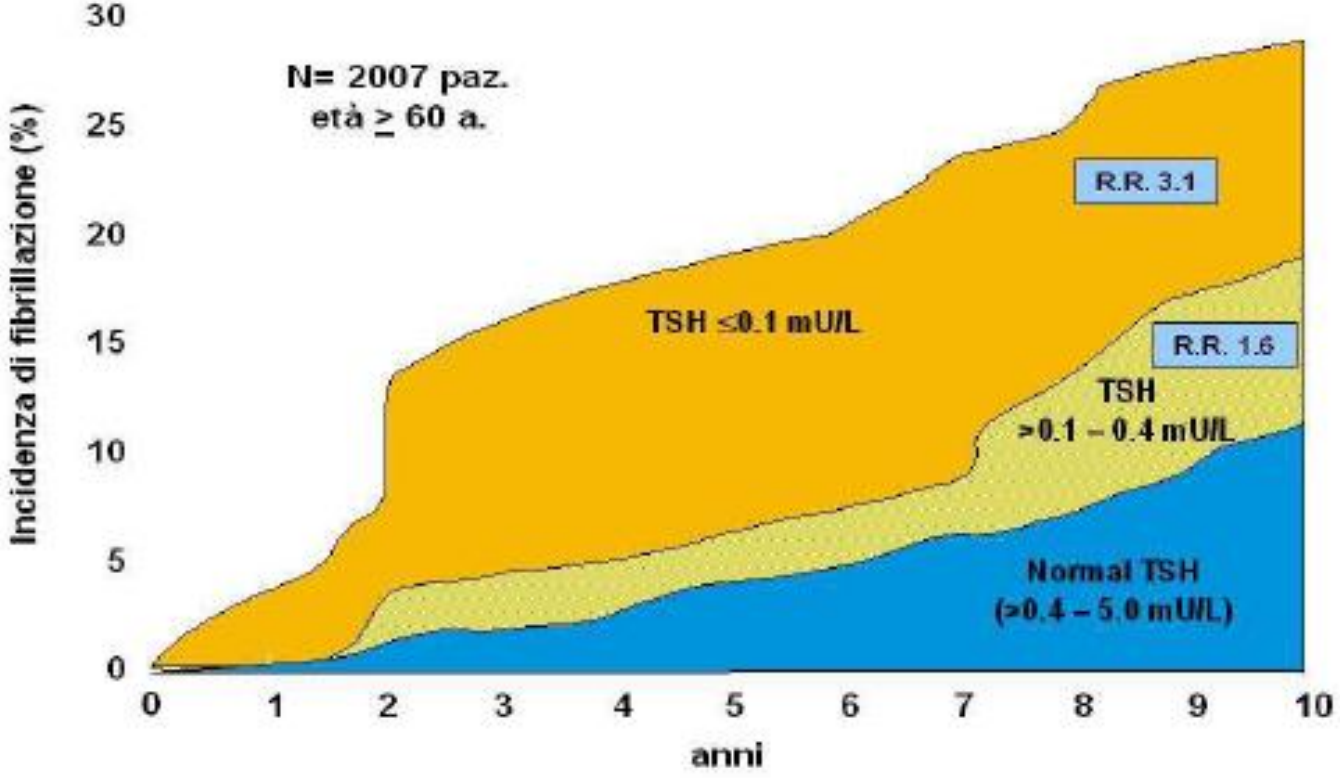
Mortality — Although subclinical hyperthyroidism has been associated with several cardiovascular risk factors, it is unknown whether there is an increase in mortality. In a meta-analysis of five population-based studies examining the association between subclinical hyperthyroidism (TSH less than 0.3 to 0.5 mU/L) and cardiovascular and all-cause mortality, the risk for all-cause and cardiovascular mortality was not significant (RRs 1.12, 95% CI 0.89-1.42 and 1.19, 95% CI 0.81-1.76, respectively) [30]. In contrast, another meta-analysis showed a significantly increased risk of all-cause mortality (HR 1.41, 95% CI 1.12-1.79) [31]. In a mathematical model designed a priori to explore mortality risk, the excess mortality after diagnosis of subclinical hyperthyroidism depended upon age, with an increase beyond the age of 60 years.

The meta-analyses included patients with both exogenous and endogenous subclinical hyperthyroidism. Serum T3 levels are higher in patients with endogenous than exogenous subclinical hyperthyroidism, and this may confer a higher mortality risk [25]. In some [32,33], but not all [20,34,35], studies evaluating patients with endogenous subclinical hyperthyroidism separately, subclinical hyperthyroidism was associated with an increase in all cause and/or cardiovascular mortality.

In a study evaluating patients with exogenous subclinical hyperthyroidism separately, there was an increased risk of cardiovascular or overall mortality only in patients with fully suppressed TSH levels [36]. In this cohort study of 17,684 patients (mean age 61.6 years) taking T4 replacement therapy, TSH levels were fully suppressed (<0.03 mU/L) or low (0.04 to 0.4 mU/L) in 6 and 21 percent of patients, respectively. Compared to patients with normal TSH, patients with suppressed TSH concentrations (<0.03 mU/L) had increased cardiovascular morbidity and mortality (Adjusted HR 1.37, 95% CI 1.17-1.60), whereas those who had serum TSH levels between 0.04 and 0.4 mU/L had a smaller increase in risk that was not significant (adjusted HR 1.10 [95% CI 0.99-1.23]).

Overall, the increased risk of mortality from subclinical hyperthyroidism appears to be small, but it may increase with age and degree of TSH suppression.

Ipertiroidismo subclinico e Fibrillazione Atriale



Sawin CT, et al. *N Engl J Med* 1994; 331:1249- 1252

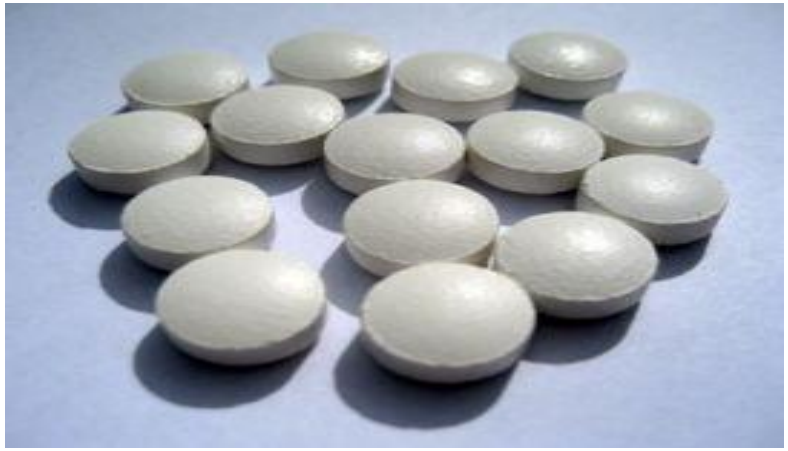
Mortality — In some [28,29,44-46], but not all [32,47-49], studies, patients with subclinical hypothyroidism have an increased risk of cardiovascular and/or all-cause mortality. In a meta-analysis of patient level data from 11 prospective cohort studies, the risk of cardiovascular mortality, but not all-cause mortality, increased with higher concentrations of TSH and was significantly increased in participants with TSH concentrations ≥10 mU/L (HR 1.58, 95% CI 1.10-2.27) [34]. In contrast, minimal elevations of TSH (4.5 to 6.9 mU/L) were not associated with cardiovascular or all-cause mortality. In one prospective study included in the meta-analysis, elderly individuals (>85 years) in the Netherlands with untreated subclinical hypothyroidism actually had a lower rate of cardiovascular and all-cause mortality [47]. In a prospective cohort study published after the meta-analysis, elderly individuals in the United States with untreated subclinical hypothyroidism had neither increased nor decreased mortality over a median follow-up period of five years [50]. (See "Diagnosis of and screening for hypothyroidism in nonpregnant adults", section on 'Effectiveness'.)

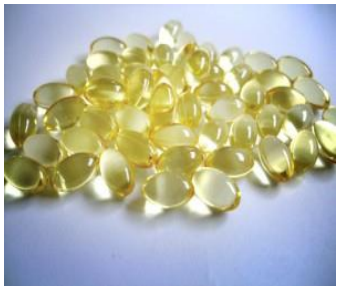
Non-alcoholic fatty liver disease — In a cross-sectional study, non-alcoholic fatty liver disease (NAFLD) was correlated with serum TSH levels. Thirty and 36 percent of individuals with subclinical or overt hypothyroidism, respectively, had typical ultrasonographic findings of NAFLD (versus 20 percent of controls) while 20 and 26 percent of individuals with subclinical or overt hypothyroidism had abnormal liver enzymes [51].

Neuropsychiatric symptoms — Several reports suggest that subclinical hypothyroidism is associated with neuropsychiatric diseases [52-55]. However, other studies (including a large study of primary care patients in England that failed to demonstrate an association of subclinical hypothyroidism with depression, anxiety, or cognitive dysfunction) do not support this observation [10,47,56-58].

Potential consequences

- In three studies, increasing serum TSH concentrations within the normal range were associated with a modest increase in body weight [59-61]. (See "Etiology and natural history of obesity", section on



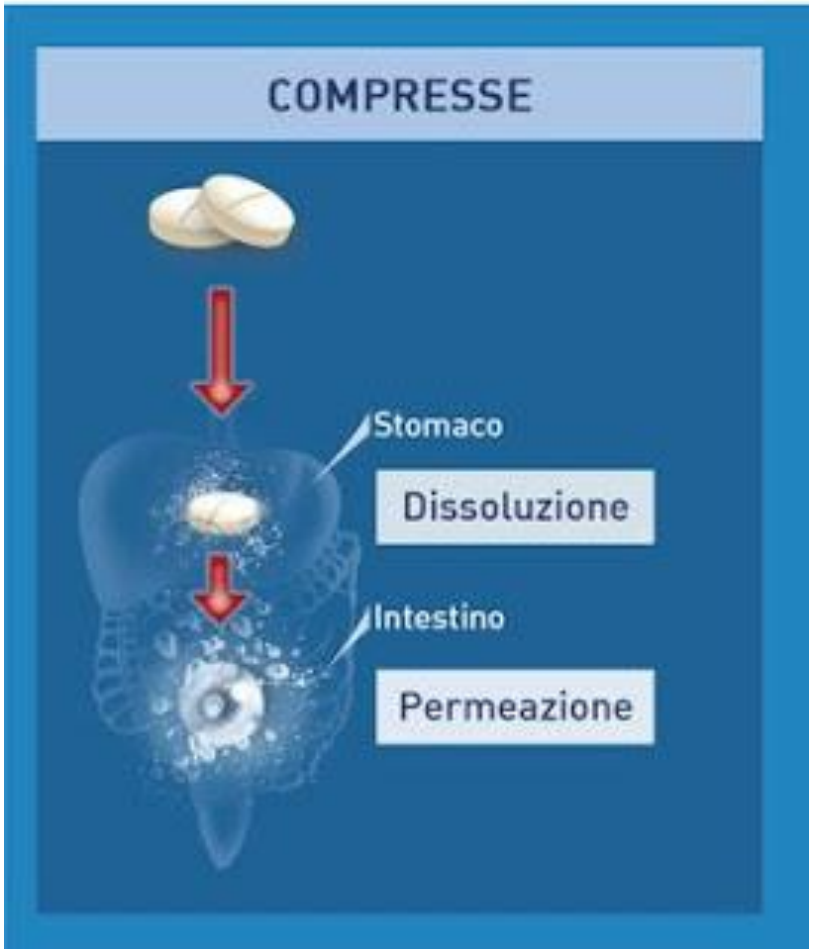


timeline

1970

2012

3 Aprile 1973



Dopo somministrazione orale il 60-90% di LT4 viene assorbita nell'intestino tenue. La fase di dissoluzione, direttamente correlata al pH gastrico, è elemento chiave per cui la terapia in compresse deve essere somministrata a stomaco vuoto la mattina a digiuno almeno 30 minuti prima di fare colazione.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thyroxine in Goiter, *Helicobacter pylori* Infection, and Chronic Gastritis

Marco Centanni, M.D., Lucilla Gargano, M.D., Gianluca Canettieri, M.D., Nicola Viceconti, M.D., Antonella Franchi, M.D., Gianfranco Delle Fave, M.D., and Bruno Annibale, M.D.

ABSTRACT

CONCLUSIONS

Patients with impaired acid secretion require an increased dose of thyroxine, suggesting that normal gastric acid secretion is necessary for effective absorption of oral thyroxine.

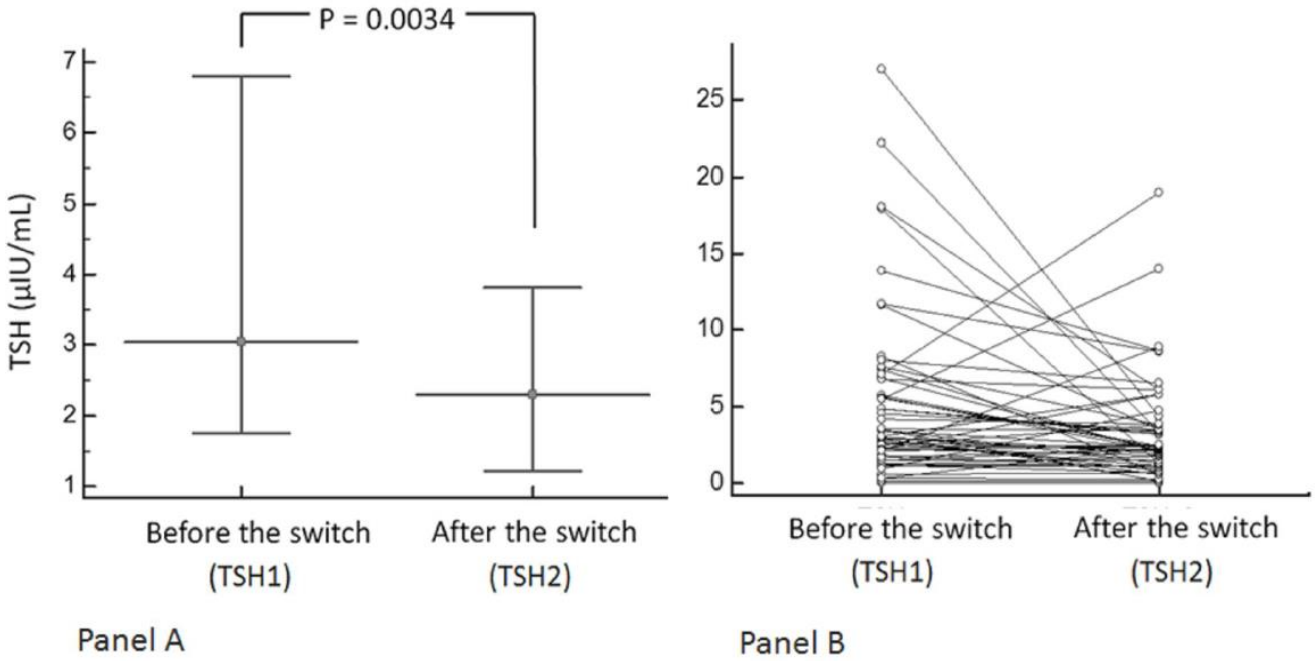
I farmaci in forma liquida non necessitano della fase di dissoluzione, si miscelano direttamente con I fluidi gastrointestinali, rendendosi subito disponibili, anche in casi di patologie come la celiachia e l'intolleranza al lattosio. Le soluzioni liquide, inoltre, garantiscono una migliore permeazione del principio attivo.

Original Article EP13418.OR

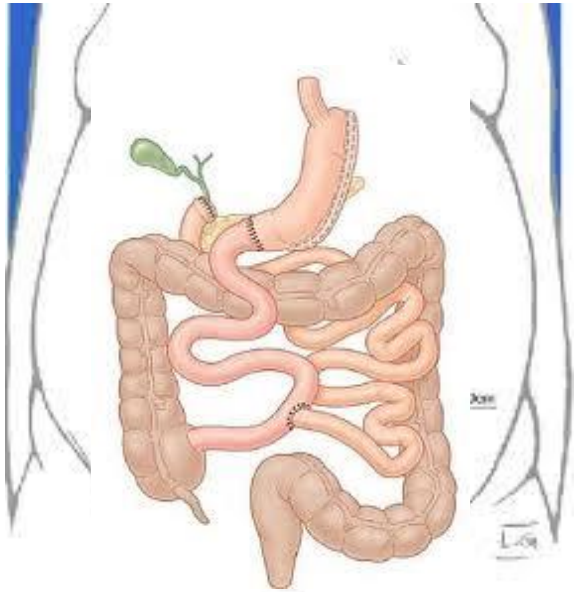
COMPARISON OF TSH LEVELS WITH LIQUID FORMULATION VERSUS TABLET FORMULATIONS OF LEVOTHYROXINE IN THE TREATMENT OF ADULT HYPOTHYROIDISM.

Running title: LT4 tablets versus oral solution

Davide Brancato, MD, Alessandro Scorsone, MD, Gabriella Saura, MD, Lidia Ferrara, MD, Anna Di Noto, MD, Vito Aiello, MD, Mattia Fleres, MD, Vincenzo Provenzano, MD.



Conclusion. Our study confirms that LT4-OS could have an increased absorption rate in comparison to LT4 tablets, especially when other factors interfering with LT4 absorption are present.



Diversione biliopancreatica

Thyroid parameters measured at the indicated times in four patients who underwent bariatric surgery between 2009 and 2011. Patients were receiving oral L-T4 in either tablet or liquid form as indicated

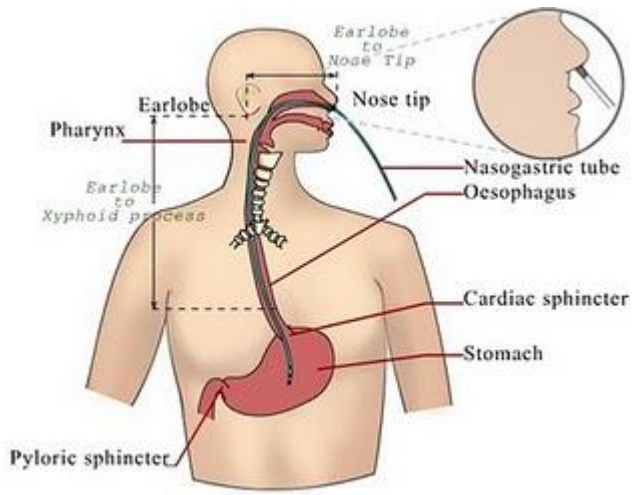
	Before surgery L-T4 in tablet form				12 Months after surgery L-T4 in tablet form				14 Months after surgeryL-T4 in liquid form				17 Months after surgery L-T4 in tablet form			
Patient	L-T4 (μg)	TSH	fT4	fT3	L-T4 (μg)	TSH	fT4	fT3	L-T4 (μg)	TSH	fT4	fT3	L-T4 (μg)	TSH	fT4	fT3
1	200	4.2	12.7	3.1	200	18.1	10.4	2.9	200	1.5	12.9	3.8	200	36.7	9.8	3.0
2	150	3.1	12.9	3.3	150	12.1	10.2	3.2	150	1.9	13.5	4.0	150	24.7	10.4	3.2
3	200	3.9	11.7	3.7	200	20.4	10.2	3.3	200	0.6	13.5	3.2	200	17.7	10.2	3.1
4	150	3.6	10.9	3.2	150	17.2	11.0	2.8	150	2.4	11.9	3.2	150	15.3	10.1	3.1

L-T4 levothyroxine, *TSH* thyrotropin, *fT4* free tyroxine, *fT3* free triiodothyronin

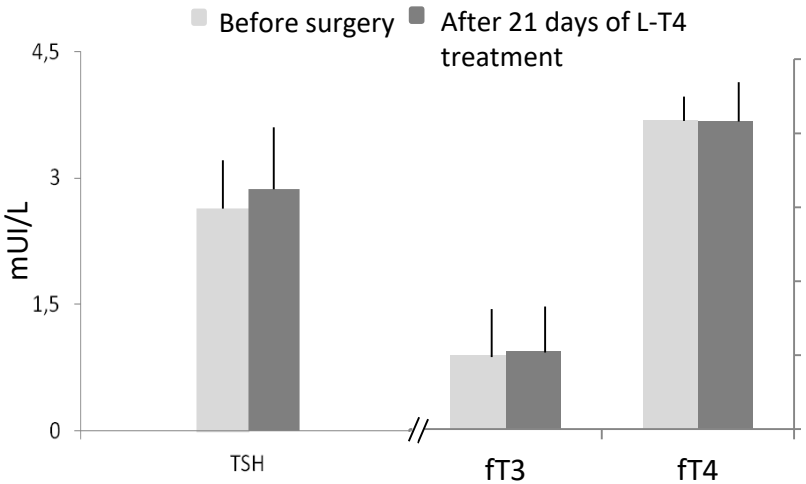
In summary, we report four patients submitted to bariatric surgery, in whom oral liquid l-thyroxine induced a reversible normalisation of thyrotropin levels. It is likely that patients affected by condition that impair l-T4 absorption (e.g., bariatric surgery) could benefit from a liquid formulation.

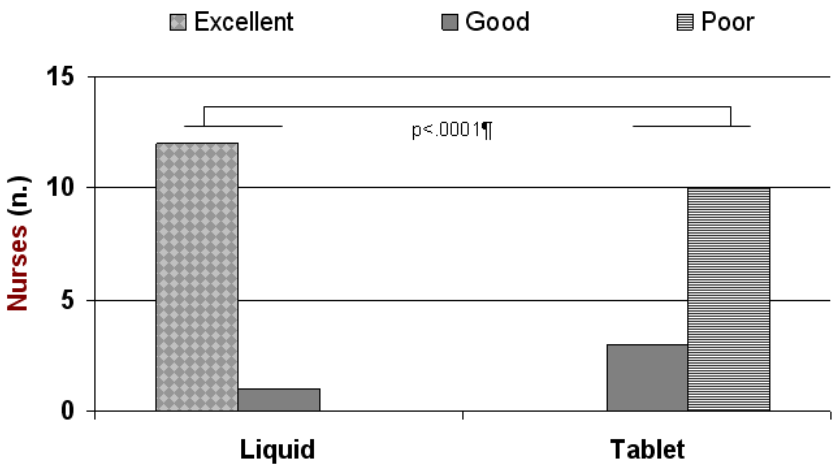
Pirola I et al, Obes Surg. 2013; 23: 1493–1496.

Comparison between liquid and tablet levothyroxine formulations in patients treated through enteral feeding tube.



	Patients treated with L-T4 *Tablet form*	Patients treated with L-T4 in *Liquid form*	P value
Patients (n.)	10	10	-
Gender (M/F)	9/1	9/1	Ns
Age (yrs)	68±5.8	69.1±5.1	Ns
BMI (Kg/cm^2)	23±2.1	23.1±1.9	Ns
TSH (mUI/L)	2.50±1.18	2.79±1.03	Ns
fT4 (pg/mL)	12.31±1.89	12.68±2.68	Ns
fT3 (pg/mL)	3.21±0.56	3.09±0.62	Ns





Pirola I et al, J Endocrinol Invest. 2014 Jun;37(6):583-7

J Clin Endocrinol Metab, December 2014, 99(12):4481–4486

ORIGINAL ARTICLE

Endocrine Care

Switching Levothyroxine From the Tablet to the Oral Solution Formulation Corrects the Impaired Absorption of Levothyroxine Induced by Proton-Pump Inhibitors

Roberto Vita, Giovanna Saraceno, Francesco Trimarchi, and Salvatore Benvenga

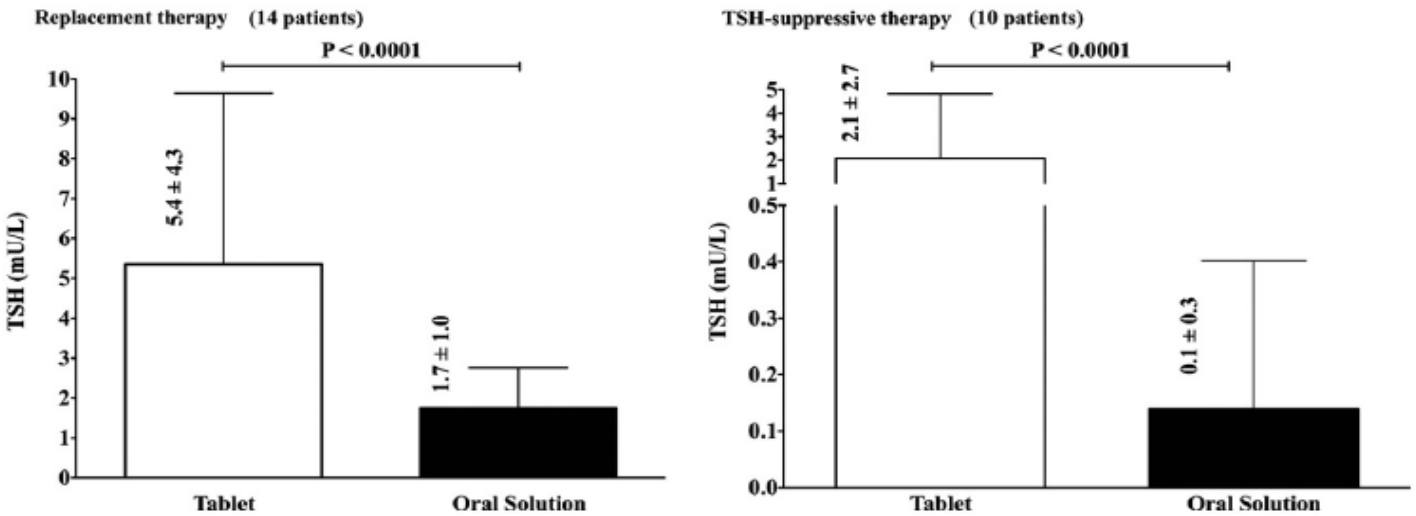


Figure 1. Serum TSH values (means ± SD) with LT4 therapy (□, tablet LT4; ■, oral solution) while maintaining therapy with PPIs. The switch was performed at the same daily dose.

Oral liquid levothyroxine treatment at breakfast: a mistake?

Carlo Cappelli, Ilenia Pirola, Elena Gandossi, Annamaria Formenti and **Maurizio Castellano**

Endocrine and Metabolic Unit, Clinica Medica, Department of Clinical and Experimental Sciences, University of Brescia, c/o 1^ Medicina Spedali Civili di Brescia, Piazzale Spedali Civili no. 1, 25100 Brescia, Italy

Correspondence should be addressed to C Cappelli
Email
cappelli@med.unibs.it

European Journal of Endocrinology

Table 1 Clinical and biochemical parameters of patients at recruitment.

	Group A ($n=41$)	**Group B** ($n=13$)	***P* value**
Age (years)	48.7±11.1	51.7±12.6	0.413
L-T_4 dosage (μg/day)	76.9±16.1	71.9±17.8	0.375
TSH (mIU/l)	2.3±1.1	2.9±0.9	0.056
fT_4 (pg/ml)	12.3±2.4	12.5±2.4	0.850
fT_3 (pg/ml)	3.4±0.6	3.4±0.5	0.734

P values based on ANOVA.

Table 2 Thyroid profile of patients consuming L-T_4 at breakfast and after 3 and 6 months of changing the time of consumption 30 min before breakfast.

	Group A ($n=41$)				**Group B** ($n=13$)			
	At recruitment[a]	3 months[b]	6 months[b]	*P*	At recruitment[a]	3 months[b]	6 months[b]	*P*
TSH (mIU/l)	2.3±1.1	2.3±1.1	2.3±1.0	0.939	2.9±0.9	2.9±0.9	2.8±0.9	0.323
fT_4 (pg/ml)	12.2±2.5	12.3±2.5	12.3±2.0	0.479	12.9±2.0	12.5±2.5	12.3±2.3	0.208
fT_3 (pg/ml)	3.4±0.6	3.3±0.6	3.2±0.6	0.079	3.4±0.7	3.5±0.6	3.5±0.4	0.615

P values based on ANOVA.
[a]Patients consuming L-T_4 with breakfast.
[b]After changing the time of L-T_4 consumption 30 min before breakfast.

Pharmaceutics **2013**, *5*, 621-633; doi:10.3390/pharmaceutics5040621

OPEN ACCESS

pharmaceutics

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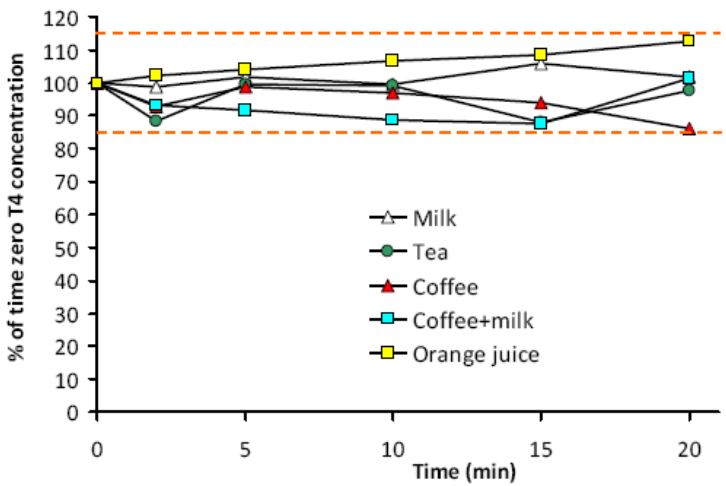
Article

Oral Liquid Formulation of Levothyroxine Is Stable in Breakfast Beverages and May Improve Thyroid Patient Compliance

Alberto Bernareggi [1,*], Elia Grata [2], Maria Teresa Pinorini [2] and Ario Conti [2]

Figure 3. Graphical representation of mean percent variation of T4 concentration as a function of time with respect to time zero concentration for all tested beverages. Dashed lines indicate the acceptance limits of ±15% of time zero concentrations.

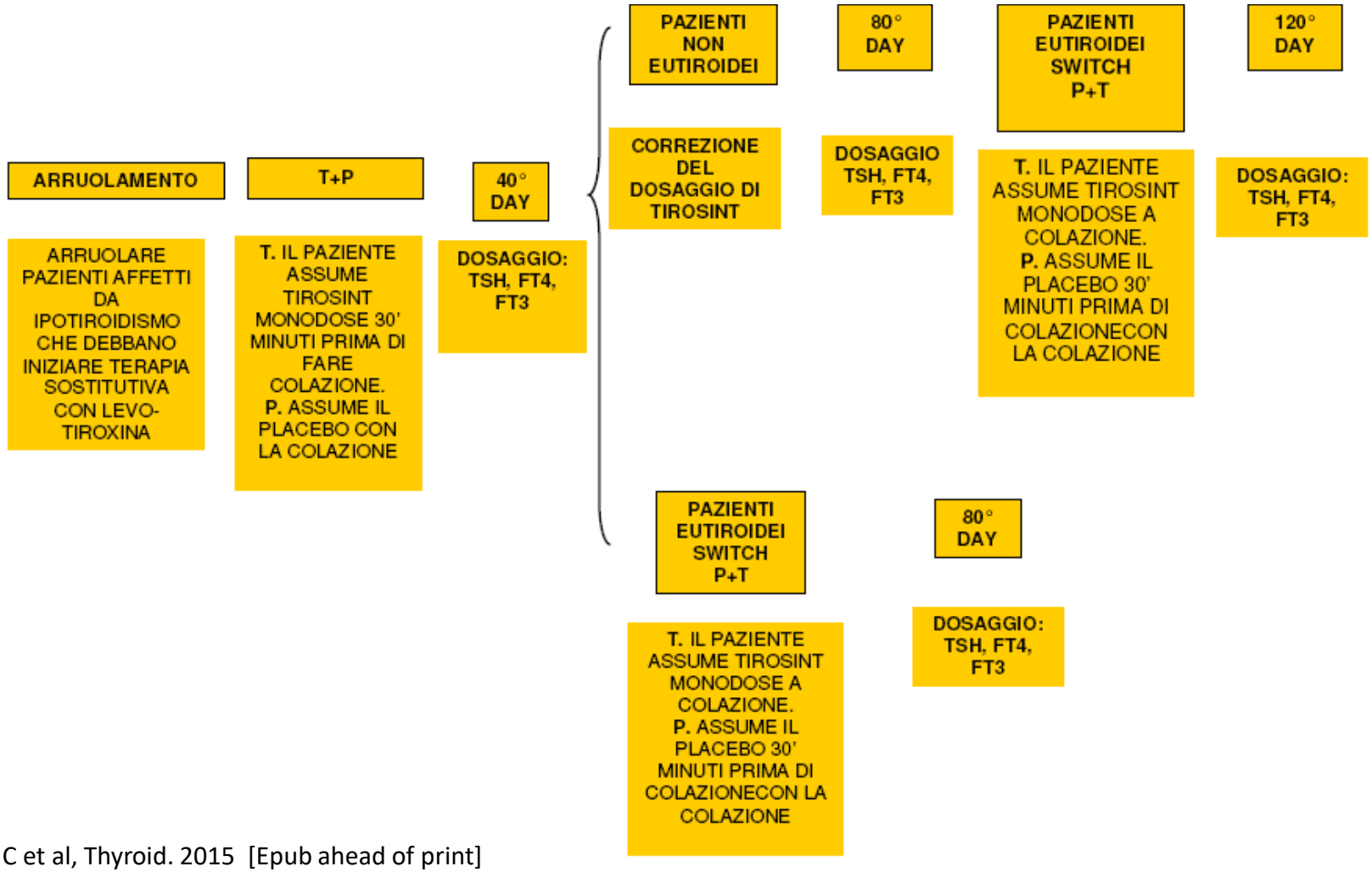


4. Conclusions

The results of the study demonstrated that T4 is stable in all beverages after 20 min incubation. Demonstration of T4 stability is a prerequisite for a thorough evaluation of the effect of breakfast beverages on the bioavailability of T4 given as oral solution and for a better understanding of the reasons underlying a decreased T4 bioavailability administered as solid formulations.

STUDIO PROSPETTICO IN CIECO SULLE CARATTERISTICHE DI ASSORBIMENTO DI LEVO-TIROXINA SOLUZIONE ORALE (Tirosint® soluzione orale monodose) IN PAZIENTI AFFETTI DA IPOTIROIDISMO

"TICO" Study



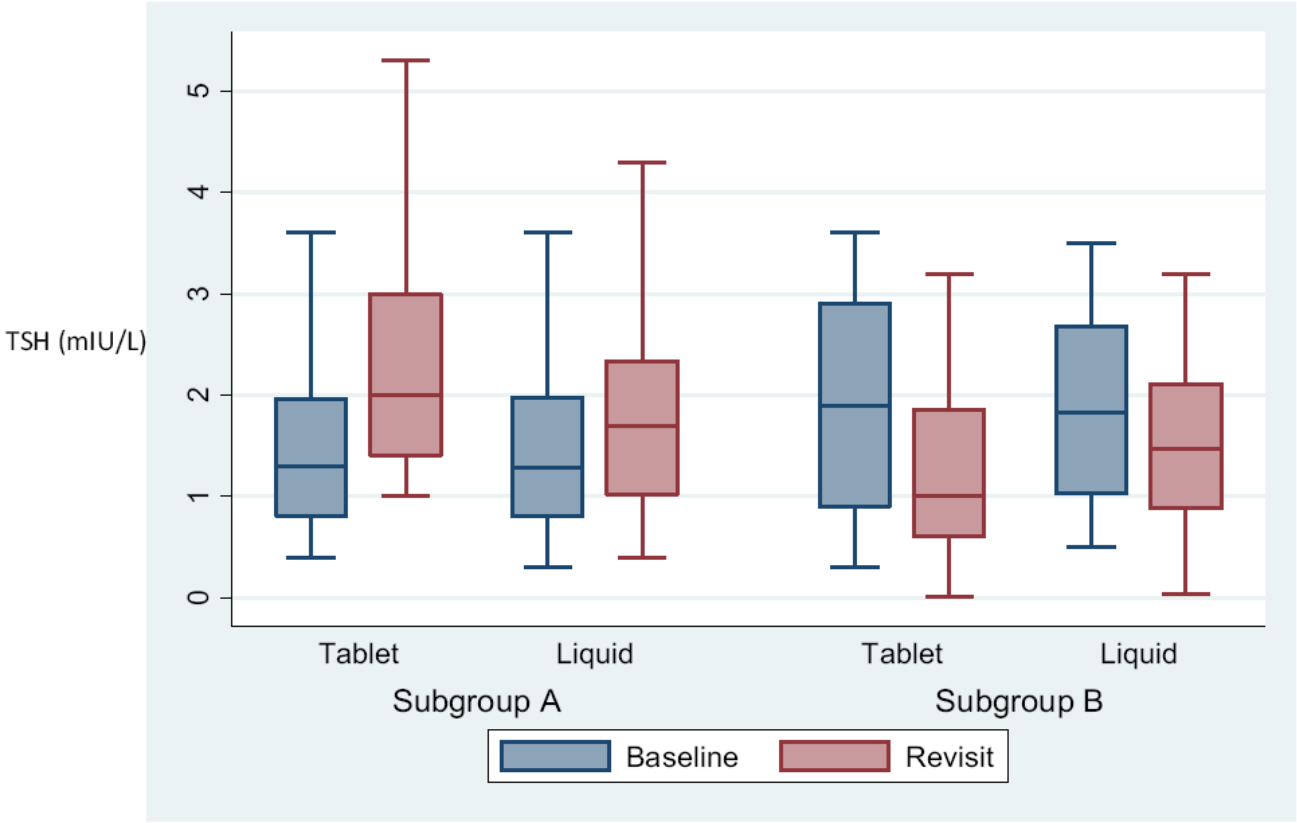
Cappelli C et al, Thyroid. 2015 [Epub ahead of print]

	ALL PATIENTS	SEQUENCE AT=>BEFORE	SEQUENCE BEFORE=>AT	P value
N. of patients	77	38	39	
Sex (female/male)	64/13	32/6	32/7	NS
Age (yrs)	45.4±13.7	46.2±14.1	44.8±13.4	NS
BMI	24.2±4.7	24.1±4.1	24.3±4.6	NS
Hashimoto thyroiditis	66	33	33	NS
Total thyroidectomy	11	5	6	
TSH (mUI/L)	16.7 (8.13-87.1)	15.1 (8.13-33.2)	18.3 (10.1-87.1)	NS
fT4 (pg/mL)	11.2 (5.3-17.5)	11.0 (5.7-17.5)	11.4 (5.3-16.1)	NS
fT3 (pg/mL)	**3.0 (2.1-4.4)**	**2.9 (2.1-4.4)**	**3.1 (2.1-4.2)**	NS

	ALL PATIENTS (n=77)		P value
	L-T4 AT BREAKFAST	L-T4 BEFORE BREAKFAST	
TSH	2.6±1.8	2.6±1.4	0.960
fT4	10.6±1.4	10.4±1.2	0.074
fT3	2.8±0.3	2.8±0.3	0.562
	SEQUENCE AT=>BEFORE (n=38)		
	L-T4 AT BREAKFAST	L-T4 BEFORE BREAKFAST	
TSH	2.3±1.3	2.4±1.5	0.574
fT4	10.7±1.4	10.4±1.3	0.025
fT3	2.8±0.3	2.8±0.3	0.445
	SEQUENCE BEFORE =>AT (n=39)		
	L-T4 AT BREAKFAST	L-T4 BEFORE BREAKFAST	
TSH	2.9±2.2	2.8±1.3	0.672
fT4	10.3±1.5	10.4±1.3	0.860
fT3	2.7±0.3	2.7±0.3	1.000

Cappelli C et al, Thyroid. 2015 [Epub ahead of print]

Levothyroxine Liquid Solution Versus Tablet for Replacement Treatment in Hypothyroid Patients.



Conclusions. The use of L-thyroxine liquid formulation compared to tablet resulted in a significantly higher number of hypothyroid patients who maintained the euthyroid state in a 12 months of follow up, and a reduced variability in TSH values.

Negro N et al. Endocr Pract, 2014, in press

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Research paper

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

C. Cappelli *, I. Pirola, L. Daffini, E. Gandossi, B. Agosti, M. Castellano

Department of Clinical and Experimental Sciences, Endocrine and Metabolic Unit, Clinica Medica, University of Brescia, c/o 1 Medicina Spedali Civili di Brescia, Piazzale Spedali Civili no 1, 25100 Brescia, Italy

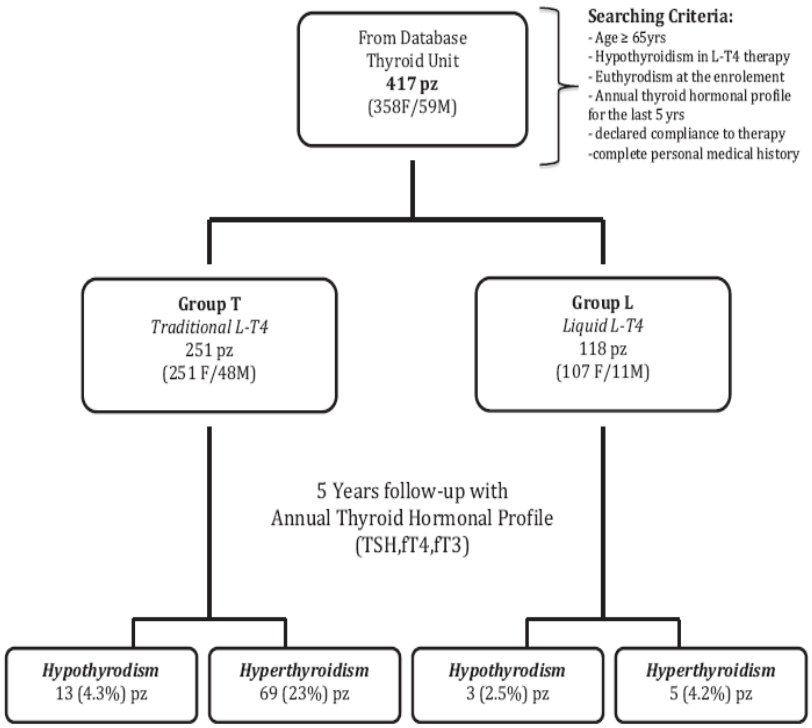
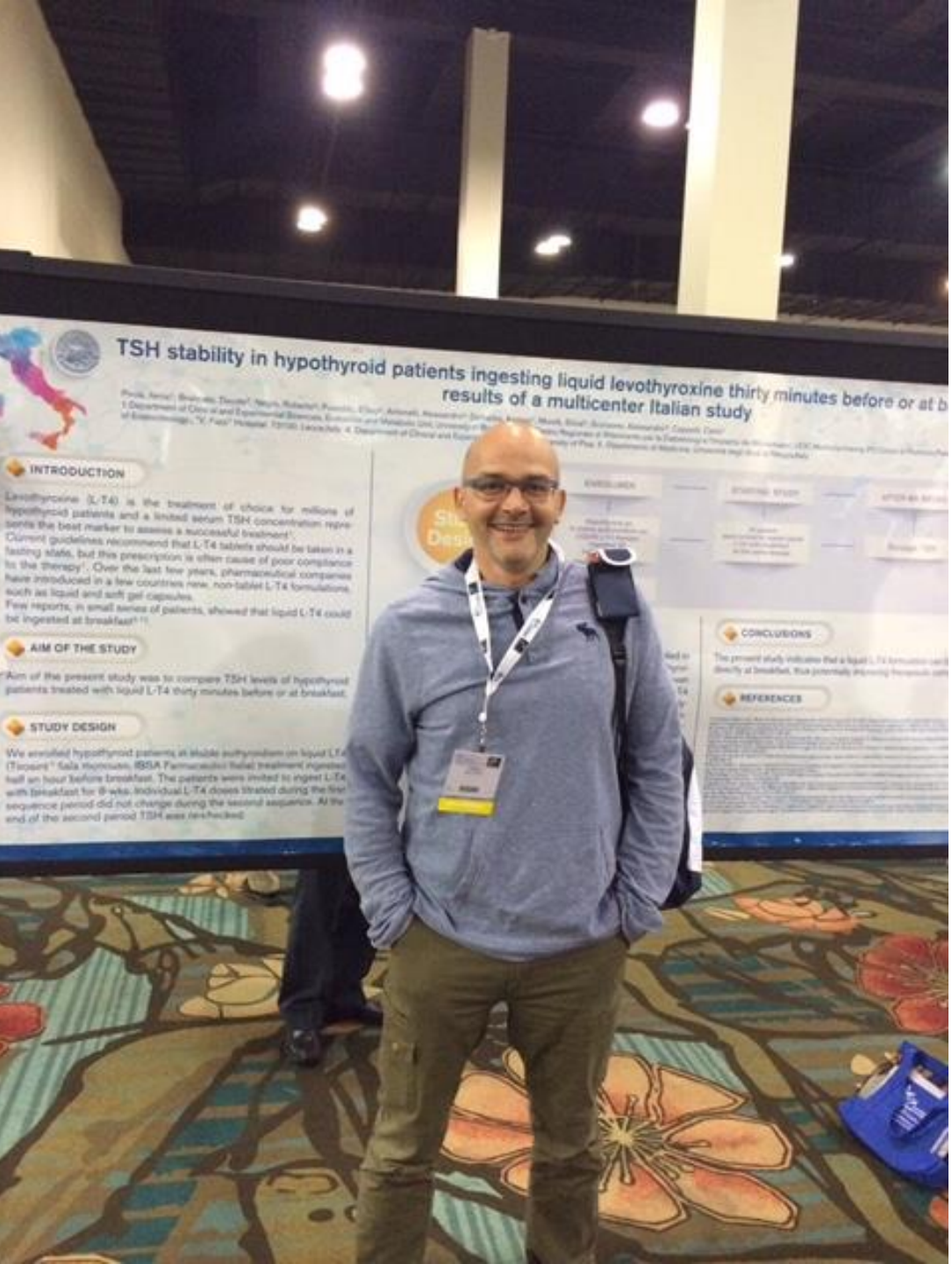


Fig. 1. Schematic diagram of the study design and data collection.

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



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CONCLUSIONI

- La terapia con L-T4 è sicura e maneggevole, ma deve essere personalizzata non solo nel dosaggio.
- La forma liquida non risente della colazione, né della concomitante assunzione di inibitori di pompa
- Il profilo tiroideo appare più stabile nel tempo con la formulazione liquida