Role of T3 in the treatment of hypothyroidism – Why, when and how?

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ביה"ח בילינסון | ביה"ח השרון

נושאים

1. יתרונות וחסרונות LT4
2. מטה אנליזות ו-Guidelines
3. T3 למי ואיך

טיפול עם LT4

- Standard of care
- קל לנטילה
- T ½ ארוך
- יעיל לטיפול בסימפטומים של תת פעילות
- ניסיון ארוך שנים
- זול
- ללא תופעות לוואי משמעותיות

אבל

- **<u>חלון תרפוטי צר</u> – הרבה מהחולים בתת או יתר טיפול**

עד 20% עם יתר טיפול ועד 20% בתת טיפול

Hadlow et al. JCEM 2013; 98(7): 2936-43

- **<u>טיפול תחליפי לא מושלם</u>:**

1. **ביוכימית**
2. **מדדים מטאבוליים, קוגניטיביים**
3. **בעיית שביעות רצון מהטיפול**

J. Clin. Invest. 1995. 96:2828–2838.

Replacement Therapy for Hypothyroidism with Thyroxine Alone Does Not Ensure Euthyroidism in All Tissues, as Studied in Thyroidectomized Rats

Héctor F. Escobar-Morreale, M. Jesús Obregón, Francisco Escobar del Rey, and Gabriella Morreale de Escobar
Instituto de Investigaciones Biomédicas, Consejo Superior de Investigaciones Científicas y Universidad Autónoma, 28029 Madrid, Spain

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Endocrinology

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Printed in U.S.A.

Only the Combined Treatment with Thyroxine and Triiodothyronine Ensures Euthyroidism in All Tissues of the Thyroidectomized Rat*

HÉCTOR F. ESCOBAR-MORREALE†, FRANCISCO ESCOBAR DEL REY, M. JESÚS OBREGÓN, AND GABRIELLA MORREALE DE ESCOBAR

Molecular Endocrinology Unit, Instituto de Investigaciones Biomédicas, Consejo Superior de Investigaciones Científicas, y Facultad de Medicina, Universidad Autónoma de Madrid, 28029 Madrid, Spain

OPEN ACCESS Freely available online

August 2011 | Volume 6 | Issue 8 | e22552

PLoS one

Levothyroxine Monotherapy Cannot Guarantee Euthyroidism in All Athyreotic Patients

Damiano Gullo*, Adele Latina, Francesco Frasca, Rosario Le Moli, Gabriella Pellegriti, Riccardo Vigneri

Endocrine Unit, Department of Clinical and Molecular Biomedicine, University of Catania Medical School, Garibaldi-Nesima Hospital, Catania, Italy

Psychological well-being in patients on 'adequate' doses of L-thyroxine: results of a large, controlled community-based questionnaire study

25% vs 38%

P. Saravanan*†, W.-F. Chau†, N. Roberts‡, K. Vedhara§, R. Greenwood¶ and C. M. Dayan*†

Clinical Endocrinology, **57**, 577–585 *July 2002*

J Clin Endocrinol Metab, December 2016, 101(12):4964–4973

Is a Normal TSH Synonymous With "Euthyroidism" in Levothyroxine Monotherapy?

Sarah J. Peterson, Elizabeth A. McAninch, and Antonio C. Bianco

Division of Endocrinology and Metabolism, Rush University Medical Center, Chicago, Illinois

THYROID
Volume X, Number X, 2018

DOI: 10.1089/thy.2017.0681

ORIGINAL STUDY

An Online Survey of Hypothyroid Patients Demonstrates Prominent Dissatisfaction

Sarah J. Peterson,[1] Anne R. Cappola,[2] M. Regina Castro,[3] Colin M. Dayan,[4] Alan P. Farwell,[5] James V. Hennessey,[6] Peter A. Kopp,[7] Douglas S. Ross,[8] Mary H. Samuels,[9] Anna M. Sawka,[10] Peter N. Taylor,[4] Jacqueline Jonklaas,[11] and Antonio C. Bianco[1]

- **סקר אינטרנטי של ה-ATA**
- **שביעות רצון מהטיפול ומהרופאים**
- **12,146 מטופלים**

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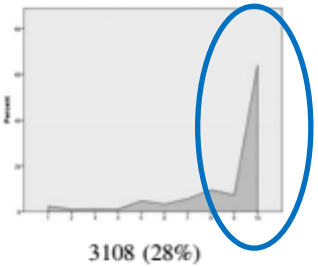
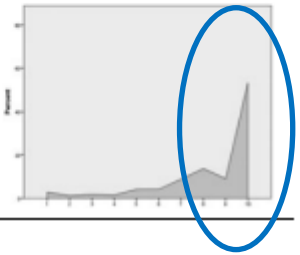
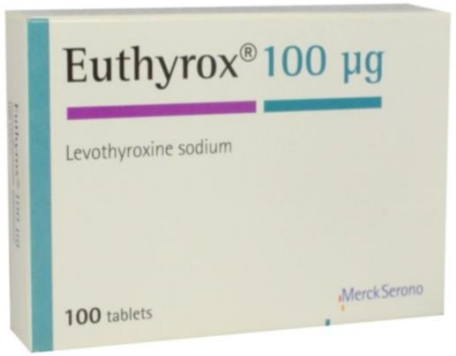
TABLE 1. (CONTINUED)

Survey section	*Survey question*	*Possible response*	*Respondents*
	How many times have you changed doctors because you were not satisfied with the treatment you were receiving?[a]	Never Once 2–4 times 5–9 times >10 times	3185 (29%) 1944 (17%) 4375 (39%) 1349 (12%) 313 (3%)
	How would you rate the need for new treatments for hypothyroidism?[b]	1 = no need 10 = strong need	10 (8–10) 
	Tried alternative hypothyroid treatment not prescribed by doctor	Yes No	3108 (28%) 8058 (71%)
	How has your life been affected by your hypothyroidism?[b]	1 = not affected 10 = strongly affected	10 (8–10) 

- תת קבוצה סימפטומטית למרות TSH מאוזן
- בסיס פזיולוגי \ ביוכימי

T4 + T3


Euthyrox® 100 µg
Levothyroxine sodium
100 tablets
Merck Serono

4 מטה-אנליזות

2014 ATA hypothyroidism guidelines

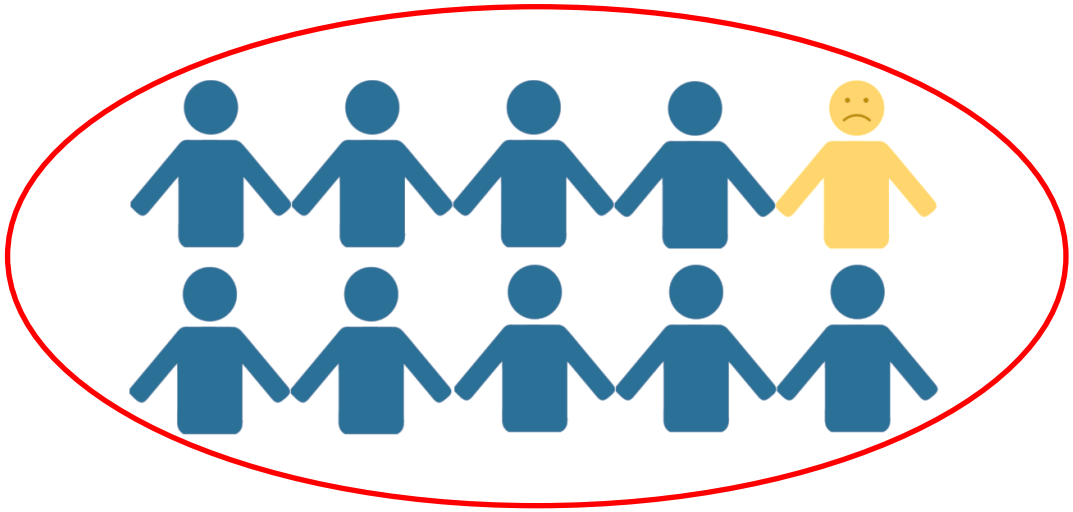
2012 ETA guidelines - T4/T3 treatment

Suggested approach

מטה-אנליזות

1. Escobar-Morreale et al. JCEM 2005 Aug;90(8):4946-54
2. Grozinsky-Glasberg et al. JCEM 2006 Jul;91(7):2592-9
3. Joffe et al. Psychosomatics. 2007 Sep-Oct;48(5):379-84
4. Ma et al. Nucl Med Commun. 2009 Aug;30(8):586-93

- 9-11 מחקרים
- אין הבדל בין T4 לשילוב T4+T3



THYROID
Volume 24, Number 12, 2014

Guidelines for the Treatment of Hypothyroidism

Prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement

Jacqueline Jonklaas,[1*†] Antonio C. Bianco,[2*‡] Andrew J. Bauer,[3†] Kenneth D. Burman,[4†] Anne R. Cappola,[5†] Francesco S. Celi,[6‡] David S. Cooper,[7†] Brian W. Kim,[2‡] Robin P. Peeters,[8‡] M. Sara Rosenthal,[9†] and Anna M. Sawka[10†]

1a. Is levothyroxine monotherapy considered to be the standard of care for hypothyroidism?

■ **RECOMMENDATION**

Levothyroxine is recommended as the preparation of choice for the treatment of hypothyroidism due to its efficacy in resolving the symptoms of hypothyroidism, long-term experience of its benefits, favorable side effect profile, ease of administration, good intestinal absorption, long serum half-life, and low cost.

Strong recommendation. Moderate quality evidence.

	Patient Satisfaction with Levothyroxine Therapy	
9a	What tools may be useful in the clinical or research setting, to measure the impact of levothyroxine replacement for primary hypothyroidism on patients' physical or psychological well-being, treatment satisfaction, or treatment preferences?	1700
9b	What approach should be taken in patients treated for hypothyroidism who have normal serum thyrotropin values but still have unresolved symptoms?	1700
	Thyroid Extracts	
12	In adults requiring thyroid hormone replacement treatment for primary hypothyroidism, is treatment with thyroid extracts superior to treatment with levothyroxine alone?	1704
	Synthetic Combination Therapy and the Rationale for Its Use	
13a	Do genetic variants in thyroid hormone pathway genes (deiodinases or thyroid hormone transporters) affect the serum or tissue levels of thyroid hormones in healthy euthyroid individuals or hypothyroid patients taking replacement therapy?	1706
13b	In adults requiring thyroid hormone replacement treatment for primary hypothyroidism, is combination treatment including levothyroxine and liothyronine superior to the use of levothyroxine alone?	1707
13c	In adults requiring thyroid hormone replacement treatment for primary hypothyroidism who feel unwell while taking levothyroxine, is combination treatment including levothyroxine and liothyronine superior to the use of levothyroxine alone?	1707
13d	Should genetic characterization according to type 2 deiodinase gene polymorphism status be used to guide the use of combination synthetic levothyroxine and liothyronine therapy in hypothyroidism, in order to optimize biochemical and clinical outcomes?	1712
	Liothyronine Monotherapy for Hypothyroidism	
14	Are there data regarding therapy with triiodothyronine alone, either as standard liothyronine or as sustained release triiodothyronine, that support the use of triiodothyronine therapy alone for the treatment of hypothyroidism?	1713
	Liothyronine Monotherapy in Euthyroid Patients	
15a	Is there a role for the use of liothyronine to treat biochemically euthyroid patients with depression?	1714
15b	Is there a role for the use of liothyronine to treat biochemically euthyroid patients with obesity?	1715
	Compounded Thyroid Hormones	
16	What is the recommendation regarding therapy with compounded thyroid hormones (either levothyroxine or liothyronine) for treatment of hypothyroidism based on current evidence?	1715

עדויות בעד T3

1. **<u>בדיקות דם</u>: תיקון רמת T4, T3, יחס T4/T3**

2. **תיקון רמת T3 ברקמות** (מודל חיה)

Eur Thyroid J 2017;6:143–151

.3

Hypothyroid Patients Encoding Combined MCT10 and DIO2 Gene Polymorphisms May Prefer L-T3 + L-T4 Combination Treatment – Data Using a Blind, Randomized, Clinical Study

Allan Carlé[a] Jens Faber[c, d] Rudi Steffensen[b] Peter Laurberg[a]
Birte Nygaard[c, d]

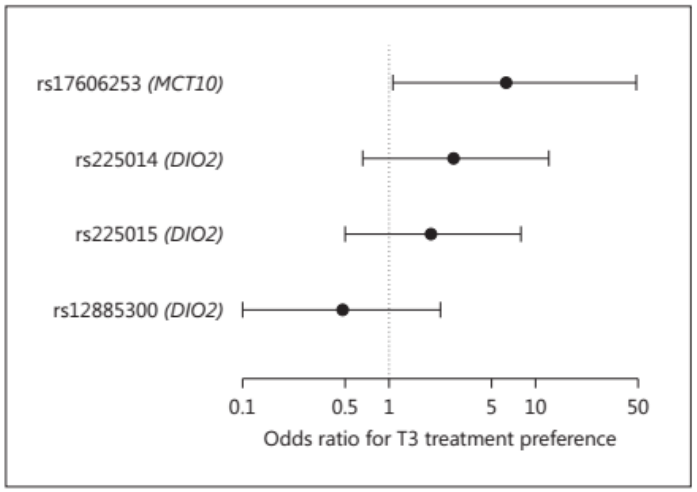


Fig. 1. Odds ratios (OR) for harbouring various single nucleotide polymorphisms (SNPs) in case of favouring the combined L-T3 +

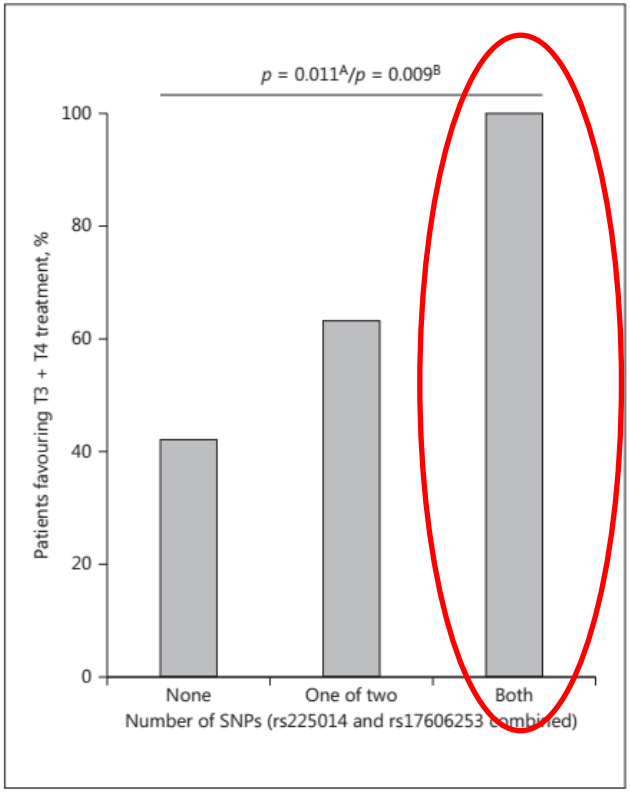


Fig. 2. Patients' preference for the combined L-T3 + L-T4 treat-

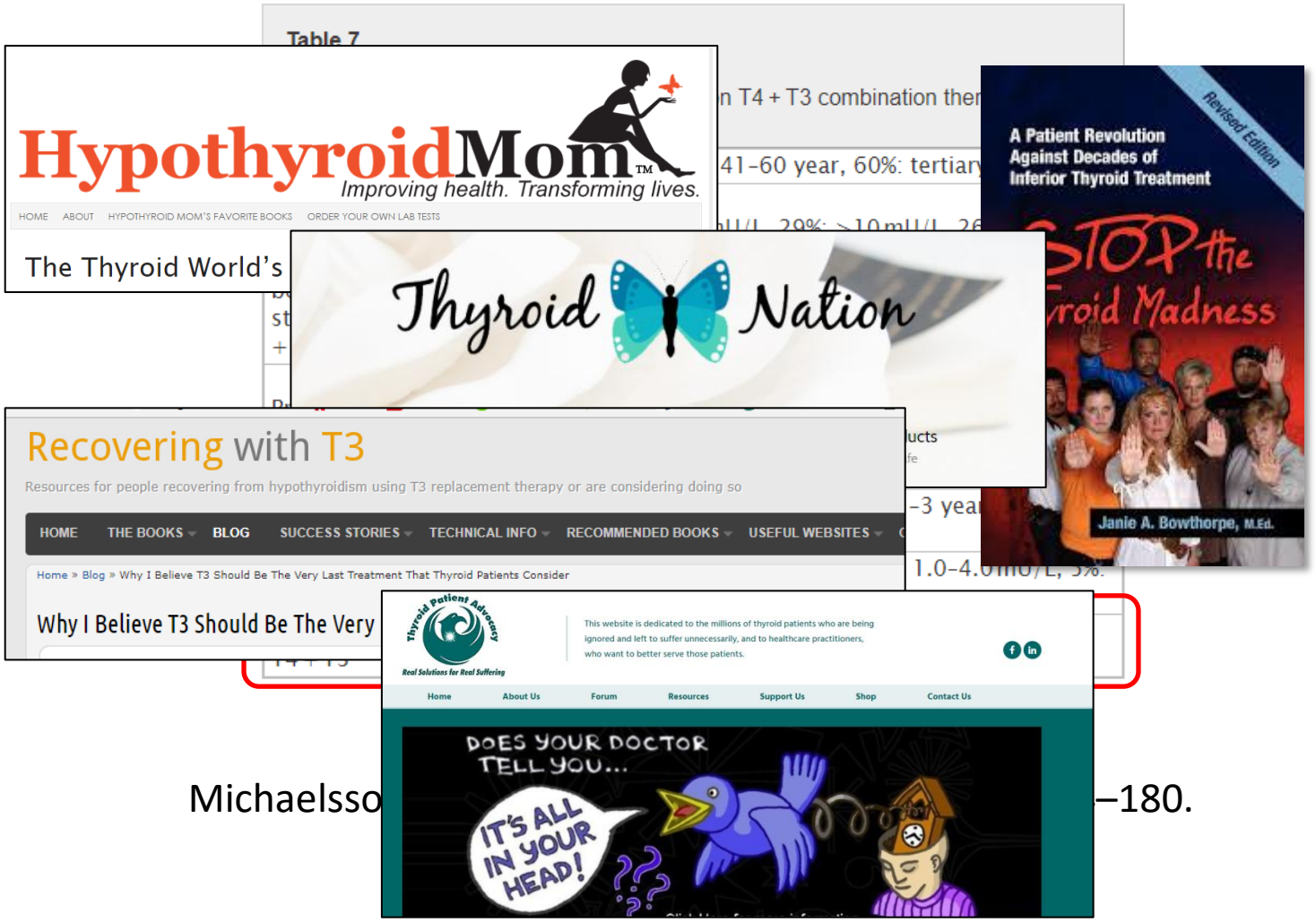
איכות חיים

- **מחקרי cross-over – 66% מעדיפים שילוב T4/T3**

Table 2. Treatment preference documented during trials of combination therapy.

Study Design	Number of Trials	Trials in which combination therapy was preferred	Trials in which combination therapy was not preferred	Number of patients	Total Number preferring vs not preferring T4/T3
Blinded, cross-over	6	Bunevicius, 1999		33	198 preferred T4/T3, 101 did not
		Bunevicius, 2002		10	
		Escobar-Morreale, 2006		26	
		Nygaard, 2009		59	
			Walsh, 2003	101	
		*Hoang, 2013		70	

טיפול ארוך טווח עם T4+T3



Michaelsso –180.

AMERICAN THYROID ASSOCIATION
FOUNDED 1923

13c. In adults requiring thyroid hormone replacement treatment for primary hypothyroidism who feel unwell while taking levothyroxine, is combination treatment including levothyroxine and liothyronine superior to the use of levothyroxine alone?

■ RECOMMENDATION

For patients with primary hypothyroidism who feel unwell on levothyroxine therapy alone (in the absence of an allergy to levothyroxine constituents or an abnormal serum thyrotopin), there is currently insufficient evidence to support the *routine* use of a trial of a combination of levothyroxine and liothyronine therapy outside a formal clinical trial or *N*-of-1 trial, due to uncertainty in long-term risk benefit ratio of the treatment and uncertainty as to the optimal definition of a successful trial to guide clinical decision-making. Additional research targeting those with relatively low serum triiodothyronine concentrations, but normal thyrotropin levels during monotherapy is needed to address whether there is a subgroup of patients who might benefit from combination therapy.

Insufficient evidence

Medscape

To T3 or Not: What's the Story on Combo Therapy in Hypothyroidism?

Nancy A Melville

December 18, 2014

Guidelines Recommend Only Against "Routine" Use of Combo


Dr Antonio Bianco


Dr Jacqueline Jonklaas

But among the most important phrases in the new ATA guidelines that should be underscored — loud and clear — is that they "recommend only against the *routine* use of combination therapy," said ATA president elect Antonio C Bianco, MD, PhD (chief, division of endocrinology and metabolism; executive vice chair, department of internal medicine, Rush University Medical Center, Chicago, Illinois), who cochaired the hypothyroidism task force along with Dr Jonklaas.

"At the same time, there are multiple instances in which combination therapy is supported," he told *Medscape Medical News*.

Those instances include when patients' serum TSH levels are normal but they are still symptomatic — which is when most clinicians are likely to consider the option.

Guidelines

European
Thyroid Journal

Eur Thyroid J 2012;1:55–71
DOI: 10.1159/000339444

Received: March 30, 2012
Accepted after revision: May 7, 2012
Published online: June 13, 2012

2012 ETA Guidelines: The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism

Wilmar M. Wiersinga[a] Leonidas Duntas[b] Valentin Fadeyev[c] Birte Nygaard[d]
Mark P.J. Vanderpump[e]

(2) Data suggest that 5–10% of L-T4-treated hypothyroid patients with normal serum TSH have persistent symptoms which can be related to the disease and L-T4 therapy

Recommendations

(4) There is insufficient evidence that L-T4 + L-T3 combination therapy serves the hypothyroid patient better than T4 monotherapy (1/++0).

(5

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Recommendations

(6) Limited data suggest that psychological well-being and preference for L-T4 + L-T3 combination therapy may be

pat

por

Recommendations

(7) It is suggested that L-T4 + L-T3 combination therapy might be considered as an experimental approach in compliant L-T4-treated hypothyroid patients who have persistent complaints despite serum TSH values within the reference range, provided they have previously given

supp

and a

(2/+0

(9) It is suggested that L-T4 + L-T3 combination therapy is discontinued if no improvement is experienced after 3 months (2/++0).

בחירת מטופלים

- TSH מאוזן מעל 6 חודשים

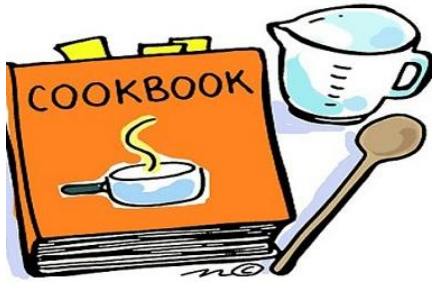
- תופעות תת פעילות + איכות חיים ירודה

- שלילת גורמים אחרים:

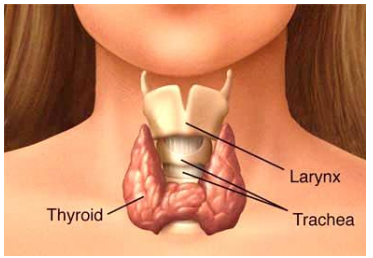
B12, פריטין, OSA, דכאון, (ויטמין D), קורטיזול

- פעילות גופנית

אין גורמים מנבאים



איך להוסיף T3?



ייצור יומי ממוצע: T4 87 מק"ג

T3 6 מק"ג (ועוד 26.5 מק"ג פריפרית)

- יחס: 1:14 (מומלץ יחס 1:13-1:20)
- T3 פוטנטי פי שלוש מ-T4
- לא Desiccated thyroid hormone – שם היחס 1:3-1:4

מרשם ל-T3:

מינון T4 סביב 100 מק"ג << T3 5 mcg

מינון T4 סביב 150 מק"ג << T3 10 mcg

T. Slow Release T3 *** mcg

Ix1/d 100

ניו-פארם

סופר-פארם

5 להוריד 50 מק"ג T4 בשבוע

10 להוריד 100 מק"ג T4 בשבוע

תחילת טיפול

שלושה ימים לא לקחת אף כדור *

ואז:

T4 במינון מופחת

+ T3 כל יום

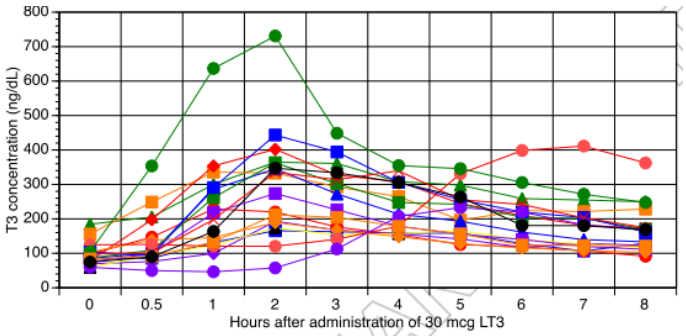
- **<u>אחרי חודש וחצי</u> – בדיקת דם והתאמת מינון T4**
- **<u>אחרי 3 חודשים</u> – פגישה עם TSH, FT4, FT3**

  + הערכת תגובה לטיפול

- **<u>איזון עדין</u>: פעמיים ביום, לעבור מ-5 מק"ג ל-10 מק"ג או הפוך**

Long term

- דאגה תיאורטית - שינויים ברמות T3 בדם



- אין עדות לתחלואת יתר (אוסטאופורוזיס, AF)

- אין נתונים על טיפול בהריון
- להיזהר בקשישים

לסיכום

- קבוצה קטנה של מטופלים – תופעות של תת פעילות למרות TSH מאוזן
- בחלקם הבעיה היא בטיפול עם T4 – בסיס ביולוגי

- תועלת בתוספת T3?
  - השאיפה – RCT גדול בחולים סימפטומטיים
  - יש עדויות נסיבתיות

- פער בין המדע ה"טהור" לבין הדאגה למטופלים כיום

- התערבות "פזיולוגית"
- גיבוי בספרות לביצוע ניסיון טיפולי

- <u>בעתיד</u> – התאמה פרקמקוגנטית

ד״ר איל רובינשטוק

058-4065363

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