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Therapie mit Schilddrüsenhormonen

Christian Trummer

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Interessenskonflikte:

Keine

82-jähriger Patient, geplante Herzkatheteruntersuchung

Thyreotropin, TSH	**4.07/+**	µU/mL	0.10-4.00
Freies Thyroxin	15.3	pmol/L	9.5-24.0
Freies Trijodthyronin	4.9	pmol/L	3.0-6.3

- Wen behandeln?
  - Manifeste Hypothyreose ✓

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Thyroxine treatment in patients with symptoms of hypothyroidism but thyroid function tests within the reference range: randomised double blind placebo controlled crossover trial

Conclusions Thyroxine was no more effective than placebo in improving cognitive function and psychological wellbeing in patients with symptoms of hypothyroidism but thyroid function tests within the reference range. Thyroxine did not improve cognitive function and psychological wellbeing in healthy participants.

Pollock et al., BMJ 2001

- Wen behandeln?
  - Manifeste Hypothyreose ✓
  - Latente Hypothyreose ?

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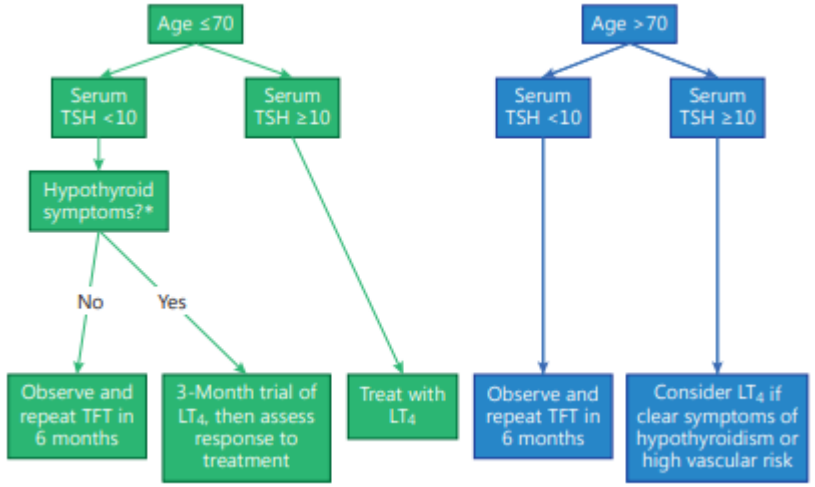
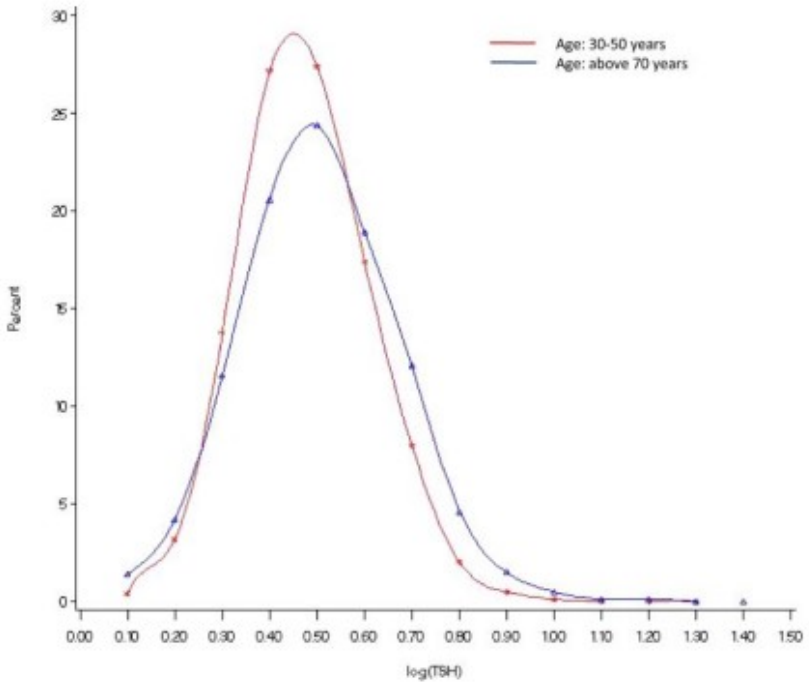
ETA European THYROID Association

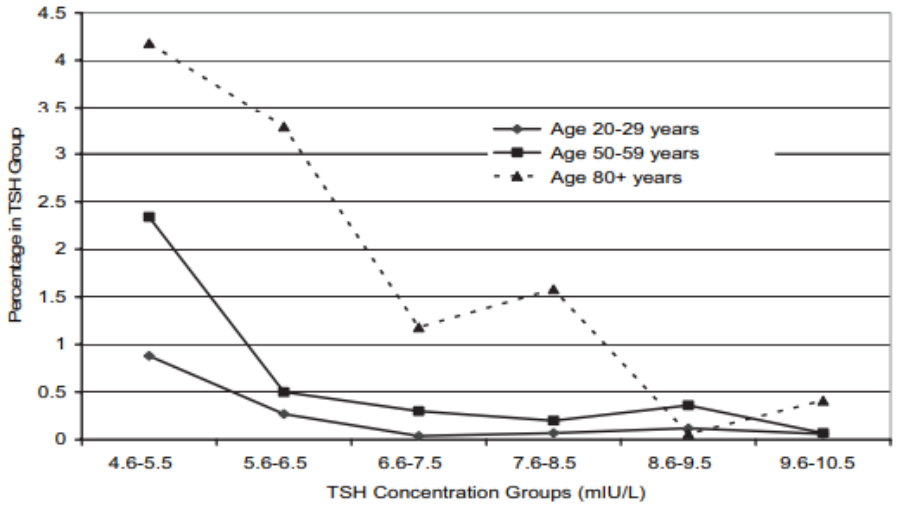


AMERICAN THYROID ASSOCIATION
ATA | *Founded 1923*

Patients whose serum TSH levels exceed 10 mIU/L are at increased risk for heart failure and cardiovascular mortality, and should be considered for treatment with L-thyroxine. **Grade B, BEL 1**

Pearce et al., Eur Thyroid J 2013 & Garber et al., Thyroid 2012





Surks et al., J Clin Endocrinol Metab 2007 & Vadiveloo et al., J Clin Endocrinol Metab 2013

1192 Patient*innen mit latenter Hypothyreose und Herzerkrankung, 136 (11,4%) behandelt mit Levothyroxin

↓

KEIN Effekt auf Mortalität, MACE oder Krankenhausaufenthalte

Andersen et al., J Clin Endocrinol Metab 2016

3093 Patient*innen zwischen 40-70 Jahren, 1642 Patient*innen über 70 Jahren mit latenter Hypothyreose

↓

Niedrigeres Risiko für ischämische kardiale Events bei Therapie und Alter zwischen 40-70

↓

ABER: kein Unterschied bei älteren Patient*innen

Razvi et al., Arch Intern Med 2012

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism

D.J. Stott, N. Rodondi, P.M. Kearney, I. Ford, R.G.J. Westendorp, S.P. Mooijaart, N. Sattar, C.E. Aubert, D. Aujesky, D.C. Bauer, C. Baumgartner, M.R. Blum, J.P. Browne, S. Byrne, T.-H. Collet, O.M. Dekkers, W.P.J. den Elzen, R.S. Du Puy, G. Ellis, M. Feller, C. Floriani, K. Hendry, C. Hurley, J.W. Jukema, S. Kean, M. Kelly, D. Krebs, P. Langhorne, G. McCarthy, V. McCarthy, A. McConnachie, M. McDade, M. Messow, A. O'Flynn, D. O'Riordan, R.K.E. Poortvliet, T.J Quinn, A. Russell, C. Sinnott, J.W.A. Smit, H.A. Van Dorland, K.A. Walsh, E.K. Walsh, T. Watt, R. Wilson, and J. Gussekloo, for the TRUST Study Group*

CONCLUSIONS

Levothyroxine provided no apparent benefits in older persons with subclinical hypothyroidism. (Funded by European Union FP7 and others; TRUST ClinicalTrials.gov number, NCT01660126.)

Subclinical Hypothyroidism and Cognitive Impairment: Systematic Review and Meta-Analysis

Giuseppe Pasqualetti, Gennaro Pagano, Giuseppe Rengo, Nicola Ferrara, and Fabio Monzani

Geriatrics Unit (G.Pas., F.M.), Department of Clinical & Experimental Medicine, University of Pisa, Pisa, Italy; King's College London (G. Pag.), Department of Clinical Neuroscience, London, United Kingdom; Department of Translational Medical Sciences (G.Pag., G.R., N.F.), Federico II University of Naples, Naples, Italy; and Salvatore Maugeri Foundation (G.R., N.F.), IRCCS Institute of Telese Terme, Benevento, Italy

Conclusions: This meta-analysis demonstrates a relationship between sHT and cognitive impairment only in individuals younger than 75 years of age and those with higher TSH concentrations. No correlation was found while considering all the studies as a whole. The lack of utilization of age-related serum TSH reference ranges and consequent potential misdiagnosis of sHT in older people may account for this. (***J Clin Endocrinol Metab* 100: 4240–4248, 2015**)

Stott et al., N Engl J Med 2017

Pasqualetti et al., J Clin Endocrinol Metab 2015

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Original Investigation

Subclinical Thyroid Dysfunction and Fracture Risk
A Meta-analysis

Manuel R. Blum, MD; Douglas C. Bauer, MD; Tinh-Hai Collet, MD; Howard A. Fink, MD, MPH; Anne R. Cappola, MD, ScM; Bruno R. da Costa, PhD; Christina D. Wirth, MD; Robin P. Peeters, MD, PhD; Bjørn O. Åsvold, MD, PhD; Wendy P. J. den Elzen, PhD; Robert N. Luben, PhD; Misa Imaizumi, MD, PhD; Alexandra P. Bremner, PhD; Apostolos Gogakos, MD, PhD; Richard Eastell, MD; Patricia M. Kearney, MD, PhD, MPH; Elsa S. Strotmeyer, MD, PhD; Erin R. Wallace, PhD; Mari Hoff, MD, PhD; Graziano Ceresini, MD, PhD; Fernando Rivadeneira, MD, PhD; André G. Uitterlinden, PhD; David J. Stott, MD, PhD; Rudi G. J. Westendorp, MD, PhD; Kay-Tee Khaw, MD; Arnuf Langhammer, MD, PhD; Luigi Ferrucci, MD, PhD; Jacobijn Gussekloo, MD, PhD; Graham R. Williams, MBBS, PhD; John P. Walsh, MBBS, PhD; Peter Jüni, MD; Drahomir Aujesky, MD, MSc; Nicolas Rodondi, MD, MAS; for the Thyroid Studies Collaboration

Subclinical Hypothyroidism and Fracture Risk

We found no association between subclinical hypothyroidism and fracture risks either overall (eFigure 2 in Supplement 1) or in stratified analyses (eTable 7 in Supplement 1), with an HR compared with euthyroid participants of 0.96 (95% CI, 0.83-

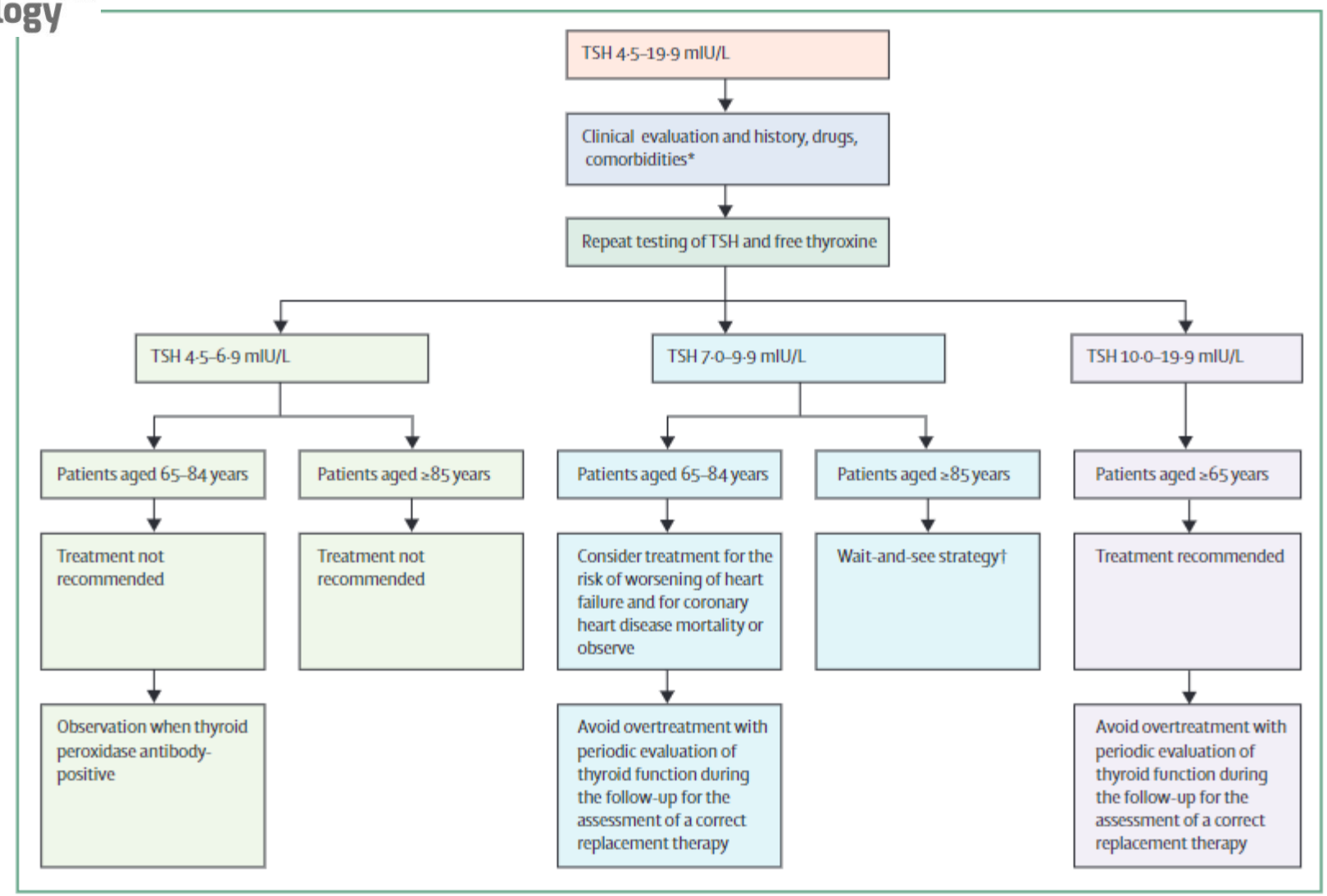
CONCLUSIONS AND RELEVANCE Subclinical hyperthyroidism was associated with an increased risk of hip and other fractures, particularly among those with TSH levels of less than 0.10 mIU/L and those with endogenous subclinical hyperthyroidism. Further study is needed to determine whether treating subclinical hyperthyroidism can prevent fractures.

Conclusions: Differentiated thyroid cancer patients have an increased CVD morbidity, which is mostly accountable to AF and to TSH suppression below 0.1 mU/L.

Conclusion

The risk of cardiovascular and all-cause mortality is increased in patients with DTC, independent of age, sex, and cardiovascular risk factors. A lower TSH level is associated with increased cardiovascular mortality, supporting the current European Thyroid Association and the American Thyroid Association guidelines of tempering TSH suppression in patients with low risk of cancer recurrence. Furthermore, patients with DTC may benefit from assessment and treatment of cardiovascular risk factors.

Pejamäki et al., Clin Endocrinol (Oxf) 2018 & Hesselink et al., J Clin Oncol 2013



Pearce et al., Eur Thyroid J 2013 & Garber et al., Thyroid 2012

Biondi et al., Lancet Diabetes Endocrinol 2022

82-jähriger Patient, geplante Herzkatheteruntersuchung

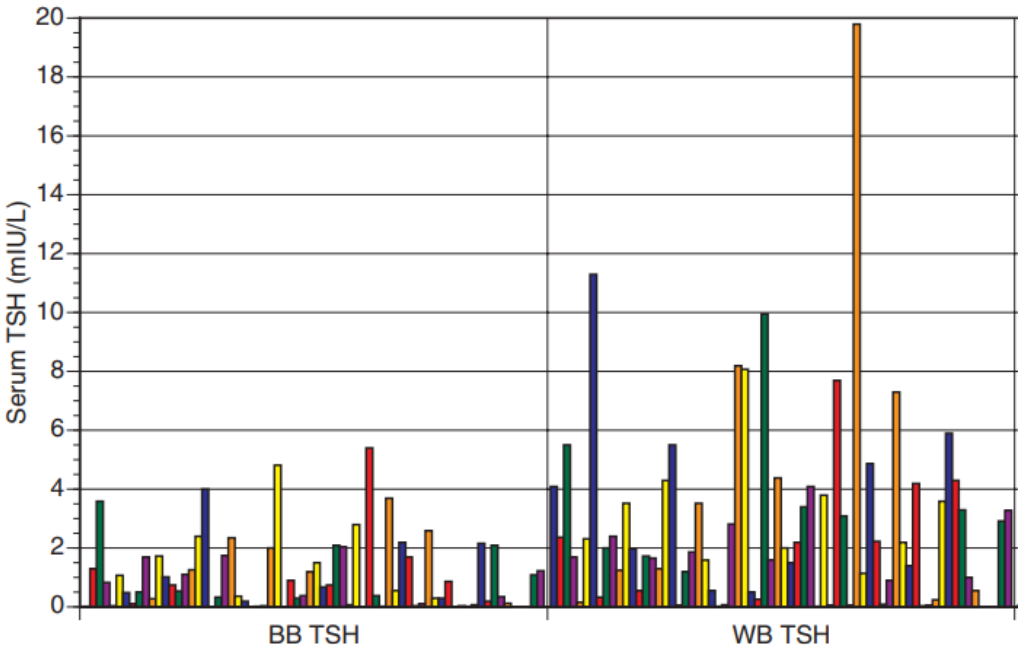
Thyreotropin, TSH	**4.07/+**	µU/mL	0.10-4.00
Freies Thyroxin	15.3	pmol/L	9.5-24.0
Freies Trijodthyronin	4.9	pmol/L	3.0-6.3

32-jährige Patientin, aktuell 9. Schwangerschaftswoche

Ausgeprägte morgendliche Übelkeit, ab mittags meist beschwerdefrei

Hashimoto-Thyreoiditis, derzeit 100 µg Levothyroxin pro Tag

- Wen behandeln?
  - Manifeste Hypothyreose ✓
  - Latente Hypothyreose ?
- Wann einnehmen?



Bach-Huynh et al., J Clin Endocrinol Metab

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?

Nüchterne Einnanme 30-60 Minuten vor dem Frühstück

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Effect of L-thyroxine administration before breakfast vs at bedtime on hypothyroidism: A meta-analysis

Xiao Pang[1] | Tao Pu[1] | Li Xu[1] | Ru Sun[2]

- 687 Patient*innen unter Levothyroxintherapie aus sieben Ländern
- prospektive oder randomisierte Studien, die eine morgendliche Einnahme mit einer abendlichen vergleichen
- KEIN Unterschied für TSH und fT3, höhere fT4-Spiegel bei Abendgabe
- in den meisten Studien wurde Levothyroxin ca. zwei Stunden nach der letzten Abendmahlzeit genommen, teilweise auch noch später

Pang et al., Clin Endocrinol (Oxf) 2020

- morgendliche Einnahme 30 (vermutlich besser 60) Minuten vor dem Frühstück
- abendliche Einnahme möglich, falls ein entsprechender Abstand zur letzten Mahlzeit eingehalten wird (mindestens zwei Stunden, optimal länger)
- Abstand zu Nahrungsaufnahme wichtiger für Patient*innen mit spezifischem bzw. engerem TSH-Ziel

- Wen behandeln?
  - Manifeste Hypothyreose ✓
  - Latente Hypothyreose ?
- Wann einnehmen?
- Was einnehmen?

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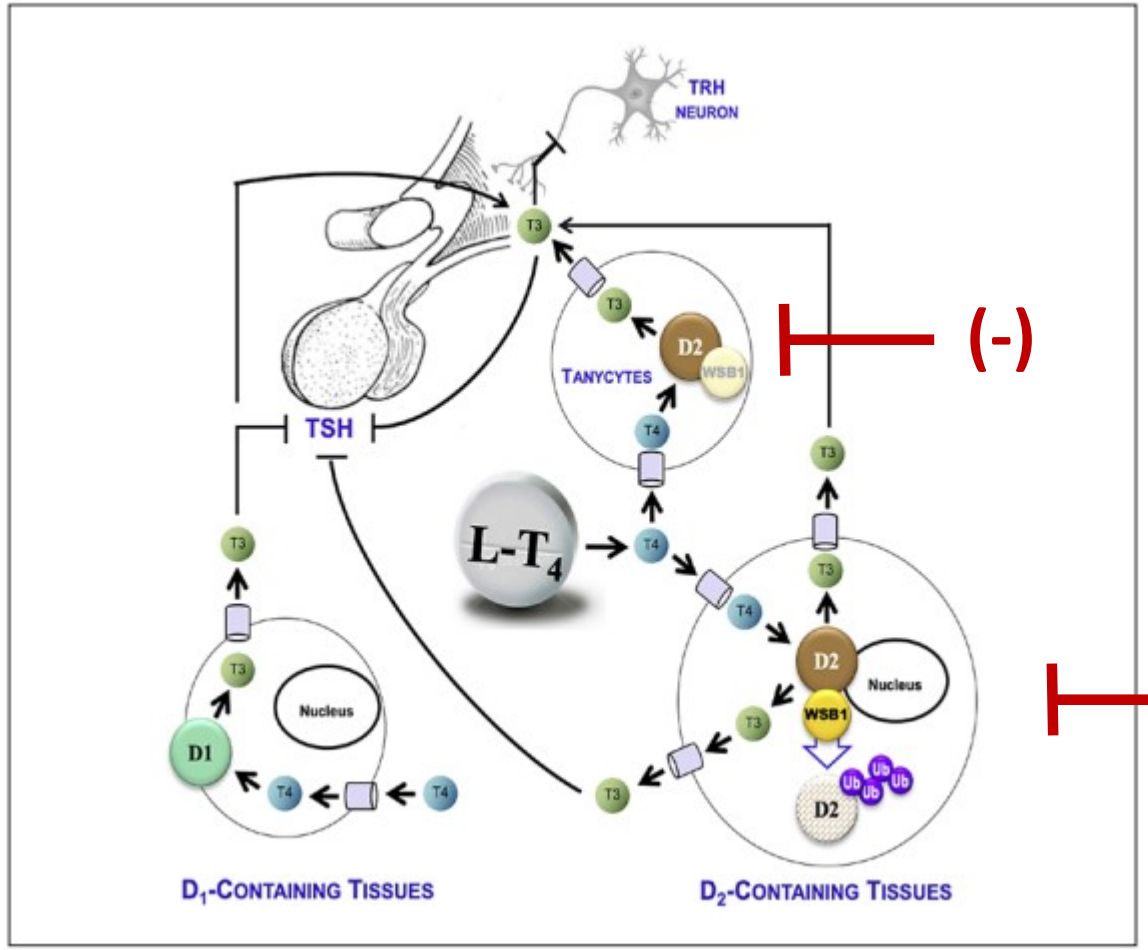
1a. Is levothyroxine monotherapy considered to be the standard of care for hypothyroidism?

- **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.

LT4 und LT3 Kombinationstherapie?

Jonklaas et al., Thyroid 2014



(-)

-

TSH normal
fT3 untere Norm oder leicht erniedrigt

Jonklaas et al., Eur Thyroid J 2021

Thr92Ala Polymorphismus im DIO2-Gen

	Pre-surgical FT3 (pg/ml)	Post-surgical FT3 (pg/ml)	p
WT			
Mean±SD	3.2±0.35	3.1±0.36	
Range	2.4-3.9	2.6-4.1	0.097
Median	3.2	3.1	
Thr/Ala			
Mean±SD	3.4±0.52	3.0±0.28	
Range	2.7-5.4	2.5-3.9	<0.0001
Median	3.3	2.9	
Ala/Ala			
Mean±SD	3.4±0.37	2.9±0.34	
Range	2.9-4.2	2.5-3.6	0.01
Median	3.4	2.9	

- schlechteres psychisches Wohlbefinden (GHQ-12)
- Verbesserung unter Kombipräparat
- kein Effekt auf Schilddrüsenhormone

Panicker et al., J Clin Endocrinol Metab 2009

- kein Effekt auf TSH, fT3, fT4
- kein Effekt auf Wohlbefinden (HRQoL)
- kein Effekt auf kognitive Funktion

Wouters et al., Thyroid 2017

Castagna et al., J Clin Endocrinol Metab 2017

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A Systematic Review and Meta-Analysis of Patient Preferences for Combination Thyroid Hormone Treatment for Hypothyroidism

Amit Akirov [1,2,3], Rouhi Fazelzad [4], Shereen Ezzat [1], Lehana Thabane [5] and Anna M. Sawka [6]*

[1] Department of Endocrine Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada, [2] Institute of Endocrinology, Beilinson Hospital, Petach Tikva, Israel, [3] Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel, [4] Princess Margaret Cancer Centre, University Health Network Library and Information Services, Toronto, ON, Canada, [5] Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada, [6] Division of Endocrinology, University Health Network and University of Toronto, Toronto, ON, Canada

- 7 verblindete RCTs
- Präferenz Kombinationstherapie 46,2%
- Positive Assoziation zwischen LT3-Dosis und Therapiepräferenz, keine Assoziation mit LT3:LT4-Ratio

Conclusions: In conclusion, in RCTs in which patients and investigators were blinded to treatment allocation, approximately half of participants reported preferring combination L-T3 and L-T4 therapy compared to L-T4 alone; this finding was not distinguishable from chance. An observed potential positive L-T3 dose effect on treatment preference deserves further study, with careful consideration of thyroid biochemical indices and patient reported outcomes.

Akirov et al., Front Endocrinol 2019

- Halbwertszeit von LT3: ca. 22h
- Monotherapie mit LT3 (1x täglich) führt zu unakzeptabel hohen T3-Konzentrationen, Monotherapie mit 3x täglicher Gabe zu einer kontinuierlichen Fluktuation der Serumspiegel
- in bisherigen Studien: meist Verwendung von 1x täglicher Verabreichung, selten 2x täglich
- Pharmakologische Äquivalenzdosis LT3 vs. LT4 liegt bei ca. 1:3
- Körpereigene Produktion T4:T3 ca. 14:1

1) Formulierung/Zusammensetzung verfügbarer Präparate

2) Einmalige tägliche Gabe unzureichend

3) Derzeit keine „slow-release“ Präparate verfügbar

4) Therapiemonitoring nicht vollständig geklärt

Kombinationspräparate für wen? Wie?

- Patient*innen mit anhaltenden hypothyreoten Symptomen trotz adäquater LT4-Therapie
- biochemische Messungen (z.B. rT3), genetische Abklärung oder neuropsychiatrische Testung derzeit nicht empfohlen
- keine Einleitung von Kombinationspräparaten bei Schwangeren, Kinderwunsch, kardialen Arrhythmien oder kardiovaskulären Erkrankungen
- Aufklärung über Behandlung außerhalb des Standards, Beenden nach 3-6 Monaten ohne Erfolg
- falls möglich, Start mit einer LT4:LT3-Ratio von 13:1 bis 20:1, falls möglich Aufteilung auf 2x täglich
- adäquate Reduktion von LT4 (Umrechnung von LT3 zu LT4 ca. 1:3)
- bei Serum T3 2-4h nach Gabe in der Norm und kein supprimiertes TSH, vermutliche sichere Dosis
- bei Langzeittherapie Osteodensitometrie, EKG, regelmäßige Pulsmessung empfohlen

Jonklaas et al., Eur Thyroid J 2021

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

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  Strong recommendation. Moderate quality evidence.

LT4 und LT3 Kombinationstherapie?

Tabletten?

Jonklaas et al., Thyroid 2014

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Tabletten

Gelkapseln

(Flüssiges LT4)

- prinzipiell bei „gesunden“ Patient*innen Tablettenform sehr wahrscheinlich suffizient
- aber: wahrscheinlich weniger Abhängigkeit vom Magen-pH bei Gelkapseln (Vita et al., Endocr Pract 2014)
- Option für Patient*innen mit vermutlich eingeschränkter Absorption (z.B. A-Gastritis, PPI)
- vielleicht auch Benefit bei Patient*innen nach bariatrischer Operation (Fallahi et al., Obes Surg 2017)

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LT4 und LT3 Kombinationstherapie?

Tabletten?

Schilddrüsenextrakt (DTE)?

Jonklaas et al., Thyroid 2014

- Extrakte aus tierischen Schilddrüsen, meistens vom Schwein
- Standardtherapie bis zu den 1960ern
- vergleichbare Bioverfügbarkeit mit synthetischen Schilddrüsenhormonen (LeBoff et al., Metabolism 1982)
- T4:T3-Ratio in DTE-Präaparaten 4,2:1 (physiologisch ca. 14:1)
- enthält außerdem unbestimmte Mengen von Diiodothyronin, Monoiodothyronin und Calcitonin
- an Platz 130 der am häufigsten verschriebenen Medikamente in den USA (2017, 5,5 Millionen Verschreibungen)

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AMERICAN THYROID ASSOCIATION
ATA | *Founded 1923*

■ **RECOMMENDATION**

We recommend that levothyroxine be considered as routine care for patients with primary hypothyroidism, in preference to use of thyroid extracts. Although there is preliminary evidence from a short-duration study that some patients may prefer treatment using thyroid extracts, high-quality controlled long-term outcome data are lacking to document superiority of this treatment compared to levothyroxine therapy. Furthermore, there are potential safety concerns related to the use of thyroid extracts, such as the presence of supraphysiologic serum triiodothyronine levels and a paucity of long-term safety outcome data.

Strong recommendation. Moderate quality evidence.

Jonklaas et al., Thyroid 2014

AACE

Thus, there are no controlled trials supporting the preferred use of desiccated thyroid hormone over synthetic L-thyroxine in the treatment of hypothyroidism or any other thyroid disease.

Garber et al., Endocr Pract 2012

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Clinical Research Article

Comparative Effectiveness of Levothyroxine, Desiccated Thyroid Extract, and Levothyroxine+Liothyronine in Hypothyroidism

Mohamed K.M. Shakir,[1,2] Daniel I. Brooks,[1] Elizabeth A. McAninch,[3] Tatiana L. Fonseca,[4] Vinh Q. Mai,[1,2] Antonio C. Bianco,[4] and Thanh D. Hoang[1,2]

- 75 Patient*innen mit Hypothyreose
- LT4, LT4+LT3 oder DTE
- TSH im Referenzbereich in allen Gruppen
- in Subgruppenanalyse Präferenz für LT3/DTE bei den Patient*innen mit den meisten Symptomen unter LT4

Shakir et al., J Clin Endocrinol Metab, 2021

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]

Conclusions: A subset of patients with hypothyroidism are not satisfied with their current therapy or their physicians. Higher satisfaction with both treatment and physicians is reported by those patients on DTE. While the study design does not provide a mechanistic explanation for this observation, future studies should investigate whether preference for DTE is related to triiodothyronine levels or other unidentified causes.

Peterson et al., Thyroid 2018

Probleme

- supraphysiologischer Gehalt an T3
- Risiko für (intermittierende) Thyreotoxikose
- kurze Halbwertszeit von T3
- keine Daten zu Langzeitwirkungen und unerwünschten Wirkungen

?

Take Home Messages

Therapieentscheidung in Abhängigkeit von Alter und Komorbiditäten ✓

Ältere Patient*innen mit milder Hypothyreose oft ohne Therapieindikation ✓

Gabe von Schilddrüsenhormonen nicht zwingend morgens notwendig ✓

Alternative Verabreichungsformen bei möglichen Aufnahmeproblemen ✓

Kombinationspräparate ?

DTE ?

Vielen Dank für Ihre Aufmerksamkeit

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