Sammendrag av statistikker bivirkninger:

Norge: (Merk at man i Norge ikke har bivirkningsrapporter i database lenger tilbake enn til 2006. Dere vil se at det er annerledes i andre land)
Ved henvendelse til Legemiddelverket fikk vi dette svaret fra dem:

For Armour Thyroid har vi ingen meldinger om bivirkninger i den norske databasen.
For Thyroid (Erfa) har vi én lite alvorlig melding om magesmerter og besvimelse.

Levaxin: Innrapportert fra 2006 til 1. april 2014
38 rapporter, 157 bivirkninger
Liothyronin: Innrapportert fra 2006 til 1. april 2014
3 rapporter, 5 bivirkninger

Danmark:
Merk: Levothyroxine i Danmark betyr enten Euthyrox eller Elthroxin
Levothyroxine: innrapportert fra 1. januar 1968 til 24. februar 2014
1358 rapporter, 7513 bivirkninger
Thyroid (vil som regel i Danmark bety Thyreoid som lages av Glostrup Apotek, samt Armour eller Erfa):
Innrapportert fra 1. januar 1968 til 24. februar 2014
5 rapporter, 5 bivirkninger

Storbritannia:
Her har vi ikke fått rapport på Levothyroxine
Liothyronine: Innrapportert fra 1. juli 1963 til 9. mai 2014
107 rapporter, 532 bivirkninger
Thyroid (er som regel Armour eller Thyroid Erfa): Innrapportert fra 1. juli 1963 til 9. mai 2014
1 rapport, 2 bivirkninger

Canada:
Levothyroxine: Innrapportert fra 1. januar 1965 til 31. mars 2014
562 rapporter
Thyroid: Innrapportert fra 1. januar 1965 til 31. mars 2014
53 rapporter

Vi mener at tendensen her er tydelig - særlig gjelder dette UK og Canada der man også kan se på statistikken fra før man begynte å bruke Levothyroxine som substitutt for NDT.

Studier som viser at ikke alle blir friske med T4-monoterapi

Dansk doktorgrad fra 2014 viser at stoffskiftesykdommer gir økt risiko for langvarig sykefravær, førtidspensjon og innkomsttap. Merk at studien er gjort på pasienter som altså allerede har en diagnose og får behandling. Likevel har de langt større sjanse for å bli satt på uførepensjon etc sammenlignet med normalpolulasjon

Mette Nexø, 2014 http://www.arbejdsmiljoforskning.dk/~/media/Boeger-og-rapporter/Mette-Nexo-phdafhandling-sept2014.pdf

Lenke til artikkel skrevet på bakgrunn av doktorgraden her:
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4207932/

Lenker til artikler skrevet om doktorgraden:
http://www.dailyrx.com/hyperthyroidism-patients-took-more-sick-leave-and-were-more-likely-be-disability-healthy-peers
http://www.healio.com/endocrinology/thyroid/news/online/%7Bffe5fb14-7914-4eab-9243-8b0ceb1d26d5%7D/thyroid-disease-diagnosis-leads-to-work-absence-disability-in-first-year
http://www.medscape.com/viewarticle/827597
http://www.eurekalert.org/pub_releases/2014-06/tes-hpm061314.php

Stofskiftesygdomme giver øget risiko for langvarigt sygefravær, førtidspension og indkomsttab
http://www.sdu.dk/Om_SDU/Fakulteterne/Sundhedsvidenskab/Nyt_SUND/stofskiftesygdomme

Norsk Masteroppgave i helse- og sosialfag fra 2008, Universitetet I Stavanger, Hilde Frafjord " Brukermedvirkning.....hva er det?" **En kvalitativ studie av hvordan unge voksne med hypothyreose opplever brukermedvirkningen I helsetjenesten**

Vi ber dere særlig se på kapittel 4.1.1. (side 46) der brukerne forteller at de stadig går til lege med ulike symptomer, men ikke blir trodd. Blant annet:

"Jeg finner meg ikke i at når de sier at når du har hypothyreose og går på medisin, så er du frisk, når jeg kommer og sier at jeg ikke er det "

" Jeg føler at legen bagatelliserer det. Nå får du behandling og nå skal alt være greit. Men jeg opplever at det ikke er slik, fordi jeg føler at jeg har en del ubehag som er relatert til dette. Og det har stor innvirkning på min hverdag"

JA Romijn, JW Smit and SW Lamberts 2003 Department of Endocrinology, Leiden University Medical Center Intrinsic imperfections of endocrine replacement therapy,

Abstract Hormonal substitution therapy has been extremely successful, with respect to morbidity and mortality, in the treatment of the major syndromes of endocrine insufficiency. However, many patients treated for endocrine insufficiencies still suffer from more or less vague complaints and a decreased quality of life. It is likely that these complaints are, at least in part, caused by intrinsic imperfections of hormone replacement strategies in mimicking normal hormone secretion. Unfortunately, these complaints are often difficult to assess by clinicometric or biochemical tests, because the effects of hormones in general, and thus of hormone replacement strategies in particular, are difficult to quantify at the tIssue level. Therefore, in clinical practice we rely mostly on plasma variables - 'plasma endocrinology' - which are a poor

reflection of hormone action at the tIssue level. Appreciation of these intrinsic shortcomings of endocrine therapy is of utmost importance to prevent incorrect labelling of the complaints of many endocrine patients and to achieve further improvement in endocrine replacement strategies.

H F Escobar-Morreale, M J Obregón, F Escobar del Rey, and G Morreale de Escobar
Replacement therapy for hypothyroidism with thyroxine alone does not ensure euthyroidism in all tissues, as studied in thyroidectomized rats.

Abstract We have studied whether, or not, tissue-specific regulatory mechanisms provide normal 3,5,3'-triiodothyronine (T3) concentrations simultaneously in all tissues of a hypothyroid animal receiving thyroxine (T4), an assumption implicit in the replacement therapy of hypothyroid patients with T4 alone. Thyroidectomized rats were infused with placebo or 1 of 10 T4 doses (0.2-8.0 micrograms per 100 grams of body weight per day). Placebo-infused intact rats served as controls. Plasma and 10 tissues were obtained after 12-13 d of infusion. Plasma thyrotropin and plasma and tissue T4 and T3 were determined by RIA. Iodothyronine-deiodinase activities were assayed using cerebral cortex, liver, and lung. No single dose of T4 was able to restore normal plasma thyrotropin, T4 and T3, as well as T4 and T3 in all tissues, or at least to restore T3 simultaneously in plasma and all tissues. Moreover, in most tissues, the dose of T4 needed to ensure normal T3 levels resulted in supraphysiological T4 concentrations. Notable exceptions were the cortex, brown adipose tissue, and cerebellum, which maintained T3 homeostasis over a wide range of plasma T4 and T3 levels. Deiodinase activities explained some, but not all, of the tissue-specific and dose related changes in tissue T3 concentrations. In conclusion, euthyroidism is not restored in plasma and all tissues of thyroidectomized rats on T4 alone. These results may well be pertinent to patients on T4 replacement therapy.

Behovet for flere behandlingsalternativer

Mehmet Asik, Fahri Gunes, Emine Binnetoglu, Mustafa Eroglu, Neslihan Bozkurt, Hacer Sen, Erdem Akbal, Coskun Bakar, Yavuz Beyazit, Kubilay Ukinc Sept 2013

Decrease in TSH levels after lactose Restriction in Hashimoto´s thyroiditis patients with lactose intolerance

Abstract

We aimed to evaluate the prevalence of lactose intolerance (LI) in patients with Hashimoto's thyroiditis (HT) and the effects of lactose restriction on thyroid function in these patients. Eighty-three HT patients taking l-thyroxine (LT4) were enrolled, and lactose tolerance tests were performed on all patients. Lactose intolerance was diagnosed in 75.9% of the patients with HT. Thirty-eight patients with LI were started on a lactose-restricted diet for 8 weeks. Thirty-eight patients with LI (30 euthyroid and 8 with subclinical hypothyroidism), and 12 patients without LI were included in the final analysis. The level of TSH significantly decreased in the euthyroid and subclinical hypothyroid patients with LI [from 2.06 ± 1.02 to 1.51 ± 1.1 IU/mL and from 5.45 ±

0.74 to 2.25 ± 1.88 IU/mL, respectively (both $P < 0.05$)]. However, the level of TSH in patients without LI did not change significantly over the 8 weeks ($P > 0.05$). Lactose intolerance occurs at a high frequency in HT patients. Lactose restriction leads to decreased levels of TSH, and LI should be considered in hypothyroid patients who require increasing LT4 doses, have irregular TSH levels and are resistant to LT4 treatment.

***Thyroid,* Manuel Muñoz-Torres, Mariela Varsavsky, and Guillermo Alonso. Thyroid. November 2006. Lactose Intolerance Revealed by Severe Resistance to Treatment with Levothyroxine**

Abstract: The most common cause of apparent ineffectiveness or resistance to treatment with oral levothyroxine (LT_4) is the result of noncompliance, known as pseudomalabsorption. However, an abnormality in the bioavailability of LT_4 should also be considered in patients requiring large doses of LT_4 to achieve euthyroidism. The incidence of lactose intolerance in Caucasian adult patients is 7%–20%, but the association with resistance to treatment with oral LT_4 is unusual. We report a 55-year-old woman in whom treatment LT_4 for hypothyroidism was found related to a previously undiagnosed oligo-symptomatic lactose intolerance, an unusual association. Although rare, intolerance to lactose should be considered in the differential diagnosis of gastrointestinal diseases that can cause malabsorption of LT_4. The possibility of correcting this disorder with simple dietary measures justifies its consideration.

Acosta B, Bianco, A C (2010). New insights into thyroid hormone replacement therapy. *Medicine Reports.* 2010; 2: 34.

Abstract: Physicians continue to report benefits from combined levothyroxine-triidothyronine therapy for some hypothyroid patients. Recently, a large prospective study reported that the benefit of the combined levothyroxine-triidothyronine therapy is associated with the Thr92Ala polymorphism in the type 2 deiodinase gene, which is present in about 15% of the general population. If confirmed, these findings indicate that personalized medicine is rapidly catching up with modern thyroidology.

Appelhof, B. C., Fliers, E., Wekking, E. M., Schene, A. H., Huyser, J., Tijssen, J. G., ... & Wiersinga, W. M. (2005). Combined therapy with levothyroxine and liothyronine in two ratios, compared with levothyroxine monotherapy in primary hypothyroidism: a double-blind, randomized, controlled clinical trial. *The Journal of Clinical Endocrinology & Metabolism*, *90*(5), 2666-2674.

Abstract: Patients preferred combined LT4/LT3 therapy to usual LT4 therapy, but changes in mood, fatigue, well-being, and neurocognitive functions could not satisfactorily explain why the primary outcome was in favor of LT4/LT3 combination therapy. Decrease in body weight was associated with satisfaction with study medication.

Dr. John C. Lowe, Thyroid Science 2009 Stability, Effectiveness, and Safety of Desiccated

Thyroid vs Levothyroxine: A Rebuttal to the British Thyroid Association,
Forskningskritikk

Department of Endocrinology and Metabolism, Academic Medical Centre, University of Amsterdam, The Netherlands, 2001 Thyroid Hormone Replacement Therapy **Utdrag**: Third, recent animal experiments indicate that only the combination of T_4 and T_3 replacement, and not T_4 alone, ensures euthyroidism in all tissues of thyroidectomized rats. It is indeed the experience of many physicians that there exists a small subset of hypothyroid patients who, despite biochemical euthyroidism, continue to complain of tiredness, lack of energy, discrete cognitive disorders and mood disturbances. As organs vary in the extent to which their T_3 content is derived from serum T_3 or locally produced T_3 from T_4, these complaints may have a biologic substrate; for example, brain T_3 content is largely determined by local deiodinase type II activity. Against this background it is of interest that a number of psychometric scores improved significantly in hypothyroid patients upon substitution of 50 µg of their T_4 replacement dose by 12.5 µg T_3. Confirmatory studies on this issue are urgently awaited. It could well be that a slow-release preparation containing both T_4 and T_3 might improve the quality of life, compared with T_4 replacement alone, in some hypothyroid patients.

Baisier, W.V., Hertoghe, J., and Eeckhaut, W. (2001). Thyroid Insufficiency: Is Thyroxine the Only Valuable Drug? *Journal of Nutritional and Environmental Medicine*, 11:159-166, 2001.
Results: A number of these patients were followed up during treatment with natural desiccated thyroid (NDT): 40 T4 treated patients and 278 untreated patients. Both groups responded equally favourably to NDT.
Conclusions: Combined T3 + T4 treatment seems to be more effective than treatment with T4 alone in hypothyroid patients.

Benevicius R, Kazanavicius G, Zalinkovicius R, Prange AJ (1999). Effects of thyroxine (T4) as compared with thyroxine (T4) plus triiodothyronine (T3) in patients with hypothyroidism. *New England Journal of Medicine.*1999; 340: 424-9.
Conclusions: In patients with hypothyroidism, partial substitution of triiodothyronine for thyroxine (medication) may improve mood and neuropsychological function; this finding suggests a specific effect of the triiodothyronine normally secreted by the thyroid gland.

Damiano Gullo,#* Adele Latina,# Francesco Frasca, Rosario Le Moli, Gabriella Pellegriti, and Riccardo Vigneri, PLOS one peer reviewed journal 2011 Levothyroxine Monotherapy Cannot Guarantee Euthyroidism in All Athyreotic Patients
Abstract
Context
Levothyroxine monotherapy is the treatment of choice for hypothyroid patients because peripheral T4 to T3 conversion is believed to account for the overall tissue requirement for

thyroid hormones. However, there are indirect evidences that this may not be the case in all patients.

Objective

To evaluate in a large series of athyreotic patients whether levothyroxine monotherapy can normalize serum thyroid hormones and thyroid-pituitary feedback.

Conclusions

Athyreotic patients have a highly heterogeneous T3 production capacity from orally administered levothyroxine. More than 20% of these patients, despite normal TSH levels, do not maintain FT3 or FT4 values in the reference range, reflecting the inadequacy of peripheral deiodination to compensate for the absent T3 secretion. The long-term effects of chronic tissue exposure to abnormal T3/T4 ratio are unknown but a sensitive marker of target organ response to thyroid hormones (serum TSH) suggests that this condition causes an abnormal pituitary response. A more physiological treatment than levothyroxine monotherapy may be required in some hypothyroid patients.

Biondi, B., & Wartofsy, L. (2012). Combination Treatment with T4 and T3: Toward Personalized Replacement Therapy in Hypothyroidism?. *The Journal of Clinical Endocrinology & Metabolism.*

Conclusions: Further prospective randomized controlled studies are needed to clarify this important issue. Innovative formulations of the thyroid hormones will be required to mimic a more perfect thyroid hormone replacement therapy than is currently available.

Giorgio Iervasi, MD; Alessandro Pingitore, MD, PhD; Patrizia Landi, BSc; Mauro Raciti, BSc; Andrea Ripoli, PhD; Maria Scarlattini, BSc; Antonio L'Abbate, MD; Luigi Donato, MD

From C.N.R. Clinical Physiology Institute and Scuola Superiore di Studi Univeritari S. Anna (A.L.A.), Pisa, Italy .**Low-T3 Syndrome: A Strong Prognostic Predictor of Death in Patients With Heart Disease American Heart Association, 2002.**

Abstract

Background— Clinical and experimental data have suggested a potential negative impact of low-T3 state on the prognosis of cardiac diseases. The aim of the present prospective study was to assess the role of thyroid hormones in the prognosis of patient population with heart disease.

Methods and Results— A total of 573 consecutive cardiac patients underwent thyroid function profile evaluation. They were divided in two subgroups: group I, 173 patients with low T3, ie, with free T3 (fT3) <3.1 pmol/L, and group II, 400 patients with normal fT3 (≥3.1 pmol/L). We considered cumulative and cardiac death events. During the 1-year follow-up, there were 25 cumulative deaths in group I and 12 in group II (14.4% versus 3%, $P<0.0001$); cardiac deaths were 13 in group I and 6 in group II (7.5% versus 1.5%, $P=0.0006$). According to the Cox model, fT3 was the most important predictor of cumulative death (hazard ratio [HR] 3.582, $P<0.0001$), followed by dyslipidemia (HR 2.955, $P=0.023$), age (HR 1.051, $P<0.005$), and left ventricular ejection fraction (HR 1.037, $P=0.006$). At the logistic multivariate analysis, fT3 was the highest independent predictor of death (HR 0.395, $P=0.003$). A prevalence of low fT3 levels was found in patients with NYHA class III-IV illness compared with patients with NYHA class I-II (χ_2 5.65,

P=0.019).

Conclusions— Low-T3 syndrome is a strong predictor of death in cardiac patients and might be directly implicated in the poor prognosis of cardiac patients.

Alessandro Pingitore, Elena Galli, Andrea Barison, Annalisa Iervasi, Maria Scarlattini, Daniele Nucci, Antonio L'Abbate, Rita Mariotti, and Giorgio Iervasi Acute Effects of Triiodothyronine (T_3) Replacement Therapy in Patients with Chronic Heart Failure and Low-T_3 Syndrome: A Randomized, Placebo-Controlled Study

Received: October 02, 2007
Accepted: December 26, 2007
Published Online: July 02, 2013

Abstract

Context: Low-T_3 syndrome is a predictor of poor outcome in patients with cardiac dysfunction. The study aimed to assess the short-term effects of synthetic l-T_3 replacement therapy in patients with low-T_3 syndrome and ischemic or nonischemic dilated cardiomyopathy (DC).

Conclusions: In DC patients, short-term synthetic l-T_3 replacement therapy significantly improved neuroendocrine profile and ventricular performance. These data encourage further controlled trials with more patients and longer periods of synthetic l-T_3 administration.

Celi, F. S., Zemskova, M., Linderman, J. D., Smith, S., Drinkard, B., Sachdev, V., ... & Pucino, F. (2011). Metabolic effects of liothyronine therapy in hypothyroidism: a randomized, double-blind, crossover trial of liothyronine versus levothyroxine. *The Journal of Clinical Endocrinology & Metabolism*,*96*(11), 3466-3474.

Results: Liothyronine (l-T3) resulted in significant weight loss [l-T4, 70.6 ± 12.5, *vs.* l-T3, 68.5 ± 11.9 kg (*P* = 0.009)] and in a 10.9 ± 10.0% decrease in total cholesterol (*P* = 0.002), 13.3 ± 12.1% decrease in low-density lipoprotein-cholesterol (*P* = 0.002), and an 18.3 ± 28.6% decrease in apolipoprotein B (*P* = 0.018). Conclusions: The substitution of l-T3 for Levothyroxine (l-T4) at equivalent doses (relative to the pituitary) reduced body weight and resulted in greater thyroid hormone action on the lipid metabolism, without detected differences in cardiovascular function or insulin sensitivity.

Chakera, A.J., Pearce, S.H., Vaidya, B. (2012) Treatment for primary hypothyroidism: current approaches and future possibilities. *Drug Des Devel Ther.*; 6: 1-11.

Conclusion: Primary hypothyroidism is the most common endocrine disease. Although the diagnosis and treatment of hypothyroidism is often considered simple, there are large numbers of people with this condition who are suboptimally treated. Even in those people with hypothyroidism who are biochemically euthyroid on levothyroxine replacement there is a significant proportion who report poorer quality of life. This review explores the historical and current treatment options for hypothyroidism, reasons for and potential solutions to suboptimal

treatment, and future possibilities in the treatment of hypothyroidism.

Chernow B, Burman KD, Johnson DL, McGuire RA, O'Brian JT, Wartofsky L, Georges LP (1983). **T3 may be a better agent than T4 in the critically ill hypothyroid patient: evaluation of transport across the blood-brain barrier in a primate model.** ***Critical Care Medicine.*** **1983 Feb;11(2):99-104**.
Conclusions: These data suggest: (a) T4, T3, and reverse T3 are all capable of bidirectional transfer across the blood brain barrier, (b) T3 may be a better agent than T4 in treating patients with myxedema coma because T3 crosses more rapidly and more completely from serum to cerebrospinal fluid (CSF).

Cooper-Kazaz, R., Apter, J. T., Cohen, R., Karagichev, L., Muhammed-Moussa, S., Grupper, D., ... & Lerer, B. (2007). **Combined treatment with sertraline and liothyronine in major depression: a randomized, double-blind, placebo-controlled trial.** ***Archives of general psychiatry***, *64*(6), 679-688.
Conclusions: These results demonstrate enhancement of the antidepressant effect of sertraline by concurrent treatment with liothyronine without a significant increase in adverse effects. The antidepressant effect of liothyronine may be directly linked to thyroid function.

The Journal of Clinical Investigation 2015
Joao Pedro Werneck de Castro[1], Tatiana L. Fonseca[1], Cintia B. Ueta, Elizabeth A.

McAninch Sherine Abdalla[1], Gabor Wittmann[3], Ronald M. Lechan, Balazs Gereben and Antonio C. Bianco **Differences in hypothalamic type 2 deiodinase ubiquitination explain localized sensitivity to thyroxine**
Abstract: The current treatment for patients with hypothyroidism is levothyroxine (L-T4) along with normalization of serum thyroid-stimulating hormone (TSH). However, normalization of serum TSH with L-T4 monotherapy results in relatively low serum 3,5,3′-triiodothyronine (T3) and high serum thyroxine/T3 (T4/T3) ratio. In the hypothalamus-pituitary dyad as well as the rest of the brain, the majority of T3 present is generated locally by T4 deiodination via the type 2 deiodinase (D2); this pathway is self-limited by ubiquitination of D2 by the ubiquitin ligase WSB-1. Here, we determined that tissue-specific differences in D2 ubiquitination account for the high T4/T3 serum ratio in adult thyroidectomized (Tx) rats chronically implanted with subcutaneous L-T4 pellets. While L-T4 administration decreased whole-body D2-dependent T4 conversion to T3, D2 activity in the hypothalamus was only minimally affected by L-T4. In vivo studies in mice harboring an astrocyte-specific *Wsb1* deletion as well as in vitro analysis of D2 ubiquitination driven by different tissue extracts indicated that D2 ubiquitination in the hypothalamus is relatively less. As a result, in contrast to other D2-expressing tissues, the hypothalamus is wired to have increased sensitivity to T4. These studies reveal that tissue-specific differences in D2 ubiquitination are an inherent property of the TRH/TSH feedback mechanism and indicate that only constant delivery of L-T4 and L-T3 fully normalizes T3-dependent metabolic markers and

gene expression profiles in Tx rats.

Thyroidea Norge mener: Denne studien viser at Levaxin kan forverre hypothyreosen i noen stoffskiftepasienter

MERK: **God artikkel om denne studien på svensk**

Utdrag: *När forskarna jämförde obehandlade individer (råttor) med hypotyreos med hypotyreota levotyroxinbehandlade råttor, så fann de att råttorna med levotyroxinbehandling hade en minskad konvertering till det aktiva hormonet T3 jämfört med de obehandlade hypotyreota råttorna.*

Forskarna fann, att endast kombinationsbehandling där både T3-hormon och T4-hormon ingår ger normal koncentration av T3 i blodet och i studerade vävnader.

Intressant i studien är även att hypotalamus inte blev påverkad av förhöjda T4-halter. Här fann man inte samma inaktivering av enzymet D2, varför konsekvensen blev att TSH var normalt i blodet.

Elizabeth A. McAninch, Sungro Jo, Nailliw Z. Preite, Erzsébet Farkas, Petra Mohácsik, Csaba Fekete, Péter Egri, Balázs Gereben, Yan Li, Youping Deng, Mary Elizabeth Patti7, Chantal Zevenbergen, Robin P. Peeters, Deborah C. Mash, and Antonio C. Bianco

The Journal of Clinical Investigation 2014 **Prevalent Polymorphism in Thyroid Hormone-Activating Enzyme Leaves a Genetic Fingerprint that Underlies Associated Clinical Syndromes**

Abstract

Context:

A common polymorphism in the gene encoding the activating deiodinase (Thr92Ala-D2) is known to be associated with quality of life in millions of patients with hypothyroidism and with several organ-specific conditions. This polymorphism results in a single amino acid change within the D2 molecule where its susceptibility to ubiquitination and proteasomal degradation is regulated.

Conclusions:

Ala92-D2 accumulates in the Golgi, where its presence and/or ensuing oxidative stress disrupts basic cellular functions and increases pre-apoptosis. These findings are reminiscent to disease mechanisms observed in other neurodegenerative disorders such as Huntington's disease, and could contribute to the unresolved neurocognitive symptoms of affected carriers.

Escobar-Morreale HF, del Rey FE, Obregon MJ, de Escobar GM (1996). Only the combined treatment with thyroxine and triiodothyronine ensures euthyroidism in all tissues of the thyroidectomized rat. *Endocrinology.* 1996 Jun;137(6):2490-502

Abstract: We have recently shown that it is not possible to restore euthyroidism completely in all tissues of thyroidectomized rats infused with T4 alone.

Results: Combined replacement therapy with T4 and T3 (in proportions similar to those

secreted by the normal rat thyroid) completely restored euthyroidism in thyroidectomized rats at much lower doses of T4 than those needed to normalize T3 in most tissues when T4 alone was used. If pertinent to man, these results might well justify a change in the current therapy for hypothyroidism.

Gautam Das, Shweta Anand & Parijat De (2007). Does synthetic thyroid extract work for everybody? ***Endocrine Abstracts*** **(2007) 13 P316.**

Introduction: Synthetic levothyroxine (L-Thyroxine) is the treatment of choice for hypothyroidism. It is safe, effective and generally well tolerated. Some patients, however, cannot tolerate L-Thyroxine. There is still some controversy about the effectiveness of combination T4 & T3 therapy. We describe 3 patients who were successfully treated with Armour thyroid (pork extract of T4 & T3) after being intolerant to L-Thyroxine. Although L-Thyroxine remains the treatment of choice in the majority, a trial of Armour could be considered in patients who have not responded to this conventional treatment and who remain symptomatic with raised serum TSH levels.

Gullo, D., Latina, A., Frasca, F., Le Moli, R., Pellegriti, G., & Vigneri, R. (2011). Levothyroxine monotherapy cannot guarantee euthyroidism in all athyreotic patients. *PLoS One, 6*(8), e22552.

Conclusions: Athyreotic patients have a highly heterogeneous T3 production capacity from orally administered levothyroxine. More than 20% of these patients, despite normal TSH levels, do not maintain FT3 or FT4 values in the reference range, reflecting the inadequacy of peripheral deiodination to compensate for the absent T3 secretion. The long-term effects of chronic tissue exposure to abnormal T3/T4 ratio are unknown but a sensitive marker of target organ response to thyroid hormones (serum TSH) suggests that this condition causes an abnormal pituitary response. A more physiological treatment than levothyroxine monotherapy may be required in some hypothyroid patients.

Hoang, T., Olsen, C., Mai, V., Clyde, P., Shakir, M. (2013). Desiccated Thyroid Extract Compared With Levothyroxine in the Treatment of Hypothyroidism: A Randomized, Double-Blind, Crossover Study. ***The Journal of Clinical Endocrinology & Metabolism***; **May 1, 2013 vol. 98 no. 5 1982-1990.**

Conclusion: Desiccated thyroid extract (DTE) therapy did not result in a significant improvement in quality of life (over levothyroxine); however, DTE caused modest weight loss and nearly half (48.6%) of the study patients expressed preference for DTE over l-T4. DTE therapy may be relevant for some hypothyroid patients.

Thyroidea Norge mener: Det som er bra med denne studien er selvsagt at den i det hele tatt har blitt utført. Den viste også klart at nær halvparten følte seg bedre på NDT og de hadde hele 70 pasienter som var med i studien (18-65 år), noe som gjør at man i større grad kan se

generelle tendenser. Og det var en randomisert, dobbelblind studie.
Problemene med studien, slik vi ser det, er følgende; De var for fokusert på TSH og vi mener de holder seg til TSH-verdier som ikke holder mål. Svært mange av de som bruker NDT til vanlig går på en dose som gjør at TSH blir helt supprimert, altså at TSH blir ikke målbar. Endokrinologisk avdeling på Aker mener dette er helt normalt, og det virker ikke som om de har problemer med dette så lenge T4 og T3-verdiene ellers er nomale. De fleste leger som behandler stoffskiftepasienter vil ønske at TSH skal ligge i nedre del av normalområdet, ca 0,3-1,5. Men i studien har de operert med TSH-verdier helt opp til 3,6. En kan derfor tenke seg at en del flere av forsøkspersonene også ville følt seg bedre på NDT om de fikk riktig dose.

Merk at også overlege for endokrinologisk avdeling ved Aker mener at det er akseptabelt at de som bruker NDT har supprimert TSH

I tillegg har de kun brukt Armour Thyroid som eneste type NDT. Det er verdt å merke seg at produsenten, det amerikanske Forest Laboratories, plutelig og uten forvarsel i 2008/2009 endret formelen på denne medisinen, noe som fikk enorme konsekvenser for hundretusenvis av pasienter (ingen vet hvor mange det er snakk om). Hele internett var fullt av desperate pasienter som enten hadde fått alle hypothyreosesymptomer tilbake, eller som fikk hjerteproblemer, nyreproblemer eller at binyrene sviktet. Alle henvendelser til Forest Labs fra pasienter, media og leger har blitt møtt med total taushet.
Thyroidea Norge mener at denne studien er prinsipielt viktig, men at det er stort behov for å sammenligne flere typer NDT samt ha en mer oppdatert holding til TSH-verdier.
Merk at RELIS finner denne studien statistisk signifikant

Hoermann, R., Midgley, J. E., Giacobino, A., Eckl, W. A., Wahl, H. G., Dietrich, J. W., & Larisch, R. (2014). **Homeostatic equilibria between free thyroid hormones and pituitary thyrotropin are modulated by various influences including age, body mass index and treatment.** ***Clinical endocrinology*****.**
Conclusions: TSH, FT4 and FT3 each have their individual, but also interlocking roles to play in defining the overall patterns of thyroidal expression, regulation and metabolic activity. Equilibria typical of the healthy state are not invariant, but profoundly altered, for example, by L-T4 treatment. Consequently, this suggests the revisitation of strategies for treatment optimization.

Stefan Sjöberg, Mats Eriksson, Sigbritt Werner, Per Bjellerup, and Conny Nordin
Department of Medicine, Karolinska Institutet, Februar 2011 **L-thyroxine treatment in primary hypothyroidism does not increase the content of free triiodothyronine in cerebrospinal fluid: A pilot study**
Abstract
The association between cerebrospinal fluid (CSF) and serum concentration of thyroid hormones and pituitary thyrotropin stimulating hormone (TSH) was studied in nine hypothyroid

patients (HT) before and in seven after L-thyroxine treatment. With L-thyroxine, median free T4 increased 4-fold in serum (3.5 pmol/L vs 17.5 pmol/L) and 3-fold in CSF, (3.9pmol/L vs 11.5 pmol/L). Correspondingly, total T3 in serum increased two-fold (0.9 nmol/L vs 2.2 nmol/L). Unexpectedly, free T3 concentration in CSF was similar (1.5 pmol/L vs.1.5 pmol/L) before and during treatment. In HT, TSH in serum correlated with TSH in CSF as did free T4 in serum and in CSF. During L-thyroxine, the correlation with TSH in serum and CSF remained. Likewise, the free T4 concentration in serum correlated with that in CSF. However, no correlation was found between T3 in serum and free T3 in CSF. It seems evident that free T4 in serum equilibrates with that in the CSF both in the HT and during L-thyroxine. Despite a two-fold increase in total serum T3, free T3 in CSF remained unchanged, which agrees with previous results in rats showing that T3 is less exchangeable between serum and CSF. Alternatively, an accelerated conversion of T4 to T3 might have maintained the concentration of T3, due to strongly increased levels of TSH found in the hypothyroid state. The notion that free T4 in serum reflects the CSF concentration of free T4 is consistent with previous reports from studies in animals.

MERK: **Artikkel på svensk om studien**
Utdrag: Omvandlat T3 från Levaxin passerar inte blod/hjärnbarriären.
Studien visar att mängden fritt T3 inte ökade i spinalvätskan (hjärn-ryggmärgsvätska) på de sju hypotyreospatienterna (som inledningsvis hade ett mycket förhöjt TSH och sänkt T4), **trots att T3** (totala mängden, dvs både fritt och bundet T3) **mer än dubblades i blodet efter behandling med Levaxin.**

Holtorf, K. (2014). Thyroid Hormone Transport into Cellular Tissue. *Journal of Restorative Medicine*, *3*(1), 53-68. Chicago.
Abstract: New research is demonstrating that thyroid hormone transport across cellular membranes plays an important role in intracellular triiodothyronine (T3) levels of peripheral and pituitary tissues and is proving to have considerable clinical significance....A combination of both clinical and laboratory assessment, which may include a T3/reverse T3 ratio and the level of sex hormone binding globulin (SHBG), should be used to determine the likely overall thyroid status and if a therapeutic trail of straight T3 or a T4/T3 combination is indicated and not based solely on standard thyroid function tests.

McDermott, M. (2012). Does Combination Therapy T3/T4 Make Sense? *Endocrine Practice. American Association of Clinical Endocrinologists*.
Conclusions: The majority of hypothyroid patients experience rapid symptomatic relief after institution of LT4 replacement therapy, but persistent symptoms remain in some despite what appears to be adequate LT4 therapy with normalization of the serum TSH level. A thorough investigation is warranted in these patients to detect and treat other responsible lifestyle issues, medical conditions and endocrine conditions. A subset of hypothyroid patients have a polymorphism of the D2 enzyme that may prevent full resolution of symptoms with LT4 therapy alone; these patients may benefit from combination LT4/LT3 therapy. When used, a physiological

LT4 to LT3 ratio of about 10:1 to 14:1 is recommended and the serum TSH should be monitored carefully to ensure that euthyroidism is maintained.

Nygaard B, Jensen EW, Kvetny J, Jarlov A, Faber J (2009). Effect of combination therapy with thyroxine (T4) and 3,5,3′-triiodothyronine versus T4 monotherapy in patients with hypothyroidism, a double-blind, randomised cross-over study. *European Journal of Endocrinology.* December 161 895-902.

Objective: To compare the effect of combination therapy with thyroxine (T4) and T3 versus T4 monotherapy in patients with hypothyroidism on stable T4 substitution.

Conclusion: In a study design, where morning TSH levels were unaltered between groups combination therapy, (treated with T3 20µg once daily) was superior to monotherapy by evaluating several QOL, depression and anxiety rating scales as well as patients own preference.

Pepper GM and Casanova-Romero PY (2014). Conversion to Armour Thyroid from Levothyroxine Improved Patient Satisfaction in the Treatment of Hypothyroidism.
Journal of Endocrinology, Diabetes & Obesity. **September, 11 2014.**

Conclusion: AT treatment was preferred over LT4 replacement therapy by 78% of patients with hypothyroidism in the sub-group with persistent subjective complaints while on T4-only therapy. No serious adverse events were noted while on AT treatment including 30 subjects aged 65 yrs or older. AT could be a reasonable alternative choice for treating this sub-group of patients with hypothyroidism.

Thyroidea Norge mener: Også denne studien er statistisk signifikant. Merk at hele 78% av forsøkspersonene foretrakk NDT fremfor T4 etter bare fire uker på NDT. Problem: Man brukte kun Armour Thyroid. Vi viser igjen til problemene somkom etter formelendringen. Studien er foretatt etter denne formelendringen.

Pritchard, E.K. (2013). Reducing the Scope of Guidelines and Policy Statements in Hypothyroidism. *Journal of Orthomolecular Medicine.* Volume 28, Number 2, 2013.

Abstract: Although practice guidelines and policy statements on hypothyroidism are generally effective, many patients do not respond to the prescribed treatment. Significantly, clinicians routinely face the conundrum of either following the guidelines, which are ineffective, or ethically prescribing alternative (but proscribed) treatment, which might bring and has brought severe punishment by boards of medicine or medical councils.

Robertas Bunevičius, M.D., Ph.D., Gintautas Kažanavičius, M.D., Ph.D., Rimas Žalinkevičius, M.D., and Arthur J. Prange, Jr., M.D. (1999). Effects of Thyroxine as Compared with Thyroxine plus Triiodothyronine in Patents with Hypothyroidism. *New England Journal of Medicine*; 340:424-429.

Conclusions: In patients with hypothyroidism, partial substitution of triiodothyronine for

thyroxine may improve mood and neuropsychological function; this finding suggests a specific effect of the triiodothyronine normally secreted by the thyroid gland.

Rosenthal, L. J., Goldner, W. S., & O'Reardon, J. P. (2011). T3 augmentation in major depressive disorder: safety considerations. ***American Journal of Psychiatry*, *168*(10), 1035-1040.**
Conclusion: Current textbooks and the 2010 APA guidelines agree that there is good evidence for the use of T3 in depressive syndromes, but largely do not mention monitoring of thyroid functioning. Schatzberg et al. suggest use of T3 in postmenopausal women or atypical depression and tapering augmentation after 60 days.

Saravanan P, Dayan C M. Understanding Thyroid Hormone Action and the Effects of Thyroid Hormone Replacement - Just the Beginning Not the End. ***Hot Thyroidology.***
Conclusions: Despite 100 years of thyroid hormone replacement, controversy still exists about the optimum replacement therapy for hypothyroid patients. Several recent studies have given insight in to the complex thyroid hormone metabolism. These support the hypothesis that serum and tissue levels of thyroid hormones may diverge significantly and vary between tissues. The dissatisfaction experienced by some individuals on thyroxine replacement despite normal TSH levels may in part relate to this.

Snyder, S., Listecki, R.E (2012) Bioidentical thyroid replacement therapy in practice: Delivering a physiologic T4:T3 ratio for improved patient outcomes with the Listecki-Snyder protocol. ***International Journal of Pharmaceutical Compound;* 16(5): 376-378.**
Conclusion: Bioidentical thyroid replacement therapy in practice: Delivering a physiologic T4:T3 ratio for improved patient outcomes with the Listecki-Snyder protocol
Effective thyroid replacement therapy may be elusive to some patients, and compounding pharmacists have an opportunity to deliver more effective therapy. Goodman & Gilman's The Pharmacological Basis of Therapeutics 12th edition states that the body usually secretes T4:T3 in an 11:1 ratio but cautions against pursuing combined thyroid replacement due to the short halflife of T3 that necessitates multiple daily dosing; no commercial availability and lack of benefit were shown in trials.

Weltman, N. Y., Ojamaa, K., Schlenker, E. H., Chen, Y. F., Zucchi, R., Saba, A., ... & Gerdes, A. M. (2014). Low-dose T3 replacement restores depressed cardiac T3 levels, preserves coronary microvasculature, and attenuates cardiac dysfunction in experimental diabetes mellitus. ***Molecular medicine (Cambridge, Mass.)*.**
Abstract: We conclude that cardiac dysfunction in chronic diabetes mellitus (DM) may be associated with tissue hypothyroidism despite normal serum thyroid hormone levels. Low-dose T3 replacement appears to be a safe and effective adjunct therapy to attenuate and/or reverse cardiac remodeling and dysfunction induced by experimental DM.

Wiersinga, W. M., & DeGroot, L. J. (2010). Adult hypothyroidism. *Thyroid Disease Manager.* Available at: www.thyroidmanager.org/chapter/adulthypothyroidism/#toc-9-2-definition-and-epidemiology-of-hypothyroidism . Accessed: Nov, 16, 2011. See section 9.8 "Treatment of Hypothyroidism".

Woeber, K. A. (2002). Levothyroxine therapy and serum free thyroxine and free triiodothyronine concentrations. ***Journal of endocrinological investigation*, *25*(2), 106-109. Abstract**: These findings indicate that in hypothyroid patients L-T4-replacement, that is sufficient to maintain a normal serum TSH, is accompanied by a serum free T4 that is higher than that in untreated euthyroid patients or normal individuals and may not result in an appropriately normal serum free T3 concentration.

Dr John Lowe, Thyroid Science, 2009 Stability, Effectiveness, and Safety of Desiccated Thyroid vs Levothyroxine: A Rebuttal to the British Thyroid Association
Abstrakt: Legger frem studier som viser at NDT er tryggere eller like trygt å bruke som T4 og at The British Thyroid Association tar feil i en del av sine konklusjoner og bør revurdere sine antakelser om T4-monoterapi som eneste anbefalte behandlingsmetode

Clinical Thyroidology 2013. Jerome M. Hershman. Patients with Hypothyroidism Taking Desiccated Thyroid Extract lose weight as compared with an equal dose of Levothyroxine
Background:1991 was the centenary of the first use of a thyroid preparation to treat successfully a previously incurable disease, myxedema ” (1). Around then, thyroid hormone preparations made up over 1% of all prescriptions filled by retail pharmacies. In 1988, one fourth of all thyroid hormone prescriptions were for natural preparations, mainly thyroid USP
Og fra konklusjonen: Many endocrinologists refuse to prescribe DTE under any circumstances, even telling the patient to find another doctor who may do it. I think that the present study shows that the switch is not so dangerous, as long as the serum TSH remains in the normal range with careful titration of the DTE dose. The many years of satisfactory therapy with synthetic levothyroxine make it the vastly preferred substitution therapy, but for the patient who insists on continuing or trying DTE, I think that it is no more dangerous than adding some additional L-T_3 in the hope that it will improve persistent “hypothyroid” symptoms in the patient taking L-T_4. (desiccated thyroid) in the United States, even though synthetic T_4 had gradually replaced the natural preparations for three fourths of patients during the previous 20 years (2). Now it is rare for physicians to prescribe desiccated thyroid extract (DTE) instead of levothyroxine (L-T_4). However, many patients report that they “don’t feel normal” while taking L-T_4, and they want the “natural preparation” that is advertised on the Web.
The current study is a careful comparison of desiccated thyroid extract and L-T_4 in the

treatment of hypothyroidism.

Gaby AR. MD, 2004[Sub-laboratory hypothyroidism and the empirical use of Armour thyroid]**Abstract** Evidence is presented that many people have hypothyroidism undetected by conventional laboratory thyroid-function tests, and cases are reported to support the empirical use of Armour thyroid. Clinical evaluation can identify individuals with sub-laboratory hypothyroidism who are likely to benefit from thyroid-replacement therapy. In a significant proportion of cases, treatment with thyroid hormone has resulted in marked improvement in chronic symptoms that had failed to respond to a wide array of conventional and alternative treatments. In some cases, treatment with desiccated thyroid has produced better clinical results than levothyroxine. Research supporting the existence of sub-laboratory hypothyroidism is reviewed, and the author's clinical approach to the diagnosis and treatment of this condition is described.

Endocrine abstracts 2007 Gautam Das, Shweta Anand & Parijat De [Does synthetic thyroid extract work for everybody?]

Tre case studies der man med suksess behandlet pasienter med Armour Thyroid. Dette er pasienter som tidligere har hatt store problemer og mange symptomer på Levaxin

Escobar-Morreale HF[1], Botella-Carretero JI, Gómez-Bueno M, Galán JM, Barrios V, Sancho J. 2005 [Thyroid hormone replacement therapy in primary hypothyroidism: a randomized trial comparing L-thyroxine plus liothyronine with L-thyroxine alone.]

Abstract

BACKGROUND:

Substituting part of the dose of l-thyroxine with small but supraphysiologic doses of liothyronine in hypothyroid patients has yielded conflicting results.

OBJECTIVE:

To evaluate combinations of L-thyroxine plus liothyronine in hypothyroid patients that match the proportions present in normal secretions of the human thyroid gland.

INTERVENTION:

Crossover trial comparing treatment with l-thyroxine, 100 microg/d (standard treatment), versus treatment with L-thyroxine, 75 microg/d, plus liothyronine, 5 microg/d (combination treatment), for 8-week periods. All patients also received L-thyroxine, 87.5 microg/d, plus liothyronine, 7.5 microg/d (add-on combination treatment), for a final 8-week add-on period.

RESULTS:

Compared with standard treatment, combination treatment led to lower free thyroxine levels (decrease, 3.9 pmol/L [95% CI, 2.5 to 5.3 pmol/L]), slightly higher serum levels of thyroid-stimulating hormone (increase, 0.62 mU/L [CI, 0.01 to 1.23 mU/L]), and unchanged free triiodothyronine levels. No improvement was observed in the other primary and secondary end points after combination treatment, with the exception of the Digit Span Test, in which the mean backward score and the mean total score increased slightly (0.6 digit [CI, 0.1 to 1.0 digit] and 0.8

digit [CI, 0.2 to 1.4 digits], respectively). The add-on combination treatment resulted in overreplacement. Levels of thyroid-stimulating hormone decreased by 0.85 mU/L (CI, 0.27 to 1.43 mU/L) and serum free triiodothyronine levels increased by 0.8 pmol/L (CI, 0.1 to 1.5 pmol/L) compared with standard treatment; 10 patients had levels of thyroid-stimulating hormone that were below the normal range. Twelve patients preferred combination treatment, 6 patients preferred the add-on combination treatment, 2 patients preferred standard treatment, and 6 patients had no preference (P = 0.015).

LIMITATIONS:

Treatment with L-thyroxine, 87.5 microg/d, plus liothyronine, 7.5 microg/d, was an add-on regimen and was not randomized.

CONCLUSIONS:

Physiologic combinations of L-thyroxine plus liothyronine do not offer any objective advantage over l-thyroxine alone, yet patients prefer combination treatment.

Thyroidea Norge mener:

Selv om 69% av de som var med i studien foretrakk kombinasjonsterapi T4+T3 foran utelukkende T4, konkluderte studien med at kombinasjonsterapien ikke har noen effekt og at man bør fortsette å ha kun T4 som behandlingsmetode for alle med hypothyreose

Det er flere problemer med studien.

Kun 28 personer var med, og to av dem droppet ut i løpet av studien. I tillegg var doseringen av T3 altfor liten i forhold til det mange erfaringsmessig trenger for å føle seg bra. Pasientene i gruppen fikk 5-7,5 mg Liothyronin, mens mange pasienter som bruker dette medikamentet må ta opptil 60 mg for å føle seg bra. I Norge får man Liothyronin kun i tabletter på 20 mg uansett. De som gikk på kombinasjonsterapi fikk også en ganske lav dose T4, maks 87,5 mg, mens vanlig dose for voksne mennesker som regel ligger fra 100-300 mg. I tillegg fikk alle den samme dosen, noe som er unormalt for ganske mange sykdommer, ikke bare stoffskiftesykdommer - det vanlige er å tilpasse dosen etter den individuelle pasient og ta høyde for vekt, alder, symptomer og ulike laboratorietester.

Studien ble likevel godkjent i Cochrane og har siden blitt referert til for å argumentere mot behandling med T3. Vi legger denne likevel med for å påpeke at ikke all forskning er god medisin.

MAURICE L. WELLBY, M.Sc., M.B., B.S.*, BRIAN F. GOOD, B.SC., JOHN S. CHARNOCK, B.SC.*, and BASIL S. HETZEL, M.D. **THE EARLY METABOLIC EFFECTS OF DESICCATED THYROID, THYROXINE AND TRIIODOTHYRONINE IN MAN: COMPARISON WITH EARLY EFFECT OF THYROTROPIC HORMONE**

Received: November 24, 1959

Published Online: July 01, 2013

ABSTRACT

In order to determine whether the early metabolic effect of thyrotropic hormone (as demonstrated previously in this laboratory) could be reproduced by certain known thyroid

hormone preparations, triiodothyronine (T_3), thyroxine (T_4) and desiccated thyroid were administered orally on four occasions in single doses to 5 normal males, and the metabolic effects observed. The dose of T_3 was 0.5 mg.; of T_4 2.5–3.0 mg.; and of thyroid, 1.3–2.0 Gm. Observations were made over an eight-hour period after an overnight fast. It was confirmed that T_3 produces a rise in metabolic rate and an increase in the levels of plasma and urinary phosphate within eight hours without significantly raising the level of plasma protein-bound iodine (PBI). There was a less marked rise in metabolic rate following administration of desiccated thyroid, with a significant rise in urinary phosphate within eight hours and a rise in the plasma PBI level to 10.2 µg. per 100 ml. within two hours. T_4 produced no elevation in metabolic rate, pulse rate or phosphate excretion, although elevation of the plasma PBI level to 9.0 µg. per 100 ml. occurred within two hours. There were no consistent effects on urine flow and sodium, potassium or creatinine excretion, and no subjective symptoms during treatment with any of the preparations. The results indicate the similarity between the early metabolic effects of triiodothyronine and desiccated thyroid. Thyroxine had no effect over the eight-hour period of observation. None of the preparations reproduced the early metabolic effects of thyrotropic hormone.

Chernow B, Burman KD, Johnson DL, McGuire RA, O'Brian JT, Wartofsky L, Georges LP. **T3 may be a better agent than T4 in the critically ill hypothyroid patient: evaluation of transport across the blood-brain barrier in a primate model. (1983)** **Abstract**: Thyroid hormone transport across the blood brain barrier in hypothyroid patients is clinically important yet poorly understood. To study this question, 200 micrograms of thyroxine (T4), 100 micrograms of 3,5,3'-triiodothyronine (T3) and 100 micrograms of 3,3',5'-triiodothyronine (reverse T3) were administered separately to 3 baboons, first iv and at a later date intrathecally (IT). Six animals were used. Three received the iv injections and three received the IT injections. In each of the 18 experiments, cerebrospinal fluid (CSF) and serum specimens were collected serially for 6 h after injection. Mean maximal elevations from baseline in CSF iodothyronine levels were 100 +/- 10 ng/dl after iv T4, 3921 +/- 293 ng/dl after iv T3 and 31 +/- 17 ng/dl after iv reverse T3. When given IT in the same dosages, the mean maximal increases in serum iodothyronine concentrations were: 1670 +/- 600 ng/dl for T4, 806 +/- 405 ng/dl for T3, and 210 +/- 43 ng/dl for reverse T3. In every animal studied, rapid bidirectional transfer of T3 from serum to CSF and CSF to serum occurred, whereas iv T4 resulted in delayed minimal increments in CSF T4 concentration. Isotopic experiments were also performed and the results analyzed using a kinetic model. When 125I-T3 was given iv, the equilibrium point in CSF was observed within 90 min with 1.7% of the administered dose/L able to be counted in CSF at any moment in time. When labeled T4 was given iv, only 0.6% of the administered dose/L was counted in CSF and the equilibrium point was not reached until 360 min. These data suggest: (a) T4, T3, and reverse T3 are all capable of bidirectional transfer across the blood brain barrier, (b) T3 may be a better agent than T4 in treating patients with myxedema coma because T3 crosses more rapidly and more completely from serum to CSF.

Norsk Legetidsskrift 2000 P Gulbrandsen **Trijodtyronin fysiologisk viktig?**
Det er usikkert om trijodtyronin har fysiologisk betydning. Ved å erstatte deler av tyroksindosen til 33 pasienter med hypotyreose med trijodtyronin, kunne en forskergruppe i Litauen påvise bedring i stemningsleie og nevropsykologisk funksjonsnivå.
I undersøkelsen, som er publisert i *New England Journal of Medicine* , ble 33 pasienter som hadde stått på tyroksin i gjennomsnittlig 73 måneder behandlet enten med tyroksin alene eller med en kombinasjon av tyroksin og trijodtyronin (50 mg tyroksin erstattet med 12,5 mg trijodtyronin) i fem uker, dernest ble behandlingsregimene byttet om (1). Rekkefølgen av behandlingstypene for pasientene var tilfeldig. Ved enden av hver femukersperiode gjennomgikk pasientene en rekke fysiologiske og nevropsykologiske tester.
Doseringen ble reflektert i serumnivåene for tyroksin og trijodtyronin etter de respektive behandlingene, men man fant ikke forskjell i TSH-nivå. Etter kombinasjonsbehandlingen hadde pasientene statistisk signifikant høyere hvilepuls og nivå av kjønnshormonbindende protein (SHBG), men generelt var det beskjedne forskjeller i de fysiologiske variablene.
Resultatet av de nevropsykologiske testene var klart forskjellig. Etter kombinasjonsbehandlingen fant man bedre innlæringsevne, mental fleksibilitet og oppmerksomhetsnivå. Pasientene var mindre deprimert, utmattet og kjente mindre sinne enn etter perioden med ren tyroksinbehandling. Av de 33 pasientene foretrakk 20 kombinasjonsbehandlingen, to tyroksin alene og 11 hadde ingen preferanse. De to som foretrakk tyroksin alene, gav uttrykk for å føle seg mer nervøse under kombinasjonsbehandlingen.
Forfatterne konkluderer med at det synes som om trijodtyronin har en gunstig effekt i alle fall i hjernen og kanskje i annet vev, sammenliknet med en ekvivalent mengde tyroksin.
Litteratur: Bunevicius R, Kazanavicius G, Zalinkevicius R, Prange AJ. Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. N Engl J Med 1999; 340: 424–9.

Thyroid Science 2006 **Four 2003 Studies of Thyroid Hormone Replacement Therapies: Logical Analysis and Ethical Implications**

Dr John C. Lowe

Meget god kritikk av fire studier samt god forklaring på hvorfor disse har blitt feiltolket

T2 har en biologisk effekt

Thyroidea Norge mener: Det er svært lite forskning å finne om T2. Men det lille som finnes viser at T3 og T2 fungerer på forskjellige måter og har ulik biologisk funksjon. Det er derfor viktig å se på muligheten for at en del stoffskiftepasienter kan bli bedre dersom de ikke bare får tilskudd av T3 men også av T2. Dessverre finnes det ingen medisiner der man får kun T2. Det finnes bittelitt i NDT, men ettersom T2 i en frisk kropp nesten utelukkende dannes gjennom de-jodinase utenfor skjoldbrusskjertelen er det svært lite T2 å finne selv i NDT. **Thyroidea Norge** mener derfor at man bør se på muligheten for å utvikle enten syntetisk T2 alene eller i kombinasjon med f eks T4 og T3.

Denne artikkelen beskriver godt hvordan T2 sammen med T3, rT3 og T4 er en av de stoffskiftehormonene som faktisk har en biologisk effekt, der hver av dem har forskjellige oppgaver. Merk at artikkelen henviser til artikler av F Goglia som vi har ført opp under

A. J. Hulbert, University of Wollongong, Australia, Research Online (2000)

Thyroid hormones and their effects: a newperspective

Utdrag s 22: It is the opinion of this reviewer that there are four iodothyronines that have signficant but not identical biological activities and these are T4, T3, rT3 and 3,5-T2

F. GogliaDipartimento di Scienze Biologiche ed Ambientali-Universita degli Studi del Sannio-Via Portí, Arsa, 11 82100 Benevento, Italy Biological Effects of 3,5-Diiodothyronine (T2) 2004

Abstract: This article is principally intended to describe the facts concerning the actions of 3,5-diiodothyronine (T2). Until recent years, T2, because of its very low affinity for thyroid hormone receptors (THR), was considered an inactive metabolite of thyroid hormones (TH) (thyroxine (T4) and triiodo-L-thyronine (T3)). Several observations, however, led to a reconsideration of this idea. Early studies dealing with the biological activities of this iodothyronine revealed its ability to stimulate cellular/mitochondrial respiration by a nuclear-independent pathway. Mitochondria and bioenergetic mechanisms seem to be major targets of T2, although outside the mitochondria T2 also has effects on carriers, ion-exchangers, and enzymes. Recent studies suggest that T2 may also affect the transcription of some genes, but again the underlying mechanisms seem to be different from those actuated by T3. The accumulated evidence permits the conclusion that the actions of T2 do not simply mimic those of T3 but instead are specific actions exerted through mechanisms that are independent of those actuated by T3 and do not involve THR

Biosci Rep. 2002 Feb

Thyroid hormones and mitochondria.

Goglia F[1], Silvestri E, Lanni A.

Abstract: Because of their central role in the regulation of energy-transduction, mitochondria, the major site of oxidative processes within the cell, are considered a likely subcellular target for the action that thyroid hormones exert on energy metabolism. However, the mechanism underlying the regulation of basal metabolic rate (BMR) by thyroid hormones still remains unclear. It has been suggested that these hormones might uncouple substrate oxidation from ATP synthesis, but there are no clear-cut data to support this idea. Two iodothyronines have been identified as effectors of the actions of thyroid hormones on energy metabolism: 3',3,5-triiodo-L-thyronine (T3) and 3,5-diiodo-L-thyronine (T2). Both have significant effects on BMR, but their mechanisms of action are not identical. T3 acts on the nucleus to influence the expression of genes involved in the regulation of cellular metabolism and mitochondria function; 3,5-T2, on the other hand, acts by directly influencing the mitochondrial energy-transduction apparatus. A molecular determinant of the effects of T3 could be uncoupling protein-3 (UCP-3), while the cytochrome-c oxidase complex is a possible target for 3,5-T2. In conclusion, it is likely that iodothyronines regulate energy metabolism by both short-term and long-term mechanisms, and that they act in more than one way in affecting mitochondrial functions.

S G Ball, J Sokolov and W W Chin (1997) 3,5-Diiodo-l-thyronine (T2) has selective thyromimetice effects in vivo and in vitro

Viser at T2 er effektiv i å senke TSH og har en annen biologisk funksjon enn T3.

ABSTRACT: Recent data have suggested that the iodothyronine, 3,5-diiodo-l-thyronine (T2), has selective thyro-mimetic activity. In vivo,T2 has been shown to suppress TSH levels at doses that do not produce significant peripheral manifestations of thyroid hormone activity. Furthermore, T2 has been shown to produce smaller increments in peripheral indices of thyroid status than does T3, when doses resulting in equivalent suppression of circulating TSH are compared.

Antonelli A[1], Fallahi P, Ferrari SM, Di Domenicantonio A, Moreno M, Lanni A, Goglia F. 2011 3,5-diiodo-L-thyronine increases resting metabolic rate and reduces body weight without undesirable side effects.

Abstract Recently, it was demonstrated that 3,5-diiodo-L-thyronine (T2) stimulates the resting metabolic rate (RMR), and reduces body-weight gain of rats receiving a high-fat diet. The aim of this study is to examine the effects of chronic T2 administration on basal metabolic rate and body weight in humans. Two euthyroid subjects volunteered to undergo T2 administration. Body weight, body mass index, blood pressure, heart rate, electrocardiogram, thyroid and liver ultrasonography, glycemia, total cholesterol, triglycerides, free T3 (FT3), free T4 (FT4), T2, thyroid stimulating hormone (TSH) and RMR were evaluated at baseline and at the end of treatment. RMR increased significantly in each subject. After continuing the T2 treatment for a further 3 weeks (at 300 mcg/day), body weight was reduced significantly ($p<0.05$) (about 4 percent), while the serum levels of FT3, FT4 and TSH, were unchanged. No side effects were observed at the cardiac level in either subject. No significant change was observed in the same subjects taking placebo.

Mangiullo R[1], Gnoni A, Damiano F, Siculella L, Zanotti F, Papa S, Gnoni GV. 2010 3,5-diiodo-L-thyronine upregulates rat-liver mitochondrial F(o)F(1)-ATP synthase by GA-binding protein/nuclear respiratory factor-2.

Abstract Besides triiodothyronine (T3), 3,5-diiodo-L-thyronine (T2) has been reported to affect mitochondrial bioenergetic parameters. T2 effects have been considered as independent of protein synthesis. Here, we investigated the effect of in vivo chronic T2 administration to hypothyroid rats on liver mitochondrial F(o)F(1)-ATP synthase activity and expression. T2 increased state 4 and state 3 oxygen consumption and raised ATP synthesis and hydrolysis, which were reduced in hypothyroid rats. Immunoblotting analysis showed that T2 up-regulated the expression of several subunits (alpha, beta, F(o)I-PVP and OSCP) of the ATP synthase. The observed increase of beta-subunit mRNA accumulation suggested a T2-mediated nuclear effect. Then, the molecular basis underlying T2 effects was investigated. Our results support the notion that the beta-subunit of ATP synthase is indirectly regulated by T2 through, at least in part, the activation of the transcription factor GA-binding protein/nuclear respiratory factor-2. These findings provide new insights into the T2 role on bioenergetic mechanisms.

Mollica MP[1], Lionetti L, Moreno M, Lombardi A, De Lange P, Antonelli A, Lanni A, Cavaliere G, Barletta A, Goglia F. 2009 [3,5-diiodo-l-thyronine, by modulating mitochondrial functions, reverses hepatic fat accumulation in rats fed a high-fat diet]

Abstract

BACKGROUND/AIMS:

Mitochondrial dysfunction is central to the physiopathology of steatosis and/or non-alcoholic fatty liver disease. In this study on rats we investigated whether 3,5-diiodo-l-thyronine (T2), a biologically active iodothyronine, acting at mitochondrial level is able to reverse hepatic steatosis after its induction through a high-fat diet.

RESULTS:

Stained sections showed that T2 treatment reduced hepatic fatty accumulation induced by a high-fat diet. At the mitochondrial level, the fatty acid oxidation rate and carnitine palmitoyl transferase activity were enhanced by T2 treatment. Moreover, by stimulating mitochondrial uncoupling, T2 caused less efficient utilization of fatty acid substrates and ameliorated mitochondrial oxidative stress.

CONCLUSION:

These data demonstrate that T2, by activating mitochondrial processes, markedly reverses hepatic steatosis in vivo.

Journal of Physiology (1997),505.2,pp.529-538 [How the thyroid controls metabolism in the rat: different roles for triiodothyronine and diiodothyronines] **Maria Moreno, Antonia Lanni, Assunta Lombardi and Fernando Goglia**

These results indicate that T2s and T3 exert different effects on resting metabolism. The effects of T2s are rapid and possibly mediated by their direct interaction with mitochondria. Those of T3 are slower and more prolonged, and at least partly attributable to a modulation of the cellularity of tissues that are metabolically very active

Elena Silvestri,* Maria Coppola, Federica Cioffi, and Fernando Goglia* [Proteomic approaches for the study of tissue specific effects of 3,5,3′-triiodo-L-thyronine and 3,5-diiodo-L-thyronine in conditions of altered energy metabolism] **Conclusions and perspectives:** The biochemical and cellular mechanisms that underlie tissue specific actions of T3 and T2 are only beginning to be elucidated. However, the proteomic studies so far conducted separately analyzed the effects of T3 and T2 in different states of altered energy balance: changed thyroid state and over-nutrition, respectively To further characterize and compare the molecular and biochemical pathways that underlie T3 and T2 metabolic actions, T3 and T2 themselves should be used in the same experimental design in comparative approaches so to highlight putative common effects or iodothyronine-specific one.

Fernando Goglia, 2015 [The effects of 3,5-diiodothyronine on energy balance]

Introduction: …..This article is particularly intended to describe the effects of the 3,5 diiodo-L-thyronine (T_2) on energy balance

3,5-diiodo-L-thyronine (T_2) T_2, a naturally occurring diiodothyronine, is a product of a currently unknown enzymatic process most probably utilizing T3 as its precursor (Moreno et al., 2002). Some years ago surprising results were published showing that (among a lot of iodothyronines tested) T_2, at a very low concentration (pM), induced a rapid stimulation of oxygen consumption in perfused livers isolated from hypothyroid rats. In the same study, it was shown that T_3 showed a similar effect but this effect was largely abolished by the addition of an inhibitor of D1 deiodinase, while the effect of T_2 was not. Moreover, T_2 exerted its effect more rapidly than T_3 ….

Maria Coppola, Daniela Glinni, Maria Moreno, Federica Cioffi, Elena Silvestri, and Fernando Goglia, 2014 **Thyroid hormone analogues and derivatives: Actions in fatty liver**
Conclusion: (...) Notably, the hypolipidemic effect of T2 is associated with a potent ability in both preventing and reducing fatty liver. Increasing evidence supports TH derivatives and analogues as attractive active agents that could be taken into consideration for the establishment of new treatments in the counteraction of metabolic disorders, such as T2DM, obesity and NAFLD, thus clinical trials are desirable.

Lombardi, A.; Lanni, A.; Silvestri, E.; Lange, P. d.; Goglia, F.; Moreno, M. Immunology, Endocrine & Metabolic Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry - Immunology, Endocrine and Metabolic Agents) 2006
3, 5-Diiodothyronine: Biological Actions and Therapeutic Perspectives **Abstract**: The purpose of this review is to summarize the current state of knowledge concerning the biological activities of 3, 5-diiodothyronine (T 2) and its potential use as a pharmacological agent. Until recent years, T2 was considered an inactive metabolite of thyroid hormones thyroxine (T4) and triiodo-L-thyronine (T3). Several observations, however, led to a reconsideration of this idea. Early studies dealing with the biological activities of this iodothyronine revealed its ability to stimulate cellular/mitochondrial respiration, essentially by a nuclear-independent pathway. Mitochondria and the energytransduction apparatus seem to be major targets of T2, although outside the mitochondria T2 also has effects on carriers, ion-exchangers and enzymes. Recent studies suggest that T 2 may also affect the transcription of some genes, but again the underlying mechanisms seem to differ from those actuated by T3. The accumulated evidence permits the conclusion that the actions of T2 do not simply mimic those of T3 but instead are specific actions exerted through mechanisms that are independent of those actuated by T3 and do not involve thyroid hormone receptors. In addition, very recent evidence leads us to suggest that T2 may be a potentially useful agent for the treatment of diet-dependent overweight (and the consequent hypertriglyceridemia and high cholesterol level) without inducing thyrotoxicosis.