Til Norsk Endokrinologisk Forening

v/ Anders Jørgensen, Bjørn Olav Åsvold, Louise J. Koren Dahll, Bjørn Gunnar Nedrebø.

Thyroidea Norges innspill til det pågående arbeidet med Nasjonale Retningslinjer for Endokrin Behandling med fokus på diagnostikk og behandling av stoffskiftepasienter

Vi i Thyroidea Norge mener at de verktøy som finnes i dag for å diagnostisere ulike stoffskiftesykdommer ikke er gode nok. Særlig reagerer vi på at det finnes mange pasienter som har høye antistoffer som Anti-TPO og TRAS, samtidig som de andre verdiene er innenfor et såkalt normalområde, og som kan ha flere "ulne" symptomer, ofte over mange år eller tiår. Disse får ingen behandling. Rådende prinsipp er å vente og se, gjerne over flere år. I mellomtiden vedvarer den autoimmune reaksjonen helt til kjertelen har blitt så nedbrutt at man har fått en irreversibel stoffskiftesykdom. I ventеperioden utvikler mange i tillegg andre autoimmune lidelser.

Ettersom det finnes forskning som støtter det faktum at begynnende autoimmune reaksjoner er reversible, mener vi i Thyroidea Norge at man bør se på mulighetene for å gjøre nettopp dette.

> *Vi mener at når det gjøres så lite for å bremse sykdomsutviklingen fører det til mye unødvendig lidelse. Dette går imot fundamentale legeetiske prinisipper*

En artikkel publisert i *Thyroid* i 2001 viste at hos pasienter med høye antistoffer men ellers normale verdier (subklinisk hypothyreose), fikk reversert den autoimmune prosessen ved å leve glutenfritt i ett år.

Vi har fått med oss at det er én eller to endokrinologer i Norge som har forstått denne sammenhengen. Samtidig er vi klar over at denne kunnskapen ikke er spesielt kjent verken blant allmennleger eller endokrinologer i Norge. Mange synes å mene at skepsis til gluten er et "motefenomen". Studien vi viser til er ikke statistisk signifikant, men er likevel i korrelasjon med erfaringen til tusenvis av pasienter - svært mange stoffskiftepasienter føler seg bedre på glutenfritt kosthold. Thyroidea Norge mener derfor at det kan være nyttig å forske mer for å se om resultatene kan bekreftes.

Thyroidea Norge mener at det bør være bedre muligheter for at stoffskiftepasienter som ikke fungerer på T4-monoterapi, kan få tilgang til å prøve ut andre stoffskiftemedisiner.
MERK: Thyroidea Norge er ikke imot bruk av Levaxin, Liothyronin eller andre syntetisk fremstilte stoffskiftemedisiner. Vi vet at mange stoffskiftepasienter klarer seg helt fint på dette. Ei heller forkynner vi "naturlig" versus syntetisk. Det vi mener er at det bør finnes flere alternativer, i betydningen tilgang til flere typer stoffskiftehormoner enn kun T4, siden ikke alle pasienter responderer likt på medisiner. Som dere vil se understøttes dette av etterhvert massiv medisinsk forskning.

Det viktigste med NDT (Naturally Desiccated Thyroid, også kalt DTE, Desiccated Thyroid Extract) er at den inneholder alt en vanlig skjoldbruskkjertel vanligvis produserer i en frisk kropp

NDT viser altså til Thyroid-preparater laget av skjoldbruskkjertel fra gris, men noen steder lages det også av kjertel fra ku eller sau. De vanligst brukte typer NDT i Norge er Armour Thyroid,. Forest Labs US, eller Thyroid fra Erfa, Canada. Så vidt vi vet finnes det ikke NDT laget av sau eller ku å få tak i i Norge, noe som kan være problematisk for en del minoriteter av religiøse årsaker.

> *MERK: I 2008/2009 endret Forest Labs formelen til Armour Thyroid. Dette gjorde de uten å informere endokrinologer, pasienter eller FDA. Formelendringen førte til store problemer for hundretusenvis av stoffskiftepasienter verden over. Hele internett var fullt av desperate pasienter som fortalte at de hadde fått alle hypothyreosesymptomene tilbake, at de hadde fått lever-eller nyreproblemer, hjerteproblemer som arytmi, eller binyresvikt. Alle henvendelser til Forest Labs har blitt møtt med fullstendig taushet.*

I et intervju med Erfa om deres Thyroid-preparat sier de blant annet at de ikke har hatt en tilbakekallelse av produktet på over 30 år. Man kan dermed ikke argumentere for at medisinen er ustabil.

Vi er kjent med at innen det endokrinologiske fagmiljøet eksisterer det en stor skepsis mot å la pasienter bruke noe annet enn Levaxin (T4). For å vise at det er gode, medisinske og vitenskapelige årsaker til at en del stoffskiftepasienter fungerer bedre enten på kombinasjonsterapi T4+T3 eller på NDT, legger vi faglig tyngde til massiv empirisk data. Vi håper dere tar dere tid til å i det aller minste lese igjennom abstraktene.

Vi minner likevel om at empiri er vitenskapens første premiss: Å underkjenne eller ignorere erfaringene til millioner av pasienter verden over - og ganske mange bare i Norge - er ikke god vitenskap. Det er ihvertfall ikke god medisin. Mange føler seg så mye bedre på NDT at de forteller at de har fått livet tilbake.

"***Prøvene dine er fine, så du kan ikke være syk***" er et utsagn altfor mange stoffskiftepasienter har fått høre - enten idet de ikke får en diagnose, eller i tilfeller der T4-monoterapi ikke synes å virke tilfredsstillende for dem. Erfaringsmessig opplever mange å ikke bli trodd av sin lege, å føle seg avvist, eller at det ikke gjøres nok med tanke på å sette sammen et utvidet bilde i form av flere og grundigere prøver.

Thyroidea Norge mener at å kategorisk avvise pasienter som kommer igjen og igjen med stadig nye plager som "plagsomme" ikke er god medisin. Selv om både forskning og mange legers erfaring nettopp viser at stoffskiftepasienter ikke alltid blir friske, virker det som om det er altfor vanlig at utforskningen av sykdomsbildet stopper opp, og at legen gir opp. De pasienter som derimot er velbehandlet har ofte god dialog med sin lege og opplever å bli behandlet ut fra et bredere diagnostisk bilde enn fokus utelukkende på TSH og FT4.

Vi erfarer også at visse private klinikker med fokus på funksjonell medisin ofte har suksess i behandlingen av de stoffskiftepasientene det offentlige ikke klarer å hjelpe. Dessverre er det store økonomiske utgifter forbundet med å gå til private klinikker. Likevel får vi tilbakemeldinger

fra svært mange som går til slike steder og blir markant bedre med påfølgende øket livskvalitet - ikke bare fordi de får NDT, men også fordi de blir grundig sjekket for andre ting. Det kan være vitamin- og mineralmangel, andre hormonelle problemer og matintoleranse - og de får faktisk skikkelig behandling for dette. Et eksempel er at de fleste av disse privatklinikkene gir B12-tilskudd i form av injeksjoner heller enn i tablettform, noe som synes å virke langt bedre hos stoffskiftepasienter. Vanlig behandling er også at man skal holde seg unna visse typer mat, blant annet sukker, samt foreskrivning av ordinære kosttilskudd ved mangel. Altså ikke verken hokus-pokus eller eksperimentell medisin, men sunn fornuft. Thyroidea Norge etterlyser denne fremgangsmåten i større grad også i det offentlige helsevesen

Bivirkninger av NDT vs Levothyroxin

Hvor farlig er det å behandle med Thyroid/NDT?

Statistikker fra flere land viser helt klart at det ikke er flere bivirkninger ved bruk av NDT enn ved syntetisk T4/T3. Snarere tvert imot.

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.*

Samtidig viser vi til vedlagt oversendelse fra Legemiddelverket om innrapporterte bivirkninger av Levaxin og Liothyronin

Statistisk kan disse ikke sammenlignes. Svært få i Norge bruker NDT. Likevel kan vi se de samme tendenser i andre land, der man har et større antall pasienter som gjør tallene statistisk signifikante

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)
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.

Vi mener også at ved bruk av Levaxin bør legen gi pasienten bedre informasjon. Det står i Felleskatalogen at Levaxin ikke skal gis til pasienter med binyreinsufficiens. Det påpekes at nyere studier viser at mange stoffskiftepasienter har en fortid med traumer eller mishandling. De som har opplevd slike ting er ofte i en konstant stressituasjon, noe som igjen påvirker binyrenes funksjon over tid. Etter det Thyroidea Norge erfarer er det få leger som tar seg bryet med å sjekke binyrefunksjonen før de setter pasienter på Levaxin. Thyroidea Norge mener også at det ikke bare er når man skal diagnostisere at det er nødvendig å sjekke stoffskiftepasienters binyrefunksjon, men at det er viktig å følge med over lang tid og sjekke binyrefunksjon minst en gang hvert år.

Thyroidea Norge mener at dette bør tas nøyere opp til vurdering ved arbeidet med nasjonale retningslinjer

Om å få Thyroid/NDT på blå resept
Det har blitt en praksisendring i HELFO uten at vi har registrert noen regelendring, som har gjort at nesten alle får avslag, selv om en spesialist har søkt for dem. Tidligere fikk man avslag på å få NDT på blå resept dersom søknad ikke var innsendt av spesialist. Nå begrunnes avslag med at det ikke finnes nok studier som bekrefter effekt av NDT. HELFO sier også nå i sine avslag at Thyroid, både fra Erfa og Forest Labs, ikke er godkjent som stoffskiftemedisin i Norge. Men ifølge Verdens Helseorganisasjon (WHO) sine retningslinjer har Thyroid klassifiseringskode H03A A05 , noe som betyr at de internasjonalt og av WHO er klassifisert for bruk til å behandle stoffskiftesykdommer. Medisinene er også laget spesifikt for dette formål og blir ikke beskrevet av produsentene for bruk til behandling av andre tilstander. Også i Felleskatalogen har Thyroid denne oppføringen. At HELFO da skal nekte pasienter å få behandling med Thyroid ut ifra en oppfatning om at Thyroid ikke skal brukes til å behandle lavt stoffskifte går fullstendig imot WHO sin oppfatning av medisinen. Vi stiller spørsmålstegn ved hva slags påvirkning som har ført til denne plutselige endringen i HELFO.

Vi understreker at også Regionalt legemiddelinformasjonssenter RELIS, mener at Thyroid er trygg å bruke som substitusjonsbehandling.

RELIS trekker også frem en av studiene vi viser til lenger ned, og mener den et statistisk signifikant. Denne studien viser altså at 49% av pasientene foretrakk NDT fremfor T4-monoterapi

Vi viser også til denne artikkelen som viser at Nycomed selv, helt frem til 1996, sa at noen stoffskiftepasienter ikke ble friske av Levaxin:

Når det gjelder blodprøver for å se om man er på riktig dose når man bruker NDT svarer overlege på endokrinologisk avdeling på Aker følgende:
"TSH kan ikke brukes som måleenhet ved bruk av T3: "Vi pleier å anbefale at Levaxin justeres slik at TSH ligger mellom 0,5 og 1,5. og at FT4 blir liggende i øvre halvdel av referanseområde.
OBS: referanseområdet for stoffskiftehormonene varierer for de ulike laboratoriemetoder.
Armour inneholder både T4 og T3. T3 har kort halveringstid i blod og gir en topp i stoffskiftet ca 1 1/2 time etter tablettinntak. Hypofysen som lager TSH "måler" konsentrasjonen av FT3 og FT4 i blod. Når det er topper i stoffskiftet vil hypofysen nedregulere sin TSH-produksjon. Pasienter som bruker Armour har derfor ofte ikke målbart TSH: TSH blir derfor ikke noe brukbart mål på om dosen Armour er riktig . Pasienter som bruker Armour må få målt fritt T4 og Fritt T3. Legen må passe på at verdiene for FT4 og FT3 ligger under øvre normale referansegrense. Hvis pasienten får for mye Armour kan det føre til hjertebank, uro og varmeintoleranse.
Vennlig hilsen Louise Koren Dahll overlege, thyreoideapoliklinikken. OUS Aker.

Merk: Ny studie har vist at 75,6% av de med Hashimotos også har laktoseintoleranse. Levaxin og Liothyronin inneholder begge laktose.

Thyroidea Norge vil anta at dette kan være en av mange mulige årsaker til at mange over tid ikke fungerer tilfredsstillende på Levaxin, ei heller på kombinasjon Levaxin/Liothyronin. Vi er klar over at det er mulig å få tak i Levaxin uten laktose, men da må jo legen vite om at det er vanlig med laktoseintoleranse hos de med Hashimotos og kanskje sjekke pasienten for dette. Det er i tillegg en lang og komplisert prosedyre å søke om laktosefri Levaxin. Liothyronin finnes ikke uten laktose.

Armour Thyroid (Forest Labs, USA) og Thyroid (Erfa, Canada) bruker ikke laktose som fyllstoff, mens Nature-Throid, som noen også i Norge bruker, inneholder laktose.

Dansk Endokrinologisk Selskabs leder skriver at alle studier gjort på kombinasjonsterapi, som viser at pasienter blir bedre med NDT /(DTE) er dårlige studier der man har gitt altfor høye doser til forsøkspersonene for å få frem et visst resultat.. Han skriver blant annet at *"Nogle pasienter har svært ved at akseptere livslang afhengighed af medicin"*. Som om det er det eneste problemet…..
Vi har fått høre at han som har skrevet denne teksten den siste tiden har vært i Norge og holdt foredrag for endokrinologer og allmennleger. Dette har vi fra stoffskiftepasienter som både fra endokrinologer og allmennleger har blitt nektet å prøve ut NDT der legene oppga disse

foredragene som årsak. Han har da snakket om at det er farlig og medisinsk uforsvarlig å behandle med T3 eller NDT, noe som har gjort at det medisinske fagmiljøet i Norge er mer restriktive enn noensinne mot å la pasienter få prøve ut disse medisinene. Etter at han holdt disse foredragene registrerte vi praksisendring i HELFO. Kan det være slik at en dansk endokrinolog kan ha så stor innflytelse på medisinsk praksis i Norge?

Thyroidea Norge kommenterer: Ifølge Stofskiftesupport.dk (pasientsammenslutning) har det nå blitt slik at de få pasienter som får lov til å behandle med T3 - som regel etter en lang kamp - kun får lov til å ta en maksimumsdose på 5 ug. I Norge får man kun Liothyronin i tabletter på 20 ug, hvor gitt maksimumsdose har blitt satt til inntil tre tabletter per dag, altså 60 ug. Man kan dermed argumentere for at danske pasienter får en altfor lav dose til at det kan ha tilfredsstillende effekt. Man kan igjen tenke seg at der danske endokrinologer ser at pasienter ikke blir bedre på tilskudd av T3, kan det skyldes den sterke begrensningen i tillatt dosering. Thyroidea Norge reagerer dermed sterkt på at en dansk endokrinolog som går ut med slike holdninger, der han kategorisk underkjenner all forskning gjort som sier at pasienter blir bedre med tilskudd av T3 eller med NDT ***OG*** all pasienterfaring som sier det samme, skal ha en så plutselig og sterk innvirkning på medisinsk praksis i Norge.

Vi har også fått ganske mange henvendelser fra pasienter som får allergiske reaksjoner på medisiner for tyreotoksikose og hypertyreose, noe vi jobber med å få oversikt over. Vi vet ikke nøyaktig hva de ulike pasientene reagerer på, og derfor er det et problem at det er så lite å velge imellom av slike medisiner. Særlig ble dette et problem forrige vinter da det i en lang periode var umulig å få tak i Neo-Mercazole. Mange pasienter reagerte dårlig på erstatningene de fikk.

Thyroidea Norge minner om at enhver pasient har rett til å være med på å bestemme sin egen behandling og skal bli hørt.

Vi tror jo ikke dere kommer til å gå igjennom alle studier vi viser til under da vi vet det er snakk om svært mange. Men vi håper at dere i det minste kan ta dere bryet med å kikke på abstraktene. Vi har lagt ved ganske mange studier for å vise at det ikke bare er et par “små” studier sånn helt i senere tid som viser at pasienter blir bedre på NDT/T3, eller som viser at pasienter sliter også med utilstrekkelig behandling - det er overveldende medisinske data, og over mange tiår.

Der vi mener det er ekstra viktige studier som det er helt essensielt at dere tar hensyn til, har vi satt dem i ramme for å utheve dem.

Merk også at vi under noen studier har satt på kommentarer. Vi håper disse kan tas til etterretning.

Tilbakemelding fra dere blir satt pris på.

Vennlig hilsen

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MERK: Dette dokumentet vil etter utsendelse bli publisert i sin helhet på vår nettside

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Studier

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

Work Disability among people with benign Thyroid Diseases in Denmark. Mette Nexø, 2014

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"

Studier som viser at ikke alle blir bra med T4 monoterapi

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.

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 jobber. 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 T2do 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.

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.

Om at TSH ikke er brukbart som måleenhet alene for å diagnostisere og behandle stoffskiftesykdommer

Alevizaki, M., Mantzou, E., Cimponeriu, A. T., Alevizaki, C. C., & Koutras, D. A. (2005). TSH may not be a good marker for adequate thyroid hormone replacement therapy. *Wiener Klinische Wochenschrift*, *117*(18), 636-640.

Abstract: We conclude that patients with T4-treated hypothyroidism have lower T3 levels, lower T3/T4 ratio and lower SHBG than normal individuals with the same TSH, perhaps indicating relative tissue hypothyroidism in the liver. TSH levels used to monitor substitution, mostly regulated by intracellular T3 in the pituitary, may not be such a good indicator of adequate thyroid hormone action in all tissues.

Andersen S, Petersen KM, Brunn NH, Laurberg P (2002). Narrow individual variations in serum T4 and T3 in normal subjects: a clue to the understanding of subclinical thyroid disease. *Journal of Clinical Endocrinology and Metabolism.* 2002;87:1068–72.

Abstract: High individuality causes laboratory reference ranges to be insensitive to changes in test results that are significant for the individual. Our data indicate that each individual had a unique thyroid function. The individual reference ranges for test results were narrow, compared with group reference ranges used to develop laboratory reference ranges. Accordingly, a test result within laboratory reference limits is not necessarily normal for an individual. Our data indicate that the distinction between subclinical and overt thyroid disease (abnormal serum TSH and abnormal T4 and/or T3) is somewhat arbitrary.

Redigert av Professor of Internal Medicine James E. Griffin M.D. Diana and Richard C. Strauss Professor of Biomedical Research, and Chief of Clinical Endocrinology in the Department of Internal Medicine University of Texas Southwestern Medical Center at Dallas,Division of Neuroscience Oregon Regional Primate Research Center/Oregon Health Sciences University Sergio R. Ojeda M.D. Head Griffin James & Ojeda Sergio R, Text Book of Endocrine Physiology, Oxford University Press, 2000

Kapittel om stoffskiftesykdommer begynner på side 294 Det står blant annet at TSH ikke kan brukes som måleenhet alene for å sjekke stoffskiftefunksjonen. Det står også at ettersom grenseverdi/normalverdi hos friske mennesker for stoffskiftehormoner er så bred, kan man utmerket godt ha en stoffskiftesykdom selv om prøvene er normale.

2005 S. Karger AG, Basel

Effects on bone mineral density by treatment of benign nodular goiter with mildly suppressive doses of L-thyroxine in a cohort women study.

OBJECTIVES:

Thyroid diseases and their treatment may influence the osseous system. The influence that prolonged suppressive L-thyroxine (LT4) therapy may have on inducing subclinical hyperthyroidism on bone metabolism is still a matter of debate. The aim of the present study was to assess the effects of chronic LT4 treatment at mildly inhibiting serum thyroid-stimulating hormone (TSH) doses on bone mineral density (BMD) and biochemical bone remodeling markers in a cohort of women with benign nodular goiter, and to verify the efficacy of the treatment on nodule size

CONCLUSIONS:
This study suggests that at slightly suppressing TSH doses, LT4 therapy has no adverse effects on BMD in both pre- and postmenopausal women, while having an efficacy on nodule size comparable with that reported using an LT4 schedule able to maintain TSH near or below the assay sensitivity limit.

Becker DV, Bigos ST, Gaitan E, Morris JC, Rallison ML, Spencer CA, Sugarawa M, Van Middlesworth L, Wartofsky L. (1993). Optimal use of blood tests for assessment of thyroid function. ***Journal of the American Medical Association.*** **1993 Jun 2; 269: 273** ‘
Introduction: The decision to initiate (thyroid) therapy should be based on both clinical and laboratory findings and not solely on the results of a single laboratory test.

De Los Santos ET, Mazzaferri EL (1988). Sensitive thyroid-stimulating hormone assays: Clinical applications and limitations. ***Comprehensive Therapy.*** **1988; 14(9): 26-33.**
Abstract: Interpretation of the TSH value should be made with a clear understanding of its limitations. At present, it is uncertain whether clinically euthyroid patients with autonomously functioning thyroid nodules, or with multinodular goiters, or patients taking thyroid hormone who have suppressed TSH values, are actually euthyroid at a cellular level. Other factors that affect TSH levels are the biologic variation in its secretion, the presence of heterophilic antibodies in a patient's serum, and various drugs. The new ultrasensitive TSH assay does not yet replace other thyroid function tests, but it is clearly emerging as an important means of screening patients for thyroid dysfunction. It can usually separate patients with thyroid dysfunction from euthyroid individuals. Good clinical assessment is always necessary, and other thyroid function tests are often needed.

Després N, Grant A. (1998). Antibody interference in thyroid assays: a potential for clinical misinformation***. Clinical Chemistry March 1998 vol. 44 no. 3 440-454.***
Abstract: Measurements of thyrotropin and of total and free thyroxine and triiodothyronine are widely used diagnostic methods for thyroid function evaluation. However, some serum samples will demonstrate a nonspecific binding with assay reagents that can interfere with the measurement of these hormones. Several recent case reports have described the presence of such interferences resulting in reported abnormal concentrations of thyroid hormones inconsistent with the patient’s thyroid state. Circulating thyroid hormone autoantibodies, described in thyroid and nonthyroid disorders, are an important class of interference factor and can bind to hormone tracers used in various immunoassays.

Dickey RA, Wartofsky L, Feld S. (2005). Optimal thyrotropin level: normal ranges and reference intervals are not equivalent. ***Thyroid.*** **2005 Sep;15(9):1035-9**
Abstract: This paper marshals arguments in support of a narrower, optimal or true normal range for thyrotropin (TSH) of 0.4 to 2.5 mIU/L, based on clinical results and recent information on the relatively stable and narrow range of values in patients without thyroid disease. The terminology used for TSH results is clarified in an attempt to help physicians interpret, explain, and respond to TSH test results for their patients.

Goldberg A, Tirona R, Schwarz U, Kim RB, Van Uum SHM. (2001). Hypothyroidism with Very Low Free T3/Free T4 Ratio May Represent Decreased Peripheral Conversion of T4 to T3: Case Report and Differential Diagnosis. *Endocrine Reviews.* Vol. 32: P3-616.
Abstract: A post-thyroidectomy patient exhibits a very low free T3/free T4 ratio and high TSH, suggesting hypothyroidism most likely caused by decreased conversion of T4 to T3. In this report, we discuss a diagnostic approach to the potential mechanisms of abnormal free T3/free T4 ratio.

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.

Tolkes slik av Thyroid UK sin rådgiver: July 2014
Thyroid UK advisors Rudolf Hoermann, John E.M. Midgley and Johannes W. Dietrich have just had a new research paper published in the Clinical Endocrinology Journal.
Dr John Midgley tells us:
"What it proves is that there is no such thing as a TSH range that is suitable for everyone, and that the range is different according to the effect of independent influences such as age, body mass, size of working thyroid volume and whether someone is on T4 or not.
The T4 therapy range is very much lower than the "normal" untreated and sits around the 1 or lower mark. The 3-4 upper level that works for the normal person is not satisfactory and can indicate undertreatment.
Also we're finding that people with no thyroid working at all cannot easily regain normal FT3 with T4 alone and that TSH suppression often has to happen, and in some people no amount of T4 will regain normal FT3 levels. Recent reviews by the gurus now admit that some people cannot handle T4 only and regain health. Just thought you'd like to know that the avalanche is beginning."

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. Reduced T4 and T3 transport into the cells in peripheral tissues is seen with a wide range of common conditions, including insulin resistance, diabetes, depression, bipolar disorder, hyperlipidemia, chronic fatigue syndrome, fibromyalgia, neurodegenerative diseases, migraines, stress, anxiety, chronic dieting and aging, while the intracellular T3 level in the pituitary often remains unaffected.

Holtorf, K. (2014). Peripheral Thyroid Hormone Conversion and Its Impact on TSH and Metabolic Activity. *Journal of Restorative Medicine*, *3*(1), 30-52.
Summary: Consequently, it is inappropriate to rely on a normal or low TSH as an adequate or sensitive indicator of normal or low tissue levels of T3 in the presence of any such conditions, making the TSH a poor marker for the body's overall thyroid level.

Holtorf, K. (2012). Hormone Replacement Therapy in the Geriatric Patient: Current State of the Evidence and Questions for the Future. Estrogen, Progesterone, Testosterone, and Thyroid Hormone Augmentation in Geriatric Clinical Practice. This article, independently written and published, is a broad study of hormone replacement in geriatric patients. In the thyroid section, written by Kent Holtorf M.D ., it details the difference between serum thyroid hormone levels and tissue thyroid hormone levels, particularly in cases of chronic and acute stress.

Kalra S, Khandelwal, SK (2011). Why are our hypothyroid patients unhappy? Is tissue hypothyroidism the answer? *Indian Journal of Endocrinology and Metabolism.* 2011 July; 15(Suppl2): S95–S98.
Introduction: The improvements in laboratory diagnosis, follow-up, monitoring and treatment, however, have not necessarily improved satisfaction levels of patients. Many patients complain of persistent psychological symptoms after treatment. Others state that they do not feel normal. Some patients report inadequate weight loss or continuous weight gain in spite of normal TSH levels.
Conclusions: As we manage our patients with hypothyroidism, we not only have to maintain normal TSH levels, but also achieve symptomatic relief and satisfaction. We have to avoid being unsympathetic and dismissive of their complaints.

Pacchiarotti A, Martino E, Bartalena L, Aghini Lombardi F, Grasso L, Buratti L, Falcone M, Pinchera A (1986). Serum free thyroid hormones in subclinical hypothyroidism. *Journal of Endocrinological Investigation.* 1986 Aug;9(4):315-9.
Abstract: These results indicate that FT4 should be measured in addition to TSH for the diagnosis of impending thyroid failure, thus showing that in many cases patients with so-called subclinical hypothyroidism are actually already mild hypothyroid.

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.

Rowsemitt, C. and Najarian, T. (2011) **TSH is Not the Answer: Rationale for a New Paradigm to Evaluate and Treat Hypothyroidism, Particularly Associated with Weight Loss.** *Thyroid Science; 6(4): H1-16.*
Conclusions: Treating to normalize thyroid hormone levels and eliminate hypothyroid symptoms results in the suppression of TSH. This is understood as a normal part of treatment once we accept that the thyroid set point has been lowered. This is not an argument to use thyroid hormones to increase metabolism above normal to achieve weight loss. Our goal is to correct the hypothyroid response in a weight loss patient and return him/her to normal metabolism so that the patient feels normal and is better able to lose weight and maintain that loss.

Ruhla, S., Arafat, A. M., Weickert, M. O., Osterhoff, M., Isken, F., Spranger, J., ... & Möhlig, M. (2011). **T3/rT3-ratio is associated with insulin resistance independent of TSH.** ***Hormone and metabolic research*, *43*(02), 130-134.**
Abstract: Here we show that the triiodothyronine/reverse triiodothyronine (T3/rT3- lab test ratio), which is supposed to reflect the tissue thyroid hormone metabolism, is significantly increased in insulin resistant subjects. This further supports a link between thyroid function and IR.

Sesmilo G, Simó O, Choque L, Casamitjana R, Puig-Domingo M (2011). **Serum free triiodothyronine (T3) to free thyroxine (T4) ratio in treated central hypothyroidism compared with primary hypothyroidism and euthyroidism.** ***Endocrinología y Nutrición*. 2011 Jan;58(1):9-15**
Conclusions: Treated patients with central hypothyroidism had a lower free T3 to free T4 ratio, similar free T3 levels and higher free T4 concentrations than euthyroid controls, whereas all these parameters were similar in central and primary hypothyroid patients treated with T4. The question of whether these findings translate into adequate tissue concentrations of free thyroid hormones in all tissues remains to be answered. Further studies should aim to determine whether clinical outcomes could be improved by a treatment achieving more physiological plasma concentrations.

Skinner GRB, Holmes D, Ahmad A, Davies JA, Benitez J (2000). **Clinical Response to Thyroxine Sodium in Clinically Hypothyroid but Biochemically Euthyroid Patients.** ***Journal of Nutritional and Environmental Medicine.* Vol. 10, No. 2 , Pages 115-124.**
Conclusions: Clinically hypothyroid but biochemically euthyroid patients had favourable clinical response to thyroid replacement which correlated with the level of thyroid replacement. It is suggested that these findings be examined in a prospective placebo controlled clinical trial.

Skinner GR, Thomas R, Taylor M, Sellarajah M, Bolt S, Krett S, Wright A. (1997). **Thyroxine should be tried in clinically hypothyroid but biochemically euthyroid patients.** ***British Medical Journal*: June 14; 314(7096).**
Utdrag: We contend that an incremental three month trial of thyroxine treatment in clinically hypothyroid but biochemically euthyroid patients is a safe and reasonable strategy. The dangers of osteoporosis and cardiac catastrophe–particularly during a three month trial–are sometimes

quoted, but these worries are unfounded and condemn many patients to years of hypothyroidism with its pathological complications and poor quality of life. We urge that the question of clinical hypothyroidism in biochemically euthyroid patients should be subjected to a formal clinical trial.

van den Beld, A.W., Visser, T., Feelders, R., Grobbee, R., Lamberts, W.J., (2005) Effect of Exogenous Thyroid Hormone Intake on the Interpretation of Serum TSH Results**.** ***The Journal of Clinical Endocrinology & Metabolism*****; 90 (12): 6403-6409.**
Conclusions: In a population of independently living elderly men, higher FT4 and RT3 concentrations are associated with a lower physical function.

Wartofsky L, Dickey, R (2005). The Evidence for a Narrower Thyrotropin Reference Range Is Compelling. ***The Journal of Clinical Endocrinology & Metabolism.*** **September 1, 2005 vol. 90 no. 9 5483-5488.**
Abstract: Debate and controversy currently surround the recommendations of a recent consensus conference that considered issues related to the management of early, mild, or so-called subclinical hypothyroidism and hyperthyroidism. Intimately related to the controversy is the definition of the normal reference range for TSH. Recognition and establishment of a more precise and true normal range for TSH have important implications for both screening and treatment of thyroid disease in general and subclinical thyroid disease in particular.

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.

A. Mortoglou, H. Candiloros (2004)
The serum triiodothyronine to thyroxine (T3/T4) ratio in various thyroid disorders and after Levothyroxine replacement therapy **Department of Endocrinology, Diabetes and Metabolism, Athens Medical Centre Hospital, Athens, Greece**
Abstract: In order to examine the significance of differences in the triiodothyronine/thyroxine (T3/T4) ratio in the achievement of euthyroidism and in different thyroidal diseases, we studied 1050 subjects: 233 were euthyroid (Eu), 239 hypothyroid (Hypo) with initial TSH levels >15 mU/L, 273 hypothyroid on substitution therapy with L-thyroxine alone and TSH values of 0.35-3.5 mU/L, (hypoRx), 236 hyperthyroid (hyper) and 69 in the acute phase of subacute thyroiditis De Quervain's (DQ). The ratio of T3/T4 was calculated using the conventional values. Results: The values of T3/T4 ratio in the various categories were: Eu= 15.89, Hypo= 24.12, hyper= 19.57, hypoRx= 13.42, DQ= 15.16. The T3/T4 ratio was lower in the hypoRx group than in the EU group (P <0.001), although neither TSH values nor T3 values showed any differences between these two groups, whereas T4 levels were significantly higher in the hypoRx group

(Eu= 7.99±1.46, hypoRx = 9.11±1.58, P< 0.001). The T3/T4 ratio in the DQ group was comparable to that of the Eu group, but significantly lower than the hyper group (P=0.95 between Eu and DQ, P<0.001 between DQ and hyper).
Conclusions: These findings indicate that in hypothyroid patients, L-T4-replacement that is sufficient to maintain a normal serum TSH is accompanied by a serum T4 that is higher than in normal individuals and may not result in an appropriately normal serum T3 concentration. In Thyrotoxicosis, a ratio of total T3/T4 >18.9 suggests Graves' disease or toxic multinodular goiter whereas T3/T4 <16 suggests thyroiditis (subacute or silent).

Eur J Endocrinol. 2013 Hoermann R, Midgley JE, Larisch R, Dietrich JW.
Is pituitary TSH an adequate measure of thyroid hormone-controlled homoeostasis during thyroxine treatment?
Abstract
OBJECTIVE:
In recognition of its primary role in pituitary-thyroid feedback, TSH determination has become a key parameter for clinical decision-making. This study examines the value of TSH as a measure of thyroid hormone homoeostasis under thyroxine (T(4)) therapy.
CONCLUSION:
The data reveal disjoints between FT(4)-TSH feedback and T(3) production that persist even when sufficient T(4) apparently restores euthyroidism. T(4) treatment displays a compensatory adaptation but does not completely re-enact normal euthyroid physiology. This invites a study of the clinical consequences of this disparity.

Endocrine Abstracts (2010) 21 OC5.6, Graham Leese & Robert Flynn, University of Dundee, Tayside, UK **Is it safe for patients taking thyroxine to have a low but not suppressed serum TSH concentration?**
Conclusion: People on long-term thyroxine with a high or suppressed TSH are at increased risk of cardiovascular disease, dysrhythmias and fractures. People with a low but not suppressed TSH did not have an increased risk of these outcomes in this study. It may be safe for patients treated with thyroxine to have a low but not suppressed serum TSH concentration.

Rakesh Nair, Shriraam Mahadevan,1 R. S. Muralidharan, and S. Madhavan, Indian J Endocrinol Metab. 2014 **Does fasting or postprandial state affect thyroid function testing?**
Abstract
BACKGROUND: Thyroid stimulating hormone (TSH) levels vary with the time of the day and probably in relation to food. In this study, we addressed the question of whether a fasting or non-fasting sample would make a clinically significant difference in the interpretation of thyroid function tests.
RESULTS:
TSH was suppressed in all subjects after food irrespective of the fasting levels. Free T4 values did not change significantly. This resulted in reclassification of 15 out of 20 (75%) subjects as subclinical hypothyroidism (SCH) based on fasting values whose TSH values were otherwise within range in the postprandial sample. This may have an impact on the diagnosis and

management of hypothyroidism especially where even marginal changes in TSH may be clinically relevant as in SCH and in pregnancy.

CONCLUSION:

TSH levels showed a statistically significant decline postprandially in comparison to fasting values. This may have clinical implications in the diagnosis and management of hypothyroidism, especially SCH.

Science Daily:Date: March 15, 2010; Source: Society for Endocrinology **May be safe for patients taking thyroxine to have lower TSH levels than currently recommended, new research shows**

Summary: New research shows that it may be safe for patients taking thyroxine replacement to have low but not suppressed thyroid stimulating hormone (TSH) levels. The research shows for the first time that it may be safe for patients to take slightly higher doses of thyroxine than are currently recommended.

ARTHUR S. WEISSBEIN, CAPTAIN, MC, USA[†], and JOHN D. LAWSON, MAJOR, MC, USA

PARADOXICAL LENGTHENING OF MUSCLE CONTRACTION TIME IN HYPOTHYROID PATIENTS GIVEN SMALL DOSES OF *l*-TRIIODOTHYRONINE, THYROXINE AND DESICCATED THYROID

Received: August 04, 1959

Published Online: July 01, 2013

ABSTRACT Since the prolongation of the Achilles reflex associated with myxedema is shortened during treatment with thyroid hormone, it was surprising to find that when *small* doses of thyroid hormone were administered to hypothyroid patients, the reflex time became longer rather than shorter. Further investigation revealed that this paradoxical response occurred in all patients who were hypothyroid by standard tests of thyroid function. Several borderline hypothyroid patients were also studied. The results thus far suggest that this paradoxical muscular response may possibly provide a means for detection of milder degrees of hypothyroidism than are demonstrable by the standard clinical tests now employed. The test was standardized on 40 hypothyroid patients. It was found that the most economical and simple method consists of recording the duration of the Achilles reflex contraction time within twenty-four hours after administration of 25 µg. of *l*-triiodothyronine (liothyronine) in fractional doses.

Behovet for flere behandlingsalternativer

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
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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[1,2], Tatiana L. Fonseca[1,2], Cintia B. Ueta[1], Elizabeth A. McAninch[1,2], Sherine Abdalla[1], Gabor Wittmann[3], Ronald M. Lechan[3], Balazs Gereben[4] and Antonio C. Bianco[1,2] **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.

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.

Og videre: 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

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.

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.

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.

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

Kognitive og emosjonelle problemer ved stoffskiftesykdom

Vi ber dere ta en titt på vår nettside og artikkelen vi har om emnet der. Kilder står nederst

Boillet, D., Szoke, A. (1998). Psychiatric manifestations as the only clinical sign of hypothyroidism. Apropos of a case. *Encephale*: 24(1):65-8.
Conclusion: The endocrine investigation has documented, in spite of the absence of any suggestive physical signs, a thyroid insufficiency. After the replacement treatment, all symptoms but the cognitive dysfunction disappeared. The patient's evolution is presented clinically, also rated on MMSE and MADRS scales, and biologically (TSH and T4 determination) for a 4 months period. The absence of any pathognomonical psychiatric finding, the possibility of the absence of other signs and symptoms (namely physical) in the hypothyroid state, the presence of potentially irreversible cognitive deterioration, as well as the inocuity and sensibility of thyroid hormones examination justify the systematic thyroid evaluation for all new psychiatric patients.

Carta, MG., Hardoy, MC., Carpiniello, B., Murru, A., Marci, AR., Carbone, F., Deiana, l., Cadeddu, M., Mariotti, S. (2005). A case control study on psychiatric disorders in Hashimoto disease and Euthyroid Goitre: not only depressive but also anxiety disorders are associated with thyroid autoimmunity. *Clin Pract Epidemiol Ment Health*; 10:1-23.
Conclusion: The study seems to confirm that risk for depressive disorders in subjects with thyroiditis is independent of the thyroid function detected by routine tests and indicates that not only mood but also anxiety disorders may be associated with Hashimoto disease.

Davis, A.T. (1989). Psychotic states associated with disorders of thyroid function. *Int J Psychiatry Med*. 1989;19(1):47-56.
Conclusions: Thyroid-related psychoses continue to pose diagnostic and treatment challenges for clinicians. Two case histories illustrate diverse clinical states associated with hyper- and hypo-thyroidism respectively and highlight the need to consider the possibility of thyroid disorder in all patients presenting with acute psychotic mental disorder. They also demonstrate treatment methods directed at control of psychotic symptoms and restoration of an euthyroid state.

Gold, M.S., Pottash, A.L., Extein, I. (1982). "Symptomless" autoimmune thyroiditis in depression. *Psychiatry Res*. 1982 Jun; 6(3):261-9.
Conclusion: The magnitude of the thyroid-stimulating hormone (TSH) response induced by thyrotropin-releasing hormone (TRH) helps identify patients whosethyroid is failing. Many of these patients have been found to have Hashimoto's thyroiditis, symptomless autoimmune thyroiditis (SAT), and subclinical hypothyroidism. While patients with SAT are clinically euthyroid, what might be "symptomless" for the endocrinologist might be a syndrome presenting with psychiatric symptoms to the psychiatrist. As a preliminary test of this hypothesis, we tested 100 consecutive admissions to a psychiatric hospital who complained

of depression or lack of energy. Fifteen (15%) of 100 patients were identified from the baseline thyroxin (T4), triiodothyronine (T3) resin uptake (RU), T3 radioimmunoassay (T3RIA), TSH, and TRH test who met criteria for either subclinical, mild, or overt hypothyroidism. Of these 15 patients, 9 (60%) had positive thyroid microsomal antibodies with titers of greater than or equal to 1:10. Our data suggest that SAT is not symptomless and may be an important diagnosis to consider in the evaluation of depressed, anergic, or atypical patients.

Hage, M.P., Azar, S.T. (2011). The Link between Thyroid Function and Depression. Journal of Thyroid Research; Vol. 2012 (Article ID 590648).
Conclusion: Clinical investigators have long recognized the link between thyroid and depression. While patients with hypothyroidism commonly manifest features of depression, hyperthyroidism presents with a wider spectrum of neuropsychiatric symptoms including both depression and anxiety...Screening patients presenting with depression for thyroid dysfunction seems reasonable particularly those with refractory symptoms. However, the use of thyroid hormones as an adjunct therapy to antidepressants in the absence of subclinical or clinical hypothyroidism should be further investigated. In addition, specifying a particular patient population that might benefit from this combination as determined by individual genetic variants should be addressed.

Haggerty, J.J., Jr., Evans, D.L., Golden, R.N., Pedersen, C.A., Simon, J.S., Nemeroff, C.B. (1990). The presence of antithyroid antibodies in patients with affective and nonaffective psychiatric disorders. *Biol Psychiatry*; 27(1):51-60.
Conclusions: Our findings confirm earlier reports that thyroid disorders may be particularly common in patients with bipolar affective disorder, even in the absence of lithium exposure. However, as antithyroid antibodies also occurred at a relatively high rate in nonaffective disorders, the possible psychiatric effects of autoimmune thyroiditis do not appear to be limited to affective dysregulation.

Hall, R C W, Popkin M, Devaul R, Hall, A K, Gardner E, Beresford T (1982). Psychiatric Manifestations of Hashimoto's Thyroiditis. Psychosomatics. Volume 23, Issue 4, April 1982, Pages 337-342.
Abstract: The mental symptoms associated with Hashimoto's thyroiditis may precede the full-blown, classic picture of hypothyroidism. The psychiatric symptoms include various mental aberrations, depression, irritability, and confusion. Indeed, patients may be mislabeled as having psychotic depression, paranoid schizophrenia, or the manic phase of a manic depressive disorder. The workup must include a thorough evaluation of thyroid function, including tests for autoantibodies. Patients usually respond favorably to thyroid replacement hormone therapy.

Hendrick, V., Altshuler, L., Whybrow, P. (1998) Psychoneuroendocrinology of mood disorders. The hypothalamic-pituitary-thyroid axis. *Psychiatr Clin North Am*. 1998 Jun;21(2):277-92.
Conclusions: Abnormal thyroid functioning can affect mood and influence the course of unipolar and bipolar disorder. Even mild thyroid dysfunction has been associated with changes in mood and cognitive functioning. Thyroid hormone supplementation may have role in the treatment of certain mood disorders, particularly rapid-cycling bipolar disorder. Women are more vulnerable to thyroid dysfunction than men and also respond better to thyroidaugmentation. This article reviews the relationship between thyroid function and mood, and the use of thyroid hormones in the treatment of mood disorders. The impact of gender on these issues is also discussed.

Jackson, I.M. (1998). Thyroid Axis and Depression. *Thyroid:* 8 (10): 951-6.
Conclusion: It is known that in human depression there is a functional disconnection of the hypothalamus with impairment of the inhibitory glucocorticoid feedback pathway from the hippocampus to the hypothalamus that results in the typical elevated cortisol levels and impaired dexamethasone suppression. It is postulated that a similar situation prevails with regards to the thyroid axis and that the increased T4 in depression, as well as the blunted TSH response to exogenous TRH, reflects glucocorticoid activation of the TRH neuron leading to increased TRH secretion with resultant down regulation of the TRH receptor on the thyrotrope. Normalization of thyroid function after treatment may result in part from an inhibitory response of the TRH neuron to antidepressant medication, although other effects may also be responsible.

McGaffee, J. Barnes, MA, Lippmann, S. (1981) Psychiatric Presentations of Hypothyroidism. *American Family Physician*; 23 (5): 129-133.
Conclusion: Hypothyroidism can often be misdiagnosed as psychiatric illness. The hypothyroid patient may present with depression, an organic mental disorder, apathy and/or frank psychosis (usually with paranoid symptoms). Psychiatric manifestations of the endocrinopathy will abate with thyroid hormone replacement therapy, unless the disease state has been sufficiently prolonged to cause some irreversible brain damage. This irreversibility mandates prompt diagnosis and specific hormonal replacement therapy. Thus, thyroid function screening is recommended for patients presenting with depression, psychosis or organic mental disorder.

Placidi, G.P.A., Boldrini M., Patronelli A., Fiore E., Chiovato L., Perugi G., Marazziti D. (1998) Prevalence of Psychiatric Disorders in Thyroid Diseased Patients. *Neuropsychobiology*; 38:222–225.
Conclusion: The results showed higher rates of panic disorder, simple phobia, obsessive-compulsive disorder, major depressive disorder, bipolar disorder and cyclothymia in thyroid patients than in the general population. These findings would suggest that the co-occurrence of psychiatric and thyroid diseases may be the result of common biochemical abnormalities.

Rack, S.K., Makela, E.H. (2000) Hypothyroidism and depression: a therapeutic challenge. *Ann Pharmacother*; 34(10):1142-5.
Conclusions: Depressed patients should be screened for hypothyroidism. In hypothyroid patients, depression may be more responsive to a replacement regimen that includes T3 rather than T4 alone. Therefore, inclusion of T3 in the treatment regimen may be warranted after adequate trial with T4 alone.

Reed K, Bland RC (1977). Masked "myxedema madness". Acta Psychiatr Scand. 1977 Nov;56(5):421-6.
Abstract: Hypothyroidism can present a wide range of psychiatric manifestations, including personality disturbance, neurotic traits and psychotic features. Psychiatric treatment techniques without recognition and correction of the endocrine root of the mental disturbance will result in a failure of treatment. However, severe hypothyroidism can exist with a poverty of classical signs and symptoms such that both internist and psychiatrist may easily overlook endocrine dysfunction as a possible etiology of the mental disorder. A case of long-standing paranoid illness whose etiology was severe myxedema with such a poverty of signs and symptoms is presented.

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.

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-hypothyroidismm . Accessed: Nov, 16, 2011. See section 9.5.3 "Nervous System" and Table 9-10 "Incidence of symptoms and signs in hypothyroidism".

Journal of Aggression, Maltreatment & Trauma, 2013 Emma Fuller-Thomson et al
Exploring Gender Differences in the Association Between Childhood Physical Abuse and Thyroid Disorders
Abstract This study used a regional subsample (n = 13,070) from the 2005 Canadian Community Health Survey to explore the independent contribution of childhood physical abuse to thyroid conditions in adulthood. Gender-specific logistic regression analyses controlled for age and race, in addition to 5 clusters of variables: childhood stressors, health behaviors, general stress levels, mental health, and socioeconomic status. No significant

relationship between childhood abuse and thyroid conditions was found in men; however, childhood physical abuse was associated with higher odds of thyroid conditions among women, independent of a wide range of factors. In a fully adjusted model, abused women had 40% higher odds of thyroid conditions compared to their non abused peers, 95% CI [1.05, 1.87]. Future research on gender differences in the abuse–thyroid relationship is warranted

Artikler om studien: http://www.empr.com/for-women-child-abuse-linked-to-adult-thyroid-conditions/article/306330/

http://media.utoronto.ca/media-releases/childhood-physical-abuse-linked-to-thyroid-disorders-in-women/

http://www.health24.com/Lifestyle/Woman/News/Childhood-abuse-may-lead-to-thyroid-problems-20130805

Saravanan P[1], Chau WF, Roberts N, Vedhara K, Greenwood R, Dayan CM. 2002
Psychological well-being in patients on 'adequate' doses of l-thyroxine: results of a large, controlled community-based questionnaire study.

Abstract

OBJECTIVE:

Over 1% of the UK population is receiving thyroid hormone replacement with l-thyroxine (T4). However, many patients complain of persistent lethargy and related symptoms on T4 even with normal TSH levels. To date there has been no large study to determine whether this is related to thyroxine replacement or coincidental psychological morbidity. We have therefore attempted to address this issue using a large, community-based study.

CONCLUSIONS:

This community-based study is the first evidence to indicate that patients on thyroxine replacement even with a normal TSH display significant impairment in psychological well-being compared to controls of similar age and sex. In view of the large numbers of people on thyroxine replacement, we believe that these differences, although not large, could contribute to significant psychological morbidity in a substantial number of individuals.

Markku Linnoila, Bror-Axel Lamberg, William Z. Potter, Philip W. Gold, Frederick K. Goodwin. Psychiatry Research: Received: November 19, 1981; Received in revised form: January 23, 1982 **High reverse T_3 levels in manic and unipolar depressed women**

Abstract A relatively high percentage of patients with affective disorders have abnormalities of thyroid function, and over 60% of endogenously depressed and most manic patients show a blunted thyroid-stimulating hormone (TSH) response to thyroid-releasing hormone (TRH) injections. We now replicate earlier findings concerning relatively high 3,3',5'-triiodothyronine (reverse T_3) levels in unipolar depressives and find similarly high levels in manic women. The significance of the present finding is unknown, but measurement of reverse T_3 levels as a

potential tool in differential diagnosis of affective disorders and in psychobiological research should be exploded further.

Thyroidea Norge mener: Reverse T3 kan kun tas på Hormonlaboratoriet på Aker, men alle fastleger kan rekvirere denne prøven. rT3 bør i større grad brukes som en indikasjon på flere ting - både for å sammenligne med pasientens kognitive funksjonsnivå, det mentale, og om pasienten klarer å konvertere T4 til T3. Vi mener at rT3 i større grad bør inn som standard test i behandling og overvåkning av stoffskiftepasienter

Review ArticleJournal of Thyroid Research, Volume 2012, Mirella P. Hage and Sami T. Azar, **Division of Endocrinology and Metabolism, Department of Internal Medicine, American University of Beirut Medical Center** **The Link between Thyroid Function and Depression**

Abstract The relation between thyroid function and depression has long been recognized. Patients with thyroid disorders are more prone to develop depressive symptoms and conversely depression may be accompanied by various subtle thyroid abnormalities. Traditionally, the most commonly documented abnormalities are elevated T4 levels, low T3, elevated rT3, a blunted TSH response to TRH, positive antithyroid antibodies, and elevated CSF TRH concentrations. In addition, thyroid hormone supplements appear to accelerate and enhance the clinical response to antidepressant drugs. However, the mechanisms underlying the interaction between thyroid function and depression remain to be further clarified. Recently, advances in biochemical, genetic, and neuroimaging fields have provided new insights into the thyroid-depression relationship.

Sammenhengen mellom binyrefunksjon og stoffskiftet

Backhaus, J., Junghanns, K., Hohagen, F. (2004). Sleep disturbances are correlated with decreased morning awakening salivary cortisol
***Psychoneuroendocrinology*; Volume 29, Issue 9, Pages 1184–1191.**
Results: Cortisol after awakening was significantly decreased in primary insomnia. Salivary cortisol at the time of awakening correlated negatively with the subjective estimation of sleep quality, i.e. a low salivary cortisol level directly after awakening correlated with a higher frequency of nightly awakenings, a diminished sleep quality and a decreased feeling of recovery after awakening.

Cleare, A.J., Miell, J., Heap, E. Sookdeo, S., Young, L., Malhi, G.S., O'Keane, V. (2001). Hypothalamo-Pituitary-Adrenal Axis Dysfunction in Chronic Fatigue Syndrome, and the Effects of Low-Dose Hydrocortisone Therapy. ***The Journal of Clinical Endocrinology & Metabolism*; vol. 86 no. 8 3545-3554.**
Results: In this group, there was a significant increase in the cortisol response to human CRH, which reversed the previously observed blunted responses seen in these patients. We conclude that the improvement in fatigue seen in some patients with chronic fatigue syndrome during hydrocortisone treatment is accompanied by a reversal of the blunted cortisol responses to human CRH.

Di Giorgio, A., Hudson, M., Jerjes, W., Cleare, A. (2005). 24-Hour Pituitary and Adrenal Hormone Profiles in Chronic Fatigue Syndrome.
***Psychosomatic Medicine*; vol. 67 no. 3 433-440**
Conclusions: Patients with CFS demonstrated subtle alterations in HPA axis activity characterized by reduced ACTH over a full circadian cycle and reduced levels during the usual morning physiological peak ACTH secretion. This provides further evidence of subtle dysregulation of the HPA axis in CFS. Whether this dysregulation is a primary feature of the illness or instead represents a biologic effect secondary to having the illness itself remains unclear.

Head, K.A., Kelly, G.S. (2009) Nutrients and Botanicals for Treatment of Stress: Adrenal Fatigue, Neurotransmitter Imbalance, Anxiety, and Restless Sleep. ***Alternative Medicine Review*; Jun;14(2):114-40.**
Abstract: Research shows a dramatic increase in use of the medical system during times of stress, such as job insecurity. Stress is a factor in many illnesses - from headaches to heart disease, and immune deficiencies to digestive problems. A substantial contributor to stress-induced decline in health appears to be an increased production of stress hormones and subsequent decreased immune function. Non-pharmaceutical approaches have much to offer such patients. This article focuses on the use of nutrients and botanicals to support the adrenals, balance neurotransmitters, treat acute anxiety, and support restful sleep.

Hills, S.R., Reiss, R.S., Orsham, P.H., George, W.T. (1950) The effect of adrenocorticotropin and cortisone on thyroid function: thyroidadrenocortical interrelationships. ***The Journal of Clinical Endocrinology & Metabolism***
Excerpt: A depression of thyroid function in animals and in man has been reported following stress, the administration of cortisone acetate (11-dehydro-17-hydroxycorticosterone acetate), ACTH (adrenocorticotropic hormone) and epinephrine (25–29). In patients with Addison's disease, the thyroid depression induced by cortisone was preceded by an initial stimulation. The availability of ACTH, TSH and cortisone for clinical use and the improvement in the techniques of measuring thyroid and adrenal cortical function have stimulated further work on the thyroid-adrenal relationship.

Holtorf, K. (2007). Diagnosis and treatment of hypothalamic-pituitary-adrenal (HPA) axis dysfunction in patients with chronic fatigue syndrome (CFS) and fibromyalgia (FM). ***Journal of Chronic Fatigue Syndrome*, *14*(3), 59-88.**
Abstract: Because treatment with low physiologic doses of cortisol (<15 mg) has been shown to be safe and effective and routine dynamic ACTH testing does not have adequate diagnostic sensitivity, it is reasonable to give a therapeutic trial of physiologic doses of cortisol to the majority of patients with CFS and FM, especially to those who have symptoms that are consistent with adrenal dysfunction, have low blood pressure or have baseline cortisol levels in the low or low-normal range.

Kamilaris, C.T., Debold, C.R., Pavlous, S.N., Island, D.P., Hoursanidis, A. Orth, D.N. (1987) Effect of Altered Thyroid Hormone Levels on Hypothalamic-Pituitary-Adrenal Function. ***The Journal of Clinical Endocrinology & Metabolism*; vol. 65 no. 5 994-999.**
Conclusions: These results indicate that thyroid hormone deficiency of short duration 1) increases corticotroph sensitivity to oCRH, 2) may diminish the plasma ACTH response to metyrapone-induced hypocortisolemia, and 3) has no apparent effect on the acute adrenal response to ACTH. These data together with those of previous studies that have shown reduced responses of the hypothalamic-pituitary-adrenal axis to metyrapone and hypoglycemia in hypothyroid patients suggest that the release of hypothalamic CRH and/or other ACTH secretagogues may be decreased in hypothyroidism.

Musselman, D.L., Nemeroff, C.B. (1996). Depression and endocrine disorders: focus on the thyroid and adrenal system. ***The British Journal of Psychiatry*. 1996(30):123-128.**
Abstract: Concerning the HPT axis, depressed patients have been reported to have: (a) alterations in thyroid-stimulating hormone response to thyrotropin-releasing hormone (TRH); (b) an abnormally high rate of antithyroid antibodies; and (c) elevated cerebrospinal fluid (CSF) TRH concentrations. Moreover, tri-iodothyronine has been shown conclusively to augment the efficacy of various antidepressants. Concerning the HPA axis, depressed patients have been reported to exhibit: (a) adrenocorticoid hypersecretion; (b) enlarged pituitary and adrenal gland size; and (c) elevated CSF corticotropin-releasing factor concentrations.

Peterson, R.E. (1958) **The Influence of the Thyroid on Adrenal Cortical Function**. ***The Journal of Clinical Investigation;*** **vol 37(5).**
Conclusions: It is suggested from these data that there is a homeostatic mechanism mediated through the liver-pituitary-adrenals which results in a decreased synthesis of cortisol in patients with myxedema in whom the rate of removal of cortisol by the liver is impaired, and an increased synthesis of cortisol in patients of thyrotoxicosis in whom the rate of removal of cortisol by the liver is accelerated.

Rodríguez-Gutiérrez, R., González-Velázquez, C., González-Saldívar, G., Villarreal-Pérez, J. Z., & González-González, J. G. (2014).
Glucocorticoid Functional Reserve in Full-Spectrum Intensity of Primary Hypothyroidism.***International Journal of Endocrinology*, *2014*.**
Conclusion: Patients with different degrees of intensity of primary hypothyroidism had improved cortisol response after reaching euthyroidism. The incidence of adrenal insufficiency was 6.7–18.3% and more than 50% of the cases had a normal cortisol response after L-T4 therapy. This finding could have important clinical implications especially in the setting of acute stress situations occurring during the period while a euthyroid state is still not achieved.

Scott, L.V., Salahuddin, F., Cooney, J., Svec, F., Dinan, T. (1999). **Differences in adrenal steroid profile in chronic fatigue syndrome, in depression and in health**. ***Journal of Affective Disorders*; vol 5: issues 1-2**: **129-137**.
Results: DHEA and DHEA-S levels were significantly lower in the CFS compared to the healthy group; DHEA-S levels, but not DHEA, were lower in the depressives; cortisol and 17-alphahydroxyprogesterone did not differ between the three groups. Conclusions: A potential role for DHEA, both therapeutically and as a diagnostic tool, in CFS, is suggested.

Van Den Eede F., Moorkens G., Van Houdenhove B., Cosyns P, Claes S. (2007) **Hypothalamic-Pituitary-Adrenal Axis Function in Chronic Fatigue Syndrome**.
***Neuropsychobiology*; Vol. 55, No. 2, 2007**.
Abstract: There is evidence for a hypofunction of the hypothalamic-pituitary-adrenal (HPA) axis in a proportion of the patients with chronic fatigue syndrome (CFS), despite the negative studies and methodological difficulties. In this review, we focus on challenge studies and on the role of the HPA axis in the pathogenesis of CFS. Mild hypocortisolism, blunted adrenocorticotropin response to stressors and enhanced negative feedback sensitivity to glucocorticoids are the main findings. Several underlying mechanisms have been proposed. Currently, it is a matter of debate whether these disturbances have a primary role in the pathogenesis of CFS. However, even if the HPA axis dysfunctions are secondary to other factors, they are probably a relevant factor in symptom propagation in CFS.

Sammenhengen mellom vitamin D, vitamin B12 og jern og stoffskiftet

VITAMIN D

Bozkurt NC, Karbek, B., Ucan B, Sahin M, Cakal E, Ozbek M, Delibasi T (2013). The Association Between Severity of Vitamin D Deficiency and Hashimoto's Thyroiditis. *Endocrine Practice*; 2013 Jan 21:1-14.
Conclusions: We showed that serum 25OHD (Vitamin D) levels of patients with Hashimoto's Thyroiditis (HT) were significantly lower than controls and severity of vitamin-D deficiency correlated with duration of HT, thyroid volume and antibody levels. These findings may suggest a potential role of 25OHD in development of Hashimoto's thyroiditis and/or its progression to hypothyroidism.

Camurdan OM, Döğer E, Bideci A, Celik N, Cinaz P. (2012). Vitamin D status in children with Hashimoto thyroiditis. *Journal of Pediatric Endocrinology & Metabolism*. 2012;25(5-6):467-70.
Conclusions: The higher vitamin D deficiency rates besides lower vitamin D levels in the Hashimoto group together with the inverse correlation between vitamin D and anti-TPO suggest that vitamin D deficiency may have a role in the autoimmune process in Hashimoto thyroiditis in children.

Thyroidea Norge mener: Barn må ut og leke!

Kivity S, Agmon-Levin N, Zisappl M, Shapira Y, Nagy EV, Dankó K, Szekanecz Z, Langevitz P, Shoenfeld Y. (2011). Vitamin D and autoimmune thyroid diseases. *Cellular & Molecular Immunology*; 8(3): 243-7.
Conclusions: The prevalence of vitamin D deficiency was significantly higher in patients with autoimmune thyroid diseases (AITDs) compared with healthy individuals, as well as in patients with Hashimoto's thyroiditis compared to patients with non-AITDs. Vitamin D deficiency also correlated to the presence of antithyroid antibodies and abnormal thyroid function tests. Significantly low levels of vitamin D were documented in patients with AITDs that were related to the presence of anti thyroid antibodies and abnormal thyroid function tests, suggesting the involvement of vitamin D in the pathogenesis of AITDs and the advisability of supplementation.

McDonnell, DP, Pike, JW, O'Malley, BW (1988). The Vitamin D receptor: A primitive steroid receptor related to thyroid hormone receptor. *Journal of Steroid Biochemistry*, Volume 30, Issues 1–6, Pages 41–46.
Abstract: The vitamin D3 receptor contains a 60 amino acid portion at its carboxyl terminus (C3) which exhibits homology with the receptor for thyroid hormone. Conservation in this region of the molecule is found only between homologous or closely related receptors. This

indicates a relationship between the vitamin D3 receptor and the receptor for thyroid hormone and may suggest that they evolved from a single primordial gene.

Tetsuyuki Yasuda, Yasuyuki Okamoto, Noboru Hamada, Kazuyuki Miyashita, Mitsuyoshi Takahara, Fumie Sakamoto, Takeshi Miyatsuka, Tetsuhiro Kitamura, Naoto Katakami, Dan Kawamori, Michio Otsuki, Taka-aki Matsuoka, Hideaki Kaneto, and Iichiro Shimomura (2012). **Serum vitamin D levels are decreased and associated with thyroid volume in female patients with newly onset Graves' disease.** ***Endocrine.*** **2012 December; 42(3): 739–741.**
Introduction: It has been shown that vitamin D deficiency is associated with autoimmune diseases..and that vitamin D supplementation prevents the onset and/or development of these autoimmune diseases. Furthermore, it was reported more recently that patients with Hashimoto's thyroiditis had lower vitamin D levels. In the present study, we evaluated the vitamin D status in female patients with newly onset GD and the association of serum vitamin D levels with the clinical factors related to GD. Although further study would be necessary to conclude, these results suggest that the vitamin D status may be involved in the pathogenesis of GD.

VITAMIN B12

Carmel, R, Spencer, CA (1982). Clinical and Subclinical Thyroid Disorders Associated With Pernicious Anemia. *Archives of Internal Medicine* 1982;142(8):1465-1469.
Abstract: Of 162 patients with pernicious anemia whom we studied, 24.1% had clinical thyroid disease; 11.7% were hypothyroid and 8.6% were hyperthyroid...We conclude that TSH screening in patients with pernicious anemia uncovers frequent abnormalities, which are superimposed on a higher coincidence of overt thyroid disease than previously described.

Jabbar A, Yawar A, Waseem S, Islam N, Ul Haque N, Zuberi L, Khan A, Akhter J. (2008). Vitamin B12 deficiency common in primary hypothyroidism. *Journal of Pakistan Medical Association*. May;58(5):258-61.
Conclusions: There is a high (approx 40%) prevalence of B12 deficiency in hypothyroid patients. Traditional symptoms are not a good guide to determining presence of B12 deficiency. Screening for vitamin B12 levels should be undertaken in all hypothyroid patients, irrespective of their thyroid antibody status. Replacement of B12 leads to improvement in symptoms, although a placebo effect cannot be excluded, as a number of patients without B12 deficiency also appeared to respond to B12, administration.

Ness-Abramof, Rosane MD; Nabriski, Dan A. MD; Braverman, Lewis E. MD; Shilo, Lotan MD; Weiss, Eliahu MSc; Reshef, Tamar MSc; Shapiro, Menachem S. MD; Shenkman, Louis MD (2006). Prevalence and Evaluation of B12 Deficiency in Patients with Autoimmune Thyroid Disease.
***American Journal of the Medical Sciences*: Volume 332 - Issue 3; pp 119-122.**
Conclusions: Patients with autoimmune thyroid disease (AITD) have a high prevalence of B12 deficiency and particularly of pernicious anemia. The evaluation of B12 deficiency can be simplified by measuring fasting serum gastrin and, if elevated, referring the patient for gastroscopy.

Okuda, K., Chow, B. (1961). The Thyroid and Absorption of Vitamin B12 in Rats.
***Endocrinology* April 1, 1961 vol. 68 no. 4 607-615 .**
Abstract: The thyroidal influence on the absorption of vitamin B-2 is not mediated through the production of IF. A possible hormonal regulation acting directly on the intestinal wall for the absorption of vitamin B12 has been discussed.

Perros, P., Singh, RK, Ludlam, CA, Frier, BM (2000). Prevalence of pernicious anaemia in patients with Type 1 diabetes mellitus and autoimmune thyroid disease. *Diabetic Medicine.* Volume 17, Issue 10, pages 749-751.
Conclusions: Patients who have both Type 1 diabetes mellitus and autoimmune thyroid disease are at risk of developing pernicious anaemia.

JERN OG FERRITIN

Beard, JL, Borel, MJ, Derr, J. (1996). Impaired thermoregulation and thyroid function in iron-deficiency anemia. *The Journal of Biological Chemistry*; May 1996, 271, 12017-12023.
Conclusions: We conclude that T3 can functionally regulate the iron-responsive elements binding activity of the iron regulatory protein. These observations provide evidence of a novel mechanism for T3 to up-regulate hepatic ferritin expression, which may in part contribute to the elevated serum ferritin levels seen in hyperthyroidism.

Beard J, Tobin B, Green W. (1989). Evidence for thyroid hormone deficiency in iron-deficient anemic rats. *The Journal of Nutrition.* [1989, 119(5):772-778] .
Abstract: Iron-deficient anemic rats have previously been shown to have low plasma levels of thyroid hormone and a poor plasma thyroid hormone response to acute cold exposure. Decreased rates of T3 production in iron-deficient anemic rats, as documented by turnover studies, may be related to decreased deiodinase activity and reduced peripheral formation of T3. The dampened TSH responses to TRH further facilitate or perpetuate this T3 deficiency. We propose that this abnormal thyroid state is partially responsible for impaired thermogenesis in iron-deficiency anemia.

Fein, HG, Rivlin, RS (1975). Anemia in thyroid diseases. *Medical Clinics of North America.* Sep;59(5):1133-45.
Abstract: Pernicious anemia has been strongly associated with hypothyroidism, hyperthyroidism, and thyroiditis. Complete correction of anemia often requires restoration of thyroid function as well as specific hematinic therapy. Continued attention to hematologic status is essential in the management of patients with thyroid diseases.

Hess S, Zimmermann MB, Arnold M, Langhans, W, Hurrell, R (2002). Iron Deficiency Anemia Reduces Thyroid Peroxidase Activity in Rats. *The Journal of Nutrition.* vol. 132 no. 7 1951-1955.
Abstract: Studies in animals and humans have shown that iron deficiency anemia (IDA) impairs thyroid metabolism. However, the mechanism is not yet clear. The objective of this study was to investigate whether iron (Fe) deficiency lowers thyroid peroxidase (TPO) activity. These data indicate that Fe deficiency sharply reduces TPO activity and suggest that decreased TPO activity contributes to the adverse effects of IDA on thyroid metabolism.

Zimmermann, MB, Köhrle, J (2002). The Impact of Iron and Selenium Deficiencies on Iodine and Thyroid Metabolism: Biochemistry and Relevance to Public Health. *Thyroid.* October 2002, 12(10): 867-878.
Abstract: Several minerals and trace elements are essential for normal thyroid hormone metabolism, e.g., iodine, iron, selenium, and zinc. Coexisting deficiencies of these elements can impair thyroid function. Iron deficiency impairs thyroid hormone synthesis by reducing activity of heme-dependent thyroid peroxidase. Iron-deficiency anemia blunts and iron supplementation improves the efficacy of iodine supplementation. Combined selenium and iodine deficiency leads to myxedematous cretinism.

Watts, D. L. (1989). The nutritional relationships of the thyroid. *Journal of Orthomolecular Medicine*, *4*(3).
A number of nutritional deficiencies are known to develop in subclinical hypothyroidism. The most recognized is iron deficiency...Other related deficiencies are protein deficiency, perhaps due to accompanying hypochlorhydria; deficiency in vitamins A, C, B6,B5, B1; and mineral deficiency: phosphorus (P), manganese (Mn), magnesium (Mg), potassium (K), sodium (Na), and chromium (Cr). Keyvani, et al, found that low vitamin A levels are associated with an increase in the prevalence of goiter in subjects under 18.

Fibromyalgi: Egentlig en stoffskiftesykdom?

Årsak kan være at kroppen ikke kan nyttiggjøre seg stoffskiftehormoner

Lowe, J.C. (1995) **T3-Induced Recovery from Fibromyalgia by a Hypothyroid Patient Resistant to T4 and Desiccated Thyroid**. ***Journal Myofascial Ther.*****, 1(4):26-31.**
Conclusions: Studies have shown no other therapies for fibromyalgia to be significantly effective,[16] while millions of fibromyalgia patients suffer non-remitting symptoms.[17] Because of this, clinicians and researchers should not ignore the possible benefits of T3 therapy for their fibromyalgia patients.

Garrison RL[1], Breeding PC. 2003 **A metabolic basis for fibromyalgia and its related disorders: the possible role of resistance to thyroid hormone.**

Abstract: It has long been recognized that the symptom complex of fibromyalgia can be seen with hypothyroidism. Hypothyroidism may been categorized, like diabetes, into type I (hormone deficient) and type II (hormone resistant). Most cases of fibromyalgia fall into the latter category. The syndrome is reversible with treatment, and is usually of late onset. It is likely more often acquired than due to mutated receptors. Now that there is evidence to support the hypothesis that fibromyalgia may be due to thyroid hormone resistance, four major questions appear addressable. First, can a simple biomarker be found to help diagnose it? Second, what other syndromes similar to Fibromyalgia may share a thyroid-resistant nature? Third, in non-genetic cases, how is resistance acquired? Fourth, what other methods of treatment become available through this new understanding? Preliminary evidence suggests that serum hyaluronic acid is a simple, inexpensive, sensitive, and specific test that identifies fibromyalgia. Overlapping symptom complexes suggest that chronic fatigue syndrome, Gulf war syndrome, premenstrual syndrome, post traumatic stress disorder, breast implant silicone sensitivity syndrome, bipolar affective disorder, systemic candidiasis, myofascial pain syndrome, and idiopathic environmental intolerance are similar enough to fibromyalgia to merit investigation for possible thyroid resistance. Acquired resistance may be due most often to a recently recognized chronic consumptive coagulopathy, which itself may be most often associated with chronic infections with mycoplasmids and related microbes or parasites. Other precipitants of thyroid resistance may use this or other paths as well. In addition to experimentally proven treatment with supraphysiologic doses of thyroid hormone, the thyroid-resistant disorders might be treatable with anti-hypercoagulant, anti-infective, insulin-sensitizing, and hyaluronolytic strategies.

Dr John Lowe har forsket en del på denne sammenhengen. **Det er en utmerket artikkel av ham på Thyroid UK sine sider:**

Studien her: **Effectiveness and Safety of T_3 (Triiodothyronine) Therapy for Euthyroid Fibromyalgia (2003) A Double-Blind Placebo-Controlled Response-Driven Crossover Study**
Conclusions. In this study, supraphysiologic dosages of T3 were safe and significantly effective in the treatment of euthyroid FMS. Though these dosages produced thyroid function

test results indicative of hyperthyroidism, our patients had no clinically significant adverse target tissue effects. Results suggest that euthyroid FMS is a clinical phenotype of partial peripheral resistance to thyroid hormone. We recommend that further studies be done to answer the questions: Are euthyroid FMS patients partially resistant to thyroid hormone? And if so, what are the molecular mechanisms of the resistance? Further testing is also necessary to establish the long-term safety of T3 therapy.

En studie til av **John Lowe:** **Thyroid Status of 38 Fibromyalgia Patients: Implications for the Etiology of Fibromyalgia (2008)**

ABSTRACT Thyroid function tests were used to classify 38 fibromyalgia patients according to thyroid status. Results were consistent with euthyroidism (normal thyroid status) in 14 patients (36.8%), primary (thyroidal) hypothyroidism in 4 patients (10.5%), and central (hypothalamic or pituitary) hypothyroidism in 20 patients (52.6%). The percentages of primary and central hypothyroidism in this group of fibromyalgia patients are extremely higher than those for the general population. There was no statistical difference for the mean intensity of fibromyalgia symptoms (measured by visual analogue scales) and the mean tender point scores (measured with algometry) between any of the categories of patients. The mean algometer scores and symptom intensities being essentially the same for all three categories of patients may show that the mechanisms involved were due to the same abnormal process-inadequate thyroid hormone regulation of gene transcription. In primary and central hypothyroid patients, this would result from a frank hormone deficiency, and in euthyroid patients, possibly from cellular resistance to thyroid hormone due to mutations in the c-erbAβ_1 gene.

Thyroid Science 2007
Metabolic Failure as the Cause of Fibromyalgia Syndrome: Exploring the John C. Lowe Thesis **Bjørn Johan Øverbye,MD**
Norsk lege ser på Lowes fibromyalgi/stoffskifteforskning

Ömer Nuri Pamuk, Necati Çakir (2006) **The frequency of thyroid antibodies in fibromyalgia patients and their relationship with symptoms**

Abstract: We determined the frequency of thyroid autoantibodies in fibromyalgia (FM) patients and the relationship between FM symptoms and these antibodies. Euthyroid 128 FM patients, 64 rheumatoid arthritis (RA) patients, and 64 healthy control subjects were included in the study. The sociodemographic features and the clinical features of FM patients were determined. By using a visual analog scale, patients were questioned about the severity of FM-related symptoms. All patients were administered with Duke-Anxiety Depression (Duke-AD) scale, the physical function items of the fibromyalgia impact questionnaire scale. Thyroid autoimmunity was defined as the presence of detectable antithyroglobulin (TgAb) and/or antithyroid peroxidase (TPOAb) antibodies by the immunometric methods. Patients with a connective tissue disorder, hypo- or hyperthyroidism, and patients who had psychiatric treatment within the last 6 months were not included into the study. The frequencies of thyroid autoimmunity in FM (34.4%) and RA (29.7%) patients were significantly higher than controls (18.8%) (p<0.05). Twenty-six (20.3%) FM patients had positive TgAb and 31 (24.2%) had positive TPOAb. When

patients with thyroid autoimmunity were compared to others, it was seen that the mean age, the percentage of postmenopausal patients, the frequency of dryness of the mouth, and the percentage of patients with a previous psychiatric treatment were higher in this group (p<0.05). FM patients had thyroid autoimmunity similar to the frequency in RA and higher than controls. Age and postmenopausal status seemed to be associated with thyroid autoimmunity in FM patients. The presence of thyroid autoimmunity had no relationship with the depression scores of FM patients.

(1998) W. Riedel, H. Layka, G. Neeck **Secretory pattern of GH, TSH, thyroid hormones, ACTH, cortisol, FSH, and LH in patients with fibromyalgia syndrome following systemic injection of the relevant hypothalamic-releasing hormones**

Summary: To study the hormonal perturbations in FMS patients we injected sixteen FMS patients and seventeen controls a cocktail of the hypothalamic releasing hormones: Corticotropin-releasing hormone (CRH), Thyrotropin-releasing hormone (TRH), Growth hormone-releasing hormone (GHRH), and Luteinizing hormone-releasing hormone (LHRH) and observed the hormonal secretion pattern of the pituitary together with the hormones of the peripheral endocrine glands. We found in FMS patients elevated basal values of ACTH and cortisol, lowered basal values of insulin-like growth factor I (IGF-I) and of triiodothyronine (T_3), elevated basal values of follicle-stimulating hormone (FSH) and lowered basal values of estrogen. (....) We conclude that the observed pattern of hormonal deviations in FMS patients is a CNS adjustment to chronic pain and stress, constitutes a specific entity of FMS, and is primarily evoked by activated CRH neurons.

Jhon C. Lowe MA, DCa, Alan J. Reichman MDa & Jackie Yellin BAa
Clinical Bulletin of Myofascial Therapy 1996
The Process of Change During T3 Treatment for Euthyroid Fibromyalgia
A Double-Blind Placebo-Controlled Crossover Study
Conclusion. Repeated administration and withdrawal of T3 corresponded to significant improvement and deterioration in fibromyalgia measures during this study. It is highly probable, then, that improvement in fibromyalgia status of our four patients was functionally related to their use of supraphysiologic dosages of T3 (effective range: 118.75-to-162.50 meg). These dosages were shown to be safe at 4-month follow-up. Further testing is necessary to establish long-term safety.

Laura Bazzichi, Alessandra Rossi, Tiziana Giuliano, Francesca De Feo, Camillo Giacomelli, Arianna Consensi, Antonio Ciapparelli, Giorgio Consoli, Liliana Dell'Osso,Stefano Bombardieri, Clinical Rheumatology, 2007 **Association between thyroid autoimmunity and fibromyalgic disease severity**
In conclusion, autoimmune thyroiditis is present in an elevated percentage of FM patients, and it has been associated with the presence of typical symptoms of the disease.

Washington Times rapporterte om studier på link mellom stoffskiftet og fibromyalgi

Viktigheten av riktig behandling og konsekvensene utilstrekkelig behandling kan ha for stoffskiftepasienter

Breast Cancer Res. 2003
Breast cancer in association with thyroid disorders.
Turken O1, Narln Y, Demlrbas S, Onde ME, Sayan O, Kandemlr EG, Yaylacl M, Ozturk A.
Abstract
BACKGROUND:
The relationship between breast cancer and thyroid diseases is controversial. Discrepant results have been reported in the literature. The incidences of autoimmune and nonautoimmune thyroid diseases were investigated in patients with breast cancer and age-matched control individuals without breast or thyroid disease.
CONCLUSION:
Our results indicate an increased prevalence of autoimmune and nonautoimmune thyroid diseases in breast cancer patients.

Michalaki V1, Kondi-Pafiti A, Gennatas S, Antoniou A, Primetis H, Gennatas C. 2009
Breast cancer in association with thyroid disorders.
Abstract
PURPOSE:
The relationship between breast cancer and thyroid diseases is controversial. Conflicting results have been reported in the literature. The incidence of autoimmune and non-autoimmune thyroid diseases were investigated in patients with breast cancer who had received prior therapy as compared with age-matched control individuals without breast or thyroid disease.
CONCLUSION:
This study demonstrated a similar incidence of thyroid enlargement and the same frequency of thyroid disturbances in patients with breast cancer and controls. No relationship was found among ER and PR status, and the presence of serum thyroid autoantibodies. Although we have been unable to demonstrate any impact of breast cancer therapy on thyroid function tests, more prolonged studies with larger number of patients may be required to demonstrate significant trends.

C Giani, P Fierabracci, R Bonacci, A Gigliotti, D Campani, F De Negri, D Cecchetti, E Martino, and A Pinchera Relationship between breast cancer and thyroid disease: relevance of autoimmune thyroid disorders in breast malignancy.
The Journal of Endocrinology and Metabolism 2003
In conclusion, 1) the present study provides evidence that the overall prevalence of thyroid disorders is increased in patients with breast cancer, and 2) thyroid autoimmune disorders, especially Hashimoto's thyroiditis, account to a large extent for the increased prevalence of thyroid disease in patients with breast cancer. This feature is independent from the ER and PR status of the primary tumor. The present findings call attention to the usefulness of screening for thyroid disease in any patient with breast cancer.

Shakila Thangaratinam, Alex Tan, Ellen Knox, Mark D Kilby et al, BMJ 2011 Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence

Objectives To evaluate the association between thyroid autoantibodies and miscarriage and preterm birth in women with normal thyroid function. To assess the effect of treatment with levothyroxine on pregnancy outcomes in this group of women.

Conclusion The presence of maternal thyroid autoantibodies is strongly associated with miscarriage and preterm delivery. There is evidence that treatment with levothyroxine can attenuate the risks.

Roberto Negro, Gianni Formoso, Tiziana Mangieri, Antonio Pezzarossa, Davide Dazzi, and Haslinda Hassan, 2006 Levothyroxine Treatment in Euthyroid Pregnant Women with Autoimmune Thyroid Disease: Effects on Obstetrical Complications

Abstract

Context: Euthyroid women with autoimmune thyroid disease show impairment of thyroid function during gestation and seem to suffer from a higher rate of obstetrical complications.

Objective: We sought to determine whether these women suffer from a higher rate of obstetrical complications and whether levothyroxine (LT_4) treatment exerts beneficial effects.

Conclusions: Euthyroid pregnant women who are positive for TPOAb develop impaired thyroid function, which is associated with an increased risk of miscarriage and premature deliveries. Substitutive treatment with LT_4 is able to lower the chance of miscarriage and premature delivery.

Roberto Negro, Alan Schwartz, Riccardo Gismondi, Andrea Tinelli, Tiziana Mangieri, and Alex Stagnaro-Green 2010 Increased Pregnancy Loss Rate in Thyroid Antibody Negative Women with TSH Levels between 2.5 and 5.0 in the First Trimester of Pregnancy

Abstract

Context: The definition of what constitutes a normal TSH during pregnancy is in flux. Recent studies suggested that the first trimester upper limit of normal for TSH should be 2.5 mIU/liter

Conclusions: The increased incidence of pregnancy loss in pregnant women with TSH levels between 2.5 and 5.0 mIU/liter provides strong physiological evidence to support redefining the TSH upper limit of normal in the first trimester to 2.5 mIU/liter.

Pregnant women with high-normal TSH values are at increased risk for pregnancy loss.