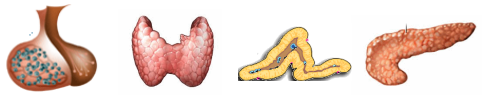
Laqueur lecture 2021



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Disclosure belangen BHRW

Voor bijeenkomst mogelijk relevante relaties (laatste 5 jaar)	Bedrijfsnamen
• Bv. Sponsoring of onderzoeksgeld • Bv. Honorarium of andere (financiële) vergoeding. • ~~Bv. Aandeelhouder~~ • **The studies on GDM have been supported by Novo Nordisk**	• DiabetesFonds NL • JDRF • NWO • Min VWS, AZ, EcZaken • Provincies Groningen, Friesland, Drenthe • Nierstichting • ZonMW • MENZIS • EASD / EFSD • Becton Dickinson • Eli Lilly • Thermo-Fisher • Pfizer • Novo Nordisk • Roche • Sanofi • Boehringer Ingelheim • Ascensia • Diagnoptics

Laqueur and ...

Groningen, Febr 5 1912 - assistant to the physiologist H.J. Hamburger.
April 15 1914 - personal lectorate
Lived in Oude Ebbingestraat 17a

sept 1914 Army Physician 46th Field Artillery Regiment in Wolfenbüttel (Harz)

JAARBOEK

DER

RIJKSUNIVERSITEIT

TE

GRONINGEN.

1913—1914.

De rij van lectoren werd met één vermeerderd. Bij Koninklijk besluit van 15 April 1914, Staatsblad No. 156, werd aan Dr. E. LAQUEUR, assistent bij het Physiologisch Laboratorium, voor zoo lang hij die betrekking zal bekleeden, den persoonlijken titel van lector verleend en hem opgedragen onderwijs te geven in de Algemeene Biologie.

FACULTEIT DER GENEESKUNDE.

Dr. J. W. van Wijhe (24 Sept. 1889). Ontleedkunde.
Dr. C. F. A. Koch (16 Dec. 1889). Heelkunde.
Dr. R. A. Reddingius (3 Febr. 1894). Ziektekunde. Ziektekundige ontleedkunde. Huid- en geslachtsziekten.
Dr. G. C. Nijhoff (15 Jan. 1898). Verloskunde. Leer der vrouwenziekten. *Voorzitter.*
Dr. H. J. Hamburger (28 Sept. 1901). Physiologie. Weefselleer. *Secretaris.*
Dr. E. D. Wiersma (4 Juli 1903 en 20 Jan. 1912). Psychiatrie. Neurologie.
A. Klein (18 Mei 1907). Gezondheidsleer. Geneeskundige politie. Gerechtelijke geneeskunde. Pharmacognosie. Pharmacodynamiek.
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LECTOREN.

Dr. K. Kooy, Physische en chemische diagnostiek.
Mej. Dr. M. E. Loke, Nieuw-Fransch.
Dr. L. S. Ornstein. Mathematische physica, hydrodynamica en mathamatische chemie.
H. H. Breuning. Nieuw-Hoogduitsch.
John A. Falconer. Nieuw-Engelsch.
Dr. E. Laqueur. Algemeene Biologie.

You'll never walk alone ....

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Erik Boersma
Rita Varkevisser

Direct colleagues & friends

Stafleden, arts-assistenten, diabetesverpleegkundigen, diëtisten en andere medewerkers

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- Interne Geneeskunde

Dijkzigt ZH / Erasmus MC
- Interne Geneeskunde

azM / MUMC
- Interne Geneeskunde
- Farmacologie
- Fysiologie
- Klinische Chemie

UMCG
- Cardiologie
- Epidemiologie
- Farmacologie
- Genetica
- Gynecologie/Obstetrie
- Interne Geneeskunde
- Interne Geneeskunde/Endocrinologie
- Heelkunde
- Kindergeneeskunde
- Klinische Chemie
- Nefrologie
- Neurologie
- Nucleaire Geneeskunde
- Pathologie

National collaborators

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Parelsnoer Initiatief / String-of-Pearl
Initiative Type 2 Diabetes, led by Petra Elders
Patient organisations SON, DVN, NVACP/Bijniernet
POEM study (Adriaan Kooy)
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Pharmaceutical & Diagnostics companies which supported our research (see disclosures slide)
ANCORA Health BV

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International consortia

DCCT/EDIC Research Group
Skin autofluorescence
Genetics of Age-at-Diagnosis

4B Study Group, GLP1 RA therapy
HOPE Study group

Long-term Type 1 Diabetes Study group

LifeLines Cohort Study

All colleagues in GWA studies on
- Coffee and Caffeine Genetics
- ECG abnormalities
- Genome of the NL
- GIANT consortium
- Healthy obesity
- Hypertension
- LARS1 consortium
- Lipids Genetics cons.
- Liver enzymes
- Thyroid consortium

International biobanks incl. HUNT, Qatar, Finnish cohorts, UK Biobank
BioSHaRE-EU consortium
MDS-Right

JDRF
Dutch Diabetes Foundation

NVE
NEDERLANDSE VERENIGING
VOOR ENDOCRINOLOGIE

DIABETES MELLITUS

E

M

21

Gestational diabetes (GDM)

Referral: Sylvia 28 yrs, 25wks pregnant, BMI 32 kg/m^2
fasting PG 5.9, after 75g-GTT 9.2 mmol/l

- Hyperglycaemia which is first detected during pregnancy
- May affect up to 10-20% of all pregnancies
- Prevalence increasing due to obesity epidemic
- Insulin resistance in 2nd part of pregnancy

- High risk of obstetric and neonatal complications such as macrosomia, birth trauma, preeclampsia and caesarean section
- Increased long-term risk of developing type 2 diabetes & CVD
- Growing evidence for long-term health consequences for the child (obesity and/or T2DM)

How does the world diagnose gestational diabetes ?

NL-2010

- Screening based on risk factors:
  - GDM in history; BMI>30 kg/m^2
  - Earlier 'big baby'
  - 1st degree relative with T2D
  - Ethnicity (Asian, Mediterranean, Caribbean, Middle East)
  - Previous unexplained intra-uterine death
  - Polycystic ovary syndrome
- Screening with 75g OGTT:
  - fasting plasma glucose ≥ 7.0 mmol/l
  - 2-h post OGTT glucose ≥ 7.8 mmol/l

Many other countries based on IADPSG 2010 guideline

- Universal screening ('all')
- Screening with 75g OGTT:
  - fasting plasma glucose ≥ 5.1 mmol/l
  - 1-h ≥ 10.0 mmol/l
  - 2-h ≥ 8.5 mmol/l
- Cut-off chosen to reflect 75% increased risk of complications (as demonstrated in 2008 HAPO Study)

Changing diagnostic criteria for GDM in 10642 'Groningen' pregnancies

Criteria	WHO 1999	IADPSG 2010 / WHO 2013
Glucose levels (mmol/l)	Fasting ≥7.0 and/or 2-h ≥7.8	Fasting ≥5.1 and/or 2-h ≥8.5
Total GDM, n (%)	**2326 (22)**	**3364 (32)**
Elevated fasting / normal 2-h, n (%)	14 (1)	**2045 (61)**
Elevated 2-h, normal fasting, n (%)	**2267 (97)**	634 (19)
Both elevated fasting and 2-h, n (%)	45 (2)	685 (20)
	Mainly diagnosed by 2-h glucose	**2/3 diagnosed by fasting glucose only**

+50%

Diabetologia (2018) 61:800–809
https://doi.org/10.1007/s00125-017-4506-x

ARTICLE

New diagnostic criteria for gestational diabetes mellitus and their impact on the number of diagnoses and pregnancy outcomes

Sarah H. Koning[1] · Jelmer J. van Zanden[2] · Klaas Hoogenberg[3] · Helen L. Lutgers[4] · Alberdina W. Klomp[1] · Fleurisca J. Korteweg[5] · Aren J. van Loon[5] · Bruce H. R. Wolffenbuttel[1] · Paul P. van den Berg[6]

Adapted from: Koning SH, et al. Diabetologia 2018;61:800-9

Big babies & many SC despite treatment

Table 3 Pregnancy outcomes according to the GDM classification groups

All women

Pregnancy outcomes	General obstetric population in the north of the Netherlands	Criteria (mmol/l)	NGT Fasting glucose <5.1 and 2HG <7.8	WHO 1999 Fasting glucose ≥7.0 and/or 2HG ≥7.8	WHO 2013 Fasting glucose ≥5.1 and/or 2HG ≥8.5	WHO 2013 fasting glucose only Fasting glucose ≥5.1-≤6.9 and 2HG <7.8	WHO 1999 2HG only Fasting glucose <5.1 and 2HG ≥7.8-≤8.4
N	29,562	4431	2851	913	1346	667	234
Treated for GDM, *n*			0	913	679	0	234
Maternal							
Gestational hypertension, *n* (%)		4427	139 (4.9)	62 (6.8)*	98 (7.3)**	52 (7.8)**	16 (6.9)
Preeclampsia, *n* (%)		4427	41 (1.4)	28 (3.1)**	35 (2.6)**	12 (1.8)	5 (2.1)
Induction of labour, *n* (%)		4405	793 (28.0)	587 (64.3)***	670 (50.0)***	230 (34.8)**	147 (62.8)***
Mode of delivery, *n* (%)		4410					
Vaginal			2051 (72.3)	618 (67.7)**	904 (67.4)**	451 (68.1)*	165 (70.5)
Emergency CS	??		327 (11.5)	116 (12.7)	177 (13.2)	89 (13.4)	28 (12.0)
Planned CS			185 (6.5)	103 (11.3)***	150 (11.2)***	68 (10.3)**	21 (9.0)
Instrumental			272 (9.6)	76 (8.3)	116 (8.2)	54 (8.2)	20 (8.5)
Gestational age at delivery (weeks)		4431	39.7 (38.7–40.6)	38.3 (38.0–39.0)***	38.7 (38.0–39.9)***	39.6 (38.3–40.4)***	38.6 (38.1–39.4)***
Neonatal							
LGA, *n* (%)	3246 (11.0)	4430	514 (18.0)	167 (18.3)	271 (20.1)	140 (21.0)	36 (15.4)
Macrosomia, *n* (%)	4275 (14.5)	4431	595 (20.9)	108 (11.8)***	226 (16.8)**	148 (22.2)	30 (12.8)**
Small for gestational age, *n* (%)	2364 (8.0)	4430	195 (6.8)	36 (3.9)**	69 (5.1)*	38 (5.7)	5 (2.1)**
Birthweight (g)		4431	3544 ± 579	3391 ± 550***	3477 ± 590**	3580 ± 596	3437 ± 493**
Birth trauma, *n* (%)		4420	64 (2.3)	27 (3.0)	43 (3.2)	20 (3.0)	4 (1.7)
Hypoglycaemia, *n* (%)[a]		4418	NA	38 (4.2)***	NA	NA	4 (1.7)
Hyperbilirubinaemia, *n* (%)[a]		4418	NA	24 (2.6)**	NA	NA	5 (2.1)
Stillbirth, *n* (%)		4431	10 (0.4)	2 (0.2)	6 (0.4)	4 (0.6)	0
Preterm delivery, *n* (%)		4431	146 (5.1)	57 (6.2)	92 (6.8)*	46 (6.9)	11 (4.7)
Respiratory support, *n* (%)		4418	116 (4.1)	34 (3.7)	51 (3.8)	27 (4.1)	10 (4.3)
Apgar score <7 at 5 min. *n* (%)		4414	74 (2.6)	30 (3.3)	57 (4.3)**	29 (4.4)*	2 (0.9)
Admission to neonatology, *n* (%)		4423	315 (11.1)	130 (14.2)*	206 (15.3)***	100 (15.0)**	24 (10.3)

Many women invited for OGTT deliver LGA neonate, also those with normal glucose tolerance

Women with fasting glucose 5.1-7.0 are obese, 21% LGA, 24% S.C.

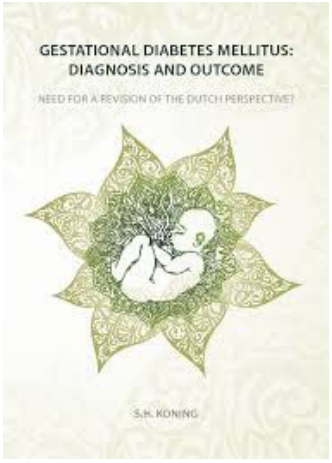
All women with post-OGTT glucose 7.8-8.5 were treated, 20% w. insulin, still 15.4% LGA, 21% S.C.

Adapted from: Koning SH, et al. Diabetologia 2018;61:800–9

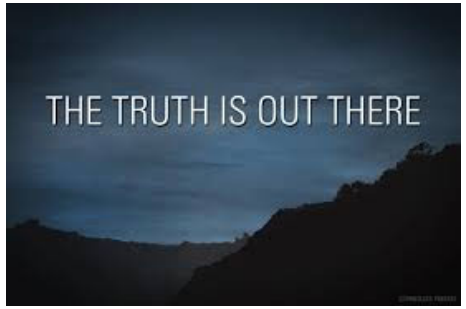
Take home message 1. *Use the evidence which is out there*

Evidence from this large Dutch study shows that NL-2010 & 2018 cut-offs for GDM diagnosis are **not appropriate**; and that risk-factor-based screening is **not optimal**

- NL-2018 guideline update
- Still screening based on risk factors:
- Still:
- Screening with 75g OGTT & 7.0/7.8 cut-off
- (6.1/7.8 when using full blood)



Nov 27, 2017



Intermezzo - 1

A 60+ internal medicine specialist with an unremarkable history (other than knee surgery & CABG) started to supplement **vitD3** because of a possible protective effect against COVID-19

He is using a statin, ezetimibe, beta-blocker & ARB, and is without GI complaints

His G.P. advised 400 IU (10 mcg) daily, but he decided to use 1000 IU (25 mcg) daily

What was his serum vitD3 levels (LC-MS, in nmol/l) after 4 months (>95% compliance) ?

1. 56
2. 76
3. 96
4. 116

www.doenoflaten.nl

D
ENDOCRINOLOGY
M
21

Hashimoto hypothyroidism

Referral: Paula, 48 yrs

- Hypothyroidism
- Persistent complaints of fatigue after 'burn out', muscle pain
- Rehabilitation program gave no improvement
- Steroid diabetes after prednisone (which did not help for her pain)

History

- Previously 'Graves' disease, TSI? 1 jaar med's, euthyroid; from 2009 primary hypothyroidism AntiTPO?
- 2012 Vitiligo (= 2e a.i. disease)
- Uses levothyroxine (TEVA) 125 mcg daily

Lab results

- TSH 1.09, FT4 16.1, FT3 3.4 (L)
- Thyroid peroxidase ab 1.179 (N<33)
- Hb 7.9, ferritin 14

Conclusion:

- Hashimoto hypothyroidism with high antiTPO

Question

- Quality of life in thyroid disorders ?
- Can we demonstrate or refute the contribution of antiTPO ??

Is the thyroid really simple ? anti-TPO

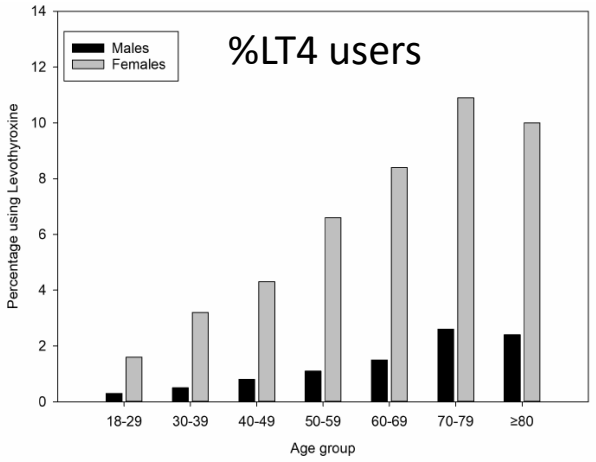
- People w. antiTPO antibodies more frequently have depression also when thyroid hormone levels are normal
- People with benign goiter: worse general health, physical functioning, vitality when increased antiTPO antibodies
- Study in monozygotic twins showed discordance in psychiatric ('bipolar') symptoms despite high antiTPO in both

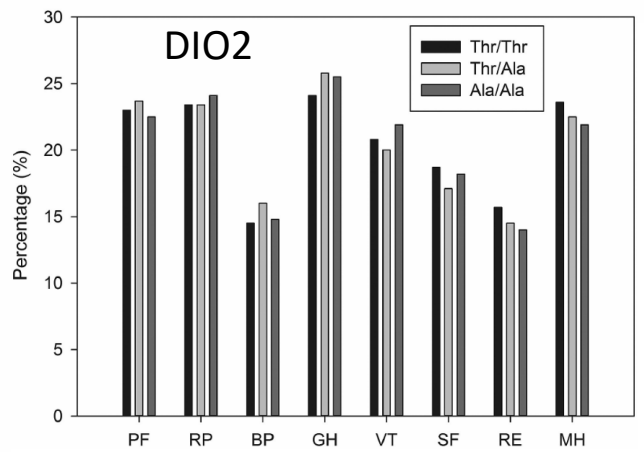
- 521 family members of thyroid patient, Amsterdam AITD cohort
- No antibodies; followed for 5 years
- Those discontinuing smoking more often developed antiTPO antibodies and hypothyroidism

- Smokers develop less anti-TPO, and more often get Graves' disease

Strieder TG et al. Clin Endocrinol (Oxf) 2003; 59: 396–401
Vonk R et al. Biol Psychiatry 2007; 62: 135-40
Effraimidis G et al. JCEM 2009; 94: 1324-8
Ott J et al. Thyroid 2011; 21: 161-7

Thyroid epidemiology & Quality-of-Life



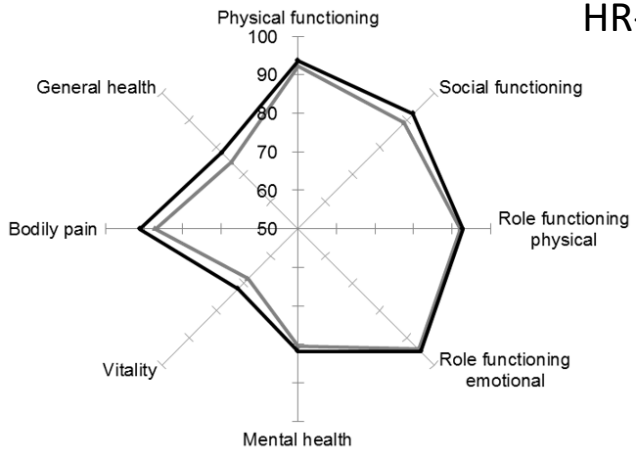


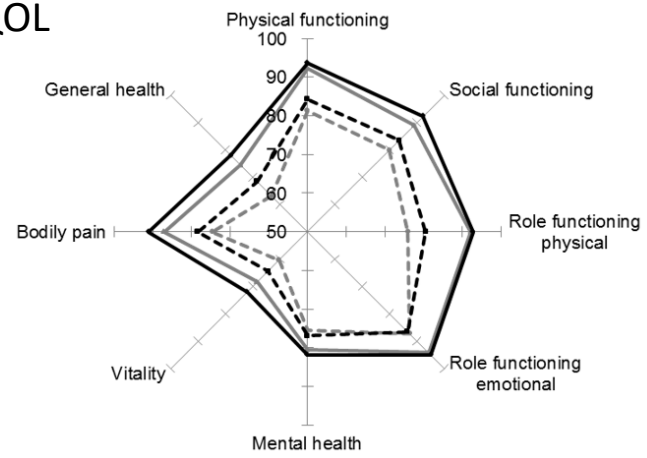
Thyroid. 2017 Feb;27(2):147-155. doi: 10.1089/thy.2016.0199. Epub 2016 Dec 15.

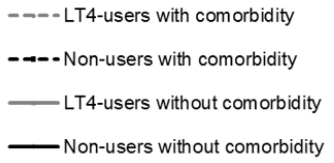
No Effect of the Thr92Ala Polymorphism of Deiodinase-2 on Thyroid Hormone Parameters, Health-Related Quality of Life, and Cognitive Functioning in a Large Population-Based Cohort Study

Hanneke J C M Wouters [1], Hannah C M van Loon [1], Melanie M van der Klauw [1], Martin F Elderson [1], Sandra N Slagter [1], Anneke Muller Kobold [2], Ido P Kema [2], Thera P Links [1], Jana V van Vliet-Ostaptchouk [1], Bruce H R Wolffenbuttel [1]

HR-QOL

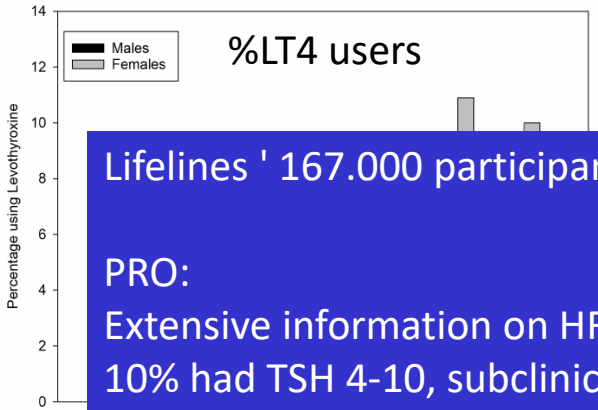


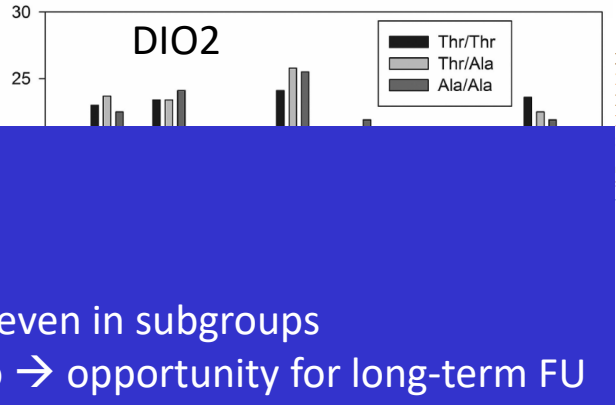




Wouters HJCM et al, Thyroid 2017; PlosONE 2020

Thyroid epidemiology & Quality-of-Life





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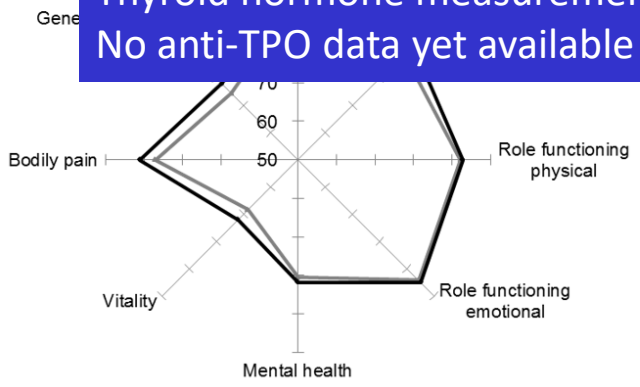
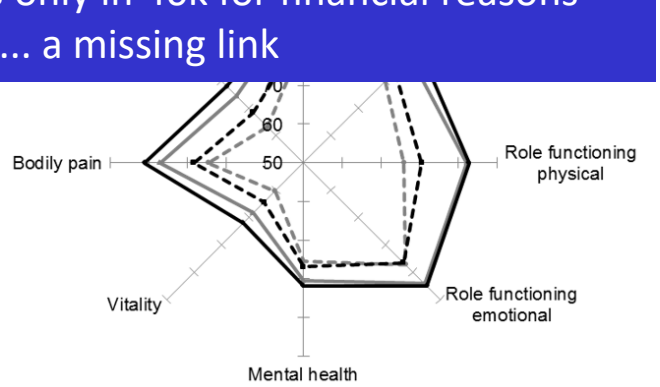
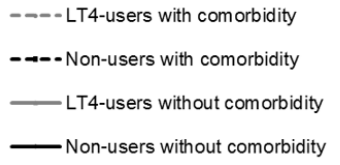
Lifelines ' 167.000 participants

PRO:
Extensive information on HR-QOL, even in subgroups
10% had TSH 4-10, subclinical hypo → opportunity for long-term FU

CON:
Thyroid hormone measurements only in 40k for financial reasons
No anti-TPO data yet available ..... a missing link



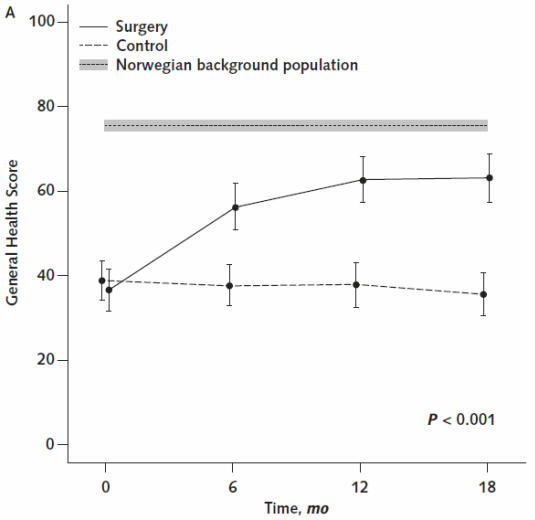


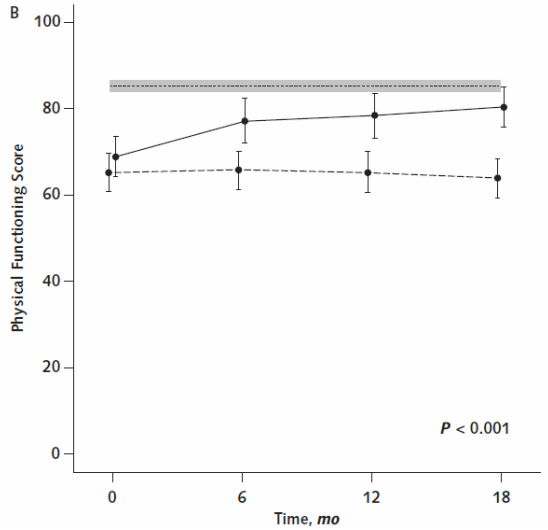


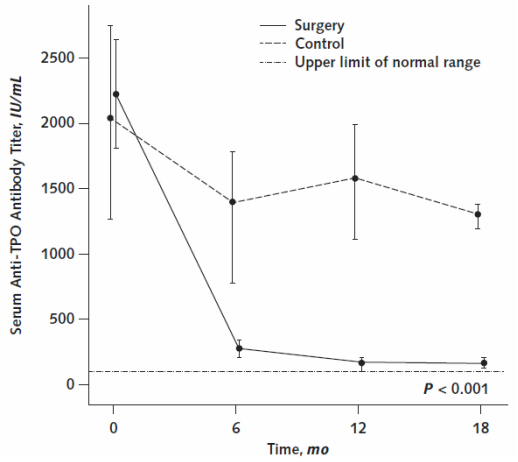
Wouters HJCM et al, Thyroid 2017; PlosONE 2020

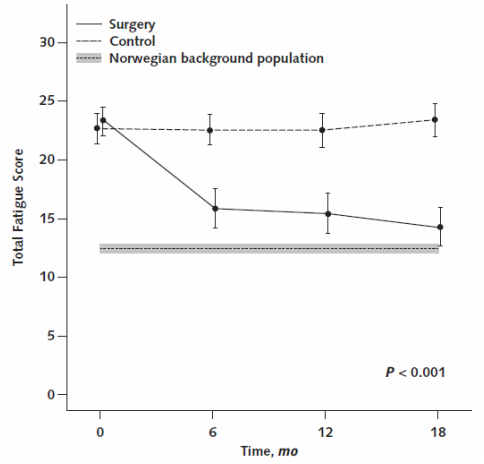
Thyroidectomy vs medical management in Hashimoto disease

- Individuals (n=147) with Hashimoto hypothyroidism, already treated with levothyroxine
- Remaining complaints & anti-TPO > 1000 …. (normal value < 100)
- Total thyroidectomy vs LT4









- Total thyroidectomy improved HR quality of life and fatigue, whereas medical therapy did not
- Improvement coincided with concomitant elimination of anti-TPO antibodies

Guldvog I, et al. Ann Int Med 2019;170:453-64

Drastic measures, but ... sham surgery ??

- Admirable study
- First in its kind
- Only very few drop-outs
- Follow-up only 1.5 years
- No sham / placebo surgery *

Thyroïdectomie bij ziekte van Hashimoto?

Gabor E. Linthorst en Miriam H.P. van Lieshout

Consequenties voor de praktijk

Thyroïdectomie is een gedurfde ingreep voor een veelvoorkomend ziektebeeld. Er werd echter geen sham-procedure verricht ter controle van de interventie. Hierdoor is niet uit te sluiten dat er sprake is van een placebo-effect van de operatie op de gezondheidsbeleving, wat in andere studies eerder is aangetoond. Het is daarom belangrijk dat alsnog een studie met sham-procedure verricht wordt voordat thyroïdectomie wegens persisterende klachten bij de ziekte van Hashimoto op grote schaal zijn intrede kan doen.

Review

Critical review of sham surgery clinical trials: Confounding factors analysis

Massimo Ciccozzi [a, b], Rosa Menga [c], Giovanna Ricci [d], Massimiliano Andrea Vitali [e, *], Silvia Angeletti [b], Ascanio Sirignano [f], Vittoradolfo Tambone [g]

- In sham surgery literature there's no assessment on confounding factors effect.
- Even if sham surgery has been used as control for over 30 years it isn't a standard.
- The validity of sham surgery is not completely supported by available literature.

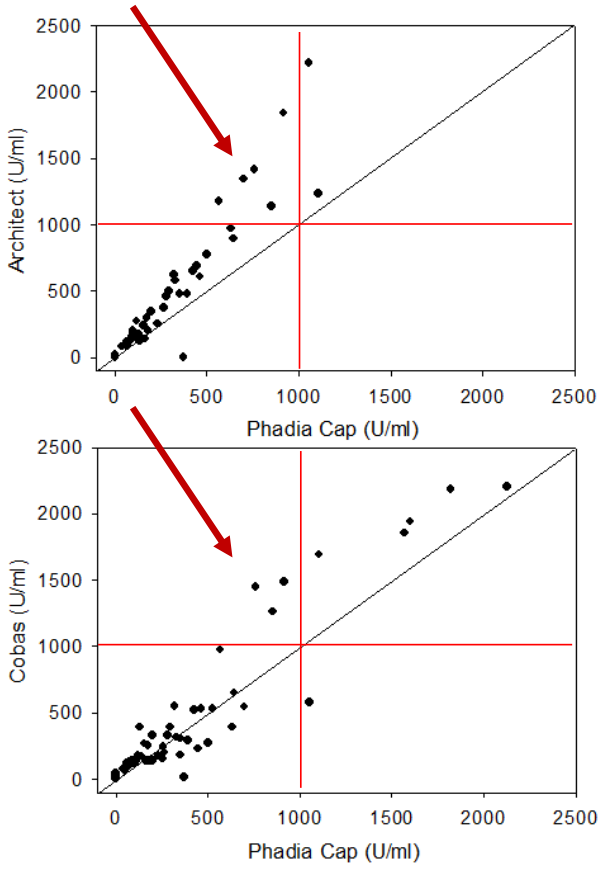
Ann Med Surg 2016; 12: 21-6

*** would you advise sham surgery to one of your parents ??**

Drastic measures, but ... how reliable is antiTPO??

- Admirable study
- First in its kind
- Only very few drop-outs
- Follow-up only 1.5 years
- No sham / placebo surgery *

Risk of misclassification



Wouters, Bruggeman, Muller Kobold, vdKlauw, Wolffenbuttel (manuscript in preparation)

Unnecessary levothyroxine switch, and then .....

- **Four LAREB ('side-effects') complaints in 2015**
- Switch (by local pharmacy) from Thyrax^{R} to 'generic' resulting in thyrotoxicosis (FT4 > 30)
- Patient with PapTC cured for > 15 yrs referred back for 'recurrence of cancer', as FT4 increased to 33 pmol/l after G.P. switched thyrax → generic

- **Then ASPEN moved its manufacture site for Thyrax, and tablets manufactured were of poor quality, leading to a STOP of thyrax supply**

- **NVE sent a 'dear colleague' letter**

NVE
NEDERLANDSE VERENIGING VOOR ENDOCRINOLOGIE

Beste NVE leden.
Wij wijzen u op een belangrijk bericht over de beschikbaarheid van schildklierhormoon. Alle endocrinologen zullen hier in de praktijk mee te maken krijgen.

Op haar website www.cbg-meb.nl heeft het College Beoordeling Geneesmiddelen het volgende bekend gemaakt:

Tekort aan Thyrax Duotab 0,025 mg (levothyroxine) vanaf februari 2016

Nieuwsbericht | 13-01-2016 | 11:00

Omdat het voor een deel van de patiënten lastig is om ingesteld te worden op de optimale dosis levothyroxine en tabletten van verschillende fabrikanten kleine variaties in sterkte kunnen hebben is er bij het veranderen van medicijnen met levothyroxine mogelijk een geringe dosis aanpassing nodig. **Daarom is het advies vanuit de Nederlandse Vereniging voor Endocrinologie om 6 weken na het over zetten op een ander schildklierhormoon preparaat een extra laboratorium controle te laten plaatsvinden.**

Thyrax gate, let's do THE study

The intentions

- Cohort study to observe effect of switch Thyrax → 'something else'
- Allow evidence-based advice on proper conversion for subsequent pat's

- Two registries w. prescription and lab data:
  1. Nivel Primary Care Database
  2. PHARMO Database Network
- Pat's on ≥25 mcg Thyrax daily for ≥1yr

- Alas, finance & data collection too slow to help clinical decision making

The conclusions (2018, publ 2020)

- Dose-equivalent switch from Thyrax to other LT4 brands induced biochemical signs of overdosing in a large proportion (24-63%) of pat's

- LT4 brand switch may necessitate dose adjustment in a large number of pat's

› Thyroid. 2020 Jun;30(6):821-828. doi: 10.1089/thy.2019.0414. Epub 2020 May 4.

Impact of a Forced Dose-Equivalent Levothyroxine Brand Switch on Plasma Thyrotropin: A Cohort Study

Linda E Flinterman [1], Josephina G Kuiper [2], Joke C Korevaar [1], Liset van Dijk [1 3], Karin Hek [1], Eline Houben [2], Ron Herings [2], Anton A M Franken [4], Johan P de Graaf [5], Annemieke Horikx [6], Marijke Janssens [7], Rietje Meijer [7], Anneke Wijbenga [7], Eugène van Puijenbroek [3 8], Bruce H R Wolffenbuttel [9], Thera P Links [9], Peter H Bisschop [10], Eric Fliers [10]

Personal experience in switching > 50 patients on levothyroxine

	Thyrax dose	Euthyrox dose	TSH (mU/l)		FT4 (pmol/l)	
	Before	After	Before	After	Before	After
< 100 mcg	67.1	67.1	1.48	0.91	17.7	18.7
≥ 100 mcg	168	-8% → 156	0.42	0.15	20.2	23.5
≥ 150 mcg	198	-9% → 181	0.35	0.13	20.9	24.3

Despite an 8-9% dose reduction, TSH drops and FT4 increases

Dose reduction of ≥10% is needed to have stable thyroid hormone levels after switch

Wolffenbuttel BHR, unpublished

Take home messages 2.

Never ever again think that the thyroid is a simple organ

- Thyroid disease significantly impairs HR-QOL
- Comorbid conditions have an additive effect on impaired HR-QOL

- Anti-TPO is associated with poorer quality of life & psychiatric conditions
- Getting rid of anti-TPO by surgery dramatically improves HR-QOL

- Thyroid hormone preparations are NOT simply interexchangeable

Intermezzo - 2

What serum vitD3 level should be reached by supplementation in order to reduce the risk of a COVID-19 infection ?

1. > 50
2. 80 - 100
3. > 100
4. VitD3 supplementation does not protect against COVID-19

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D
E
METABOLISM
21

You can't see the answer when you close your eyes

Referral: Susanne, 19 yrs old

- Referred because serum B12 >1476
- Age 14 burning sensation in tongue, paraesthesias in hand/feet, muscle cramps
- VitB12 deficiency, sB12 150 (↓), MMA 360 (↑)
- Started on i.m. OH-Cbl inj by GP, excellent effect

- Age 16, R/ stopped by G.P. "*you now have had enough*"
- Two yrs later neurologic complaints, repeatedly sB12 >1476 (↑)
- Evaluated by neurologist, tremor and peripheral neuropathy, 'no cause found'
- No supplementation during last 2.5 yrs

Additional evaluation

- sB12 >1476, Methylmalonic acid 222 (N)
- Homocysteine 7.8 (N)
- TSH 1.8, FT4 13.7, antiTPO 0
- Antibodies against parietal cells and IF negative

- What now ?

Clin Chem Lab Med 2020; 58(3): 408–415 DE GRUYTER

Reza Soleimani[a], Julien Favresse[a], Tatiana Roy, Damien Gruson* and Catherine Fillée

Macro vitamin B12: an underestimated threat

https://doi.org/10.1515/cclm-2019-0999
Received September 25, 2019; accepted October 6, 2019; previously published online October 30, 2019

Abstract

studies confirmed the presence of macro-B12 (immunoglobulin-B12 complexes).
Conclusions: The prevalence of macro-B12 in elevated B12 samples is high. We suggest to systematically screen

The team effort evaluating macro-B12

- Serum multi-assay dilution
- With dilution 1 : 10 was sB12 conc. 440 pmol/l, so total serum B12 = 4400 pmol/l

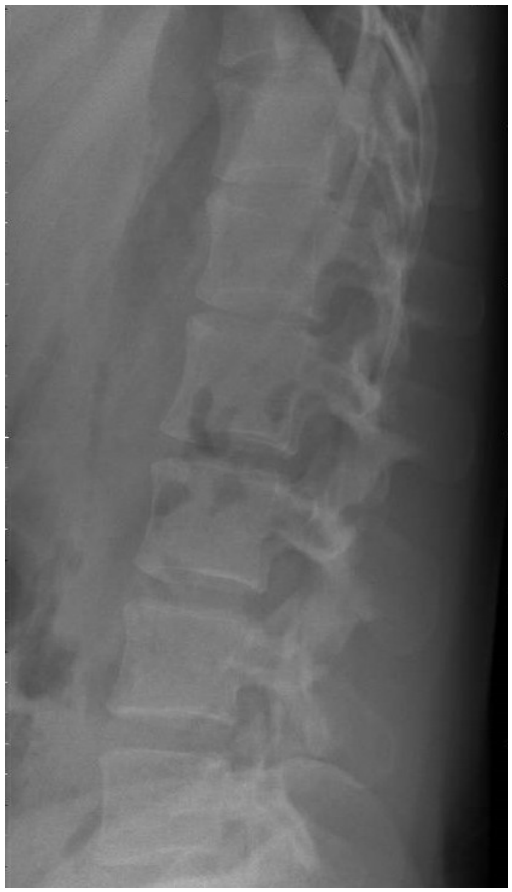
- 1:1 dilution with **PEG (40%)** and 30 min incubation at 37°C
- After PEG B12 136 pmol/l
- Preliminary conclusion >96% macro-B12, <4% 'free' B12

- Thus the patient is 'still' vitB12 deficient, and therapy restarted successfully
- ***The reason why macro-B12 develops is currently unknown***
- But it is comparable to macro-CK and macro-PRL

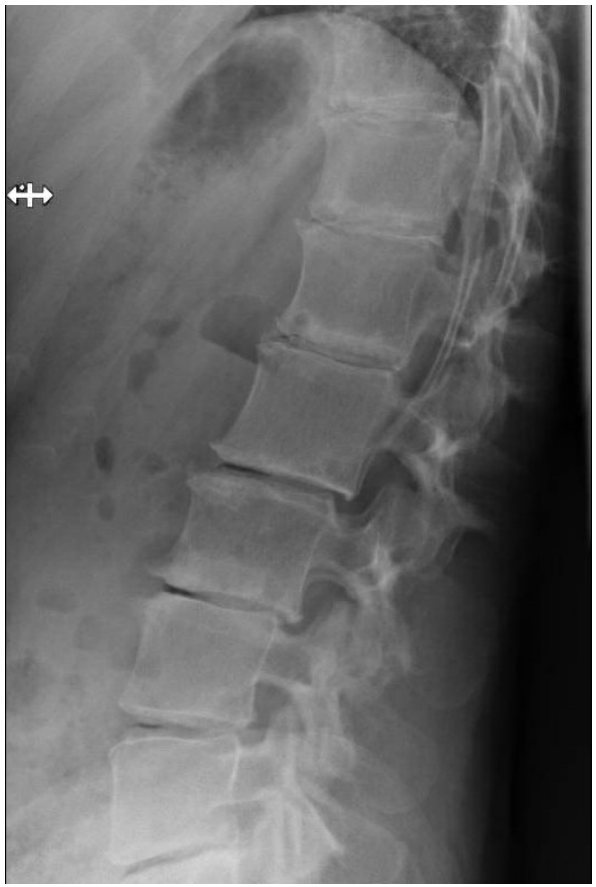
In this situation, the case was resolved by the clinical chemist & her team: many thanks to Annke Muller-Kobold, UMCG

What Is The Diagnosis ?

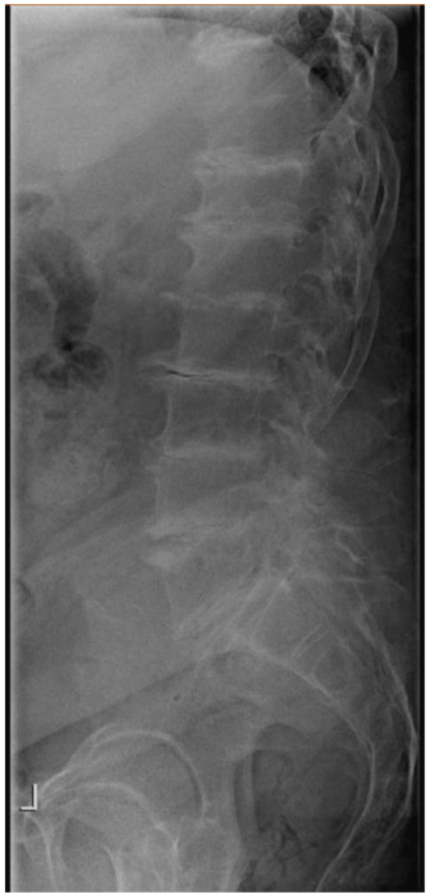
Lina, age 34



age 40



Steven age 55

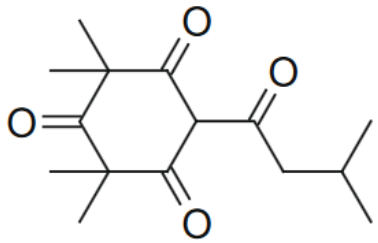


From weed removal to a valid medication

De rode lampenpoetser

- **Serendipity:** 1977 biochemist Reed Gray (Western Research Center, Ca) noted that in his garden there were no weeds (‘onkruid’) below a plant called the Callistemon citrinus (Lampenpoetser)
- Isolation yielded a substance identified as leptospermone
- Developed into ‘triketone’ herbicides

- Nitisinone (1984, codename SC-0735, NTBC)
- In animal studies gave accumulation of tyrosine, shown to inhibit the enzyme HPPD, p-hydroxyphenylpyruvate dioxygenase



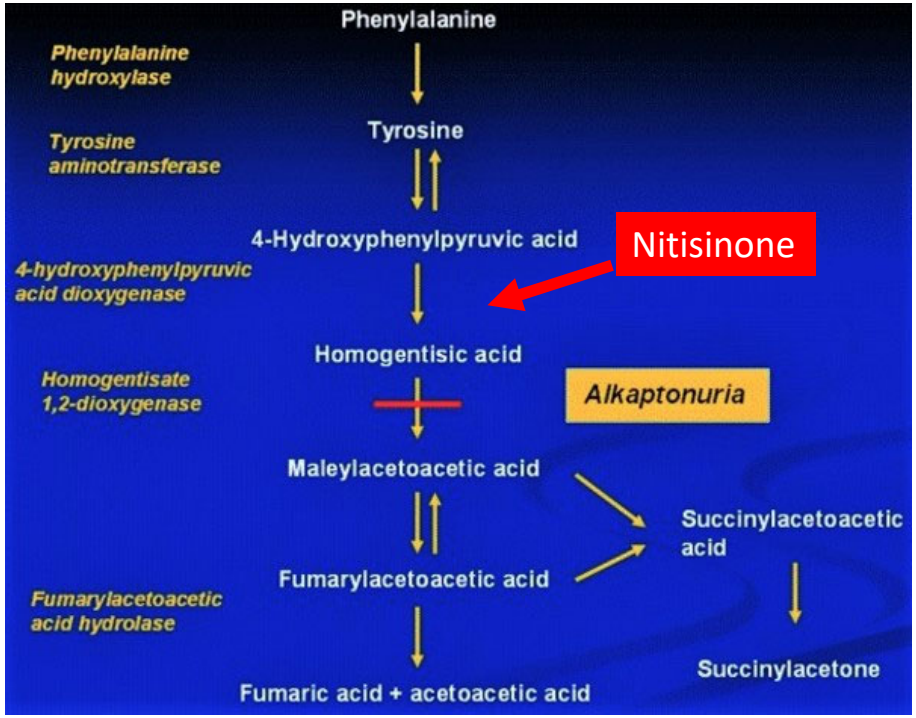
Lina & Steven face the: **Consequences of alkaptonuria**

Joint replacement & valve reconstruction

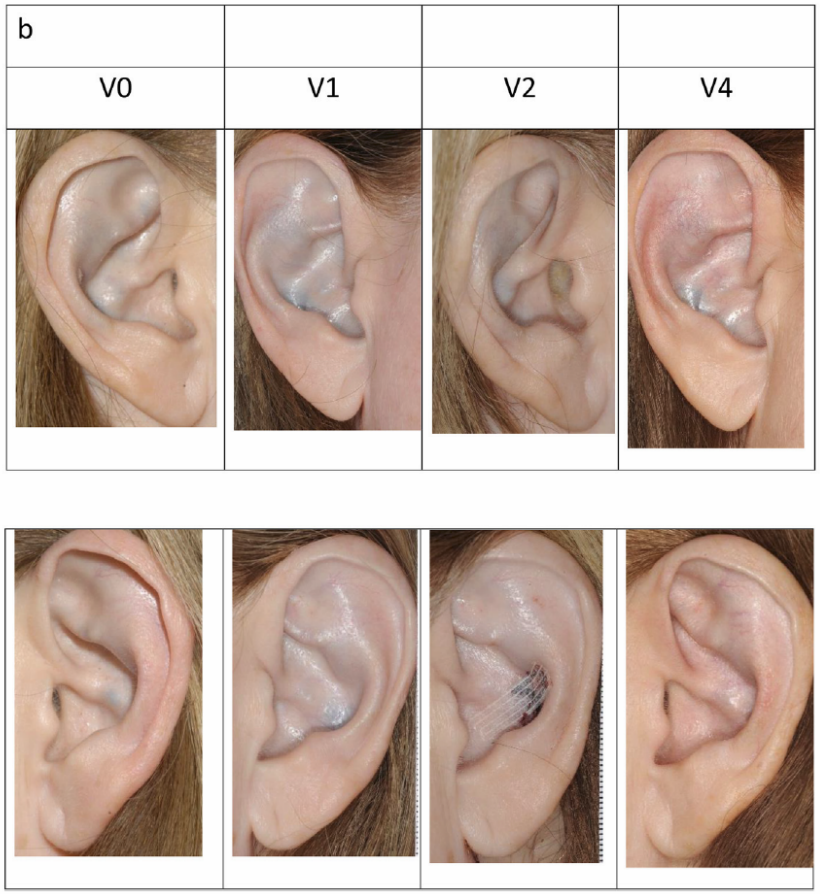
Current status on nitisinone

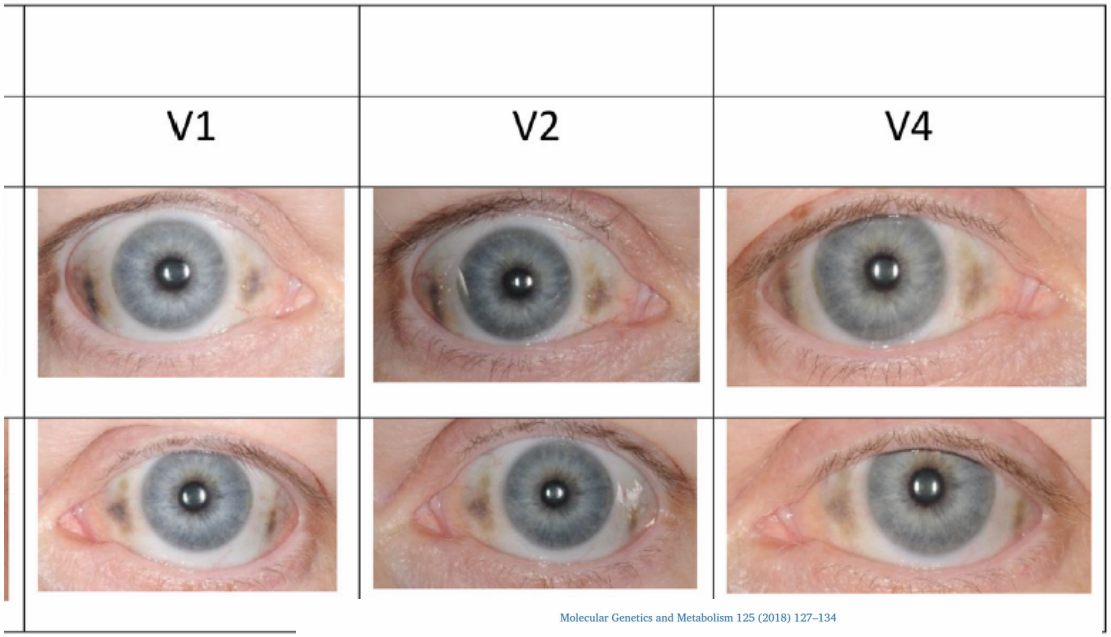
- Used (50+ mg) to treat tyrosinaemia type I
- Inhibits 4-hydroxyphenylpyruvate dioxygenase
- Drastic reduction of homogentisic acid, the toxic compound in alkaptonuria
- Small scale & one larger European study show beneficial effects in CLINICAL alkaptonuria: less pain, joint damage, clinical improvement, ochronosis
- Still ‘off-label‘ use
- 'Well tolerated'

- Side-effects: cornea crystals, cognitive complaints (high dose, pTyr > 1000)



Improvement of ochronosis in patients with alkaptonuria





Molecular Genetics and Metabolism 125 (2018) 127–134

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

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

Nitisinone arrests ochronosis and decreases rate of progression of Alkaptonuria: Evaluation of the effect of nitisinone in the United Kingdom National Alkaptonuria Centre

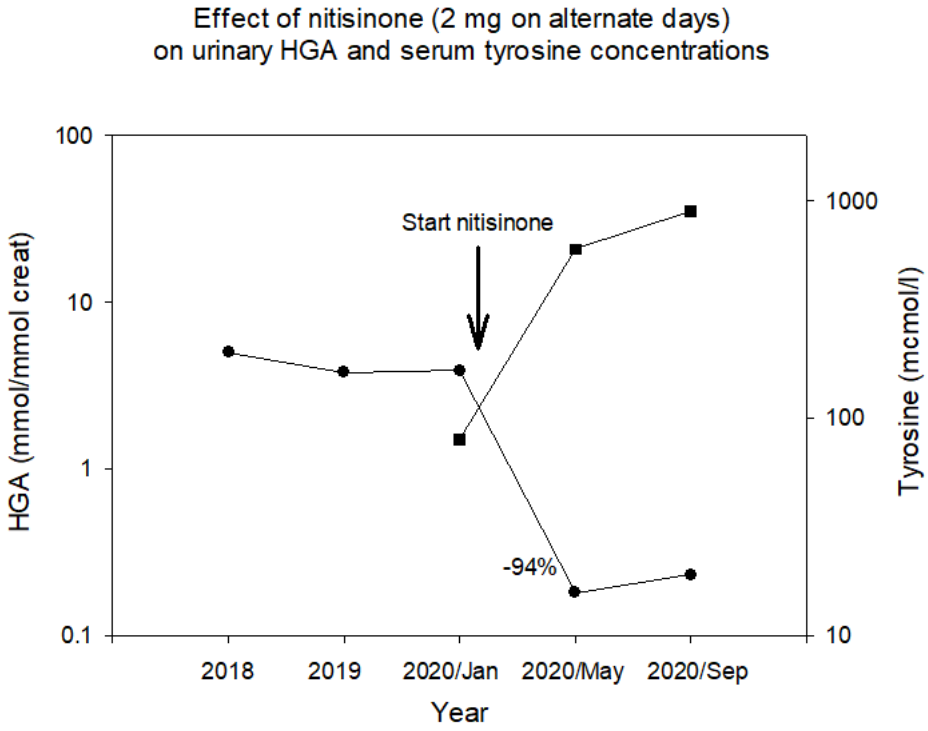
Ranganath L.R.[a,*], Khedr M.[a], Milan A.M.[a], Davison A.S.[a], Hughes A.T.[a], Usher J.L.[a], Taylor S.[b], Loftus N.[b], Daroszewska A.[c,m], West E.[d], Jones A.[e], Briggs M.[f], Fisher M.[g], McCormick M.[h], Judd S.[i], Vinjamuri S.[j], Griffin R.[k], Psarelli E.E.[k], Cox T.F.[k], Sireau N.[l], Dillon J.P.[m], Devine J.M.[m], Hughes G.[n], Harrold J.[n], Barton G.J.[o], Jarvis J.C.[o], Gallagher J.A.[m]

The time for prophylactic nitisinone therapy has come

Preventive use protocol UMCG

- Basal measurement of amino acids & HGA
- Nitisinone alternate days 2 mg for 3 months, aiming to reduce HGA > 95%
- Evaluation of amino acids (pTyr)
- Possible dose increase to 1 dd 2 mg
- Follow-up after 6, 9 & 12 months
- Questionnaires & quality of life BL & 12 mo
- Dietary measures when pTyr too high

- Many questions remain: pregnancy, threshold for HGA, natural course
- **A national prospective registry is urgently needed**



Take home messages

GDM: Use the available evidence to properly define GDM diagnosis

Thyroid: Treat as a complex organ with great impact on HR-QOL
Big data is only good data when the data are complete and reproducible (anti-TPO)
The best doctor for some Hashimoto's patients may be a surgeon

Metabolic: An open mind & open eye can make the diagnosis
Preventive medicine is an important feature of metabolic diseases

Ernst Laqueur
1880-1947

Gerry Marsden
1942-2021