The Effect of Thyroid Hormone Defficiency and Replacement on Lipoprotein Metabolism

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Adult Endocrinology

Disclosures

- No conflict of Interest

Mayor Topics

- Brief Review of Thyroid Hormones Synthesis/Actions
- Thyroid Hormone Related Cholesterol Synthesis Alterations
- Associated important direct systemic effects
- Treatment: Beyond Levothyroxine replacement

Hypothyroidism Prevalence

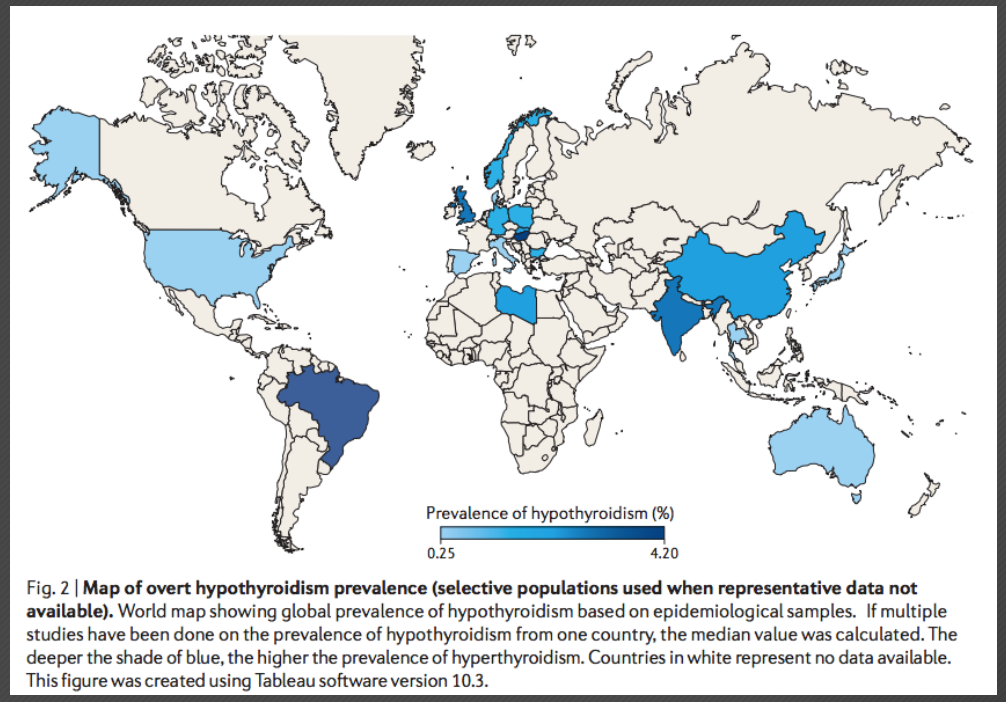


Fig. 2 | **Map of overt hypothyroidism prevalence (selective populations used when representative data not available).** World map showing global prevalence of hypothyroidism based on epidemiological samples. If multiple studies have been done on the prevalence of hypothyroidism from one country, the median value was calculated. The deeper the shade of blue, the higher the prevalence of hyperthyroidism. Countries in white represent no data available. This figure was created using Tableau software version 10.3.

- USA
  - OH: 0.1-2.0%
  - SCH: 4-10%
  - Women 8x >> Men
- Dyslipidemia + HypoThyroidsm
  - Up to 14%
- While Overt HypoT
  - >90% have dyslipidemia

Taylor et al, 2018: Global epidemiology of hyperthyroidism and hypothyroidism

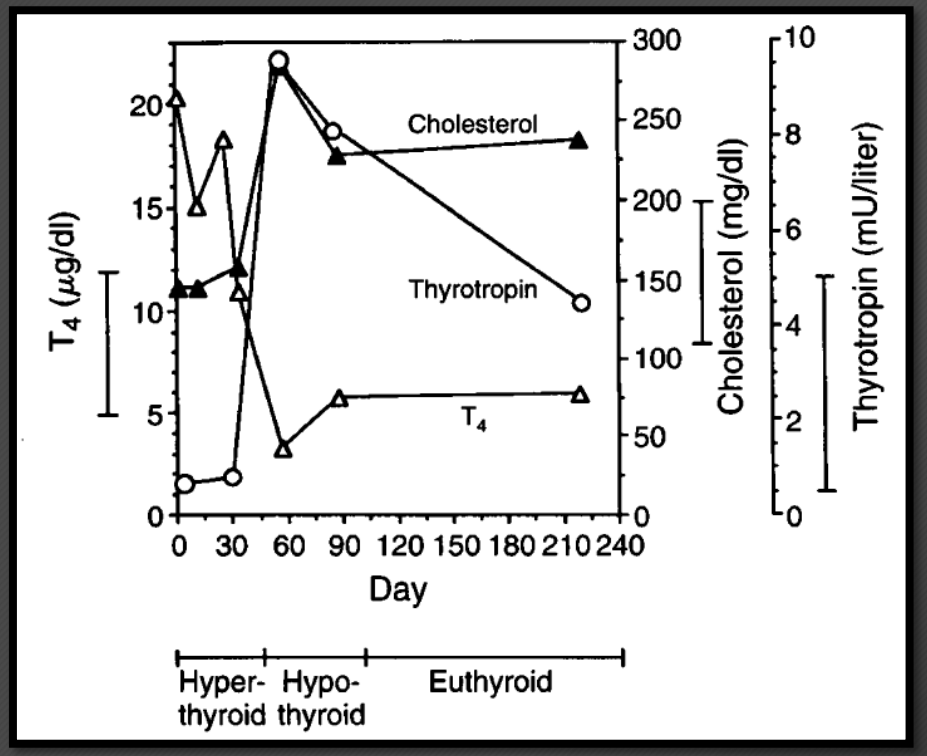
Hypothyroidsm and Dyslipidemia

- Coronary Artery Disease and Hypothyroidsm Relationship described 1967
  - No TSH or free T4 available
  - 194 subjects died of MI, of whom 1/3 males and half women had obesity, DM and HBP
  - Of those above 20% males and ~50% women had CLT
  - CLT also noted on those with MI and no obesity, hbp or diabetes

CLT: Chronic Lymphocytic Thyroiditis

O'Brien T, Mayo Clin Proc. 1993, Hyperlipidemia in patients with primary and secondary hypothyroidism

Phenothype of Dyslipidemia in Hypothyroidsm

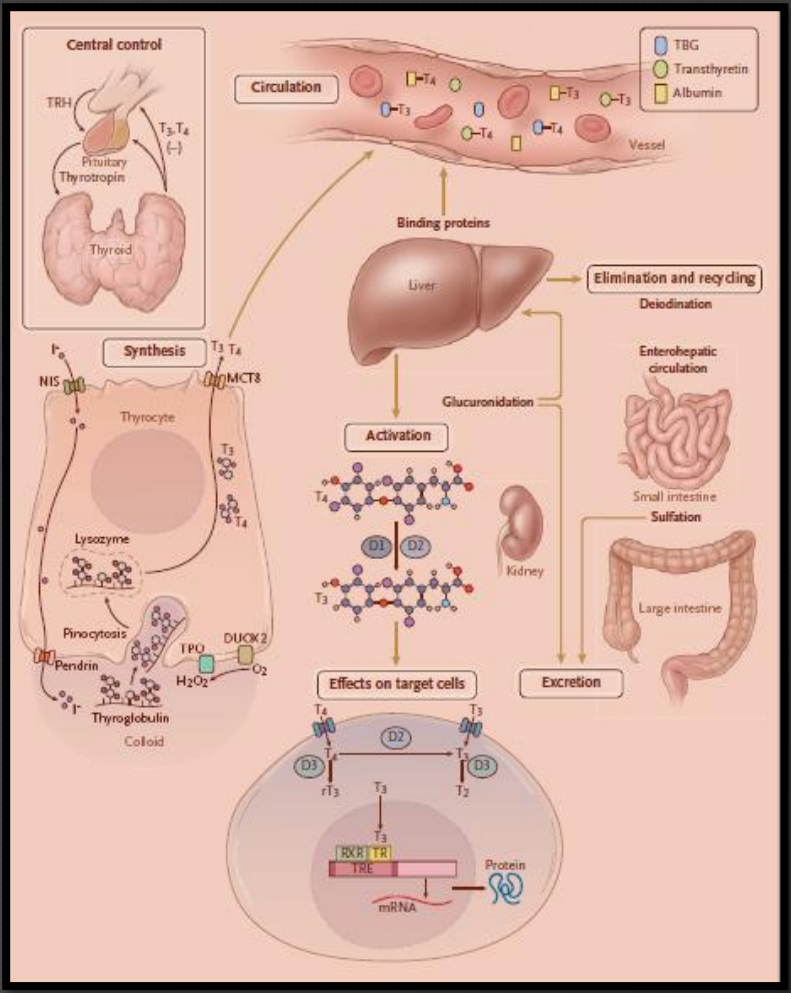


Frederickson Classification

- Type IIa (hypercholesterolemia) – 56 %
- Type IIb (hypercholesterolemia and hypertriglyceridemia) – 34 %
- Type IV (hypertriglyceridemia) – 1.5 %
- No abnormality – 8.5 %

Left: Brent, MD., The Molecular Basis of Thyroid Hormone Action
Right: O'Brien T, Mayo Clin Proc. 1993, Hyperlipidemia in patients with primary and secondary hypothyroidism

Thyroid Hormone Activity

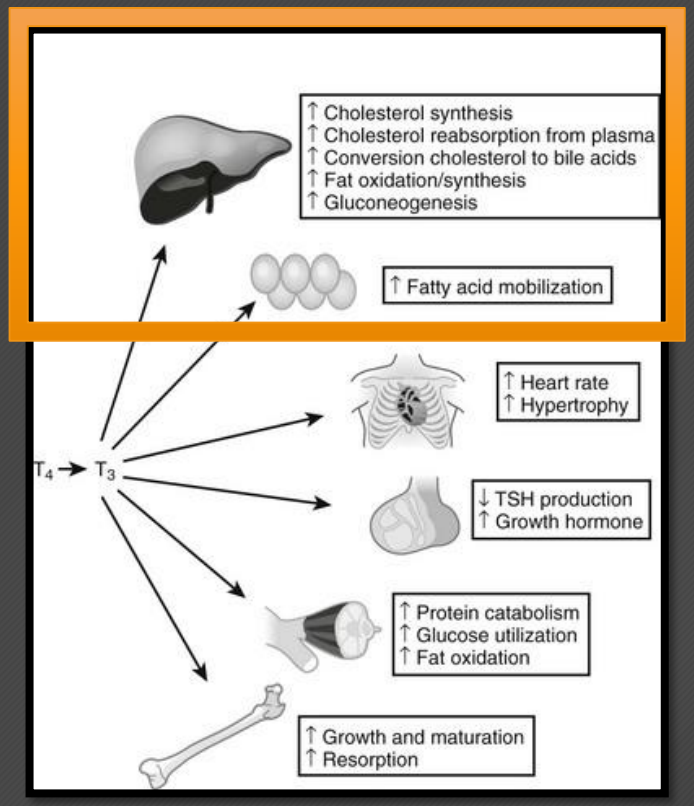


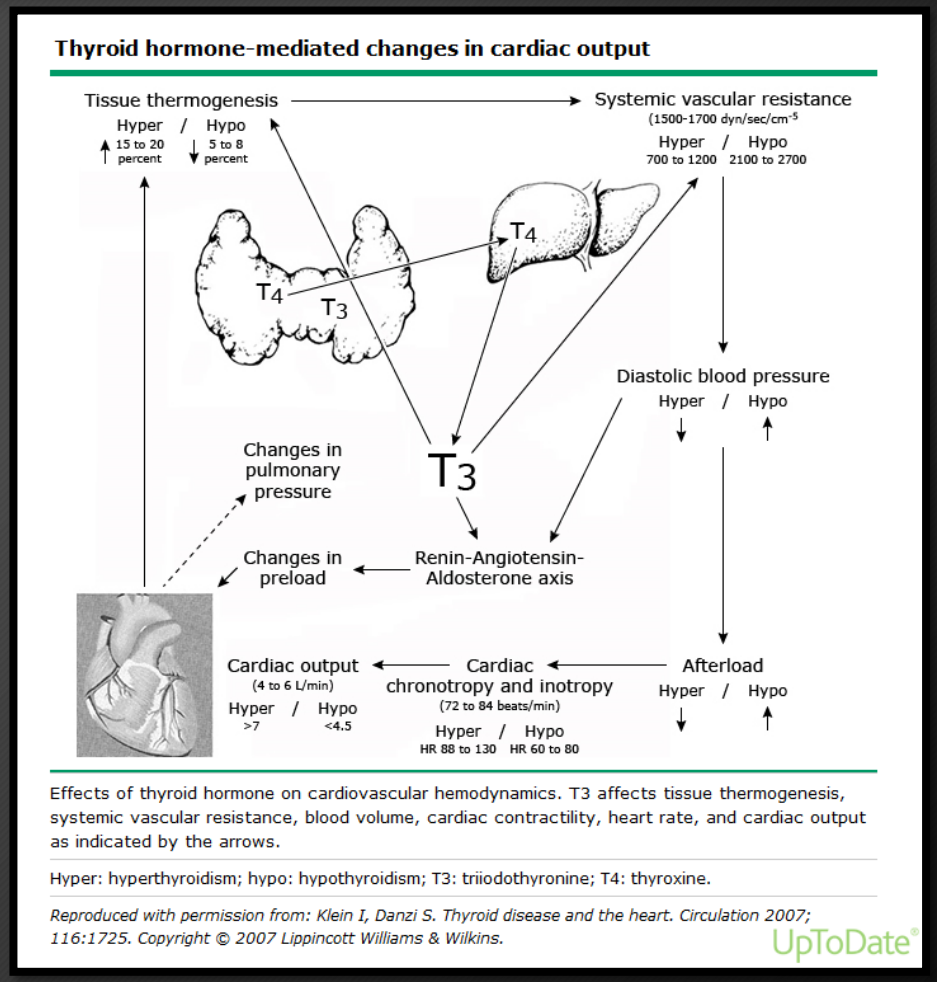
Genomic Actions

- T3 interacts with its nuclear receptors to regulate gene activity
- T3 binds to a specific nuclear thyroid hormone receptor (TR), which in turns bind to DNA at specific sequences called **thyroid hormone response elements (TREs**)
- T3 has a 15-fold higher binding affinity for TRs than T4
- There are **tissue-specific preferences** in expression of the various TRs (difference expression in hypothalamus vs kidney, liver, brain and heart)

TR isoforms	Predominant Distribution	Proposed role
TR α1	Heart, skeletal muscles, brain	Cardiac stimulation with increase in metabolic rate due to increase in heart rate and force of contraction
TR β1	Brain, liver,	Normal brain development Increased LDL and cholesterol clearance Increase in basal metabolic rate
TR β2	Hypothalamus, pituitary, retinal cone photoreceptors, cochlea	Negative feedback for TSH secretion

Thyroid Hormone Activity



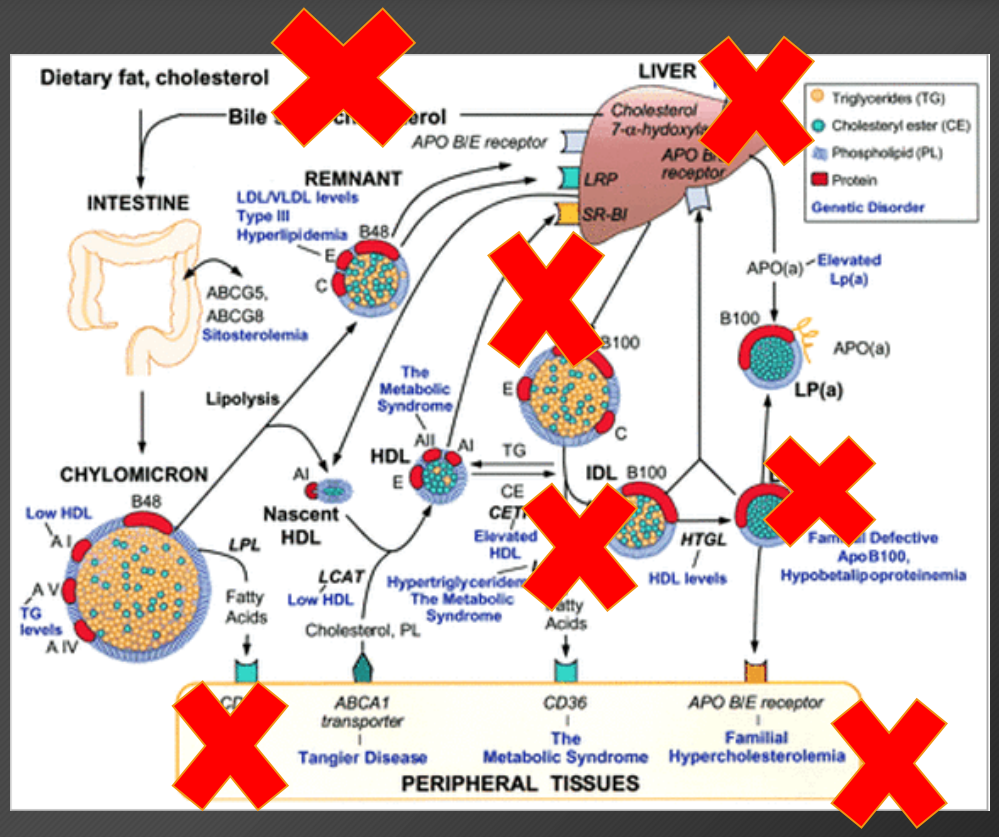


OVERVIEW OF CHOLESTEROL SYNTHESIS

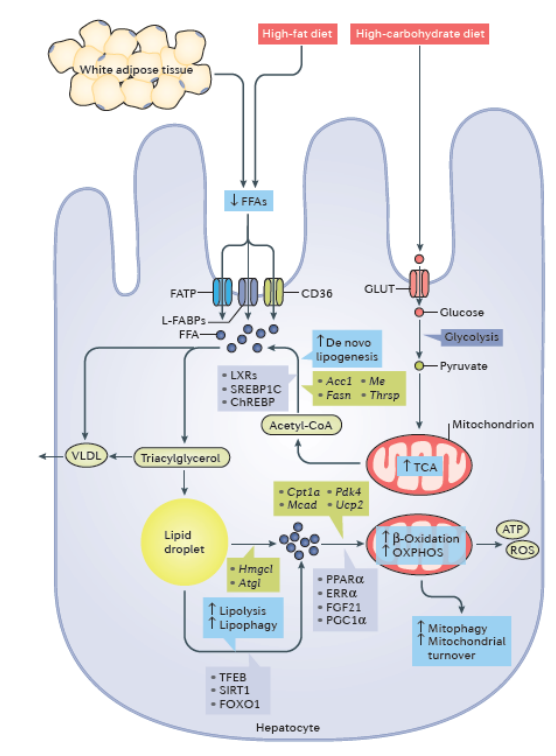
Main Cholesterol Particles

Lipoprotein	Apolipoproteins	Function
Chylomicrons, Chylo-remnants	B-48 (A-I, C-II, C-III, and E)	Delivers TG & Chol (intestinal or exog. path)
VLDL, IDL	B-100 (C-II, C-III, E)	Delivers TG & Chol (endogenous path)
LDL	B-100	Delivers Chol (endogenous path)
Lp(a)	B-100, apo (a)	Delivers Chol (endogenous path)
HDL	A-I, A-II (C-II, C-III, E)	RCT; Anti-athero;

Exogenous/Endogenous Pathways



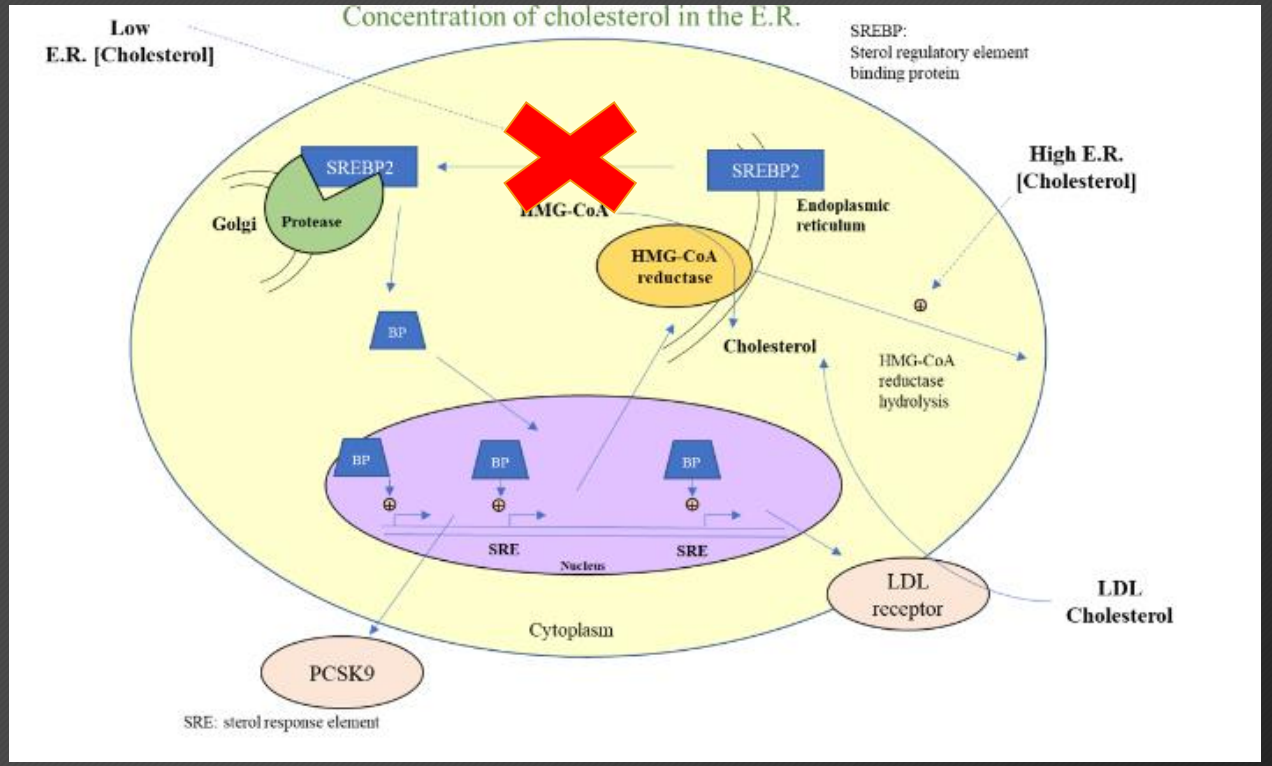
Effects of Thyroid Hormone at the Hepatocyte



- Lipolysis → Increase FFA
- Stimulates De novo lipogenesis
- Regulates *SREBP1C*, *LXRs*, *ChREBP*
- *Enhances glucose conversion to FFA to Tg's and B oxidation of Tg's*

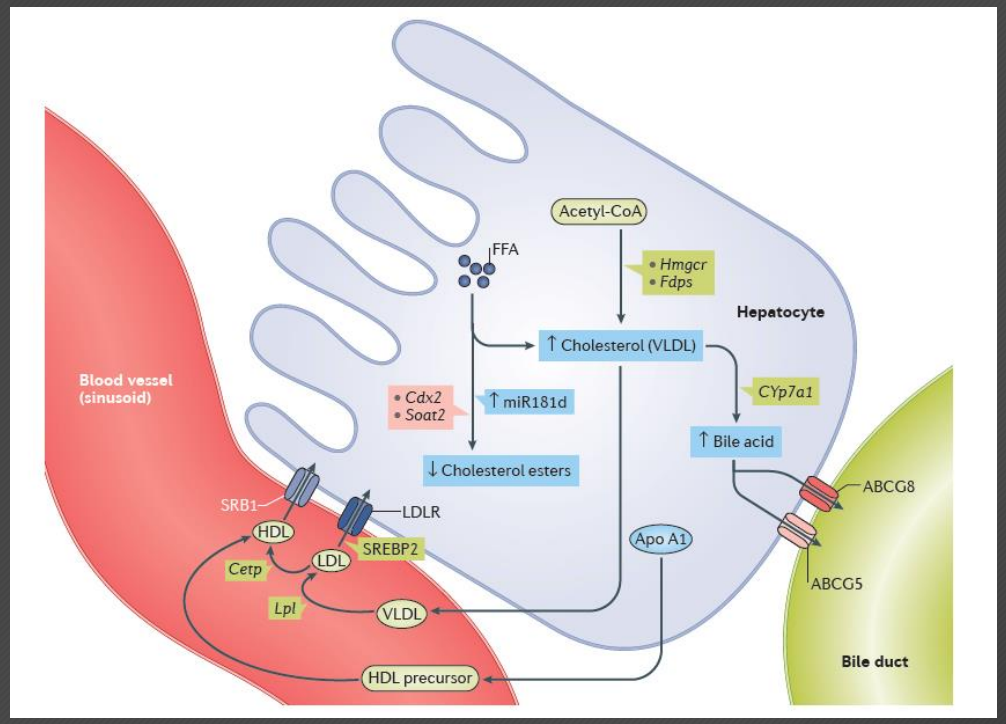
Rohit A. Sinha, 2018: Direct effects of thyroid hormones on hepatic lipid metabolism

Inhibition of SREBP by T3 defficiency



NET EFFECT IS INHIBITION OF SREBP1 → DECREASED INTRAHEPATIC CHOLESTEROL SYNTHESIS AND DECREASED LDL-R EXPRESION

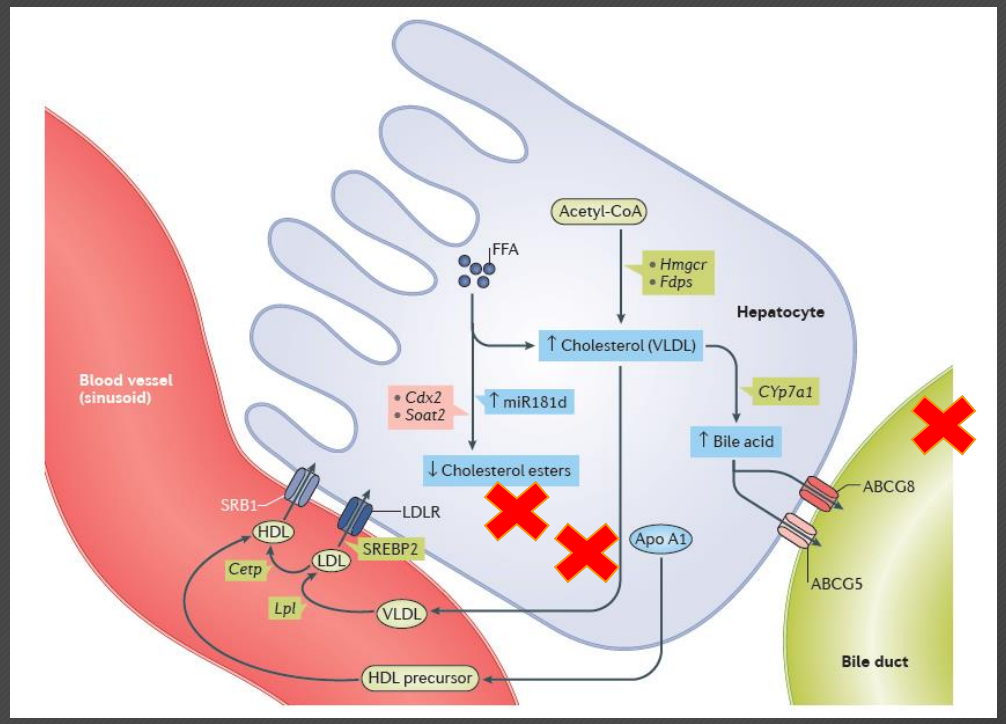
Reverse Cholesterol Transport Pathway



- Process by which HDL takes cholesterol back to liver
- TH induces SRBP1, apo-A1 and SRBEP2 expression
- Upregulates ABCG8/5 for increased bile acid secretion out of liver

Rohit A. Sinha, 2018: Direct effects of thyroid hormones on hepatic lipid metabolism

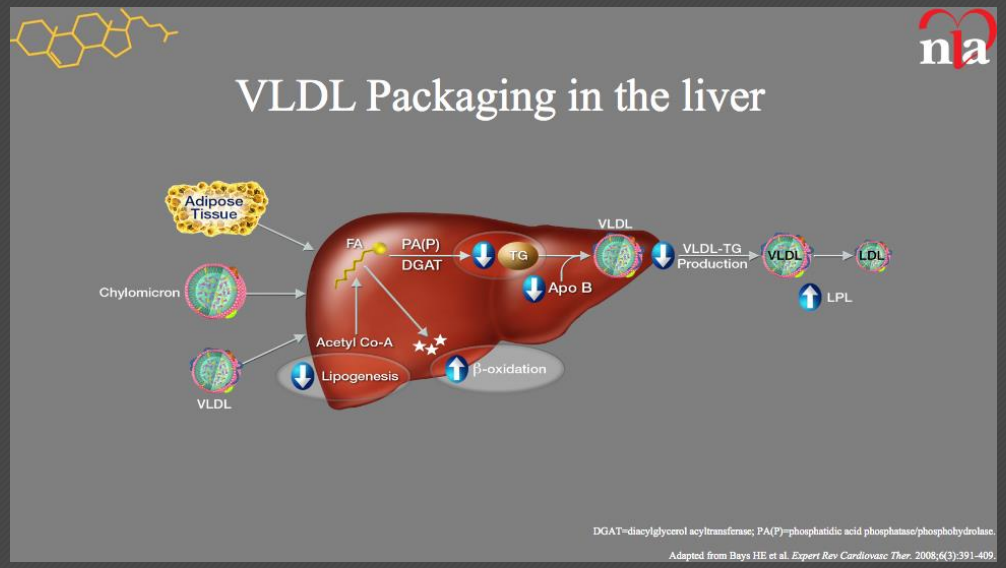
Reverse Cholesterol Transport Pathway: Lack of Thyroid Hormone



- Decreases C7aOH enzyme activity →
  - Decrease Bile Acids secretion from liver →
  - Increased Intrahepatic fatty infiltration
- Decreases SRB1 →
  - HDL non functional in RCT pathway
  - Increased HDL3 subfraction

Rohit A. Sinha, 2018: Direct effects of thyroid hormones on hepatic lipid metabolism

Apo B100 and Thyroid Hormone



- Thyroid Hormone reduce apolipoprotein B100, which decreases VLDL and LDL in rats
- Variable response due to other factors in humans
- Not entirely clear how is hepatic FFA's uptake in humans under TH defficiency

Rohit A. Sinha, 2018: Direct effects of thyroid hormones on hepatic lipid metabolism
Leonidas H. Duntas, 2018: A Renewed Focus on the Association Between Thyroid Hormones and Lipid Metabolism

Intrahepatic Fatty Acids Metabolism

Lipophagy – process of delivery of triacylglycerols to lysosomes for degradation and hydrolysis to FFA's

Thyroid hormone by means of THRB, increases available autophagosomes and lysosomes for this process

TH induces mitochondrial FF's oxidation

Rohit A. Sinha, 2018: Direct effects of thyroid hormones on hepatic lipid metabolism
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Why LDL-C is not extremly high?

- Decrease activity of various lipases:
  - CEPT (cholesterol ester transfer protein)
    - VLDL+HLD → IDL
  - Heptic Lipase
    - Regulates hydrolysis of HDL2 to HDL3
  - Lipoprotein Lipase
    - Catabolizes serum triglycerides

Rohit A. Sinha, 2018: Direct effects of thyroid hormones on hepatic lipid metabolism
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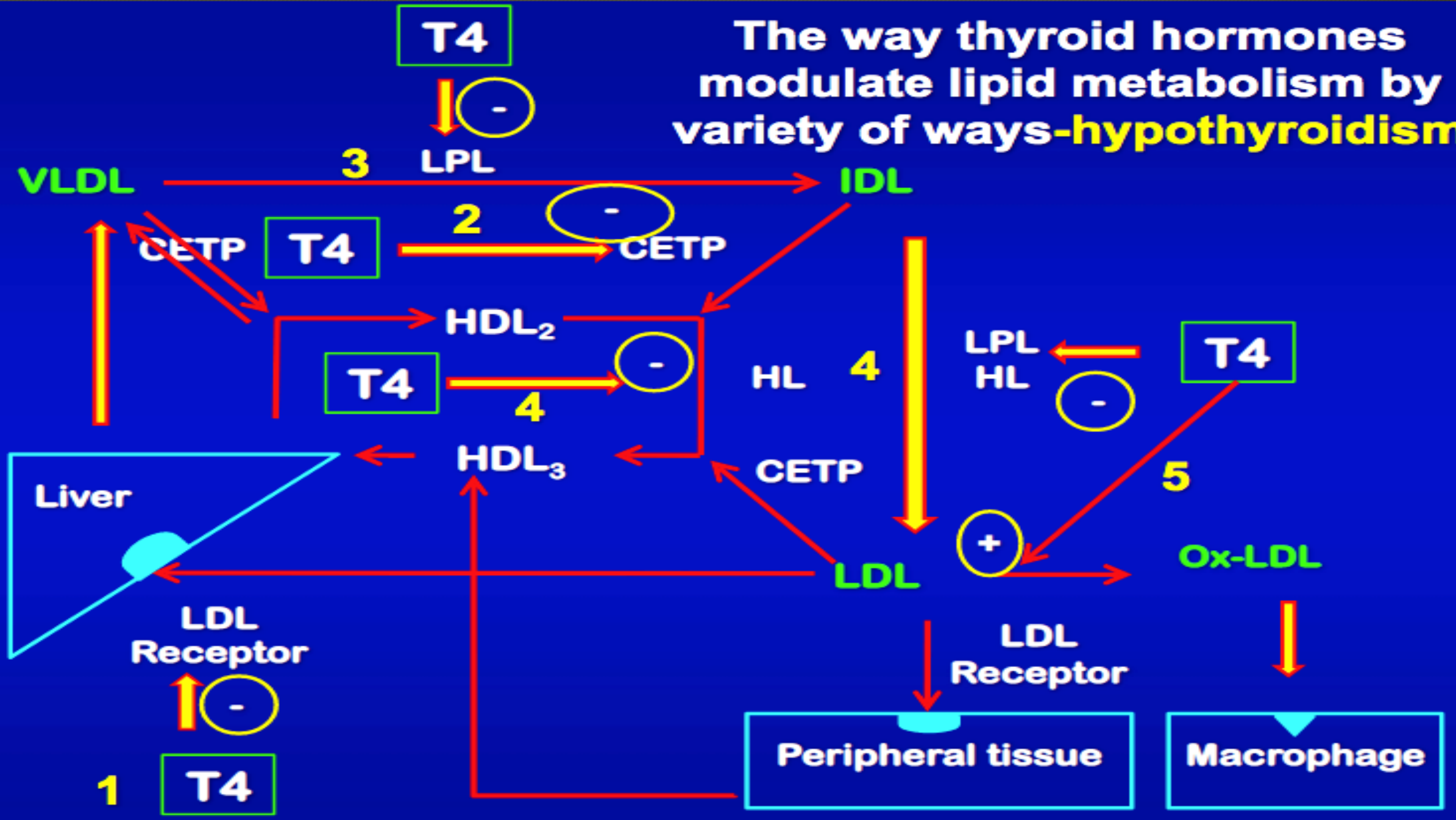
The way thyroid hormones modulate lipid metabolism by variety of ways-hypothyroidism



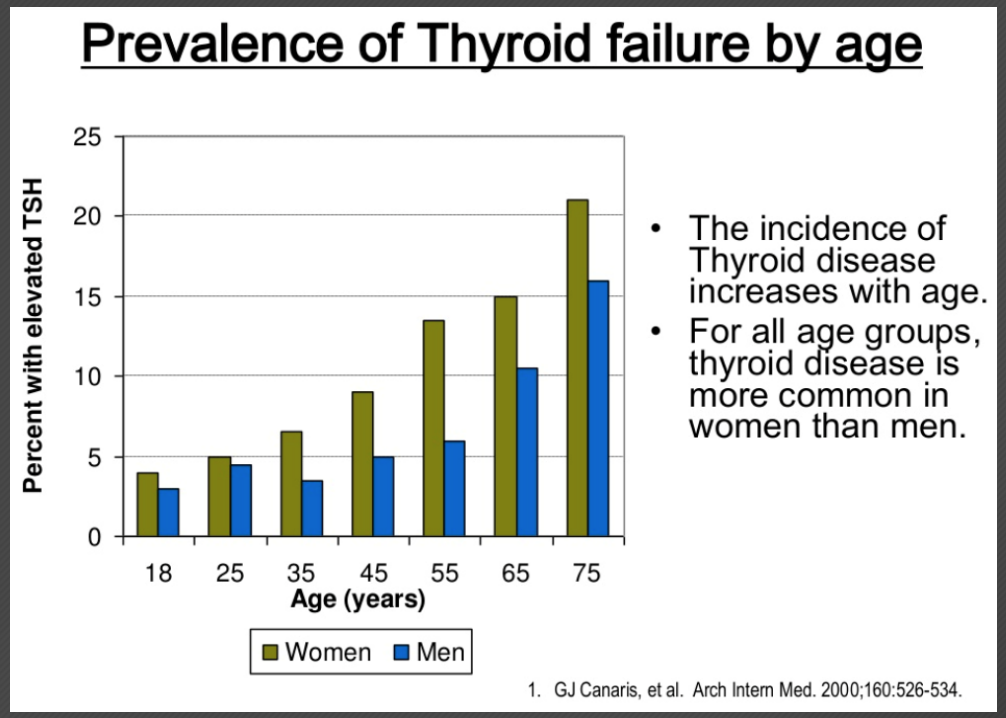
Liberopoulos EN. Hormones 2002, 1(14): 218-223

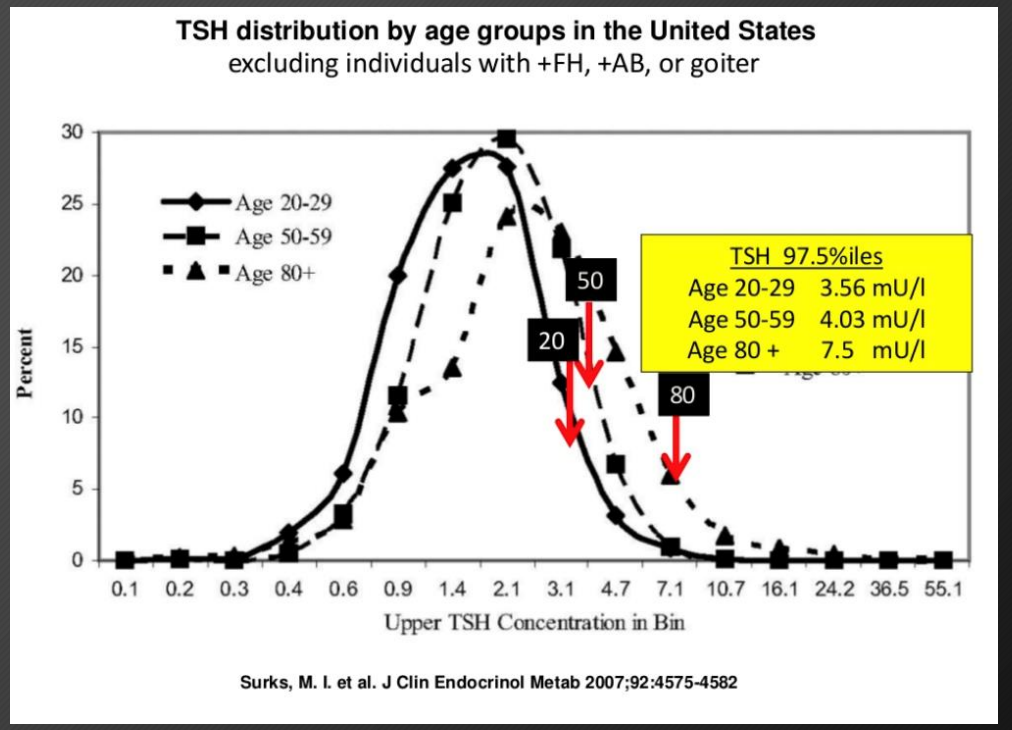
AGE, LIPID METABOLISM, AND THE THYROID

- As age advances, decline in thyroid function test may be apparent
- Physiological vs pathologycal
  - Degree of TSH elevation, TPOAB titers
- Thyroid disfunction has been associated with metabolic syndrome and increased CVD risk

Meng Zhao, 2015: Subclinical Hypothyroidism Might Worsen the Effects of Aging on Serum Lipid Profiles: A Population-Based Case-Control Study

AGE, LIPID METABOLISM, AND THE THYROID





THYROID
Volume 22, Number 11, 2012

DOI: 10.1089/thy.2012.0013

ORIGINAL STUDIES, REVIEWS, AND SCHOLARLY DIALOG
THYROID FUNCTION AND DYSFUNCTION

Age and Gender Substantially Influence the Relationship Between Thyroid Status and the Lipoprotein Profile: Results from a Large Cross-Sectional Study

Sara Tognini,[1] Antonio Polini,[1] Giuseppe Pasqualetti,[1] Silvia Ursino,[1] Nadia Caraccio,[1] Marco Ferdeghini,[2] and Fabio Monzani[1]

TABLE 2. CLINICAL AND BIOCHEMICAL FEATURES OF THE WHOLE COHORT ACCORDING TO AGE GROUPS

	1st group (n=306)	*2nd group (n=894)*	*3rd group (n=838)*	*4th group (n=270)*
Gender (% female)	85.6%	76.7%	84.5%	80.0%
Age (years)	24.7±3.6	40.5±5.8	55.7±4.2	70.4±5.0
BMI (kg/mq)	23.7±5.5	25.6±5.1	27.2±5.1*	26.4±4.4
Systolic BP (mm/Hg)	113.3±12.5	121.4±15.6	132.1±17.1	136.3±16.1
Diastolic BP (mm/Hg)	71.5±8.5	77.0±9.6	81.9±9.6	79.7±8.9
Autoimmunity (%)	56.1%	52.5%	51.2%	50.0%
TSH[a] (mIU/L)	3.09 (0.1–119.87)	1.97 (0–200)	1.46 (0–150)	1.32# (0–46)
FT4 (pg/mL)	9.8±3.6	10.7±3.5	11.1±3.6	11.1±3.7
FT3 (pg/mL)	3.3±1.4	3.1±1.0	3.1±0.9	3.0±1.2
TC (mg/dL)	188.0±40.3	209±44.0	233.9±42.1*	225.8±50.1*
LDLc (mg/dL)	109.6±31.6	131.7±39.1	149.6±39.0*	145.3±43.0*
HDLc (mg/dL)	56.4±13.1	56.0±13.4	57.4±16.4	55.9±15.5
TRIG (mg/dL)	91.0±5.3	111.6±83.9	133.5±80.4*	129.6±63.3*
LDL/HDL	2.06±0.82	2.48±0.94	2.81±1.00*	2.78±1.02*

Age groups were defined as: 1st, 10–29 years; 2nd, 30–49 years; 3rd, 50–64 years; 4[illegible], >65 years.
Data represent mean±SD, and were analyzed by *ANOVA ($p<0.0001$ vs. 1st and 2[illegible]d age groups) or #Kruskal–Wallis test ($p<0.0001$).
[a]Expressed as median and range.

Tognini S, Thyroid. 2012: Age and gender substantially influence the relationship between thyroid status and the lipoprotein profile: results from a large cross-sectional study

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TABLE 3. CLINICAL AND BIOCHEMICAL FEATURES OF THE WHOLE COHORT ACCORDING TO TSH GROUPS

	1st group (n=290)	*2nd group (n=1370)*	*3rd group (n=474)*	*4th group (n=174*
Women (%)	82.1	80.1	81.8	83.9
Age (years)	52.8±11.9*	48.1±13.7	42.2±14.1	46.6±15.1
BMI (kg/mq)	26.3±4.3	26.2±5.5	25.2±4.9	25.8±5.1
Systolic BP (mm/Hg)	125.8±15.6	127.9±17.3	125.9±19.3	125.9±20.1
Autoimmunity (%)	28.2	35.8	59.1	88.5×
TSH[a] (mIU/L)	0.14 (0.0–0.35)	1.43 (0.36–3.59)	5.06 (3.6–9.87)	19.8 (10.1–200)
FT4 (pg/mL)	14.6±5.1	11.0±2.6	9.4±2.3	6.5±3.9**
FT3 (pg/mL)	3.7±2.0	3.2±0.8	3.0±0.6	2.4±0.9**
TC (mg/dL)	213.9±47.3	215.7±43.3	215.5±44.0	243.2±65.4**
LDLc (mg/dL)	131.8±39.8	134.1±36.7	134.7±41.2	154.5±58.9**
HDLc (mg/dL)	55.1±14.9	57.0±14.7	56.5±15.3	54.7±13.2
TRIG (mg/dL)	123.8±65.9	118.7±78.5	116.1±71.7	140.8±117.6**
LDL/HDL	2.50±0.98	2.51±0.95	2.53±0.94	2.91±1.25**

TSH groups were defined as: 1st, <0.36 mIU/L; 2nd, >0.36 and <3.6 mIU/L; 3rd, >3.6 and <10.0 mIU/L; 4th, >10.0 mIU/L.
Data represent mean±SD, and were analyzed by ANOVA (*$p<0.001$ 1st group vs. 2nd and 4th group, $p<0.0001$ vs. 3rd group; **$p<0.000$1 4th group vs. each other group) or ×χ^2 test ($p=0.0002$).
[a]Expressed as median and range.

Tognini S, Thyroid. 2012: Age and gender substantially influence the relationship between thyroid status and the lipoprotein profile: results from a large cross-sectional study

Subclinical Hypothyroidism Might Worsen the Effects of Aging on Serum Lipid Profiles: A Population-Based Case-Control Study

Meng Zhao,[1,2,*] Tao Yang,[3,*] Li Chen,[4,*] Xulei Tang,[5,*] Qingbo Guan,[1,2,*] Bingchang Zhang,[6,*] Xu Zhang,[1,2,*] Haiqing Zhang,[1,2] Chenggang Wang,[7] Jin Xu,[1,2] Xinguo Hou,[4] Qiu Li,[1,2] Chunxiao Yu,[1,2] Yuanfei Zhao,[1,2] Li Fang,[1,2] Zhongshang Yuan,[8] Fuzhong Xue,[8] Guang Ning,[9] Ling Gao,[2,10] Chao Xu,[1,2] and Jiajun Zhao[1,2]

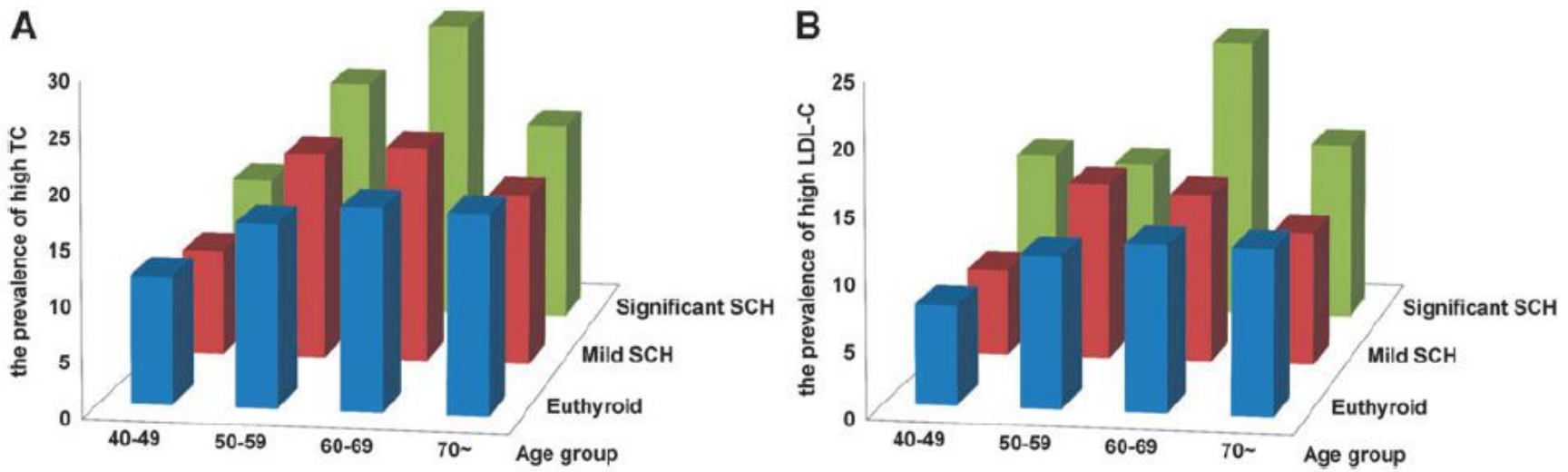

FIG. 3. The prevalence of high total cholesterol (TC) and high low-density lipoprotein cholesterol (LDL-C) according to age and thyroid status. Analysis of the lipid profile according to age and thyroid status revealed that the prevalence of high TC **(A)** and high LDL-C **(B)** progressively increased with age and TSH elevation. Based on the serum TSH level, SCH was divided into mild (TSH ≤ 10 mIU/L) and significant SCH (TSH > 10 mIU/L). Color images available online at www.liebertpub.com/thy

Meng Zhao, 2015: Subclinical Hypothyroidism Might Worsen the Effects of Aging on Serum Lipid Profiles: A Population-Based Case-Control Study

Systemic complications of altered lipid metabolism

Non-Alcoholic Fatty Liver Disease

- Global epidemic with an incidence of ~30%
- Considered to be part of Metabolic Syndrome
- Subtle progress from hepatosteatosis to NASH
- If left untreated may lead to cirhosis and/or hepatocellulr carcinoma
- NAFLD is the most common cause for liver transplantation in the USA
- Higher NAFLD prevalence associated with low T4 states

Subclinical and clinical hypothyroidism and non-alcoholic fatty liver disease: a cross-sectional study of a random population sample aged 18 to 65 years

Ulla Ludwig[1†], Daniela Holzner[1†], Christian Denzer[2], Artur Greinert[1], Mark Martin Haenle[1], Suemeyra Oeztuerk[1], Wolfgang Koenig[3,4,5], Bernhard Otto Boehm[6,7], Richard Andrew Mason[8], Wolfgang Kratzer[1*], Tilmann Graeter[9] and the EMIL-Study

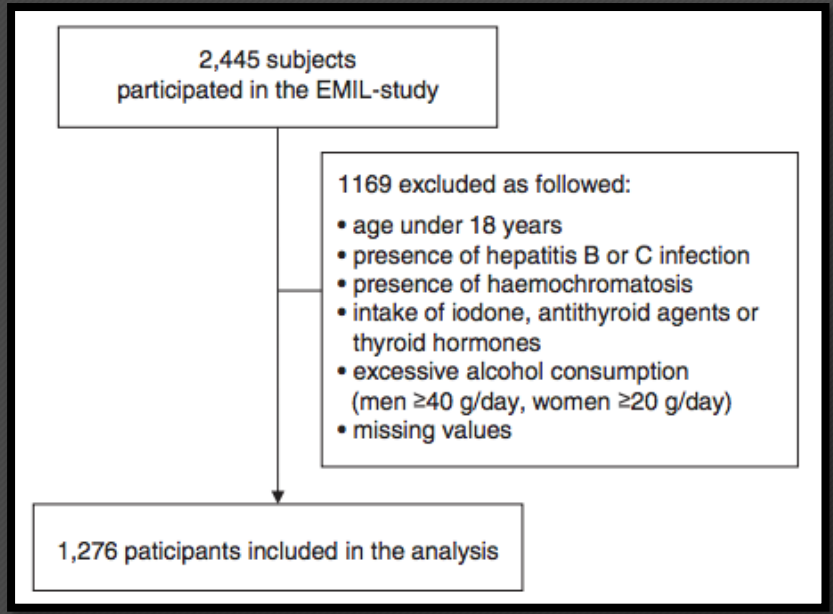

Table 1 Breakdown of thyroid hormone parameters in quartiles in the present study

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
TSH	<1.0	1.01-1.49	1.50-2.18	>2.19
TT4	<74.5	74.6-83.9	84.0-94.2	>94.3
TT3	<1.40	1.41-1.57	1.58-1.81	>1.82

Table 2 Characteristics of study subjects with and without NAFLD

Variables	Subjects with NAFLD (n = 349) Mean ± SD	Subjects without NAFLD (n = 927) Mean ± SD	*P* value
Gender, *n (%)*			
female	102 (29.2)	500 (53.7)	<.0001
male	247 (70.8)	427 (46.1)	
Age	47.7 ± 11.5	38.0 ± 12.1	<.0001
BMI	29.7 ± 4.7	24.0 ± 3.7	<.0001
WHR	0.9 ± 0.1	0.8 ± 0.1	<.0001
ALT	20.9 ± 10.3	13.5 ± 5.8	<.0001
AST	11.2 ± 5.1	9.0 ± 2.6	<.0001
GGT	20.5 ± 20.6	11.0 ± 10.5	<.0001
TSH (μU/ml)	1.8 ± 1.4	1.8 ± 3.5	0.6381
TT3 (nmol/l)	1.6 ± 0.3	1.6 ± 0.3	0.3293
TT4 (nmol/l)	83.2 ± 15.6	92.0 ± 17.4	0.0004
Anti-TPO (IU/ml)	23.9 ± 72.1	23.9 ± 74.0	0.4063
Diabetes, n (%)	22 (6.3)	8 (0.9)	<.0001
Metabolic syndrome, n (%)	65 (18.6)	15 (1.6)	<.0001
Hypertension, n (%)	99 (28.4)	67 (7.2)	<.0001

BMI = body-mass-index; WHR = waist to hip ratio; ALT = Alanine transaminase; AST = Aspartate transaminase; GGT = Gamma-glutamyl transferase; TSH = thyroid-stimulating hormone; TT3 = triiodothyronine; TT4 = thyroxine; Anti-TPO = anti-thyroid autoantibodies

Subclinical and clinical hypothyroidism and non-alcoholic fatty liver disease: a cross-sectional study of a random population sample aged 18 to 65 years

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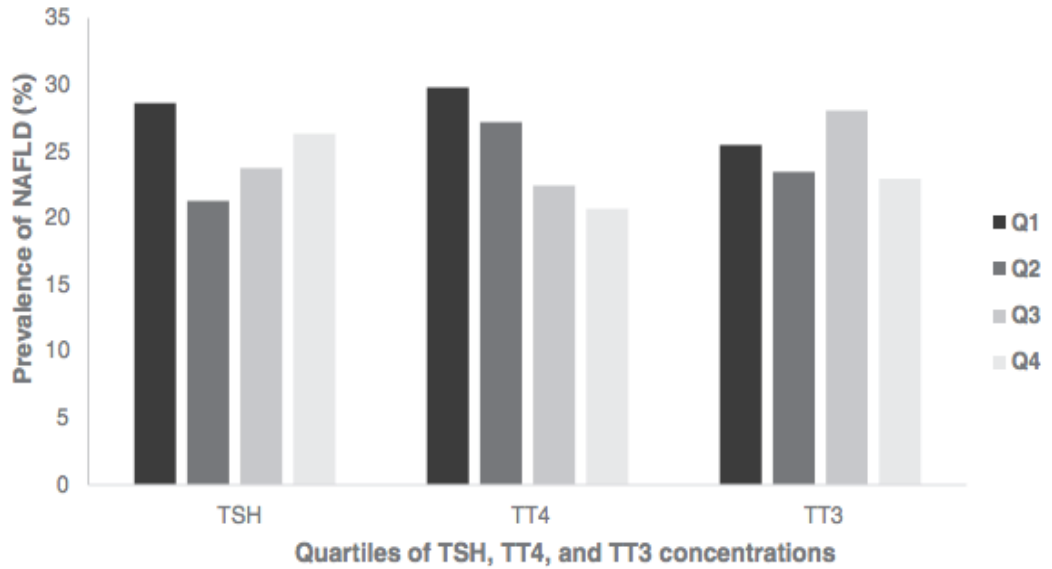


Fig. 2 Prevalence of non-alcoholic fatty liver disease (NAFLD) in relation to thyroid function in the present study. The figure plots the thyroid hormone concentrations in their respective quartiles (*x*-axis) against NAFLD prevalence rates in percent (*y*-axis). NAFLD prevalence rates show a downward trend with increasing TT4 concentrations. In addition, a positive trend is also seen for NAFLD prevalence rates with increasing TSH levels in the first quartile

NAFLD and Thyroid Hormone possible pathways

Abnormal lipid metabolism

Increased TSH might promote lipogenesis in the liver

Decreased TH concentration and signaling

Decreased expression and activity of intrahepatic DIO1

Metabolic syndrome

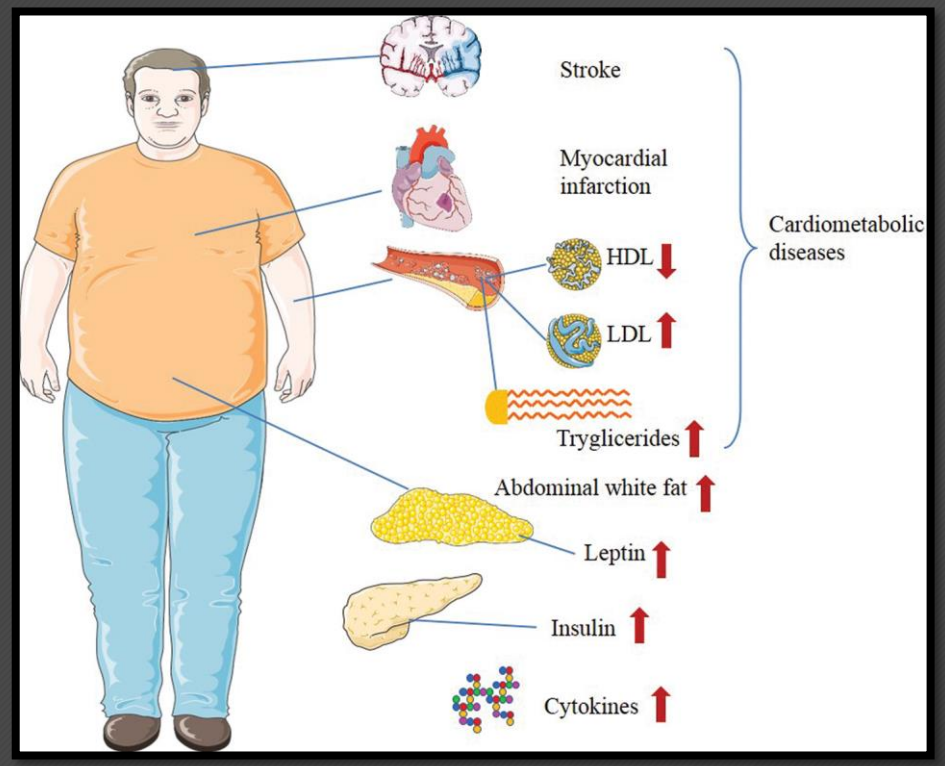


Table 1

NCEP ATP III Proposed Diagnostic Criteria of Metabolic Syndrome

Diagnostic Criteria (any 3 below)	Defining Points
Elevated waist circumference[a]	Men: >102 cm (>40 in) Women: >88 cm (>35 in)
Elevated TG	≥150 mg/dL *OR* Drug treatment for elevated TG
Reduced HDL-C	Men: <40 mg/dL Women: <50 mg/dL *OR* Drug treatment for reduced HDL-C
Elevated blood pressure	≥130 mmHg systolic blood pressure *OR* ≥85 mmHg diastolic blood pressure *OR* Drug treatment for hypertension
Elevated fasting glucose	≥100 mg/dL *OR* Drug treatment for elevated glucose

NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol.

[a] In non-Asian men and women with a marginally increased waist circumference (37-39 inches in men and 31-34 inches in women), there may be a strong genetic contribution to insulin resistance, and they should benefit from changes in lifestyle. In Asian Americans, there appears to be a lower cutoff point in waist circumference of 35 inches in men and 31 inches in women.

Source: References 2, 6.

Metabolic Syndrome and Thyroid Hormone

Thyroid Function and Prevalent and Incident Metabolic Syndrome in Older Adults: The Health, Aging, and Body Composition Study

Avantika C. Waring, Nicolas Rodondi, Stephanie Harrison, Alka M. Kanaya, Eleanor M. Simonsick, Iva Miljkovic, Suzanne Satterfield, Anne B. Newman, and Douglas C. Bauer for the Health, Aging, and Body Composition (Health ABC) Study

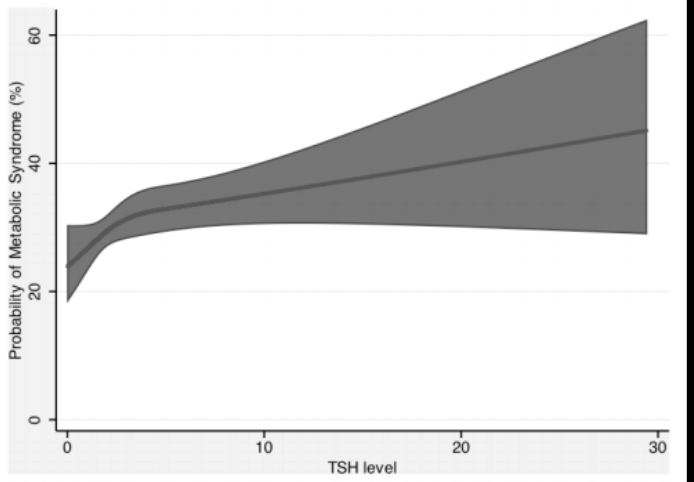


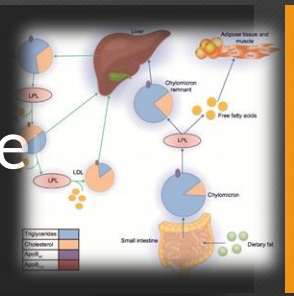
Figure 1.
Fitted prevalence of metabolic syndrome as a function of TSH levels, with 95% confidence interval, holding age, sex, race, BMI, smoking status, and HOMA-IR constant at their sample means

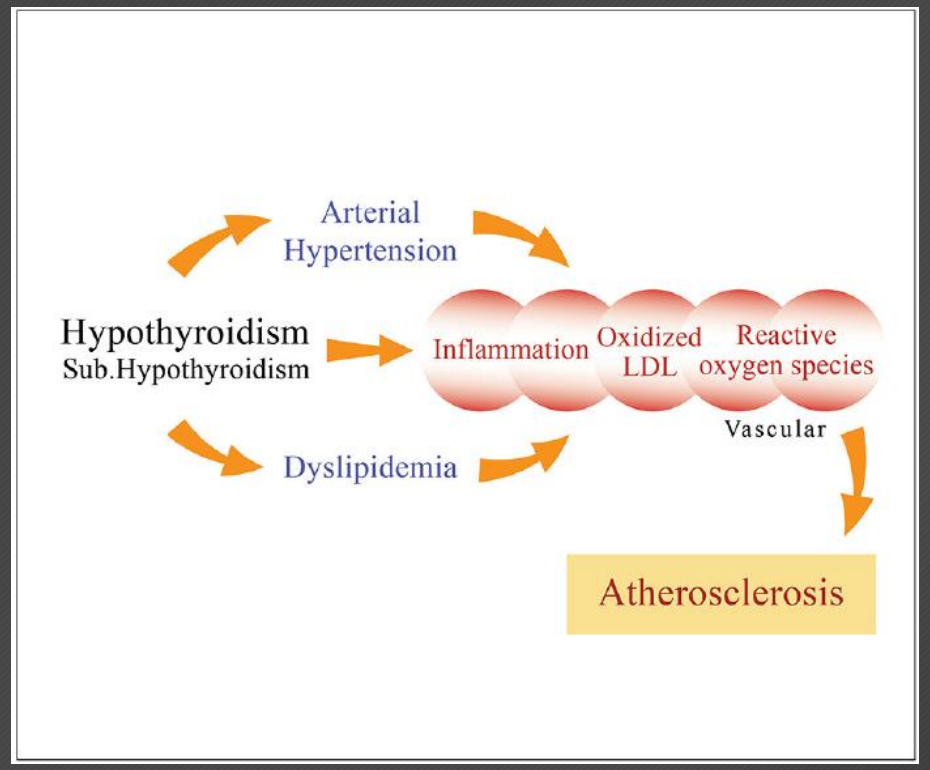
- At the MJ Health Screening database was noted:
  - 94,434 patients
  - MetS were at 21 % excess risk of developing SCH
  - After 4.2 years, an increased risk of SCH was associated with high serum triglycerides

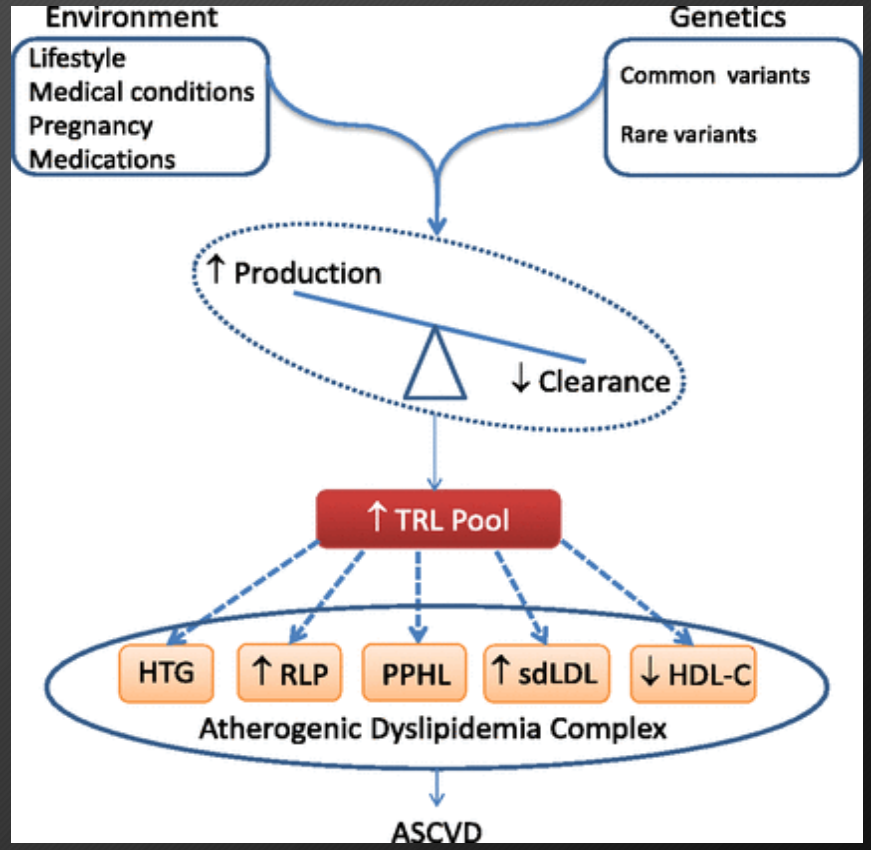
ODD ratio of 2.3 if TSH >10

Chia-Hsuin Chang, 2017: **Metabolic syndrome is associated with an increased incidence of subclinical hypothyroidism - A Cohort Study**

Increased Cardiovascular Risk and Thyroid Hormone Defficie



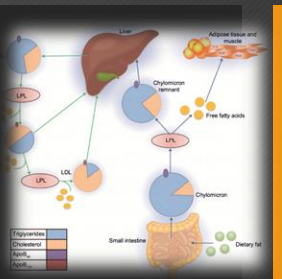




Clin Endocrinol (Oxf). 2003 May;58(5):621-6.

Serum concentrations of remnant-like particles in hypothyroid patients before and after thyroxine replacement.

Ito M[1], Takamatsu J, Matsuo T, Kameoka K, Kubota S, Fukata S, Tamai H, Miyauchi A, Kuma K, Hanafusa T.



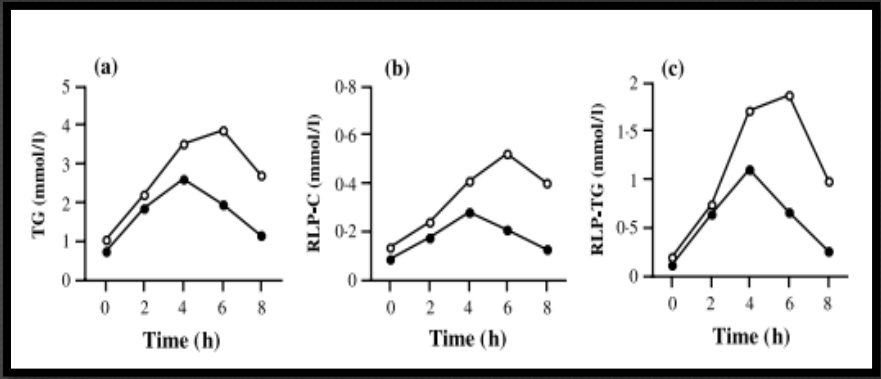


Fig. 1 Changes in serum triglyceride (a), RLP-C (b) and RLP-TG (c) after fat-loading. Open circles represent mean value when patients were hypothyroid; closed dots represent mean value when euthyroid following T_4 replacement.

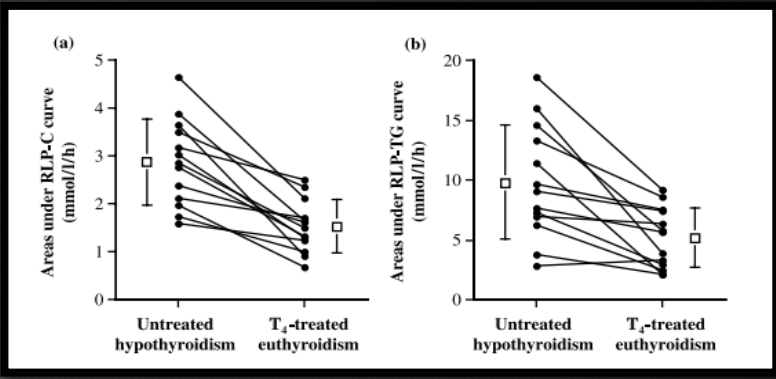


Fig. 2 Individual changes in area under RLP-C (a) and RLP-TG (b) curve 0–8 h after fat-loading test before and after T_4 replacement therapy. Open squares represent mean value level; bars represent the SD.

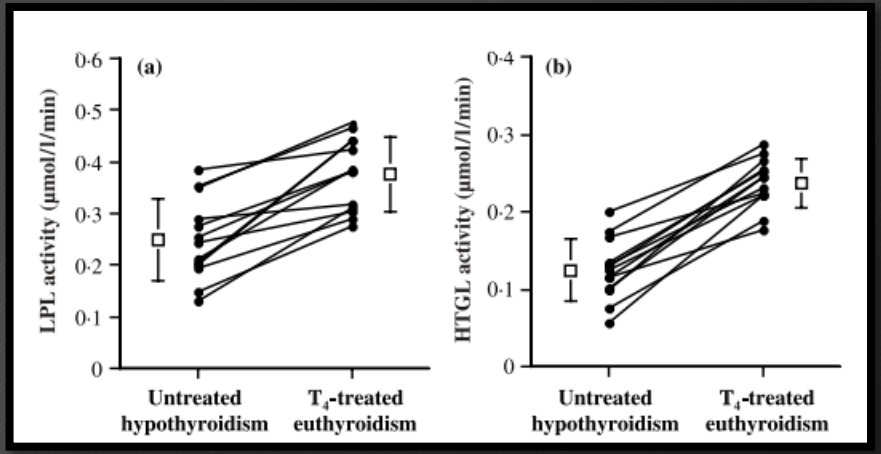


Fig. 3 Individual changes in activities of LPL (a) and HTGL (b) before and after T_4 replacement therapy. Squares represent mean value; bars represent the SD.

Study	Population (sample size)	Key findings
ERFC: individual record analysis of 68 long-term prospective studies[64]	No prior CHD (n=302,430)	After adjustment for nonlipid risk factors, TG levels were significantly associated with the incidence of CHD (HR 1.37, 95% CI 1.31–1.42). The association was no longer significant after adjustment for HDL-C and non-HDL-C (HR 0.99, 95% CI 0.94–1.05).
Post hoc analysis of two statin trials: IDEAL and TNT[65]	CHD and ACS, on potent statin therapy (n=15,779)	Risk of CVE occurring after the first year of the trials increased as a function of increasing on-treatment TG, with patients in the 5th quintile of TG having a 63% increase in events versus patients in the first quintile after adjusting for age and sex ($P<0.001$). After adjustment for HDL-C and apoB/apoAI, the association was attenuated ($P=0.044$).
PROVE IT-TIMI 22[10]	Hospitalized for ACS, on potent statin therapy (n=4,162)	On-treatment fasting TG <150 mg/dL was associated with a reduction in CHD risk versus high TG (HR 0.73, 95% CI 0.62–0.87; $P<0.001$). For each on-treatment 10-mg/dL decrement in TG, the incidence of death, MI, and recurrent ACS was lowered by 1.6% or 1.4% after adjustment for LDL-C ($P<0.001$) or non-HDL-C ($P=0.01$), respectively.
Prospective Copenhagen City Heart Study: ischemic stroke[66]	General population of Denmark (n=13,956)	The cumulative incidence of ischemic stroke increased with increasing levels of baseline nonfasting TG in both sexes ($P<0.001$). For men, age-adjusted HRs ranged from 1.4 (95% CI 0.9–2.1) in those with baseline TG of 89–176 mg/dL to 3.2 (95% CI 1.7–6.2) in those with TG ≥443 mg/dL versus men with TG <89 mg/dL. For women, HRs ranged from 1.3 (95% CI 1.0–1.8) in those with baseline TG of 89–176 mg/dL to 5.1 (95% CI 1.7–14.8) in those with TG ≥443 mg/dL versus women with TG <89 mg/dL.
Women's Health Study[67]	Healthy US women (n=26,509)	Baseline fasting and nonfasting TG were both strongly associated with CVE. Fasting TG was not significantly associated with CVE after adjustment for TC and HDL-C and measures of insulin resistance. However, nonfasting TG remained significantly associated with CVE after adjustment for TC and HDL-C ($P=0.006$).
Prospective Copenhagen City Heart Study: MI, IHD, and all-cause mortality[68]	General population of Copenhagen, Denmark (n=13,981)	Levels of remnant lipoprotein cholesterol increased with increasing non-fasting TG. The cumulative incidence of MI, IHD, and all-cause mortality increased with increasing nonfasting TG ($P<0.001$). For men, HRs for MI increased from 1.6 (95% CI 1.1–2.3) for TG of 88.5–176.1 mg/dL to 4.6 (95% CI 2.7–8.0) for TG ≥442.5 mg/dL versus those with TG <88.5 mg/dL. For women, HRs for MI increased from 2.2 (95% CI 1.6–3.2) for TG of 88.5–176.1 mg/dL to 16.8 (95% CI 6.8–41.6) for TG ≥442.5 mg/dL versus those with TG <88.5 mg/dL.
Post hoc analysis of the Framingham Heart Study[119]	Participants of the Framingham Heart Study without CVD at baseline (n=3,501)	High plasma TG levels (>150 mg/dL), in the absence of high LDL-C (>130 mg/dL) or low HDL-C (<40 mg/dL) levels, were not significantly associated with an increased risk of CVD events ($P=0.13$).
ARIC study[120]	Participants of the ARIC Study without CVD at baseline (n=12,339)	In women, TG was significantly associated with CHD risk after adjustment for age, race, LDL-C, apoB, apoA-1, and HDL-C subfractions (RR 1.29, $P<0.01$). However, TG was not significantly associated with CHD risk in men.
PROCAM study[121]	Men and women aged 16–65 years (n=19,698)	In a logistic function analysis, log-transformed TG levels showed a significant association with CHD incidence ($P<0.01$). However, after adjustment for HDL-C, this association was no longer significant.

Homocysteine, Hypothyroidism, and Effect of Thyroid Hormone Replacement

B. CATARGI,[1] F. PARROT-ROULAUD,[2] C. COCHET,[1] D. DUCASSOU,[3] P. ROGER,[1] and A. TABARIN[1]

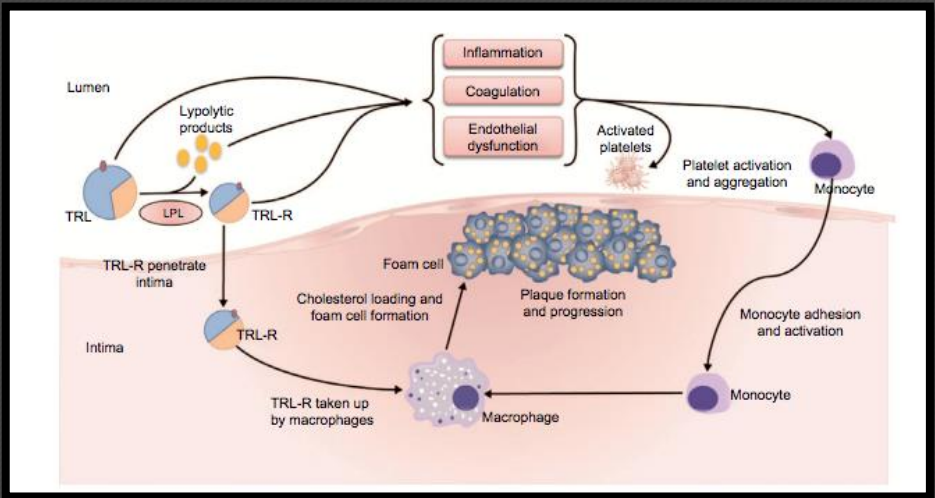


TABLE 1. BASELINE CHARACTERISTICS, FASTING AND POSTLOAD Hcy IN PATIENTS WITH HYPOTHYROIDISM AND IN CONTROLS

	Hypothyroidism (n = 40)	*Control* (n = 26)	p
Gender (no. of women)	35	7	—
Age, yr	47.7 ± 11.5	41.2 ± 6.6	<0.05
Fasting Hcy (μmol/L)	13.0 ± 7.5	8.5 ± 2.6	<0.01
Postload Hcy (μmol/L)	46.5 ± 30.0	29.6 ± 8.4	<0.01
TSH (mU/L)	80.1 ± 79.2	1.7 ± 0.6	<0.0001
Folates (nmol/L)	11.5 ± 5.2	21.0 ± 19.7	<0.05
B_{12} (pmol/L)	488.2 ± 229.0	409.6 ± 174.3	0.2
Total cholesterol (mmol/L)	8.0 ± 1.6	5.5 ± 1.1	<0.05
LDL cholesterol (mmol/L)	4.6 ± 1.1	3.7 ± 1.0	<0.05
Creatinine (μmol/L)	97.5 ± 17.5	102.1 ± 12.2	0.26

Data are mean ± SD.
Hcy, homocysteine; TSH, thyrotropin; LDL, low-density lipoprotein.

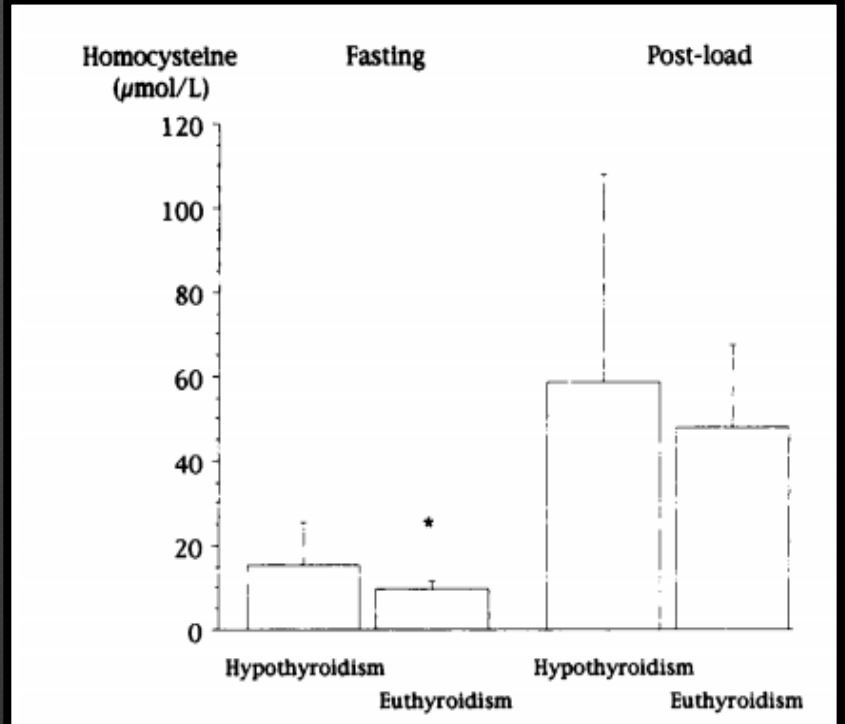


FIG. 1. Plasma homocysteine concentrations, fasting and after methionine loading, before and after thyroid hormone replacement in group 1. *$p < .05$ vs. hypothyroidism.

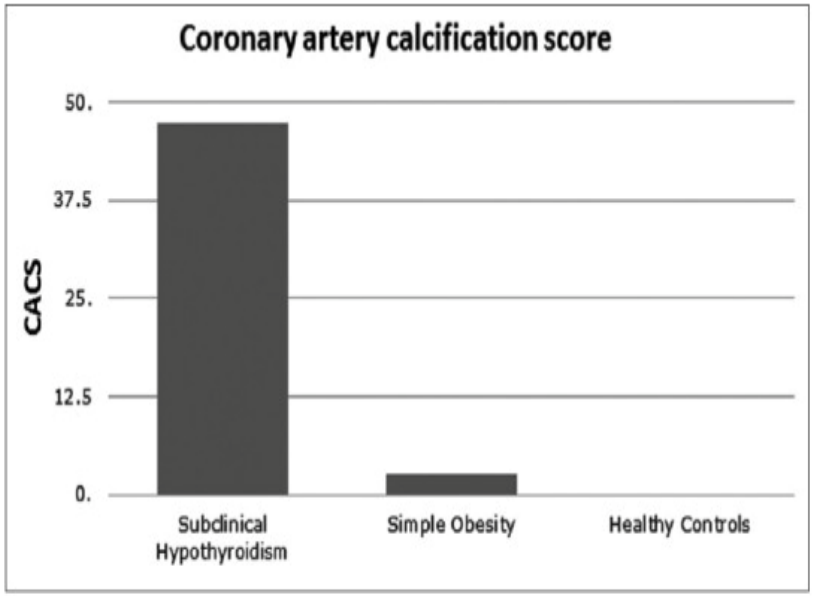
Indian Journal of Endocrinology and Metabolism
Wolters Kluwer -- Medknow Publications

Coronary artery calcium scoring is a better predictor of cardiac risk in subclinical hypothyroidism patients with low-risk Framingham score

Rajesh Verma, Ashish Verma, [...], and N. K. Agrawal

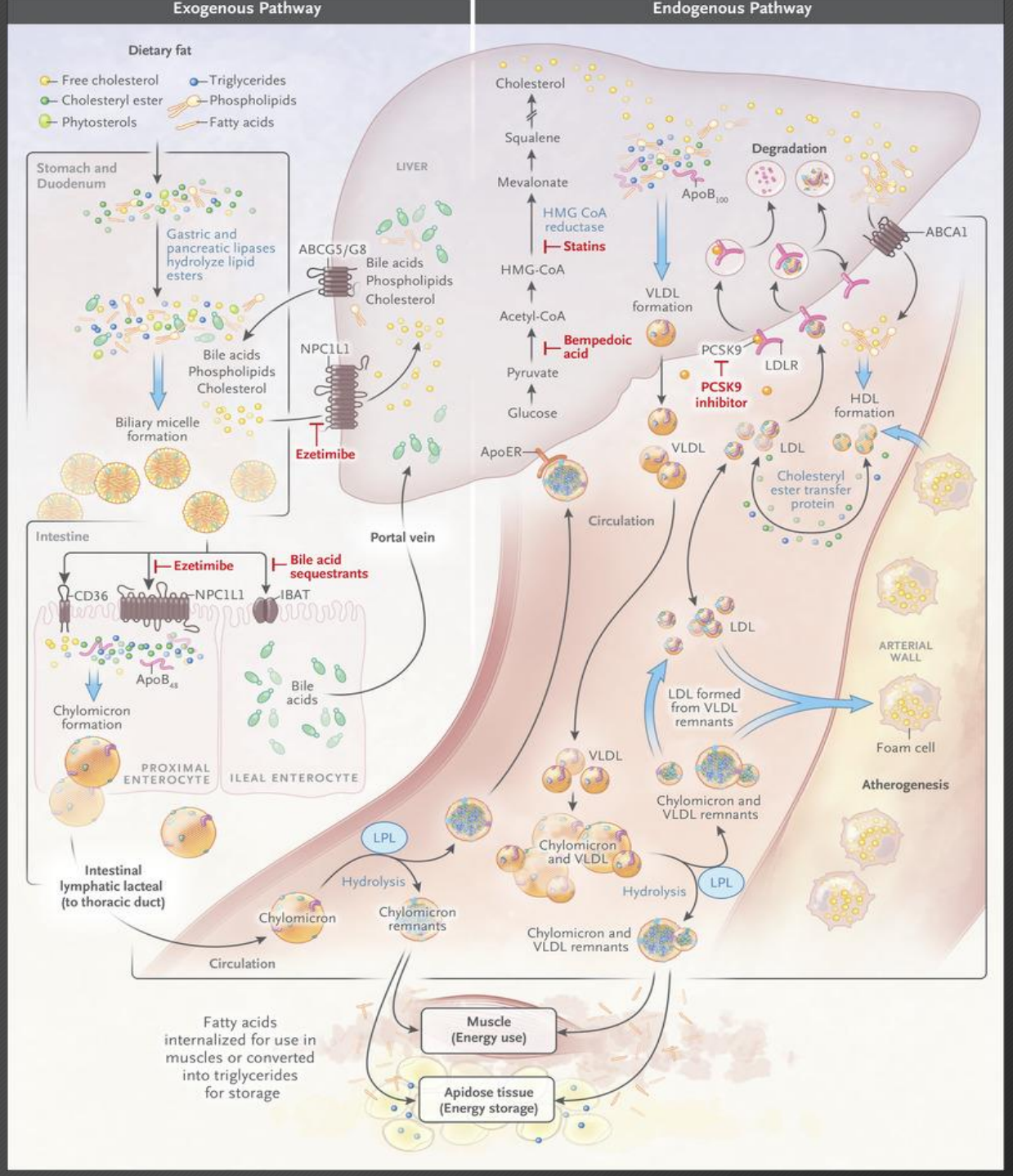
Parameter	Mean±SD			P
	Group 1 (SCH, n=30)	Group 2 (simple obesity, n=30)	Group 3 (healthy controls, n=10)	
Age (years)	42.7±10.3	42.5±7.5	47.6±7.9	0.26
Height (cm)	155.99±8.19	153.38±6.42	157.29±8.16.2	0.25
Weight (kg)	70.49±11.56	65.93±10.62	51.42±5.43	0
BMI (kg/m²)	29.0±4.22	28.0±4.37	20.74±1.13	0
Waist (male)	91.70±6.04	92.33±2.51	80.90±7.74	0.036
Waist (female)	94.51±11.51	91.57±12.09	65.78±4.95	<0.001
SBP (mmHg)	121.47±5.63	120.80±5.72	120.00±5.25	0.757
DBP (mmHg)	82.77±8.91	81.47±10.41	79.80±5.03	0.658
Fasting plasma glucose (mg/dl)	93.52±9.47	90.33±11.77	92.38±8.89	0.498
Plasma glucose 2 h post-OGTT (mg/dl)	116.54±15.10	116.48±13.39	121.36±10.05	0.590
HbA1c (%)	5.09±0.36	5.07±0.56	5.03±0.29	0.914
Urea (mg/dl)	23.44±6.43	24.48±7.24	22.50±4.93	0.676
Creatinine (mg/dl)	0.88±0.16	0.87±0.17	1.01±0.39	0.150
AST (U/L)	30.00±4.78	29.47±6.39	32.50±3.31	0.306
ALT (U/L)	29.27±6.53	30.75±6.77	27.50±6.39	0.377
Total bilirubin (mg/dl)	0.76±0.27	0.71±0.23	0.87±0.17	0.190
Direct bilirubin (mg/dl)	0.21±0.11	0.21±0.10	0.24±0.07	0.663
Alkaline phosphatase (U/L)	80.30±21.13	99.77±34.84	97.10±22.81	0.006
Total proteins (g/dl)	7.86±0.62	7.64±0.82	7.76±0.42	0.495
Albumin (g/dl)	4.42±0.37	4.43±0.39	4.45±0.41	0.975
Total cholesterol (mg/dl)	194.40±36.54	188.47±32.65	177.90±30.15	0.410
Triglyceride (mg/dl)	161.86±69.88	123.01±54.93	114.10±18.91	0.018
HDL (mg/dl)	47.44±11.59	48.150±11.52	56.30±9.20	0.092
LDL (mg/dl)	133.39±47.57	121.12±32.84	103.60±19.39	0.103
VLDL (mg/dl)	31.34±8.19	26.38±10.38	21.50±4.55	0.007
Free T4 (ng/dl)	1.23±0.22	1.12±0.23	1.09±0.13	0.086
TSH (μIU/ml)	7.53±1.67	2.99±1.60188	3.59±2.14	0
Serum anti-TPO antibody (IU/ml)	367.46±70.84	54.44±24.12	24.20±18.03	0

SD: Standard deviation, SCH: Subclinical hypothyroidism, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, OGTT: Oral glucose tolerance test, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very low-density lipoprotein, TSH: Thyroid stimulating hormone, TPO: Thyroid peroxidase, HbA1c: Glycated hemoglobin, Free T4: Free thyroxine



	Subclinical hypothyroidism	Simple obesity	Healthy controls
Coronary artery calcium score	47.17	2.67	0

TREATMENT: BEYOND LT4 REPLACEMENT



- TH have proven to reduce TC, LDL-C, TG's when replaced
- Although not proven to lower CVD risk as statins

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Subclinical Hypothyroidism

Robin P. Peeters, M.D., Ph.D.

Table 2. Associations Between Subclinical Hypothyroidism and Clinical Outcome, and Consequences of Treatment.*

Outcome of Subclinical Hypothyroidism	Strength of the Association		Benefits of Treatment
	Thyrotropin 4.5–9.9 mIU/liter	Thyrotropin ≥10 mIU/liter	
Progression to overt hypothyroidism	Strong	Stronger	Early treatment before development of overt hypothyroidism with more severe symptoms
Symptoms of hypothyroidism (e.g., tiredness, decreased cognition)	Strong	Stronger	Inconsistent, with large trial involving persons with mildly elevated thyrotropin levels (<10 mIU/liter) and very few symptoms showing no effects, and small trials involving persons with thyrotropin levels >10 mIU/liter showing benefits
Surrogate markers of cardiovascular risk (e.g., elevation in total cholesterol and LDL cholesterol levels, increased carotid-wall intima–media thickness, and decreased cardiac function)	Strong	Stronger	Moderate for reduction in total cholesterol and LDL cholesterol levels but unclear whether this is accompanied by a decreased risk of cardiovascular events
Risk of coronary heart disease	Weak	Stronger	Insufficient data to inform benefits
Risk of congestive heart failure	Weak	Stronger	Insufficient data to inform benefits
Risk of stroke	Weak	Weak	Insufficient data to inform benefits
Cognitive decline	Weak	Weak	Insufficient data to inform benefits

* This table is adapted and updated from Surks et al.[3] LDL denotes low-density lipoprotein.

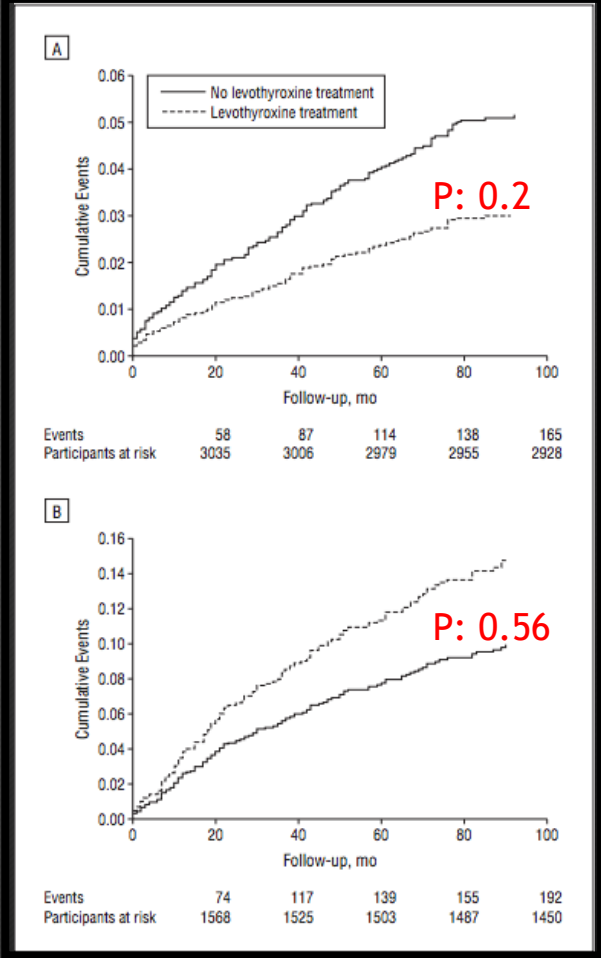
Levothyroxine Treatment of Subclinical Hypothyroidism, Fatal and Nonfatal Cardiovascular Events, and Mortality

Salman Razvi, MD, FRCP; Jolanta U. Weaver, PhD, FRCP; Timothy J. Butler, MRCGP; Simon H. S. Pearce, MD, FRCP

- United Kindome General Practitioner Research data base
- TSH 5-10 mIU/L and normal thyroxine
- 2 groups
  - A: 40-70 y/o
  - B: >70 y/o

Conclusion:

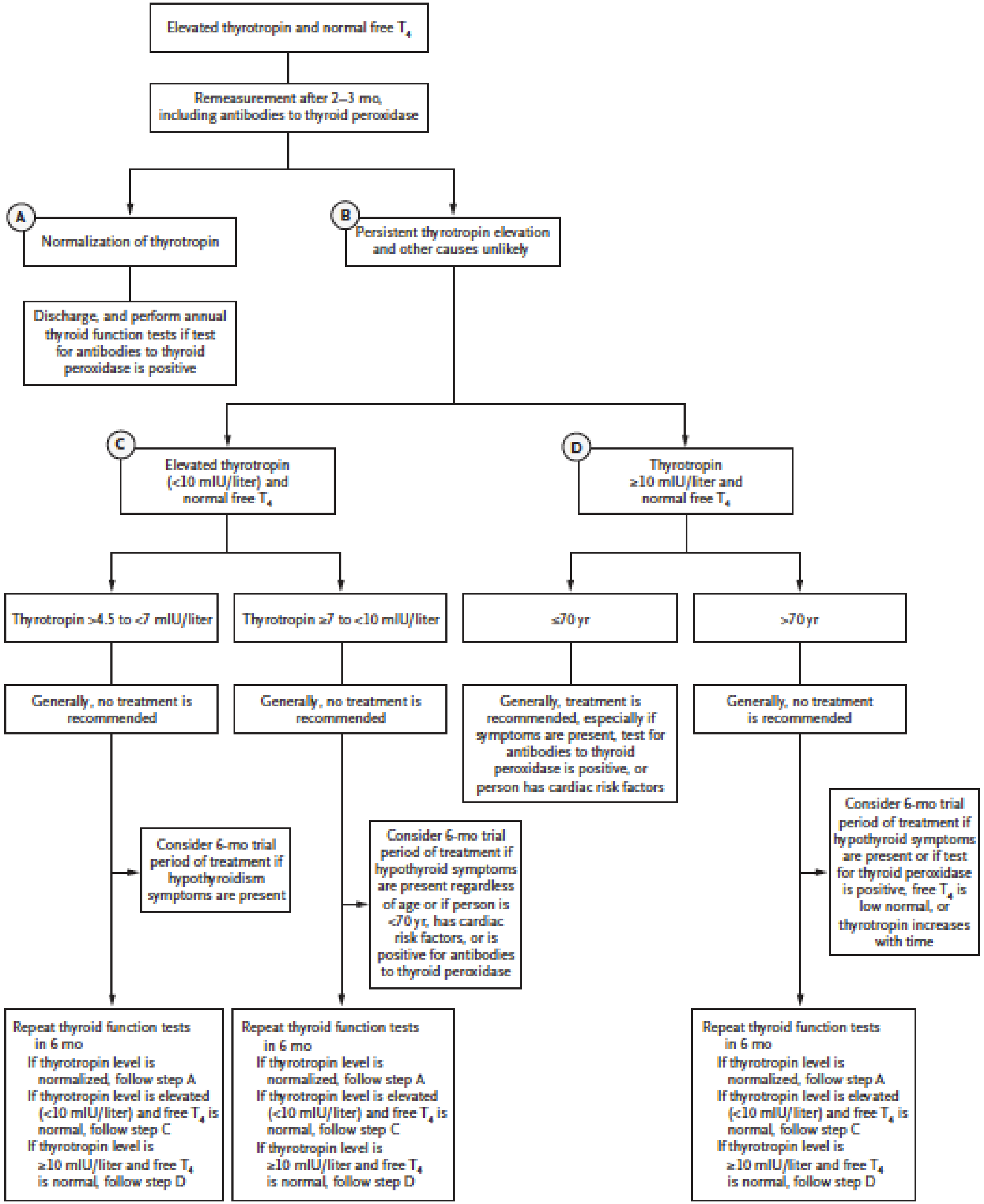
Younger individuals had fever IHD events in the tx arm



Young:
68/1634 vs
97/1459 events
tx vs no tx

Old:
104/819 vs
88/823 events
tx vs no tx

Salman Razvi, 2012: Levothyroxine Treatment of Subclinical Hypothyroidism, Fatal and Nonfatal Cardiovascular Events, and Mortality



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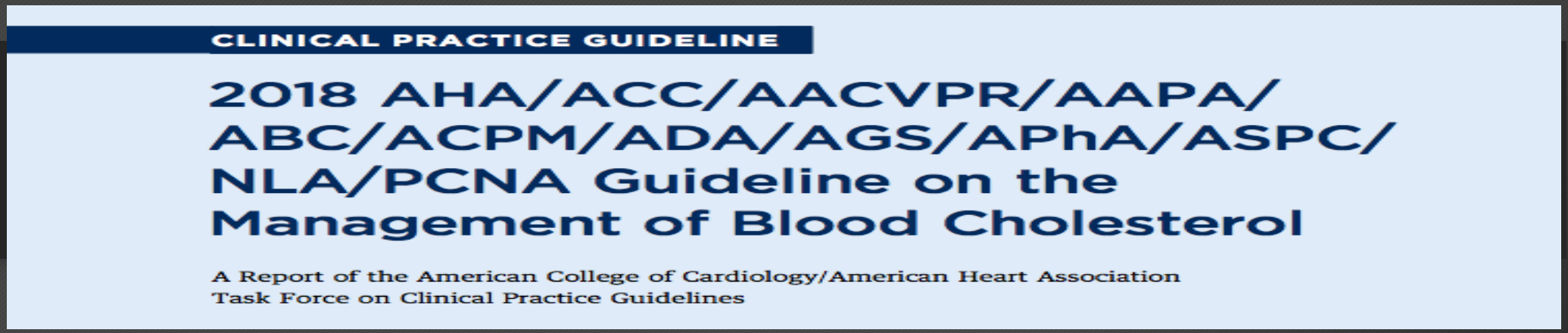

- Section 4.4.4.2
  - Group: Young adults (20 to 39 years of age)

    "*Secondary causes of elevated cholesterol—hypothyroidism (TSH), obstructive liver disease (liver panel), renal disease and nephrosis (creatinine and urine analysis) as well as dietary and medication history—should be addressed appropriately*"

- Coexisting factors that may potentiate Statin induced sidde effects:
  - DM, vitamin D deficiency, renal/liver disease, drug-drug interactions, female
  - Undiagnosed Hypothyroidism

TH induced cholesterol reduction

Mayo Clinic 1993
268 patients with primary hypoT and 27 with secondary hypothyrodism
Treatment with Lt4 significantly reduced TC and LDL

Table 1.—**Serum Lipid Values in 295 Study Patients With Primary or Secondary Hypothyroidism***

Lipid	Primary hypothyroidism (N = 268) Median†	Range	Secondary hypothyroidism (N = 27) Median†	Range	*P*
Total cholesterol (mg/dl)	257 (255)	106-541	256 (256)	116-439	NS
Triglycerides (mg/dl)	125 (118)	26-1,107	163 (163)	54-525	0.026
HDL cholesterol (mg/dl)	50 (52)	23-102	35 (35)	25-55	<0.001
LDL cholesterol (mg/dl)	180 (185)	89-403	177 (161)	123-238	NS

*HDL = high-density lipoprotein; LDL = low-density lipoprotein; NS = not significant.
†Values in parentheses are median values excluding patients who had diabetes or were receiving medications known to affect lipids.

Table 2.—**Serum Lipid Values, Total Thyroxine, and Thyrotropin Before and After Treatment of Patients With Primary Hypothyroidism***

Measurement	No. of patients	Before treatment Median†	Range	After treatment Median†	Range	*P*
Total cholesterol (mg/dl)	70	264 (272)	148-440	222 (225)	146-298	<0.001
Triglycerides (mg/dl)	69	114 (108)	26-1,107	100 (101)	42-606	0.019
HDL cholesterol (mg/dl)	44	54	27-86	51	19-78	0.012
LDL cholesterol (mg/dl)	42	187	110-335	152	76-233	<0.001
Total T4 (µg/dl)	65	4.1	0.5-8.0	8.5	4.9-13.4	<0.001
TSH (mIU/L)	62	32.3 (43)	8-467	1.2 (1.2)	0-6.6	<0.001

*Only patients with measurements before and after treatment are included in this tabulation. HDL = high-density lipoprotein; LDL = low-density lipoprotein; T4 = thyroxine; TSH = thyroid-stimulating hormone (thyrotropin).
†Values in parentheses are median values excluding patients who had diabetes or were receiving medications known to affect lipids.

Association between thyroid function and lipid profiles, apolipoproteins, and high-density lipoprotein function

Kyong Yeun Jung, MD[a,1], Hwa Young Ahn, MD, PhD[b,1], Sun Kyoung Han, BSc[c], Young Joo Park, MD, PhD[d], Bo Youn Cho, MD, PhD[b], Min Kyong Moon, MD, PhD[d,e,*]

- Atherogenic Particles Decrease as Well
- 27 patients with PTC who underwent TT + RAIU
- Time 1 at the day of sx
- Time 2 before RAI tx (overt hypo)
- Time 3, 12 weeks on LT4 tx

Table 2. Changes of lipid profile and HDL function according to thyroid function state

	Time 1	Time 2	Time 3	*p* value
Thyroid function test				
Free T4 (ng/dl)	1.75 ± 0.37	0.24 ± 0.06 *	1.60 ± 0.27 †	<0.001
TSH (μIU/ml)[a]	0.03 (0.02–0.24)	91.2 (77.8–118.2) *	0.03 (0.01–0.16) †	<0.001
Lipid levels				
Total cholesterol (mg/dl)	169.4 ± 31.1	236.5 ± 46.9 *	172.0 ± 31.0 †	<0.001
Triglyceride (mg/dl)[a]	85.8 (66.8-117.6)	141.0 (113.2-198.4)*	104.8 (74.4-118.5) †	<0.001
HDL-C (mg/dl)	36.8 ± 8.4	40.4 ± 10.7 *	38.9 ± 8.5 *	0.005
LDL-C (mg/dl)	93.5 ± 21.5	133.3 ± 30.2 *	94.1 ± 21.4 †	<0.001
Apolipoproteins				
Apo A-I (mg/dl)	140.8 ± 25.7	157.1 ± 25.5 *	145.6 ± 22.4 †	<0.001
Apo A-II (mg/dl)	29.3 ± 4.0	28.8 ± 3.5	29.6 ± 3.9	0.436
Apo A-I/A-II ratio	4.8 ± 0.8	5.5 ± 0.8 *	4.9 ± 0.6 †	<0.001
Apo B (mg/dl)	81.7 ± 23.6	127.8 ± 27.3 *	84.4 ± 20.9 †	<0.001
Apo E (mg/dl)	2.9 ± 1.7	5.1 ± 2.3 *	4.8 ± 1.3 *	<0.001
Cholesterol efflux (%)	21.5 ± 5.1	18.9 ± 2.9 *	18.9 ± 3.3 *	0.021
PON1 activity / Apo A-I	0.14 ± 0.04	0.13 ± 0.02 *	0.14 ± 0.02 †	0.009

* *p* values < 0.05 vs. period 1, † *p* values < 0.05 vs. period 2 by repeated ANOVA or Friedman test

Effect of Thyroxine Therapy on Serum Lipoproteins in Patients with Mild Thyroid Failure: A Quantitative Review of the Literature*

MARK D. DANESE, PAUL W. LADENSON, CURTIS L. MEINERT, AND NEIL R. POWE

TABLE 2. Overview of 13 studies of levothyroxine therapy on serum lipids

First author	Yr	Design	Sample size	Mean age (yr)	Selection criteria for patients	Initial TSH (mU/L)[a]	Final TSH (mU/L)[a]	Design score (of 13)
Arem (50)	1990	Before-after	13	32	Hypothyroidism	16.6	3.2	4
Arem (51)	1995	Before-after	14	41	Hypothyroidism	9.1	1.8	6
Bell (52)	1985	Before-after	18	42	Hyperthyroidism	17.9	3.2	7
Bogner (48)	1993	Before-after	7	60	Hypercholesterolemia	4.8	0.7	5
Caron (53)	1990	Before-after	29	35	NR	12.0	1.2	5
Cooper (12)	1984	Parallel RCT	33	54	Hyperthyroidism	10.8	2.6	8
Franklyn (54)	1993	Before-after	11	63	Hyperthyroidism	13.8	1.1	3
Jaeschke (57)	1996	Parallel RCT	31	68	NR	12.3	4.6	7
Miura (49)	1994	Before-after	15	47	Mixed, mostly hyperthyroidism	6.0	3.0	5
Nilsson (55)	1976	Before-after	29	54	Hyper- and hypothyroidism	19.0	5.0	3
Nyström (11)	1988	Crossover RCT	17	58	Community-based screening	7.7	1.9	8
Paoli (58)	1998	Before-after	15	32	NR	5.3	0.6	6
Powell (56)	1989	Before-after	15	71	Arterial clinic	9.8	2.9	4
Median	1990	NA	15	54	NA	10.8	2.6	6

Before-after, Uncontrolled, single-group study; RCT, randomized, placebo-controlled trial; NR, not reported; NA, not applicable.
[a] For controlled studies, TSH data reported for T_4-treated group or period.

Effect of Thyroxine Therapy on Serum Lipoproteins in Patients with Mild Thyroid Failure: A Quantitative Review of the Literature*

MARK D. DANESE, PAUL W. LADENSON, CURTIS L. MEINERT, AND NEIL R. POWE

TABLE 4. Raw data from studies

First author	Total cholesterol (mmol/L)			LDL cholesterol (mmol/L)			HDL cholesterol (mmol/L)		
	Before	Change	% change	Before	Change	% change	Before	Change	% change
Arem 90 (50)	5.34	−0.52	−10%	3.57	−0.60	−17%	1.14	0.13	11%
Arem 95 (51)	5.18	−0.41	−8%	3.50	−0.54	−15%	1.17	0	0%
Bell (52)	6.40	−0.21	−3%	NA	NA	NA	1.66	−0.26	−16%
Bogner (48)	7.17	−0.98	−14%	5.28	−0.91	−17%	1.45	−0.08	−6%
Caron (53)	5.15	0.16	3%	3.65	−0.08	−2%	1.17	0.21	18%
Cooper (12)									
T_4	6.57	−0.34	−5%	NA	NA	NA	NA	NA	NA
Placebo	6.05								
Franklyn (54)	7.41	−0.36	−5%	5.26	−0.34	6%	1.04	−0.18	−17%
Jaeschke (57)									
T_4	5.68	0.31	5%	3.64	0.18	5%	1.36	0.04	3%
Placebo	6.51			4.11			1.45		
Miura (49)	5.96	−0.13	−2%	3.76	0.16	4%	1.48	−0.08	−5%
Nilsson (55)	5.75	−0.18	−3%	NA	NA	NA	NA	NA	NA
Nyström (11)									
T_4	6.78	−0.23	3%	NA	NA	NA	NA	NA	NA
Placebo	6.67								
Paoli (58)	5.08	−0.31	−6%	3.19	−0.34	−11%	1.19	0.08	7%
Powell (56)	8.03	−0.80	−10%	4.82	−0.78	−16%	1.30	0.16	12%

NA, Data not available.

Different Effects of Atorvastatin on Metabolic and Cardiovascular Risk Factors in Hypercholesterolemic Women with Normal Thyroid Function and Subclinical Hypothyroidism

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- 48 woman from Poland
- Subclinical hypo treated and not treated
- Atorvastatin 20 mg daily x 12 weeks

Variable	Group A[2]	Group B[3]	Group C[4]
Number of patients	14	16	16
Age [years; mean (SD)]	47 (5)	49 (4)	50 (5)
Body mass index [kg/m^2; mean (SD)]	27.5 (2.3)	27.0 (2.0)	26.8 (1.9)
Waist circumference [cm; mean (SD)]	92 (6)	91 (5)	90 (5)
Smokers [%]	21	25	19
Autoimmune thyroid disease [%][5]	71[b]	69[b]	0
Thyroidectomy [%]	29[b]	31[b]	0
Daily L-thyroxine dose [μg; mean (SD)]	0 (0)	88 (15)[a,b]	0 (0)

[1]only data of individuals who completed the study were included in the final analyses (2 patients were withdrawn from the study)
[2]patients with untreated subclinical hypothyroidism
[3]patients with hypothyroidism treated with L-thyroxine
[4]patients without thyroid disorders
[5]the reduced echogenicity of the thyroid parenchyma on thyroid ultrasonography and positive antibodies (>35 U/mL) against thyroid peroxidase
[a]$p<0.001$ vs. group A, [b]$p<0.001$ vs. group C

Variable	Group A[2]	Group B[3]	Group C[4]
TSH [mIU/L; mean (SD)]			
Baseline	7.5 (1.3)	1.3 (0.6)[c]	1.2 (0.6)[c]
After 12 weeks	7.3 (1.4)	1.5 (0.5)[c]	1.4 (0.6)[c]
Free thyroxine [pmol/L; mean (SD)]			
Baseline	13.1 (2.0)	15.6 (1.9)[b]	16.0 (2.3)[b]
After 12 weeks	13.4 (1.8)	16.1 (2.5)[b]	15.8 (2.0)[b]
Free triiodothyronine [pmol/L; mean (SD)]			
Baseline	3.1 (0.5)	3.9 (0.6)[b]	4.1 (0.8)[b]
After 12 weeks	3.2 (0.6)	4.2 (0.8)[b]	4.3 (0.7)[b]
Total cholesterol [mg/dL; mean (SD)]			
Baseline	258 (20)	269 (27)	247 (25)
After 12 weeks	193 (18)[f]	172 (20)[a,f,g]	161 (21)[a,f,g]
LDL-cholesterol [mg/dL; mean (SD)]			
Baseline	180 (22)	187 (19)	175 (26)
After 12 weeks	119 (16)[f]	105 (14)[a,f,g]	101 (14)[a,f,g]
HDL-cholesterol [mg/dL; mean (SD)]			
Baseline	47 (6)	50 (6)	46 (7)
After 12 weeks	48 (5)	56 (7)[a,d,g]	53 (5)[a,d,g]
Triglycerides [mg/dL; mean (SD)]			
Baseline	146 (22)	150 (25)	142 (23)
After 12 weeks	151 (27)	130 (30)	125 (32)
Glucose [mg/dL; mean (SD)]			
Baseline	93 (7)	95 (7)	94 (6)
After 12 weeks	95 (5)	94 (6)	94 (5)
HOMA-IR			
Baseline	2.9 (0.6)	2.6 (0.5)	2.8 (0.5)
After 12 weeks	3.6 (0.8)[d,i,j]	2.8 (0.7)[a]	2.9 (0.6)[a]
Uric acid [µmol/L; mean (SD)]			
Baseline	315 (43)	325 (53)	309 (38)
After 12 weeks	321 (39)	273 (40)[a,d,g]	260 (46)[a,d,g]
hsCRP [mg/L; mean (SD)]			
Baseline	3.4 (0.7)	2.6 (0.7)[a]	2.6 (0.6)[a]
After 12 weeks	2.9 (0.5)	1.5 (0.4)[c,f,h]	1.6 (0.3)[c,f,h]
Homocysteine [µmol/L; mean (SD)]			
Baseline	47 (11)	29 (10)[b]	31 (11)[b]
After 12 weeks	43 (10)	19 (6)[c,d,g]	17 (8)[c,e,h]
Fibrinogen [mg/dL; mean (SD)]			
Baseline	380 (65)	312 (60)[a]	294 (56)[b]
After 12 weeks	408 (64)	252 (41)[c,d,h]	236 (46)[c,d,h]

Thyromimetics/Analogs

- GC-1 (Sobetirome)
  - Selectie THR-B1 agonist – same clinical activity as T3
  - Stimulates steps of the reverse cholesterol transport
  - Prevents and reverses hepatosteatosis in rat fed a diet that induced NASH
  - Reduced liver weight, serum triglycerides
  - Decreased lipoperoxidation and liver injury, efect noted by reduced ALT/AST

  - Phase I study in humans
    - 2 weeks treatment reduced LDL-C by up to 41%

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Use of the Thyroid Hormone Analogue Eprotirome in Statin-Treated Dyslipidemia

Paul W. Ladenson, M.D., Jens D. Kristensen, M.D., Ph.D., E. Chester Ridgway, M.D., Anders G. Olsson, M.D., Ph.D., Bo Carlsson, M.Sc., Irwin Klein, M.D., John D. Baxter, M.D., and Bo Angelin, M.D., Ph.D.

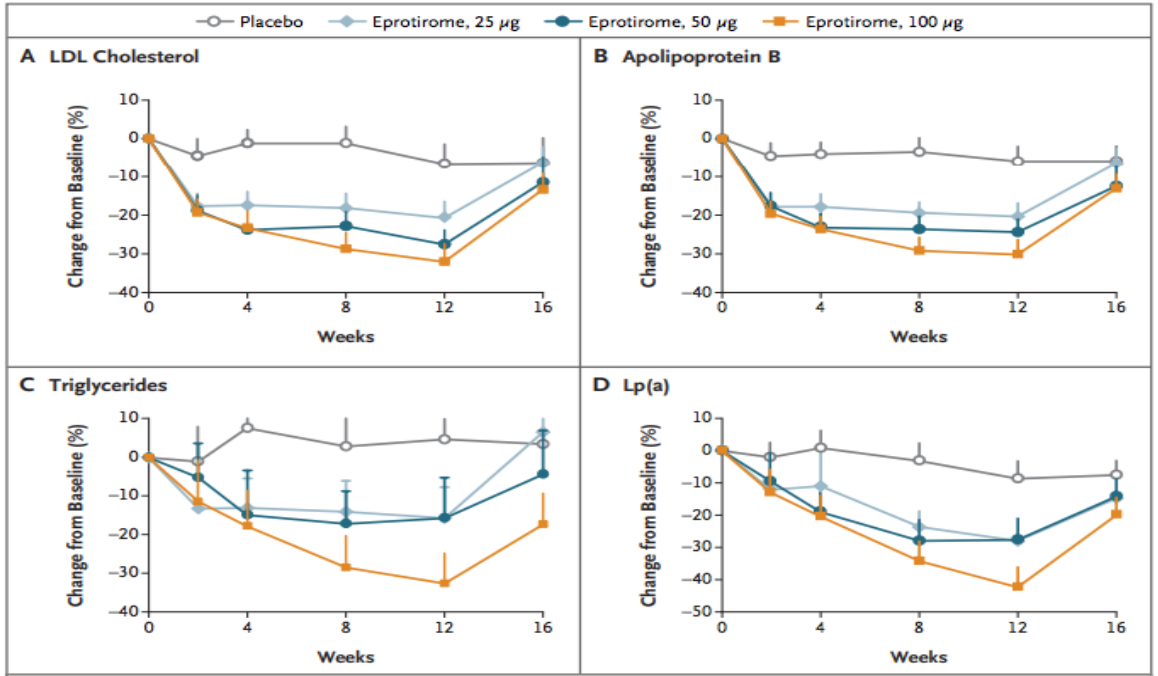

Figure 1. Effects of Eprotirome on Serum Levels of Cholesterol, Lipoproteins, and Triglycerides.

Mean changes in levels of serum low-density lipoprotein (LDL) cholesterol (Panel A), apolipoprotein B (Panel B), triglycerides (Panel C), and Lp(a) lipoprotein (Panel D) over the 16-week study period are shown. The dose of eprotirome was adjusted upward during the first 4 weeks, and the study drug was discontinued after 12 weeks. The bars represent 95% confidence intervals.

- Eprotirome
  - THR-B specific analoge
- Placebo vs Eprotirome at a dose of 25, 50, or 100 μg daily to statin
- LDL mean reduction from baseline, 7%, 22%, 28%, and 32%

Future Area of Research

Thyroid hormone analogues and/or mimetics	Biological effects	Species
L-94901	Lowers cholesterol	Mouse
CGH-509A	Lowers cholesterol	Rat
CGS-23425	Lowers cholesterol	Rat
T-0681	Lowers cholesterol	Mouse
DITPA	Lowers cholesterol	Human
GC-1 (sobetirome)	Lowers cholesterol, triglyceride, blood glucose, adipose tissue and atherosclerosis	Mouse
KB-141	Lowers cholesterol, triglyceride, adipose tissue and blood glucose	Monkey, rat and mouse
KB2115 (eprotirome)	Lowers cholesterol and triglyceride	Human
MGL-3196	Lowers cholesterol and triglyceride	Human
MB07811	Lowers cholesterol, triglyceride and blood glucose	Human
3,5-Diiodothyronine	Lowers blood glucose and triglyceride and improves hepatic insulin resistance	Rat

Take Home Message

- Thyroid hormone defficiency on lipid metabolism may cause:
  - Increased TC, LDL-C; +/- HDL/TG's
  - Decrease LDL-R quantity/activity, LCAT/CEPT, LPL/HL activity
  - Decrease bile acids flow

- Thyroid hormone replacement will
  - Improve TC, LDL-C, +/- TG
  - More important improves RLP-C, RLP-TG's

Muchas Gracias por su Atención!