THYROID DISORDERS: A METABOLIC APPROACH

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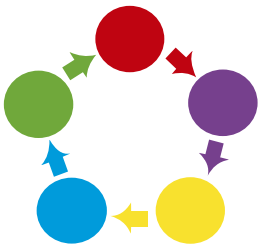
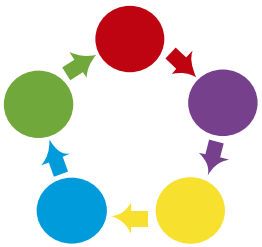


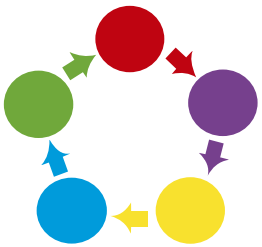
DISCLOSURE

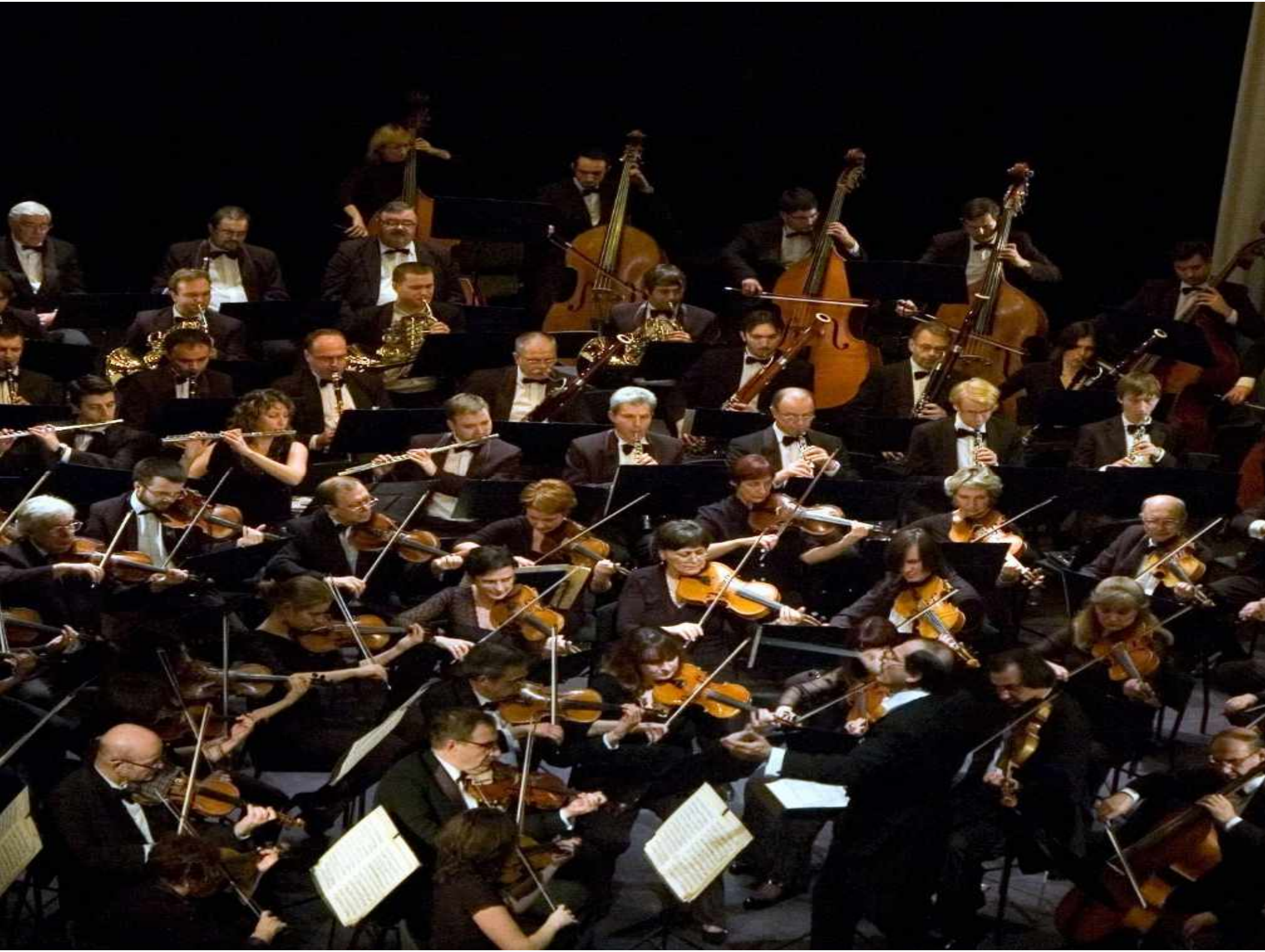
- Disclosure of Financial Relationships:
  - None
- Off-Label Usage
  - None



OBJECTIVES

- Describe normal thyroid function and the HPAT axis
- Review inhibitors and promoters of normal thyroid function
- Explain specific subjective and objective signs, symptoms and physical exam findings
- Review several thyroid conditions and approaches to treat them





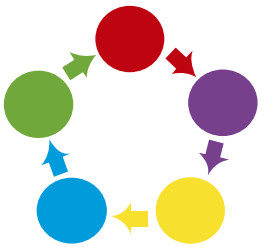
Insulin

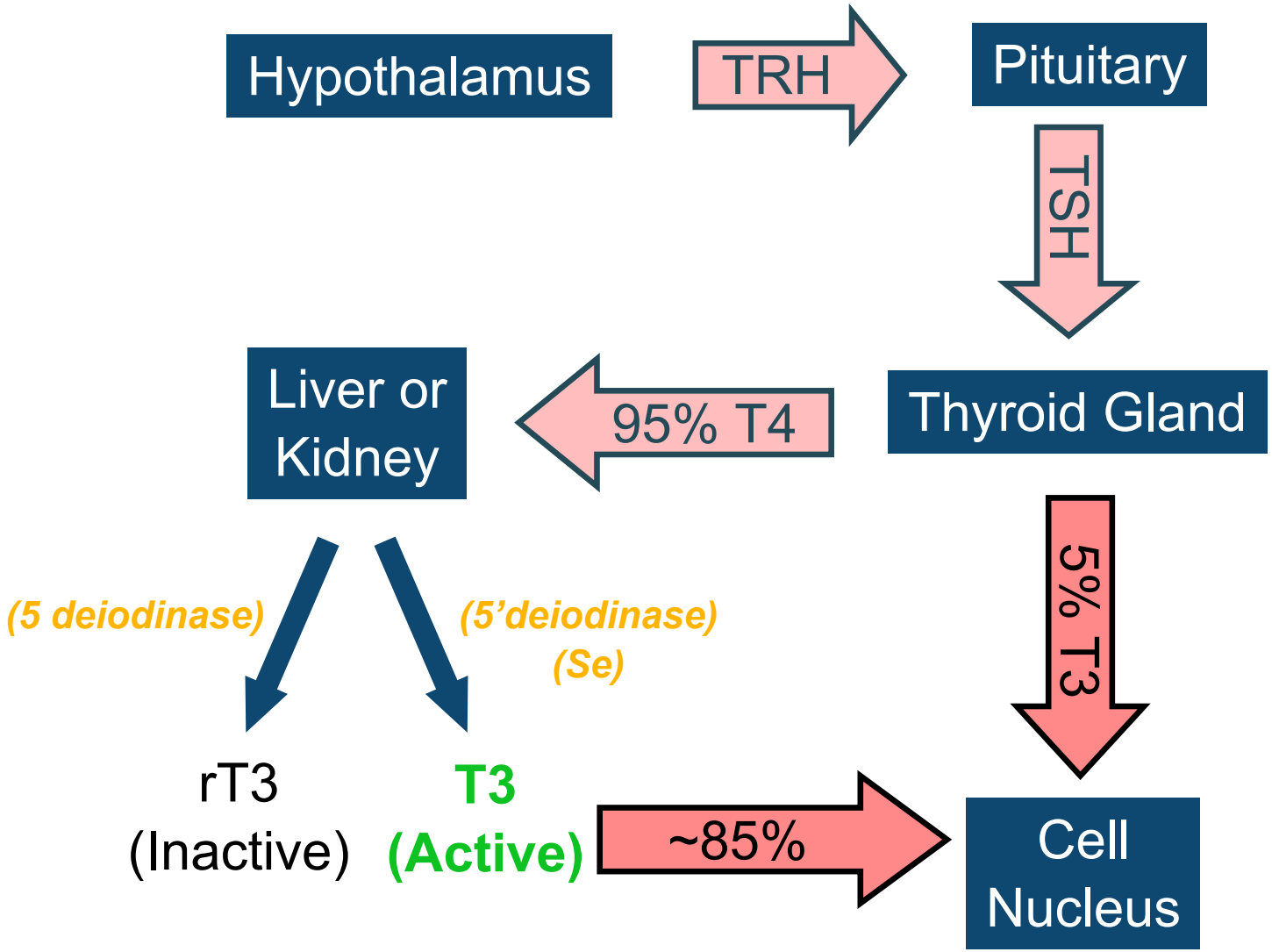
HPA Axis/ Adrenal

Thyroid

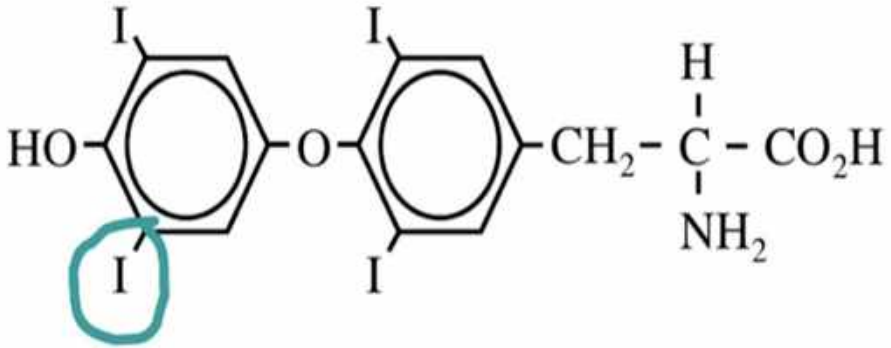
Sex Steroids

WHAT IS NORMAL THYROID FUNCTION?



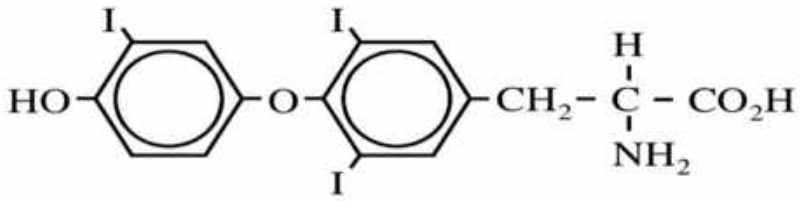

Hypothalamus
TRH
Pituitary
TSH
Thyroid Gland
95% T4
Liver or Kidney
5% T3
(5 deiodinase)
(5'deiodinase) (Se)
rT3 (Inactive)
T3 (Active)
~85%
Cell Nucleus

Thyroxine (T4)
(3,5,3',5' tetraiodo-L-thyronine)



- Derived entirely from the thyroid gland
- Is a pro-hormone

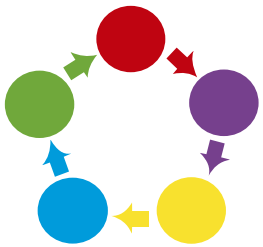
T3 (3,5,3' triiodo-L-thyronine)

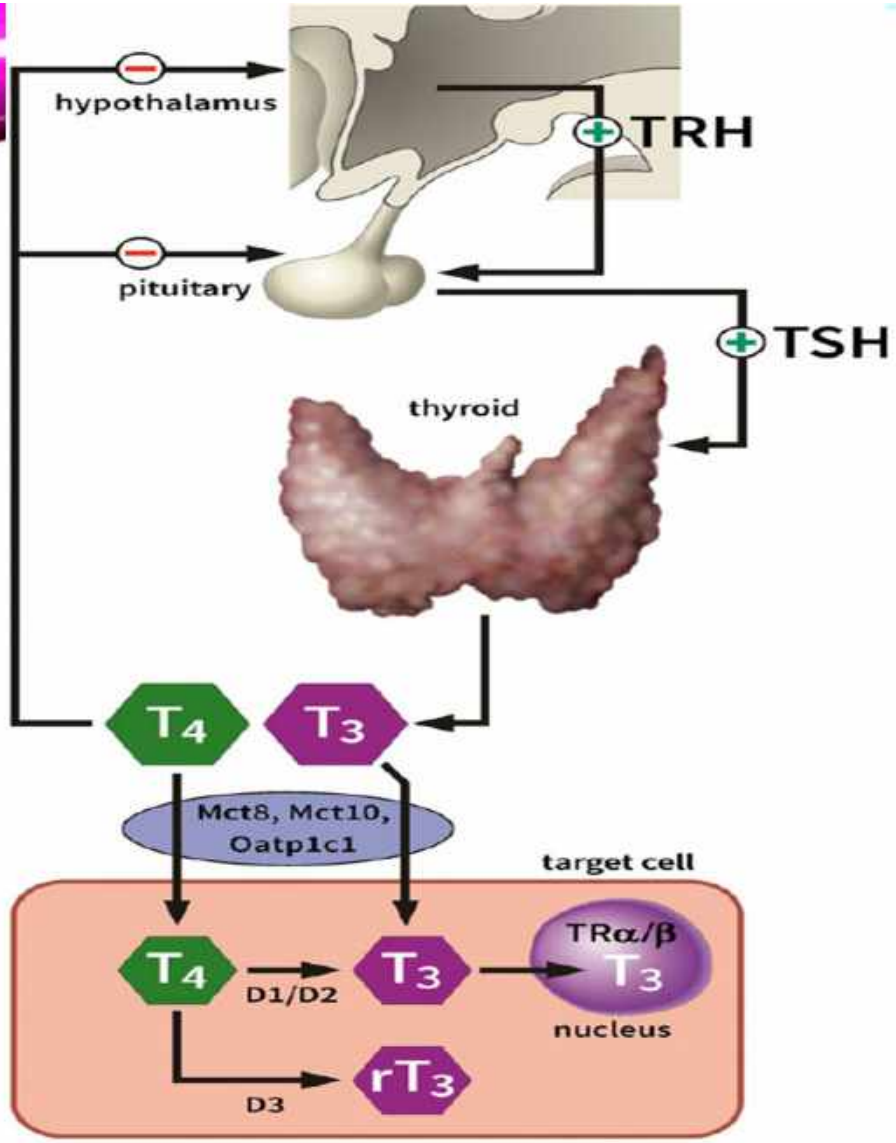


- Is the biologically active thyroid hormone
- 5% of plasma T3 comes from thyroidal secretion
- 95% comes from T4 5'-deiodination in peripheral organs

Thyroid Hormones

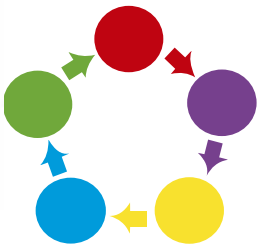
- T4
- T3
- T2
- Calcitonin



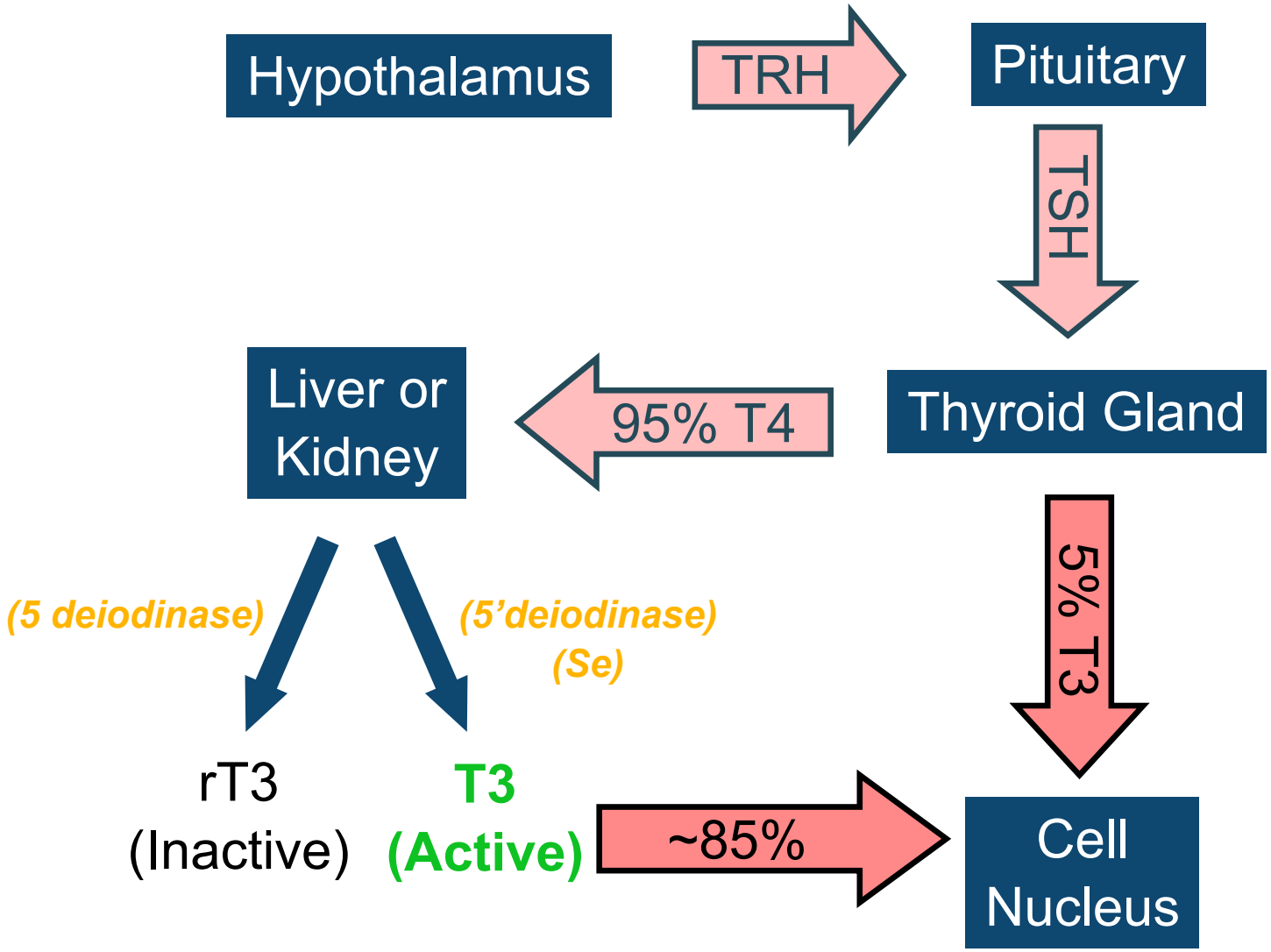


Thyroid hormone physiology. Circulating thyroid hormone concentrations are regulated via a negative feedback system at the level of the hypothalamus and the pituitary. The production of thyroid hormone by the thyroid is regulated by thyroid-stimulating hormone (TSH) produced by the anterior pituitary, which itself is regulated by thyrotropin-releasing hormone (TRH) produced by the hypothalamus. Thyroid hormone circulates as the inactive prohormone thyroxine (T4) and as the active hormone triiodothyronine (T3). Thyroid hormone can only enter target cells by virtue of specific transporters (MCT8, MCT10 and Oatp1c1). In target cells, thyroid hormone can be activated (T4 to T3) or inactivated (T4 to rT3 or T3 to T2) depending on the local activity of specific deiodinases (D1, D2 and D3). Subsequently, active T3 can bind to the nuclear thyroid hormone receptors (TR-alpha and TR-beta) and induce transcription.

https://www.researchgate.net/figure/Thyroid-hormone-physiology-Circulating-thyroid-hormone-concentrations-are-regulated-via_fig1_271592550



REVIEW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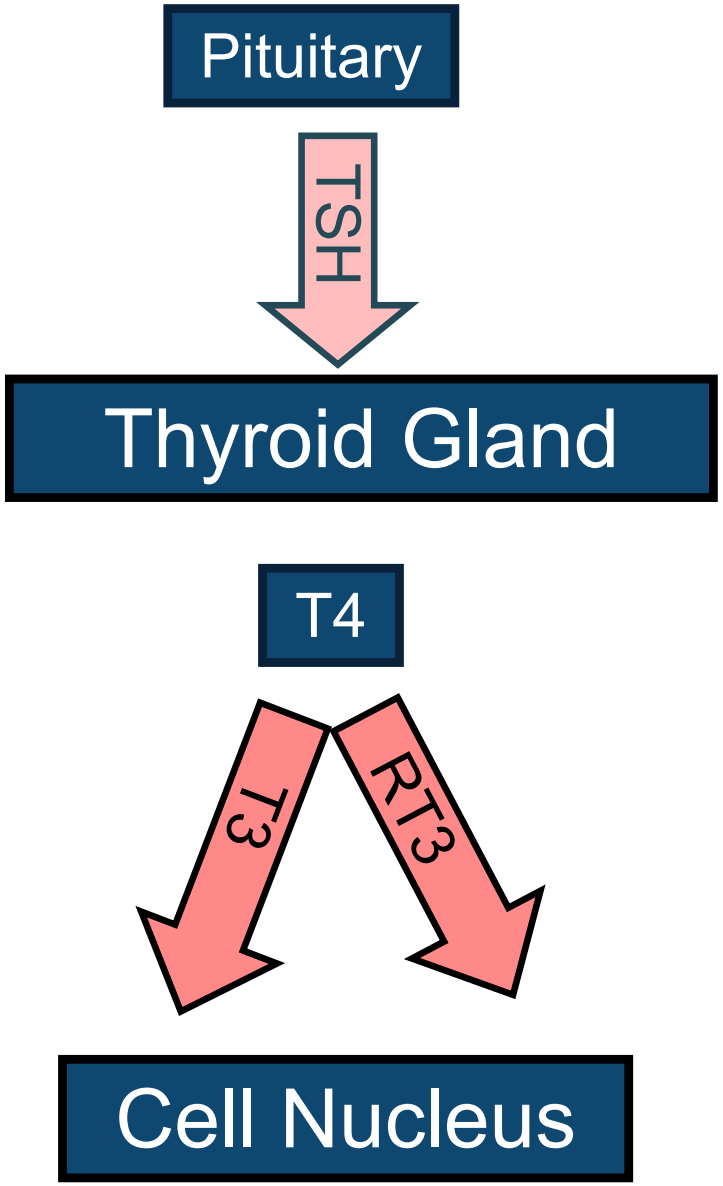
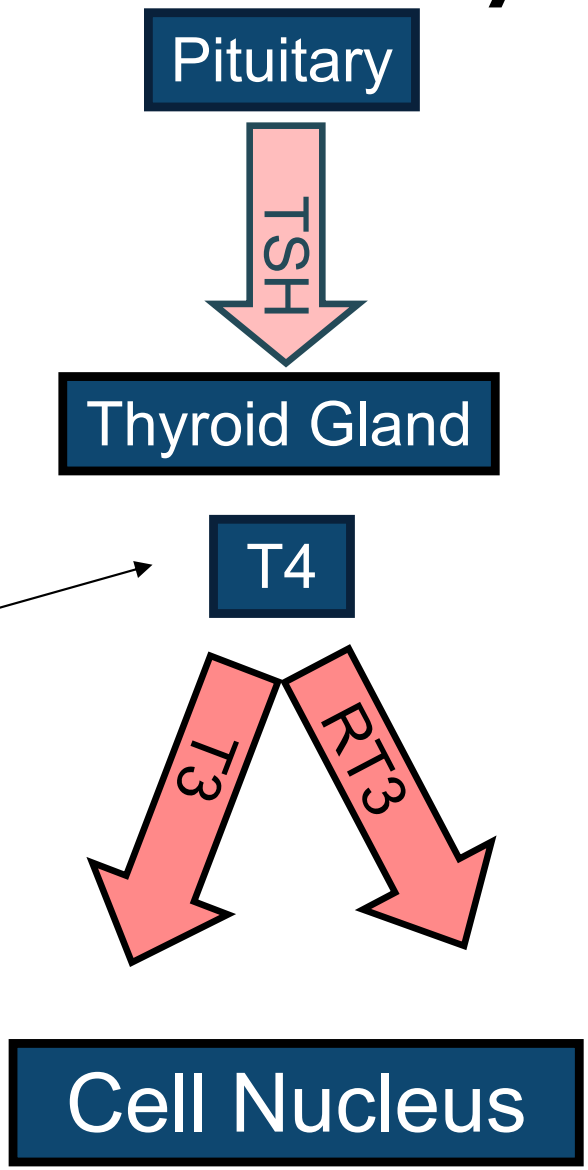
What Effects Thyroid Function?

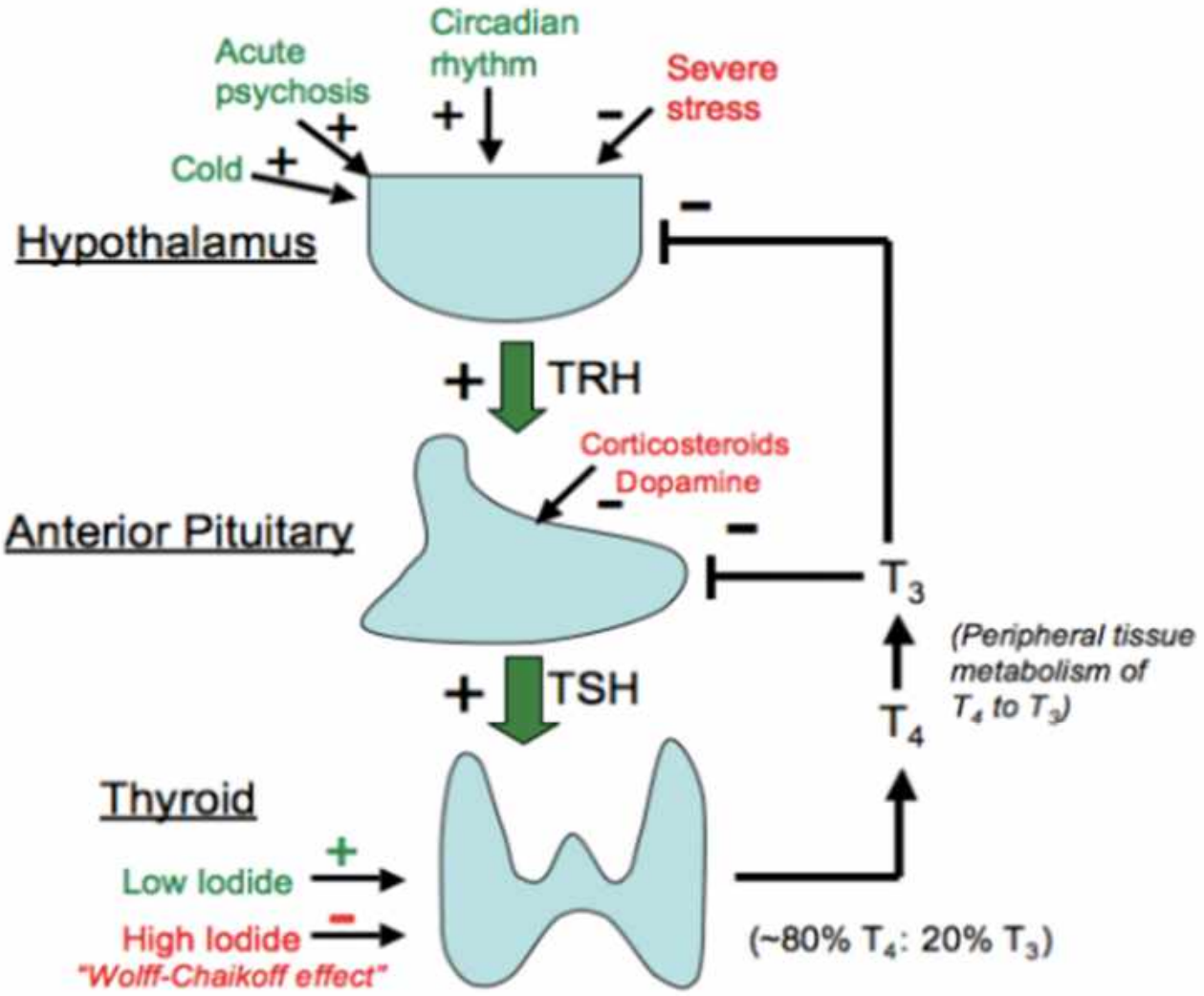


What Effects Thyroid Function: Production of Thyroid Hormones

- Nutrients:
  Iron, iodine, tyrosine, zinc, selenium vitamin E, B2, B3, B6, C, D



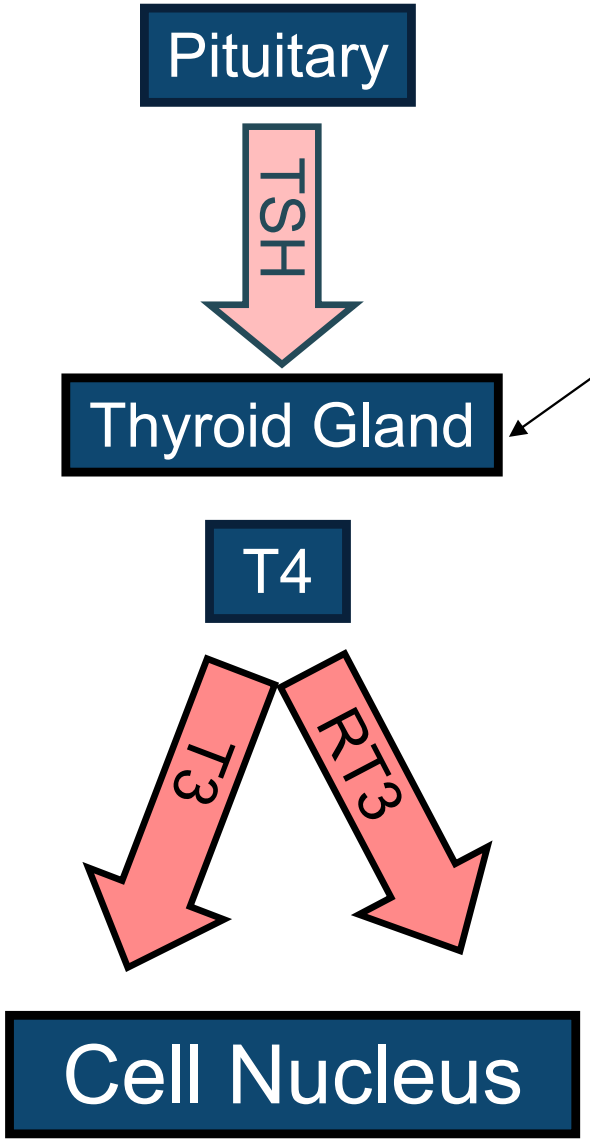
TRH (hypothalamus) => TSH (pituitary) => T4 (thyroid) => T3 (peripheral conversion) => target physiology



Thyroid hormone signaling pathway (source)

https://www.stepwards.com/?page_id=2473

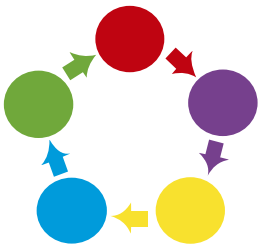
Thyroid Function: Inhibitors of Thyroid Hormone Production:



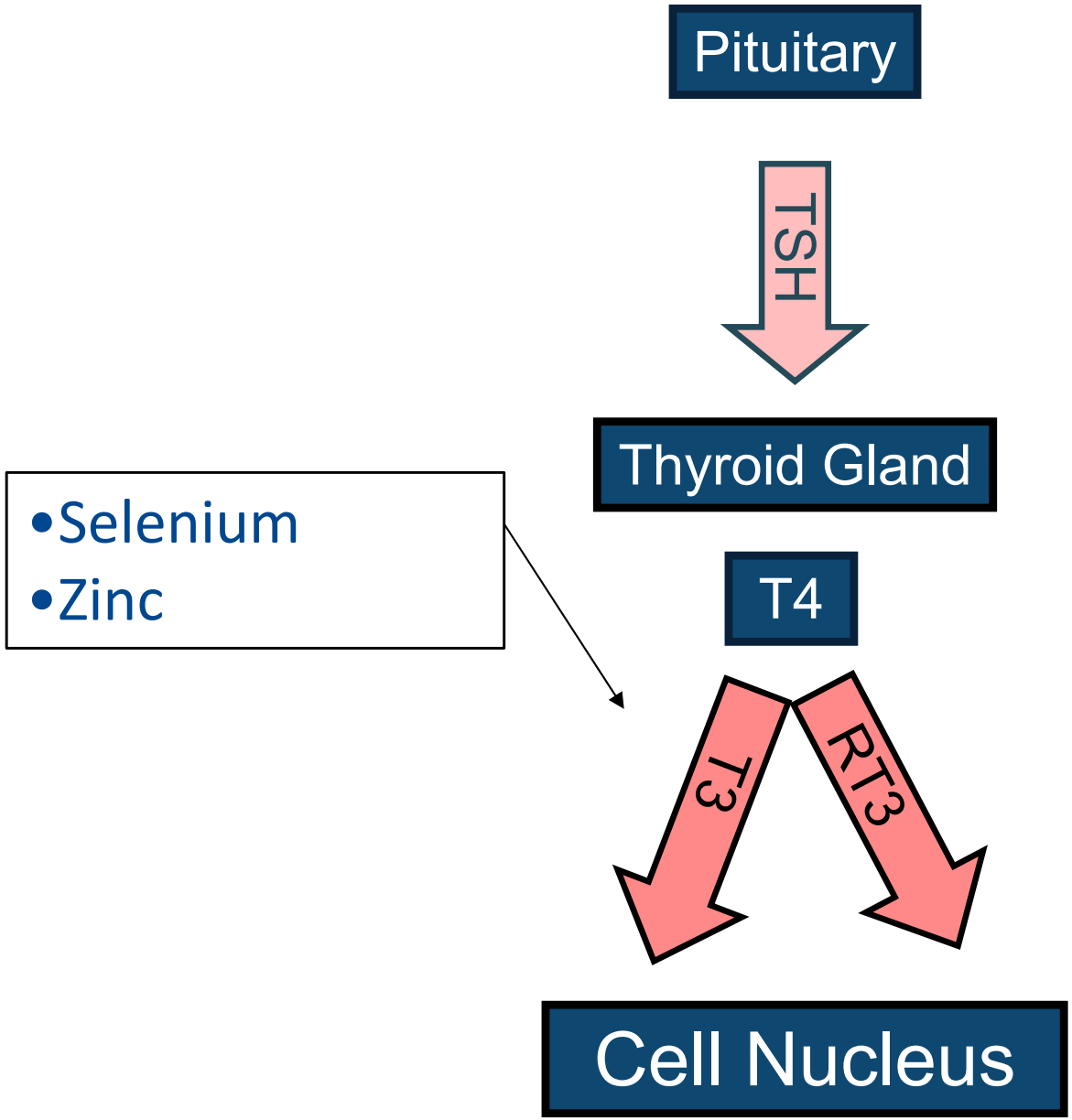
- Stress
- Infection, trauma, radiation, medications
- Fluoride (antagonist to iodine)
- Toxins: pesticides, Hg, Cd, Pb
- Autoimmune disease: celiac
- Selenium deficiency
- Cadmium, mercury, or lead toxicity
- Starvation
- Low protein intake
- High CBO diet
- Elevated cortisol
- Chronic illness
- Decreased kidney or liver function

FACTORS PROMOTING CONVERSION OF T_4 TO T_3

- **Micro-nutrients**
  - Selenium, potassium, iodine, iron, zinc
- **Vitamins**
  - A, E, riboflavin
- **Hormones**
  - Cortisol (physiologic doses)
  - Growth hormone, testosterone
  - Insulin, glucagon, melatonin

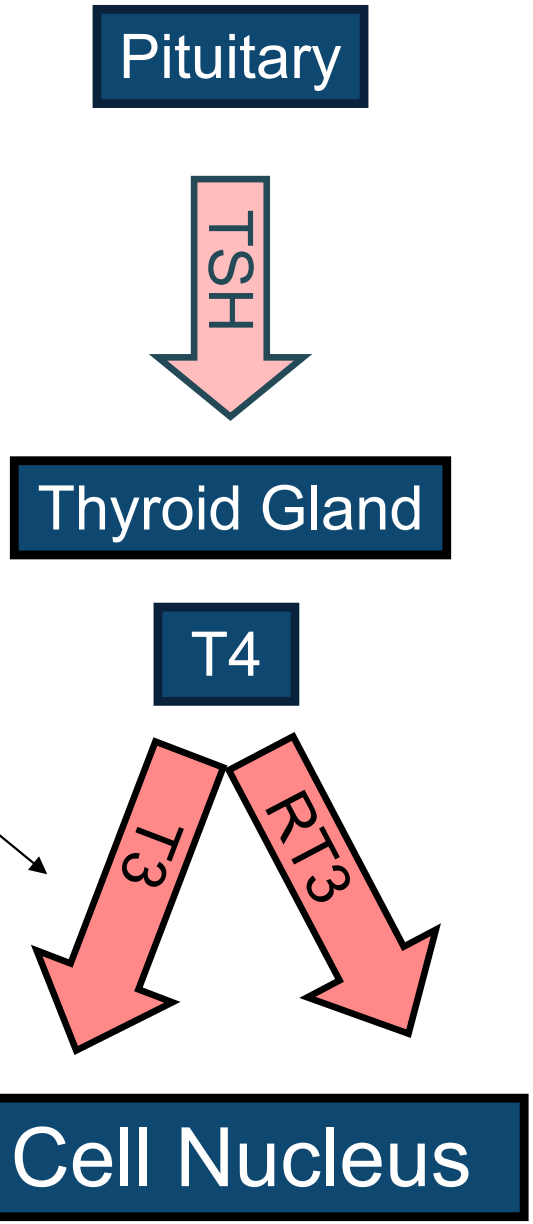


Thyroid Function:
Factors increasing conversion of T4 to T3



Thyroid Function:
Factors Decreasing conversion of T4 to T3

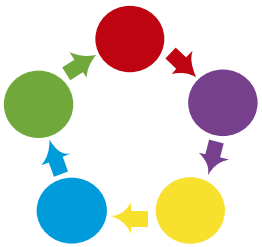
- Stress
- Trauma
- Low-calorie diet
- Inflammation (cytokines, etc.)
- Toxins
- Infections
- Liver/kidney dysfunction
- Rx medications



Rx medications Decreasing T4-T3 Conversion

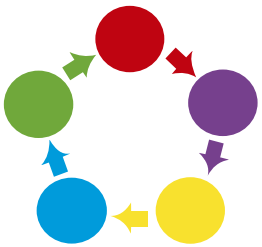
- Beta blockers
- Propranolol
- Birth control pills
- Estrogen
- Lithium
- Phenytoin
- Theophylline
- Chemotherapy

Propranolol and thyroid hormone metabolism, Thyroid. Summer 1991;1(3):273-7. doi: 10.1089

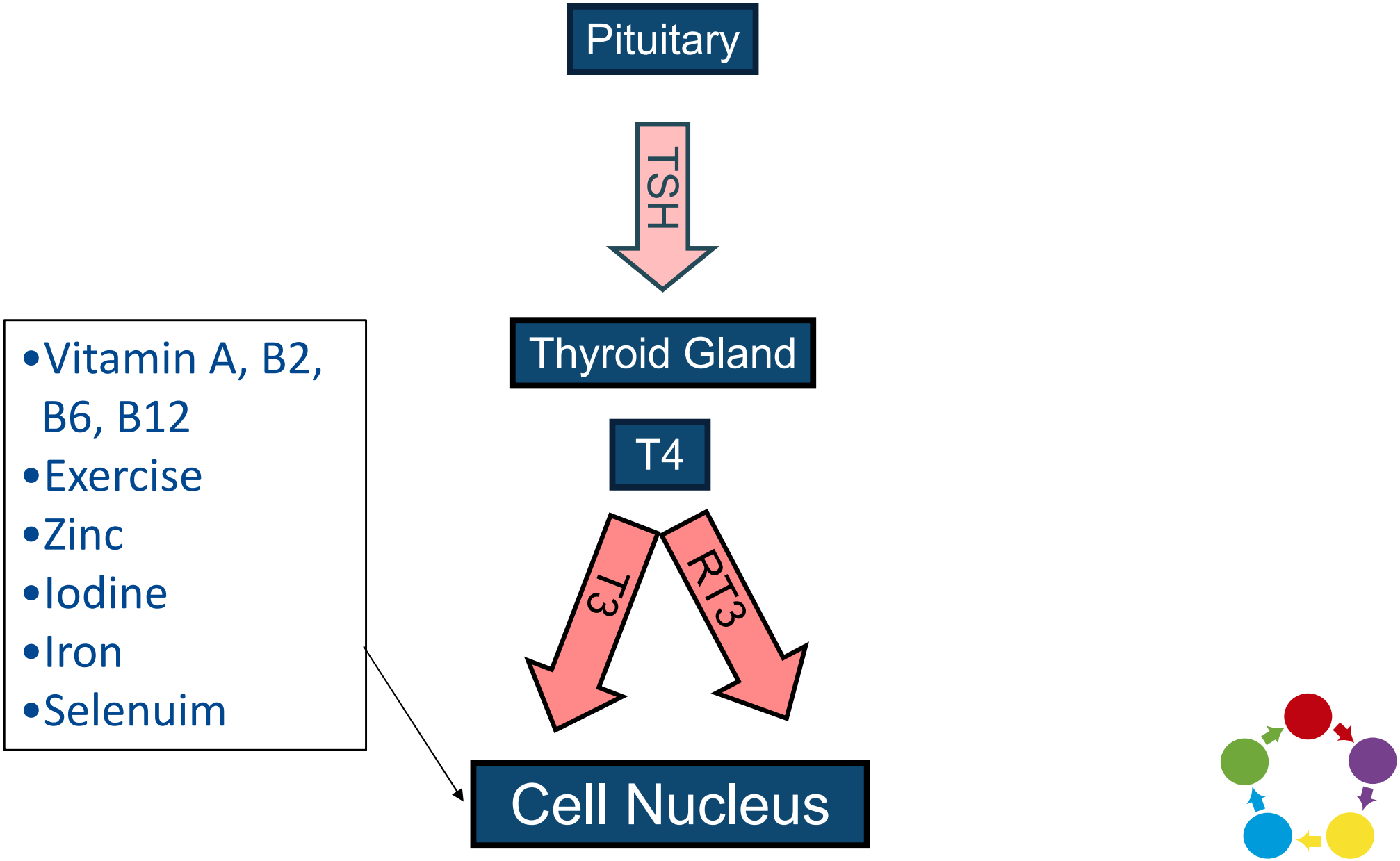


PERIPHERAL REGULATION

- T4 is converted to T3 in the liver or kidney
- T3 binds to nuclear receptors, up regulating metabolism
- 95% of all circulating T3 is of peripheral origin (liver or kidney)

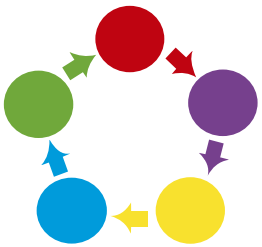


Thyroid Hormones: Factors Improving cellular sensitivity to thyroid hormones

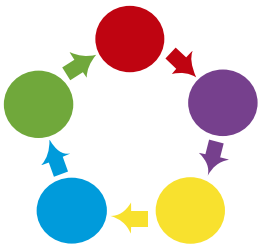


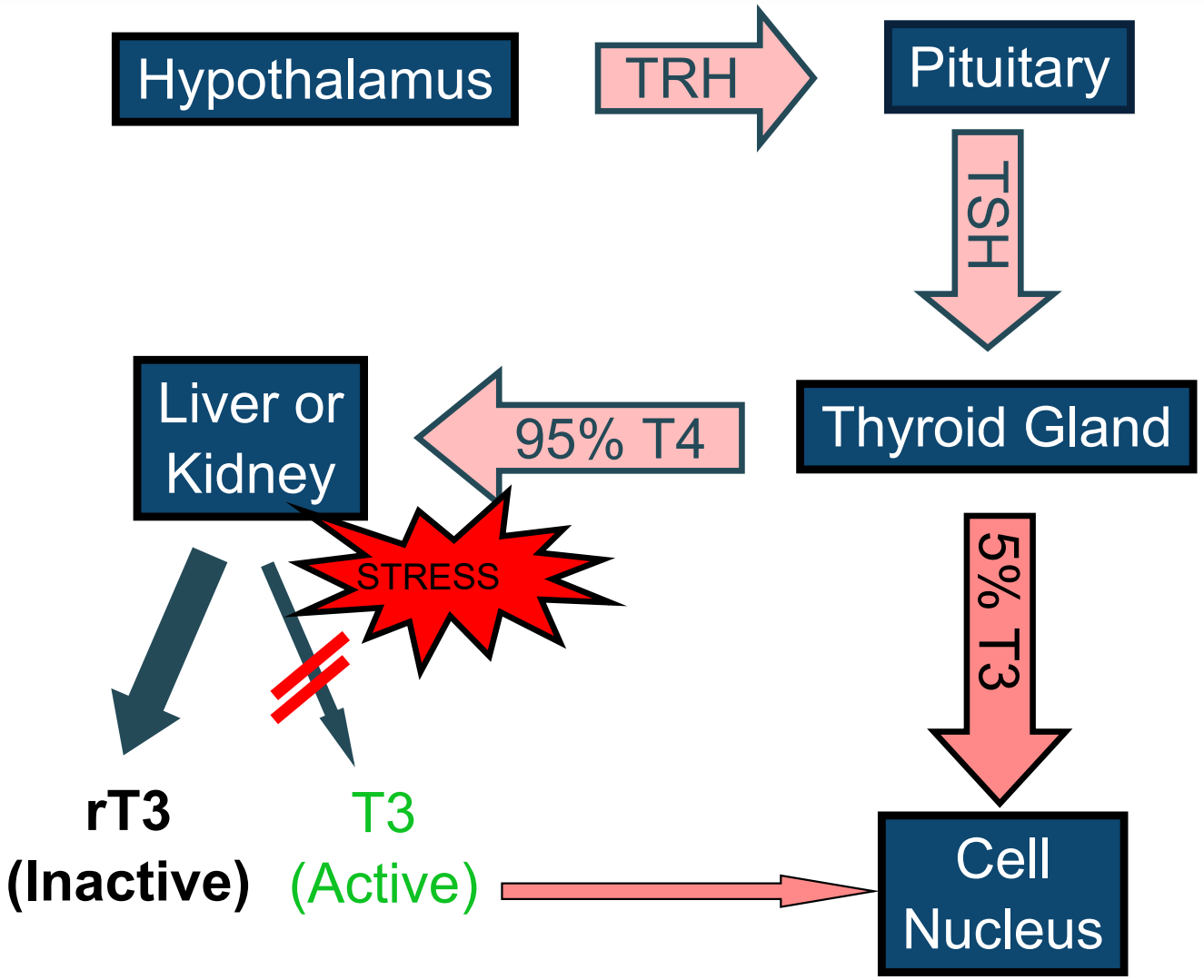
DISRUPTORS OF THYROID FUNCTION

- Food allergy, intolerance or sensitivity
- Infections (i.e. occult)
- Exogenous toxins
  - EDC's, heavy metals, etc.
- Chronic sleep deprivation
- Inflammatory diseases
- Oxidative Stress
- Pharmaceutical Drugs
- Hormone Imbalance
- Acute physical stress
- Diet: ↑ CBO/↓ protein
- Physical trauma
- Autoimmune diseases
- Nutritional insufficiencies
- Nutrient Excesses (Fl, Fe)
- Traumatic emotional events
- Aging
- Changes in gut microbiota
- Altered biotransformation
- Mitochondrial Dysfunction
- Single Nucleotide Polymorphisms (SNP's)



TOXINS AND THE THYROID

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95% T4
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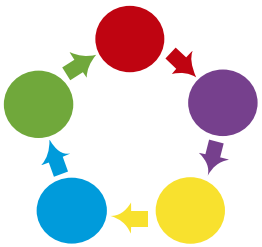
(Inactive)
T3
(Active)
Cell Nucleus

5' –DEIODINASE INHIBITORS

- Excess cortisol, catecholamines
- Selenium deficiency
- Deficient protein, excess sugar diet
- Chronic illness (cytokines, free radicals)
- Compromised liver or kidney function
- Heavy Metal (Cd, Hg, Pb) toxicity
- Herbicides, pesticides
- Endocrine Disruptors
- Polycyclic aromatic hydrocarbons
- Oral contraceptives, other drugs
- Excess estrogen/estrogen dominance

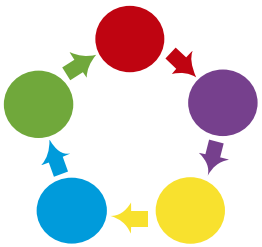


TOXINS CAN BE A PRIMARY TRIGGER

At least 150 industrial chemicals have been shown to result in the reduction in TSH and/or T4.

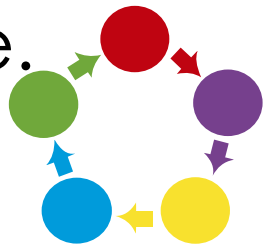
Howdeshell KL. (2002). A model of the development of the brain as a construct of the thyroid system. *Environ Health Perspect,* Jun;110 Suppl 3:337-48

HOW DO TOXINS AND ENDOCRINE DISRUPTORS EFFECTS THYROID FUNCTION?



WHAT ARE ENDOCRINE DISRUPTORS?

- Endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations.
- A **potential endocrine disruptor** is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub) populations.
- In February 2013, UNEP and WHO released the report State of the Science of Endocrine Disrupting Chemicals - 2012 which identifies concerns, including evidence in humans, laboratory animals, and wildlife that exposure to endocrine-disrupting chemicals can result in adverse effects and highlighted that an important focus should be on reducing exposure.

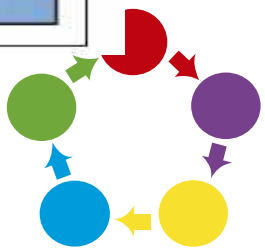


https://www.unenvironment.org/pt-br/node/1190

Table 1. Mechanisms and Effects of Thyroid Disruptors[55,60]

Thyroid Disruptors	Mechanism	Effect
Perchlorates, thiocyanate, nitrate, bromates, phthalates	Blocking uptake of iodide into thyroid cell	Decreased synthesis of T3 and T4
Methimazole, amitrole, soy isoflavones, benzophenone 2	Blocking production of TPO in thyroid follicles	Decreased synthesis of T3 and T4
PCBs, pentachlorophenol, flame retardants, phthalates	Competitive binding to thyroid transport protein (TTR)	Possible effect on fetal brain T4 production
Dioxin, PBDE, chlordane	Altering transport across cell membrane	Increased biliary elimination of T3 and T4
Acetochlor (herbicide), PCBs	Enhanced hepatic metabolism	Increased biliary metabolism of T3 and T4
PCBs, triclosan, pentachlorophenol, dioxin, difuran	Inhibition of sulfation	Decreased sulfation of thyroid hormones leading to possible decrease of peripheral T3 synthesis
FD&C red dye #3, PCBs, octyl-methoxycinnamate	Inhibition of deiodinase activity	Decreased peripheral T3 synthesis
PCBs, bisphenol A, hexachlorobenzene, flame retardants	Altering binding to thyroid receptor	Altered thyroid hormone directed gene transcription
DDT, PCBs	Inhibiting TSH receptor	Decreased production of T3 and T4

Alternative Medicine Review Volume 14, Number 4 2009



International Journal of *Molecular Sciences*

MDPI

Review

Thyroid Disrupting Chemicals

Valeria Calsolaro [1,2], Giuseppe Pasqualetti [1], Filippo Niccolai [1], Nadia Caraccio [1] and Fabio Monzani [1,*]

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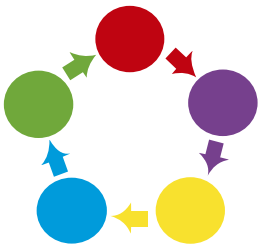
Abstract: Endocrine disruptor compounds are exogenous agents able to interfere with a gland function, exerting their action across different functional passages, from the synthesis to the metabolism and binding to receptors of the hormone produced. Several issues, such as different levels and time of exposure and different action across different ages as well as gender, make the study of endocrine disruptors still a challenge. The thyroid is very sensitive to the action of disruptors, and considering the importance of a correct thyroid function for physical and cognitive functioning, addressing this topic should be considered a priority. In this review, we examined the most recent studies, many of them concentrating on maternal and child exposure, conducted to assess the impact of industrial chemicals which showed an influence on thyroid function. So far, the number of studies conducted on that topic is not sufficient to provide solid conclusions and lead to homogeneous guidelines. The lack of uniformity is certainly due to differences in areas and populations examined, the different conditions of exposures and the remarkable inter-subject variability. Nonetheless, the European

"The thyroid is very sensitive to to the action of disruptors, and considering the importance of a correct thyroid function for physical and cognitive functioning, addressing this topic should be considered a priority."

In fact, a subsequent scientific statement from the Endocrine Society defined the EDC as "an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action" [2]. Mixtures in particular constitute a complex problem; in the late 70s, the production of Polychlorinated Biphenyls (PCB) in the US was banned by the Congress, because commercial mixture of PCB showed a dioxine-like effect [2]. The studies conducted on the matter are mainly concentrated to the exposition to single compounds, or more compounds but separately analyzed, even if the environmental exposure is



Frontiers in Endocrine Disruption: Impacts of Organotin on the Hypothalamus-Pituitary-Thyroid Axis

Ana Paula Santos-Silva [1], Marcelle Novaes Andrade [2], Paula Pereira-Rodrigues [3], Francisca Diana Paiva-Melo [3], Paula Soares [4], Jones Bernardes Graceli [5], Glaecir Roseni Mundstock Dias [1], Andrea Claudia Freitas Ferreira [6], Denise Pires de Carvalho [1], Leandro Miranda-Alves [7]

Affiliations + expand

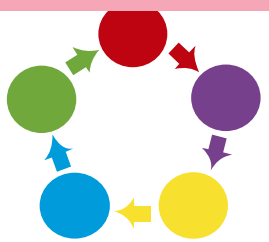
PMID: 28774778 DOI: 10.1016/j.mce.2017.07.038

Abstract

Endocrine disruptors (EDs), chemical substances widely used in industry and

Endocrine disruptors(EDs) are able to interfere with the synthesis, release, transport, metabolism, receptor binding, action or eliminatin of endogenous hormones. EDs bind thyroid hormone receptors.

energy homeostasis, it is crucial to clarify the effects of TBT on the hypothalamus-pituitary-thyroid axis. Therefore, we review herein the main effects of TBT on important metabolic pathways, with emphasis on disruption of the thyroid axis that could contribute to the development of endocrine and metabolic disorders, such as insulin resistance and obesity.



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Environmental Research xxx (xxxx) xxx

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

Association between mixture of persistent organic pollutants and thyroid pathologies in a Belgian population

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[b] Center for Interdisciplinary Research on Medicines (C.I.R.M.), University of Liege (ULg), CHU (B35), 4000, Liege, Belgium
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Keywords
Hyperthyroidism
Hypothyroidism
Endocrine disruptors
Persistent organic pollutants
Mixture effect

ABSTRACT

Previous years, the incidence of autoimmune thyroid diseases has increased worldwide. The presence of many pollutants in the environment suspected to be thyroid disruptors may have contributed to the observed increase. Unfortunately, the results from epidemiological studies assessing the association between pollution and thyroid disorders remain inconsistent, maybe due to a nearly complete neglect of the mixture effect. The blood levels of 12 brominated flame retardants, 3 polychlorinated biphenyls, 16 organochlorine pesticides, 7 perfluoroalkyl substances and 16 phenolic organohalogens were measured in 35 hypothyroid and 44 hyperthyroid volunteers and in 160 individuals from the general population designed as controls. Weighted quantile sum (WQS) regressions were performed to compute indexes representing the mixture of POPs, and we assessed the relations with thyroid disorders. Nineteen pollutants were detected in more than 40% of the individuals and were thus

"The incidence of autoimmune thyroid diseases has increased worldwide. The presence of many pollutants in the environment suspected to be thyroid disruptors may have contributed to the observed increase."

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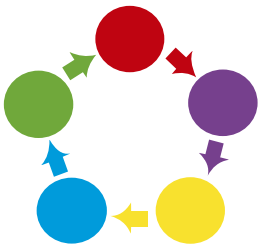
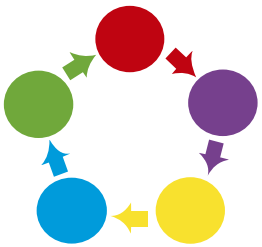


THYROID DISRUPTORS: HEAVY METALS



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Combined effects of cadmium and tetrabromobisphenol a (TBBPA) on development, antioxidant enzymes activity and thyroid hormones in female rats

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ARTICLE INFO

Keywords:
Tetrabromobisphenol A
Cadmium
Co-exposure
Subchronic effect
Rat

ABSTRACT

Tetrabromobisphenol A (TBBPA) is one of the world's most widely used brominated flame retardants (BFRs) and considered as persistent halogenated contaminant. E-wastes contain a range of toxic chemicals, including BFRs and heavy metals, exerting adverse impacts to human health and environment. Nevertheless, comprehensive evaluation on combined toxicity of these co-existing pollutants is limited. This study conducted a subchronic effects of cadmium and TBBPA on the development and antioxidative defense system as well as thyroid functions in female rats through single and combined exposure at environmentally relevant doses for a 20-day consecutive

"This study represents the toxic effects of Cd and TBBPA co-exposure through oral administration in pubertal rats, which may provide useful information for health risk assessment for young exposed individuals."

Cd remain poorly understood.

Heavy metals are also persistent in the environment and could be

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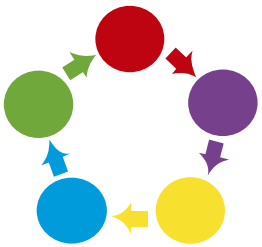

International Journal of *Molecular Sciences*

MDPI

Review

Overview of Cadmium Thyroid Disrupting Effects and Mechanisms

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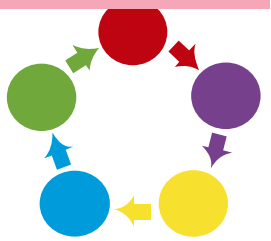
Abstract: Humans are exposed to a significant number of chemicals that are suspected to produce disturbances in hormone homeostasis. Hence, in recent decades, there has been a growing interest in endocrine disruptive chemicals. One of the alleged thyroid disrupting substances is cadmium (Cd), a ubiquitous toxic metal shown to act as a thyroid disruptor and carcinogen in both animals and humans. Multiple PubMed searches with core keywords were performed to identify and evaluate appropriate studies which revealed literature suggesting evidence for the link between exposure to Cd and histological and metabolic changes in the thyroid gland. Furthermore, Cd influence on thyroid homeostasis at the peripheral level has also been hypothesized. Both in vivo and in vitro studies revealed that a Cd exposure at environmentally relevant concentrations results in biphasic Cd dose-thyroid response relationships. Development of thyroid tumors following exposure to Cd has been studied mainly using in vitro methodologies. In the thyroid, Cd has been shown to activate or stimulate the activity of various factors, leading to increased cell proliferation and a

"In the thyroid, Cd has been shown to activate or stimulate the activity of various factors, leading to increased cell proliferation and a reduction in normal apoptotic activity."

The thyroid system plays a pivotal role in the body homeostasis and functioning of the nervous, cardiovascular and reproductive systems, and of body growth control [4–6]; hence, putative thyroid disruptors can cause significant impairments in living organisms. Thyroid function is controlled by the hypothalamic-pituitary-thyroid axis, with the mediation of Thyrotropin-Releasing Hormone (TRH), Thyroid-Stimulating Hormone (TSH), thyroxine (T4), and triiodothyronine (T3). These hormones are



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Sex-specific effects of blood cadmium on thyroid hormones and thyroid function status: Korean nationwide cross-sectional study

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ARTICLE INFO

Keywords:
Cadmium
Endocrine disrupting chemicals
Heavy metal
Hypothyroidism
Thyroid

ABSTRACT

Previous studies on blood cadmium (BCd) and changes in thyroid hormone levels are controversial. We investigated whether thyroid hormone levels and thyroid function status were associated with BCd according to sex in the Korean population. Our study included 1972 participants based on the 2013 Korea National Health and Nutrition Examination Survey (KNHANES) data. Participants whose thyroid-stimulating hormone (TSH) and free thyroxine (fT4) levels were altered physiologically or medically were excluded. Changes in TSH, fT4, and anti-thyroid peroxidase antibody (TPOAb) in men and women were analyzed by different characteristics: age, body mass index (BMI), smoking status, drinking status, BCd, and urine iodine-to-creatinine ratio (UI/Cre). Thyroid function status was classified as hypothyroidism, euthyroidism, and hyperthyroidism as defined by TSH and fT4 levels. Among the total participants, there was a negative correlation between BCd and fT4 ($r = -0.067$, $p = 0.003$). In men ($n = 1057$), fT4 levels decreased with increasing BCd quartile (p-for-trend = 0.002). After adjustment for age, BMI, smoking status, UI/Cre, and TPOAb, the association between BCd and hypothyroidism was significant in men (odds ratio = 1.813, $p = 0.032$) but not in women. These results suggest that cadmium accumulation is closely associated with thyroid dysfunction, and there is a difference in metabolic capacity according to sex.

"These results suggest that cadmium accumulation is closely associated with thyroid dysfunction, and there is a difference in metabolic capacity according to sex."

Abbreviations: BCd, blood cadmium; BMI, body mass index; EDC, endocrine-disrupting chemical; fT3, free T3; fT4, free thyroxine; KNHANES, Korea National Health and Nutrition Examination Survey; OR, odds ratio; SD, standard deviation; T3, triiodothyronine; T4, thyroxine; Tg, thyroglobulin; TGAb, thyroglobulin antibody; TPOAb, anti-thyroid peroxidase antibody; TSH, thyroid-stimulating hormone; UCd, urine cadmium; UI/Cre, urine iodine-to-creatinine ratio; US, United States

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Lead and cadmium exposure, higher thyroid antibodies and thyroid dysfunction in Chinese women☆

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ABSTRACT

Background: Exposure to lead(Pb) or cadmium(Cd) has been related to decreasing thyroxine in many previous studies. The underlying mechanisms have not been clarified. Heavy metal-induced thyroid autoimmunity in pregnant women has been found, despite having been rarely explored in the general population.

Objectives: We aimed to determine whether the blood levels of lead(BPb) or cadmium(BCd) related to the levels of sera antibodies to thyroid proteins and thyroid dysfunction in the general population.

Methods: Our study included 5628 Chinese adults and was based on the 2014 SPECT-China study. Thyroid dysfunction and subclinical thyroid dysfunction were defined by total triiodothyronine (TT3), total thyroxine(TT4) and thyroid stimulating hormone (TSH).Thyroid peroxidase antibody (TPOAb), thyroglobulin antibodies (TGAb). TT3, TT4, and TSH were measured by immunochemiluminometric as-

"In women, BPb and BCd levels were related to higher TSH and hypothyroid status, respectively, suggesting a Pb and Cd induction of sex-biased thyroid autoimmunity."

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and thyroid cancers has increased (McLeod and Cooper, 2012; Chen et al., 2016), and rising TPOAb and TGAb levels are a concern. Although a study on Danish twins demonstrated that genetic factors are approximately 73% responsible for the presence of TPOAb and TGAb (Hansen et al., 2006), the remaining 20%–30% is related to environmental factors and is still worthy of attention.

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Taylor & Francis

Association between arsenic exposure and thyroid function: data from NHANES 2007–2010

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The association of arsenic variables in urine, total arsenic (UAS), arsenobetaine (UAB), dimethylarsinic acid (UDMA), and arsenic adjusted for arsenobetaine (UAAS) with thyroid-stimulating hormone (TSH), free and total serum thyroxine (FT4, TT4), free and total triiodothyronine (FT3, TT3), and thyroglobulin (TGN) was evaluated by analyzing data from 2007–2010 National Health and Nutrition Examination Survey. For iodine deficient males, there was a positive association between TSH and UDMA ($p < 0.01$) and a negative association between the levels of TT4 and UDMA ($p < 0.01$). Levels of UAAS were inversely associated with the levels of TT4 for both iodine-deficient ($p = 0.054$) and iodine-replete females ($p < 0.01$). For iodine-replete females, levels of both TSH and TGN increased with decrease in the levels of both UAB ($p < 0.01$) and UAS ($p < 0.01$). There was also a negative association between TSH and UAB as well as UAS ($p < 0.01$). For iodine-replete males, increased levels of UDMA were associated with decreasing levels of FT4 ($p = 0.03$).

"Consequently, exposure to high levels of arsenic should be a cause for concern since it may disrupt thyroid homeostasis and lead to low levels of FT3, TT3, or TT4."

shown to be associated with urinary cancer (Chen et al. 2010), lung function/cancer (Putila & Guo 2011; Ferreccio et al. 2013; Parvez et al. 2013; Sawada et al. 2013), bladder cancer (Ferreccio et al. 2013), head and neck cancer (Khlifi et al. 2014), peripheral vascular disease (Tseng et al. 1996), and respiratory diseases (Parvez et al. 2010; Dauphine et al. 2011). Cardiovascular effects related to the exposure of arsenic have also been documented (Mumford et al. 2007; Moon et al. 2013). Exposure to arsenic

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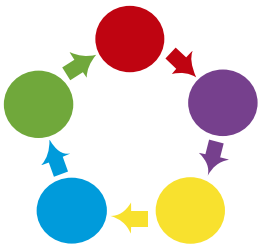

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Thyroid disruption and reduced mental development in children from an informal e-waste recycling area: A mediation analysis

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HIGHLIGHTS

- Median values of Pb, Cd, FT_4 and TSH in Guiyu were higher than that of the reference area.
- Guiyu children had lower cognitive Scores than those in the reference area.
- Pb was negatively correlated with both cognitive and language scores.
- Thyroid disruption isn't involved in the neurotoxicity induced by Pb-Cd co-exposure.

ARTICLE INFO

ABSTRACT

"Results suggest exposure to heavy metal (Pb) reduces cognitive and language skills, and affects thyroid function, but fail to confirm that thyroid disruption is involved in the neurotoxicity induced by PbCd co-exposure."

children has been extensively studied (Chan and Kilby, 2000). The

neonate are quite sensitive to TH, and neurological growth and maturation can be compromised when disruptions in TH occur during fetal development (Zoeller et al., 2002). Studies have also revealed that relatively subtle deficits in circulating levels of TH, in pregnant women, could affect the neurological outcome of children (Ghassabian et al., 2011).

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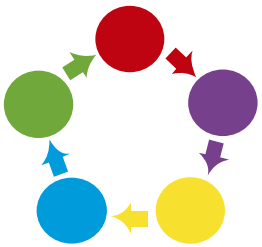

Thyroid Hormones in Relation to Lead, Mercury, and Cadmium Exposure in the National Health and Nutrition Examination Survey, 2007–2008

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Background: Heavy metals, such as lead (Pb), mercury (Hg), and cadmium (Cd), are known toxicants, but their associations with the thyroid axis have not been well quantified at U.S. background levels.

Objectives: We investigated the relationships between thyroid hormones (total and free thyroxine [TT_4 and FT_4], total and free triiodothyronine [TT_3 and FT_3], thyroid-stimulating hormone [TSH], and thyroglobulin [Tg]) and levels of Pb, Hg, and Cd in blood and Cd in urine.

Methods: We separately analyzed a sample of 1,109 adolescents (12–19 years of age) and a sample of 4,409 adults from the U.S. National Health and Nutrition Examination Survey (NHANES) 2007–2008. We estimated associations after adjusting for age, sex, race, urinary iodine, body mass index, and serum cotinine.

Results: The geometric mean (GM) levels of blood Pb (BPb), total Hg, and Cd were 0.81 μg/dL, 0.47 μg/L, and 0.21 μg/L in adolescents and 1.43 μg/dL, 0.96 μg/L, and 0.38 μg/L in adults, respectively. The GMs of urinary Cd were 0.07 and 0.25 μg/g creatinine in adolescents and adults, respectively. No consistent pattern of metal and thyroid hormone associations was observed in adolescents. In adults, blood Hg was inversely related to TT_4, TT_3, and FT_3 and urinary Cd was positively associated with TT_4, TT_3, FT_3, and Tg, but there were no associations with Pb. Associations were relatively weak at an individual level, with about 1–4% change in thyroid hormones per interquartile range increase in Hg or Cd.

Conclusions: Our analysis suggests an inverse association between Hg exposure and thyroid hormones, and a positive association between Cd exposure and thyroid hormones in adults.

Key words: cadmium, heavy metals, lead, mercury, thyroid hormones. *Environ Health Perspect* 121:181–186 (2013). http://dx.doi.org/10.1289/ehp.1205239 [Online 16 November 2012]

Thyroid hormones (THs) play a critical role in the functions of nervous, reproductive, and cardiovascular systems in both children and adults (Danzi and Klein 2012; Williams 2008; Yazbeck and Sullivan 2012). The hypothalamus–pituitary–thyroid (HPT) axis regulates thyroid function through thyrotropin releasing hormone, thyroid-stimulating hormone (TSH), and the THs [thyroxine (T_4) and triiodothyronine (T_3)]. Circulating

development (Ghassabian et al. 2011; Pop et al. 2003), blood pressure (Asvold et al. 2007), cholesterol, triglycerides, and insulin resistance (Roos et al. 2007).

Environmental chemicals might alter TH levels via several mechanisms, including disruption of iodine (I) transport, thyroid peroxidase, TH-binding proteins, hepatic catabolism, deiodinases, and receptor binding (Miller et al. 2009). Studies of human populations have focused primarily on chemicals that are structurally similar to T_4, such as polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers, and bisphenol A (BPA), with little attention on heavy metals (Boas et al. 2006; Pearce and Braverman 2009). Lead (Pb), mercury (Hg), and cadmium (Cd) are known environmental toxicants, but only a few studies

patients (Zheng et al. 2001). Previous studies of populations with high exposure to Pb (indicated by BPb levels of > 20 μg/dL) suggested negative associations with circulating T_4, FT_4, or T_3 (López et al. 2000; Robins et al. 1983; Singh et al. 2000; Tuppurainen et al. 1988); however, associations were not evident in other similar study populations (Erfurth et al. 2001; Schumacher et al. 1998; Siegel et al. 1989). Fewer studies have investigated associations of BPb levels of < 10 μg/dL with THs. Dundar and colleagues reported a negative association between BPb and FT_4 levels in adolescents with mean BPb of 7 μg/dL (Dundar et al. 2006). A recent study (Meeker et al. 2009) has suggested an inverse association between BPb (median, 1.5 μg/dL) and TSH levels in men of the couples presenting at infertility clinics. Another study, in the lakeside communities of Quebec, Canada, found no association between BPb (median, 3.1 μg/dL) and THs in men, but identified a positive association with T_3 and an inverse association with TSH in females with median BPb of 1.7 μg/dL (Abdelouahab et al. 2008).

Hg has adverse effects on a variety of systems that vary with the level, length of exposure, and time window of exposure (Tan et al. 2009). Proposed mechanisms of Hg-related TH disruption involve selective binding to sulfhydryl (SH)-containing ligands in the thyroid, reduced TSH production, and inhibition of deiodination (Soldin et al. 2008; Tan et al. 2009). FT_3 levels were reduced in association with occupational exposure to Hg vapor among chloralkali plant workers (Barregard et al. 1994; Ellingsen et al. 2000). Studies of populations with environmental exposure, for example, from fish consumption and from dental amalgams, have had mixed findings (Abdelouahab et al. 2008; Meeker et al. 2009; Schell et al. 2008; Takser et al. 2005). A study in a Canadian lakeside community with

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Supplemental Material is available online (http://dx.doi.org/10.1289/ehp.1205239).

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The authors declare they have no actual or potential competing financial interests.

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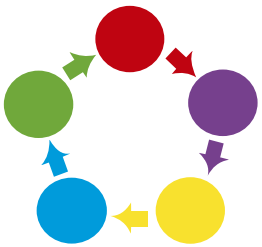
"Our analysis suggests an inverse association between Hg exposure and thyroid hormones in adults."



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Review

Children with health impairments by heavy metals in an e-waste recycling area

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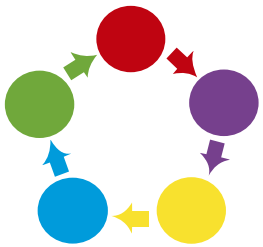
HIGHLIGHTS GRAPHICAL ABSTRACT

Heavy metals derived from electronic waste (e-waste), such as, Pb, Cd), Cr, Mn, Ni, Hg, As, Cu, Zn, Al and cobalt (Co), influence a number of diverse systems and organs, resulting in both acute and chronic effects on children's health, ranging from minor upper respiratory irritation to chronic respiratory, cardiovascular, nervous, urinary and reproductive disease, as well as aggravation of pre-existing symptoms and disease.

DISRUPTORS OF THYROID FUNCTION

- Food allergy, intolerance or sensitivity
- Infections (i.e. occult)
- Exogenous toxins
  - EDC's, heavy metals, etc.
- Chronic sleep deprivation
- Inflammatory diseases
- Oxidative Stress
- Pharmaceutical Drugs
- Hormone Imbalance
- Acute physical stress
- Diet: ⇑ CBO/↓ protein
- Physical trauma
- Autoimmune diseases
- Nutritional insufficiencies
- Nutrient Excesses (Fl, Fe)
- Traumatic emotional events
- Aging
- Changes in gut microbiota
- Altered biotransformation
- Mitochondrial Dysfunction
- Single Nucleotide Polymorphisms (SNP's)



Alternative Medicine Review Volume 14, Number 4 2009

Thyroid Disruption: Mechanisms and Clinical Implications in Human Health

Lyn Patrick, ND

Abstract

Exposure to specific environmental toxins, including polychlorinated biphenyls, dioxins, phthalates, polybrominated diphenyl ethers (PBDEs), and other halogenated organochlorines, has been shown to interfere with the production, transportation, and metabolism of thyroid hormones by a variety of mechanisms. A broad range of chemicals, with structural similarity to thyroid hormone, have been shown to bind to thyroid receptors with both agonist and antagonist effects on thyroid hormone signaling. The incidence of thyroid disease in the United States, particularly for thyroid cancer and thyroid

in the last two decades on the relationship between environmental exposure to a specific class of chemicals and its effects on the endocrine and nervous system. Chemicals that affect thyroid metabolism, either through the hypothalamic-pituitary axis or directly via nuclear receptors, are termed "thyroid disruptors" (TD). A review of at least 150 industrial chemicals summarizes the evidence in animal studies that these chemicals can cause a reduction in thyroid-stimulating hormone (TSH) as well as thyroxine.[2] An extensive review by Brucker-Davis cites 381 wildlife and experimental animal and human studies analyzing the effects of specific drugs and chemicals on thyroid metabolism and subsequent neurodevelopmental and endocrine effects in offspring and children.[3]

Evidence linking polychlorinated biphenyls

"Chemicals effect thyroid metabolism through HP axis or directly via nuclear receptors are termed thyroid disruptors (TD). At least 150 industrial chemicals cause a reduction in TSH as well as thyroxine. "

which through environmental or inappropriate developmental exposures alter the hormonal and homeostatic systems that enable the organism to communicate with and respond to its environment." The statement is a response to the large body of evidence accumulated

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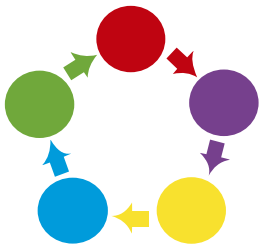

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Review

Microbiome impact on metabolism and function of sex, thyroid, growth and parathyroid hormones

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Commensal bacteria and their genes associated with host are known as microbiome. In recent years, microbial influence on host endocrine system has been under detailed investigation. The role of microbiome in the pathogenesis of insulin resistance and obesity, the function of hypothalamic-pituitary-adrenal axis and secretion of hormones regulating appetite is well described in world literature. In this article we discuss poorly reviewed issues: the microbiome role in modulation of non-peptide (sex and thyroid) and peptide (growth hormone and parathyroid hormone) functions. Understanding complex bidirectional relations between host endocrine system and bacteria is of fundamental importance to understanding microbial impact on host reproduction, risk of endocrine-related cancers, pathogenesis of non-thyroidal illness syndrome, growth failure in children and hormonal changes during chronic kidney disease. This article also highlights effects of dietary compounds on microbiome composition and bacterial enzymes activity, and thus host hormonal status.

Key words: microbiome, lipopolysaccharide, estrogens, thyroid hormones, growth hormone

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pituitary-adrenal axis have been published (Sudo *et al.*, 2004; Gao *et al.*, 2009; Vrieze *et al.*, 2010; Burcelin *et al.*, 2011; Zimomra *et al.*, 2011; Holzer *et al.*, 2012; Norris *et al.*, 2013). In this review, we focus on less well described issues: the microbiome role in modulation of non-peptide (sex and thyroid) and peptide (growth hormone - GH and parathyroid hormone — PTH) functions.

In animals, bacteria influence their endocrine system *via* various mechanism, i.e. intestinal metabolism of bile-excreted hormones, intestinal conversion of exogenous molecules to endocrine-active derivatives, production/release of endocrine-active molecules like short chain fatty acids (SCFAs) and lipopolysaccharide (LPS). The first way concerns steroid and thyroid hormones, which are metabolized in the liver and excreted with bile. A large number of intestine bacteria are capable of hydrolysis of hormone conjugates and afterward modify chemical structure of free molecules. Another important aspect concerns the ability of microorganisms associated with plants to produce phytohormones and hormone-like substances, which may modify host metabolism (Tsavkelova *et al.*, 2006).

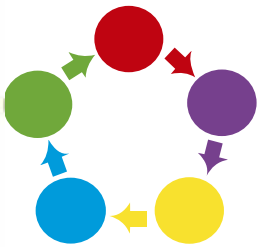
"human-microbiome superorganism" also in hormonal system. Microbes sense and react for example to host adrenaline, noradrenaline, triiodothyronine and sex hormones, which changes their metabolism, growth and virulence (Sperandio *et al.*, 2003; Hughes & Sperandio, 2008; García-Gómez *et al.*, 2013). In turn, many reviews and original papers analyzing the influence of microbiota on hormones regulating appetite, insulin sensitivity, pathogenesis of diabetes and obesity and hypothalamic–

or other microbiomes, such as *Eubacterium lentum*, Bac-

✉e-mail: jawit@gumed.edu.pl

Abbreviations: E2, estradiol; EHC, enterohepatic circulation; GH, growth hormone; hCG, human chorionic gonadotropin ; hPL, human placental lactogen ; HSD, hydroxysteroid dehydrogenase; IL, interleukin; LBP, LPS-binding protein; LPS, lipopolysaccharide; P4, progesterone; PAH, polycyclic aromatic hydrocarbons; PTH, parathyroid hormone; SCFA, short chain fatty acid; T, testosterone; TLR, Toll-like receptor

The microbiome has a role in metabolism of bile excreted hormones such as thyroid hormones which are metabolized in the liver and excreted in the bile.



nutrients

MDPI

Review

Celiac Disease and Glandular Autoimmunity

George J. Kahaly [1,*], Lara Frommer [1] and Detlef Schuppan [2,3]

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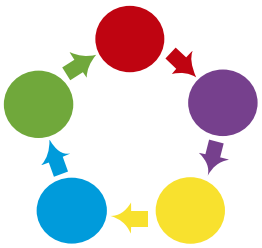
Abstract: Celiac disease is a small intestinal inflammatory disease with autoimmune features that is triggered and maintained by the ingestion of the storage proteins (gluten) of wheat, barley, and rye. Prevalence of celiac disease is increased in patients with mono- and/or polyglandular autoimmunity and their relatives. We have reviewed the current and pertinent literature that addresses the close association between celiac disease and endocrine autoimmunity. The close relationship between celiac disease and glandular autoimmunity can be largely explained by sharing of a common genetic background. Further, between 10 and 30% of patients with celiac disease are thyroid and/or type 1 diabetes antibody positive, while around 5–7% of patients with autoimmune thyroid disease, type 1 diabetes, and/or polyglandular autoimmunity are IgA anti-tissue transglutaminase antibody positive. While a gluten free diet does not reverse glandular autoimmunity, its early institution may delay or

"Patients with CeD show a high prevalence of glandular autoimmune disorders. CeD is associated with T1D, AITD i.e., Hashimoto's thyroiditis (HT), Graves' disease (GD), and the polyglandular autoimmune syndrome (PAS)."

autoimmune diseases, prominently with autoimmune thyroid disease (AITD) and type 1 diabetes mellitus (T1D), but also rheumatoid diseases including systemic lupus erythematodes, Sjoegren's syndrome, autoimmune liver diseases, and others [5]. Severe complications, like refractory CeD type 2, a premalignant condition, and overt enteropathy-associated T-cell lymphoma, occur in patients with longstanding undetected and untreated CeD, but remain rare [6,7]. Iron, zinc, vitamin D, vitamin B12, or folic acid deficiency, iron deficiency or overt anemia are the most common laboratory finding.



Filis et al. BMC Medicine (2018) 16:194
https://doi.org/10.1186/s12916-018-1183-7

BMC Medicine

RESEARCH ARTICLE Open Access

Maternal smoking and high BMI disrupt thyroid gland development

Panagiotis Filis[1*], Sabine Hombach-Klonisch[3], Pierre Ayotte[4], Nalin Nagrath[1], Ugo Soffientini[2], Thomas Klonisch[3], Peter O'Shaughnessy[2] and Paul A. Fowler[1]

Abstract

Background: Maternal lifestyle factors, including smoking and increased body weight, increase risks of adult diseases such as metabolic syndrome and infertility. The fetal thyroid gland is essential for the control of fetal metabolic rate, cardiac output, and brain development. Altered fetal thyroid function may contribute to increased disease onset later in life. Here, we investigated the impact of maternal smoking and high maternal weight on human fetal thyroid function during the second trimester.

Methods: Thyroid glands and plasma were collected from fetuses electively terminated in the second trimester (normally progressing pregnancies). Plasma total triiodothyronine (T3) and total thyroxine (T4) were measured by solid-phase extraction-liquid chromatography-tandem mass spectrometry. Fetal plasma thyroid-stimulating hormone (TSH) levels were measured using a multiplex assay for human pituitary hormones. Histology and immunolocalization of thyroid developmental markers were examined in thyroid sections. Transcript levels of developmental, functional, apoptotic, and detoxification markers were measured by real-time PCR. Statistical analyses were performed using multivariate linear regression models with fetal age, sex, and maternal smoking or maternal body mass index (BMI) as covariates.

Results: Maternal smoking was associated with significant changes in fetal plasma T4 and TSH levels during the

"For the first time, we show that maternal BMI are associated with disturbed fetal thyroid gland development and endocrine function in a sex-specific manner during the second trimester. These findings suggest that predisposition to post-natal disease is mediated, in part, by altered fetal thyroid gland development."

Bone Research (2013) 2: 146-161.
www.boneresearch.org

REVIEW

Role and Mechanisms of Actions of Thyroid Hormone on the Skeletal Development

Ha-Young Kim[1,2,3], Subburaman Mohan[1,2]*

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The importance of the thyroid hormone axis in the regulation of skeletal growth and maintenance has been well established from clinical studies involving patients with mutations in proteins that regulate synthesis and/or actions of thyroid hormone. Data from genetic mouse models involving disruption and overexpression of components of the thyroid hormone axis also provide direct support for a key role for thyroid hormone in the regulation of bone metabolism. Thyroid hormone regulates proliferation and/or differentiated actions of multiple cell types in bone including chondrocytes, osteoblasts and osteoclasts. Thyroid hormone effects on the target cells are mediated via ligand-inducible nuclear receptors/transcription factors, thyroid hormone receptor (TR) α and β, of which TRα seems to be critically important in regulating bone cell functions. In terms of mechanisms for thyroid hormone action, studies suggest that thyroid hormone regulates a number of key growth factor signaling pathways including insulin-like growth factor-I, parathyroid hormone related protein, fibroblast growth factor, Indian hedgehog and Wnt to influence skeletal growth. In this review we describe findings from various genetic mouse models and clinical mutations of thyroid hormone signaling related mutations in humans that pertain to the role and mechanism of action of thyroid hormone in the regulation of skeletal growth and maintenance.

Keywords: thyroid hormone; bone; cartilage; growth factors; bone cells

Bone Research (2013) **2**: 146-161. doi: 10.4248/BR201302004

Introduction

considerable evidence regarding the importance of TH in skeletal development, the molecular mechanisms of

There is a key role for thyroid hormone in the regulation of bone metabolism.

short stature and craniosynostosis (3). Although there is

Systemic TH levels are maintained by the classical negative feedback loop involving the hypothalamus-pituitary--thyroid (HPT) axis (Figure 1). Thyrotropin releasing hormone (TRH) is synthesized in the paraventricular nucleus (PVN) of the hypothalamus and stimulates synthesis and secretion of thyroid stimulating hormone (TSH) from

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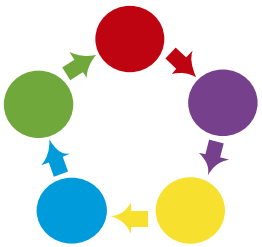

Endocrine Journal 2021, 68 (2), 129-136

REVIEW

Thyroid complications of SARS and coronavirus disease 2019 (COVID-19)

Gábor Speer[1)] and Péter Somogyi[2)]

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[2)] Department of Orthopaedics, Municipal Clinic Biatorbágy, H-2051, Biatorbágy, Hungary

Abstract. We have reviewed the available literature on thyroid diseases and coronavirus disease 2019 (COVID-19), and data from the previous coronavirus pandemic, the severe acute respiratory syndrome (SARS) epidemic. We learned that both SARS and COVID-19 patients had thyroid abnormalities. In the limited number of SARS cases, where it was examined, decreased serum T3, T4 and TSH levels were detected. In a study of survivors of SARS approximately 7% of the patients had hypothyroidism. In the previous evaluation evidence was found that pituitary function was also affected in SARS. Others suggested a hypothalamic-pituitary-adrenal axis dysfunction. One result published recently indicates that a primary injury to the thyroid gland itself may play a key role in the pathogenesis of thyroid disorders in COVID-19 patients, too. Subacute thyroiditis, autoimmune thyroiditis and an atypical form of thyroiditis are complications of COVID-19. Thyroid hormone dysfunction affects the outcome by increasing mortality in critical illnesses like acute respiratory distress syndrome, which is a leading complication in COVID-19. Angiotensin-converting enzyme 2 is a membrane-bound enzyme, which is also expressed in the thyroid gland and the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) uses it for docking, entering as well as replication. Based on the available results obtained in the SARS-CoV-2 pandemic, beside others, we suggest that it is necessary to monitor thyroid hormones in COVID-19.

Key words: Coronavirus disease 2019 (COVID-19), Severe acute respiratory syndrome (SARS), Thyroid, Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), Acute respiratory distress syndrome (ARDS)

The SARS-cov-2 virus affects thyroid function and needs to be monitored.

of case fatality for COVID-19 is approximately 3.4%, while for SARS and MERS it was 9.6% and 34%, respectively [1]. SARS is an acute respiratory disease with significant morbidity and mortality, consisting of two phases: initially an influenza-like period, followed very commonly by the outbreak of respiratory and gastrointestinal symptoms [2]. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the original virus of COVID-19, described as the seventh type of coronavirus infecting humans (86.9% of the genome of

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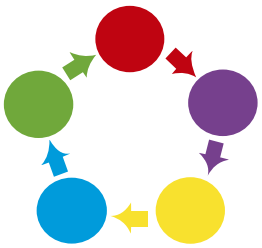
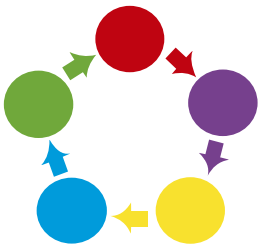
presumed that SARS could have a detrimental effect on the thyroid gland, as well [3]. However, there are only a few publications reporting data on clinical observations based on blood samples from SARS patients' specimens examined for thyroid function. Also, there are only a few direct researches published on the hypothalamic-pituitary-thyroid (HPT) axis of SARS patients [3, 4]. It has been assumed that the adenohypophyseal endocrine cells in SARS patients may be destructed [4]. Some surveys in connection with the former outbreak of SARS suggest that coronavirus can affect thyroid activity in people not previously diagnosed with thyroid disorders [5]. A study found that SARS patients had low triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH) levels [5]. Some other viruses may also



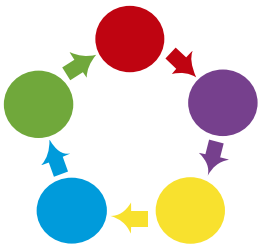
CLINICAL APPROACH TO THE THYROID PATIENT:

How did this person develop a thyroid disorder?



DISRUPTORS OF THYROID FUNCTION

- Food allergy, intolerance or sensitivity
- Infections (i.e. occult)
- Exogenous toxins
  - EDC's, heavy metals, etc.
- Chronic sleep deprivation
- Inflammatory diseases
- Oxidative Stress
- Pharmaceutical Drugs
- Hormone Imbalance
- Acute physical stress
- Diet: ↑ CBO/↓ protein
- Physical trauma
- Autoimmune diseases
- Nutritional insufficiencies
- Nutrient Excesses (Fl, Fe)
- Traumatic emotional events
- Aging
- Changes in gut microbiota
- Altered biotransformation
- Mitochondrial Dysfunction
- Single Nucleotide Polymorphisms (SNP's)



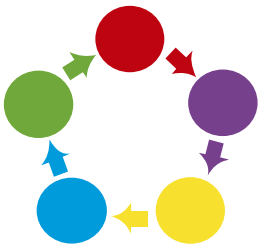
MY PROTOCOL STEP1: GET THE HISTORY!

GET THE STORY: TYPICALLY TOLD AS…

- Chief Complaint (CC)
- History of Present Illness (HPI)
- Past Medical History (PMH)
- Family History (FH)
- Dietary History
- Supplement and Medication History
- Lifestyle, Social, and Exercise History
- Physical Exam Findings
- Laboratory Evaluation

OVERVIEW OF MY APPROACH TO THYROID

- Thorough history including past history and family history.
- Complete physical exam looking for signs of dysfuncion
- Laboratory Evaluation: thyroid, but also other hormones (HPA axis, sex hormones (including ovarian function), steroidogenic cascade and estrogen metabolism
- Balance all hormones in specific order
- Consider metabolism/genomics/downstream effects
- Assessment of impact of hormones
- Can affect hormones without drugs
- Decision to give hormones and informed consent
- Route of delivery
- Reassessment of hormone levels and symptoms



Thyroid Questionnaire

By Sara Gottfried, MD | September 30, 2013

I love this questionnaire from Dr. Hotze, another integrative physician. It gets to the heart of whether you should be tested for thyroid dysregulation, even if your conventional doc has dismissed your concerns. I also like to use these questions to build a tracker for how you improve with different therapies, as trial-and-error continues to be the best route for choosing the best thyroid optimization.

If the question addresses a concern that applies to you, record the number. When done, total the numbers.

1. Do you experience fatigue (4)?
2. Is your cholesterol elevated (4)?
3. Do you have difficulty losing weight (2)?
4. Do you have cold hands and feet (2)?
5. Are you sensitive to cold (2)?
6. Do you have difficulty thinking (2)?
7. Do you find it hard to concentrate (2)?
8. Do you have poor short-term memory (2)?
9. Are your moods depressed (2)?
10. Are you experiencing hair loss (2)?
11. Do you have fewer that one BM per day (2)?
12. Do you have dry skin (2)?
13. Do you have itchy skin in winter (1)?
14. Do you have fluid retention (2)?
15. Do you have recurrent headaches (1)?
16. Do you sleep restlessly (1)?
17. Do you experience afternoon fatigue (2)?
18. Are you tired when you awaken (2)?
19. Do you experience tingling in hands or feet (2)?
20. Have you had infertility or miscarriages (2)?
21. Do you have decreased sweating (2)?
22. Do you have muscle aches (2)?
23. Have you had recurrent infections (2)?
24. Do you have joint pain (2)?
25. Do you have thinning of your eyebrows or eyelashes (2)?

By Sara Gottfried, MD | September 30, 2013, by questionnaire from Dr. Hotze

Score < 11? You are unlikely to have a thyroid problem.
Score 11-30? Low thyroid function is a possibility.
Score >30? Low thyroid function is probable.
Get tested if your score is > 11, including a free T3 and TSH.

European Journal of Endocrinology (2010) **162** 161–167 ISSN 0804-4643

CLINICAL STUDY

Validity and reliability of the novel thyroid-specific quality of life questionnaire, ThyPRO

Torquil Watt[1,2], Laszlo Hegedüs[3], Mogens Groenvold[2,4], Jakob Bue Bjorner[2,5], Åse Krogh Rasmussen[1], Steen Joop Bonnema[3] and Ulla Feldt-Rasmussen[1]

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(Correspondence should be addressed to T Watt at Department of Endocrinology, Copenhagen University Hospital Rigshospitalet; Email: t.watt@rh.dk)

Abstract

Background: Appropriate scale validity and internal consistency reliability have recently been documented for the new thyroid-specific quality of life (QoL) patient-reported outcome (PRO) measure for benign thyroid disorders, the ThyPRO. However, before clinical use, clinical validity and test–retest reliability should be evaluated.

Aim: To investigate clinical ('known-groups') validity and test–retest reliability of the Danish version of the ThyPRO.

Methods: For each of the 13 ThyPRO scales, we defined groups expected to have high versus low scores ('known-groups'). The clinical validity (known-groups validity) was evaluated by whether the ThyPRO scales could detect expected differences in a cross-sectional study of 907 thyroid patients. Test–retest reliability was evaluated by intra-class correlations of two responses to the ThyPRO 2 weeks apart in a subsample of 87 stable patients.

Results: On all 13 ThyPRO scales, we found substantial and significant differences between the groups expected to have high versus low scores. Test–retest reliability was above 0.70 (range 0.77–0.89) for all scales, which is usually considered necessary for comparisons among patient groups, but below 0.90, which is the usual threshold for use in individual patients.

Conclusion: We found support for the clinical validity of the new thyroid-specific QoL questionnaire, ThyPRO, and evidence of good test–retest reliability. The questionnaire is now ready for use in clinical studies of patients with thyroid diseases.

European Journal of Endocrinology **162** 161–167

Introduction

Measurements applying standardized self-reports to capture the impact of health on patients' lives are termed health-related quality of life (HRQL) measurements (1). They usually conceptualize HRQL as a multidimensional concept encompassing various aspects of physical, mental, and social functioning and well-being. To an increasing extent, the broader, but also more neutral term 'patient-reported outcomes (PROs)' is replacing HRQL. Today, PROs or HRQL measurements are recognized as inevitable and important outcomes in high quality clinical studies. Further, they can provide important documentation for evidence-based patient information and may even be implemented in clinical management of the individual patient, as has been done within, e.g. oncology (2), where randomized trials have documented significant improvement of patient–clinician interaction, without prolonging consultations, and impact on patient management (3). HRQL measurements may be either generic, i.e. applicable to any patient group regardless of diagnosis, or specific, i.e. targeted to a specific disease group. Specific HRQL measurements are usually more sensitive than generic, which on the other hand have the advantage of allowing comparisons across dissimilar populations.

Some questionnaires have been developed for specific thyroid diseases (4–12). However, a thoroughly validated questionnaire only exists for thyroid-associated ophthalmopathy (TAO) patients (5–7). Another TAO questionnaire has been developed, but has not been validated (8). One questionnaire for patients with hyperthyroidism was developed, but has never been validated (4). Three questionnaires for hypothyroid patients have been developed (9–12), but studies

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Online version via www.eje-online.org

Basal Metabolic Temperature vs. Laboratory Assessment in "Posttraumatic Hypothyroidism"

K W Sehnert [1], A C Croft

Affiliations + expand

PMID: 8903695

Abstract

Objectives: To compare standard laboratory analytical methods with measurement of basal metabolic temperature in cases of hypothyroidism arising posttraumatically.

Setting: Private medical office.

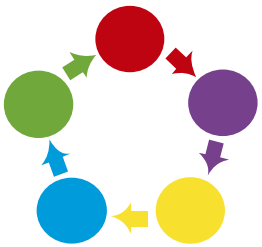
Subjects: One hundred and one consecutive status post-whiplash trauma patients.

Design: All subjects were evaluated with standard laboratory tests (T3RU, T4, FT4I, TSH) for thyroid function. Ninety-four were also evaluated with the newer fluorescence-activated microsphere assay test (FAMA) and basal metabolic temperature (BMT) was measured in all. Correlations were investigated between BMT, age, gender, standard laboratory values and the FAMA test. The differences between low and high BMT vs. normal and abnormal standard

"Measurement of BMT seems to be a sensitive screening test, in combination with laboratory analysis, for the hypothyroidism seen after whiplash trauma."

our posttraumatic hypothyroid group (30%) were not identified with either standard laboratory tests or the FAMA test-a group we referred to as lab-normal.

Conclusions: Measurement of BMT seems to be a sensitive screening test, in combination with laboratory analysis, for the hypothyroidism seen after whiplash trauma. Whiplash seems to result in a form of hypothyroidism suggesting direct injury to central tissues.



SYMPTOMS OF LOW THYROID FUNCTION

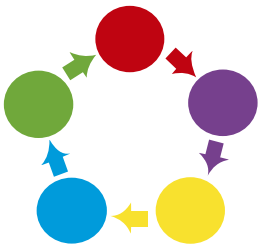
- Hypotension
- Hypoglycemia or Reactive hypoglycemia
- Myalgias
- Poor tolerance to stress and exercise
- Fatigue
- Hair loss
- Poor concentration
- Cold extremities
- Irritability/mood changes
- Shortness of breath
- Impaired kidney function

SYMPTOMS OF LOW THYROID FUNCTION-CONTINUED

- Memory and concentration problems
- Diffuse headache, migraines
- Depression; melancholia
- Constipation: hard bowel movements and decreased frequency
- Low libido
- Arthralgias/joint stiffness
- Menorrhagia
- Recurrent miscarriage
- Nocturia
- Easy bruising
- Erectile dysfunction

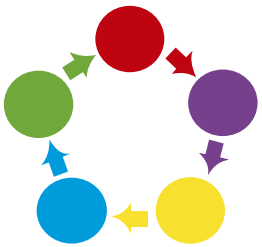
Diagnoses Associated with Low Thyroid Production

- Gallstones
- Bladder and kidney infections
- Deposition of mucin in connective tissues
- Hypercholesterolemia
- Hyperhomocysteinemia
- High c-reactive protein



WHAT TO LOOK FOR ON PHYSICAL EXAM:

LOW THYORID



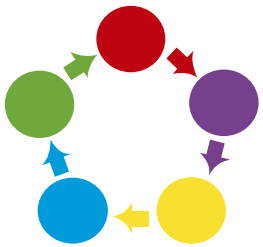
Int J Endocrinol Metab. 2014 January; 12(1): e13759. DOI: 10.5812/ijem.13759
Published online 2014 January 5. Review Article

Clinical Conundrums in Management of Hypothyroidism in Critically Ill Geriatric Patients

Vishal Sehgal [1,*]; Sukhminder Jit Singh Bajwa [2]; Rinku Sehgal [3]; Anurag Bajaj [3]

Table 1. Common Clinical Presentation of Hypothyroidism in Critically Ill Geriatric Population

Systems	Clinical Manifestations
Cardiac	
	Congestive heart failure
	Pericardial effusion
	Hypertension
	Decreased cardiac output
	Angina
Pulmonary	
	Decrease response to hypercapnia and hypoxia
	Macroglossia
Gastrointestinal	
	Constipation
	Non-alcoholic fatty liver
Hematologic	
	Pernicious anemia
	Anemia of chronic disease
Neurologic	Complex mental status changes
Metabolic	
	Hyperlipidemia
	Hyponatremia
	Metabolic syndrome



SOME PHYSICAL FINDINGS OF LOW THYROID FUNCTION

- Dry skin, elbow keratosis, brittle nails
- Diffuse hair loss
- Puffy face, swollen eyelids; edema in legs, feet, hands
- Loss of hair in varying amounts from legs, axilla, and arms
- Poor night vision
- Loss of eyelashes, or eyelashes that are not as thick
- Blepharospasm
- Easy bruising
- Prolonged Achilles tendon reflex
- Keratoderma
- Enlarged thyroid gland

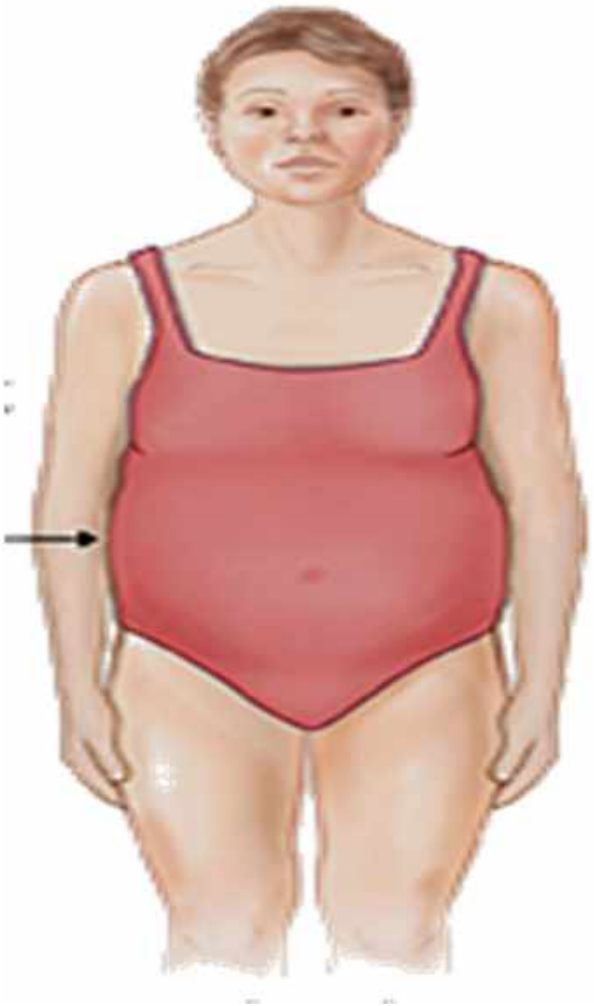
PHYSICAL EXAM FINDINGS IN LOW THYROID

During physical exam, pay particular attention to the following:

General:	Weight gain and bradycardia
HEENT:	Dull expression, swollen face, periorbital edema, decreased auditory acuity, swollen tongue, hoarseness, enlarged thyroid gland (goiter), glandular atrophy and thyroid nodules.
CV:	Bradycardia, LV hypertrophy, mild hypotension or diastolic hypertension, decreased heart sounds.
Respiratory:	Bradypnea, diminished vital capacity and total lung capacity, dyspnea
Abdominal:	Hypoactive bowel sounds and abdominal bloating
MSK:	Swollen hands, swollen feet and leg edema
NEURO:	Dementia, paranoid ideation, slow delayed reflexes and cerebellar ataxia
PSYCHE:	Depression
SKIN:	Dry skin, pale, course dry hair, brittle nails, hair loss, and temporal thinning of eyebrows

ANDROID BODY TYPE

COMMON BIOMARKER PATTERNS TO RECOGNIZE



Increased Inflammation Through Adipocytokine Communication

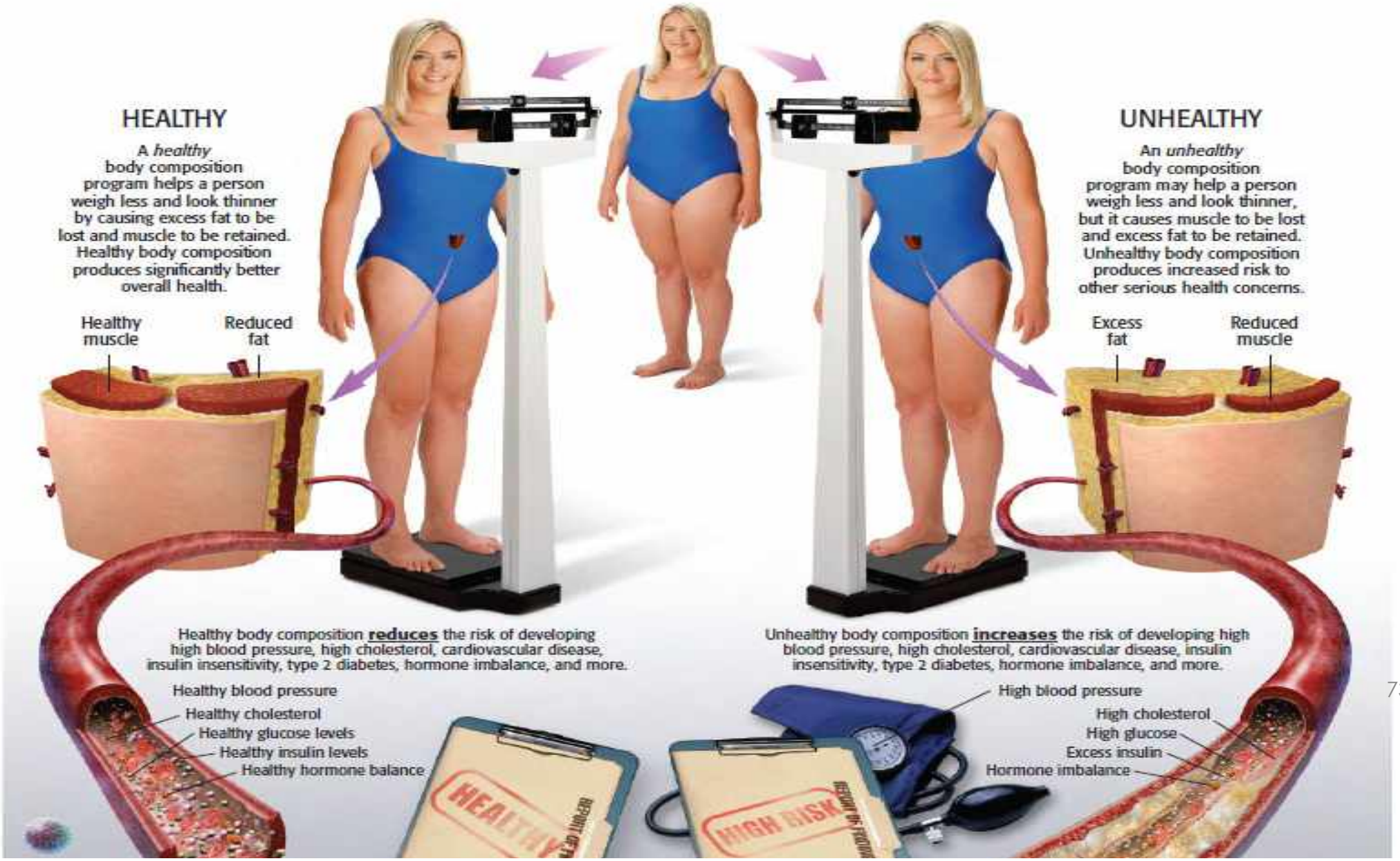
Insulin Resistance/Hyperinsulinemia and Reduced Adiponectin

HIGH INSULIN

- Overweight
- Inflammation (arthritis, skin rash, urge incontinence)
- Metabolic Syndrome (high blood pressure, obesity, high cholesterol)
- Any of the high adrenaline or high cortisol symptoms

HIGH INSULIN

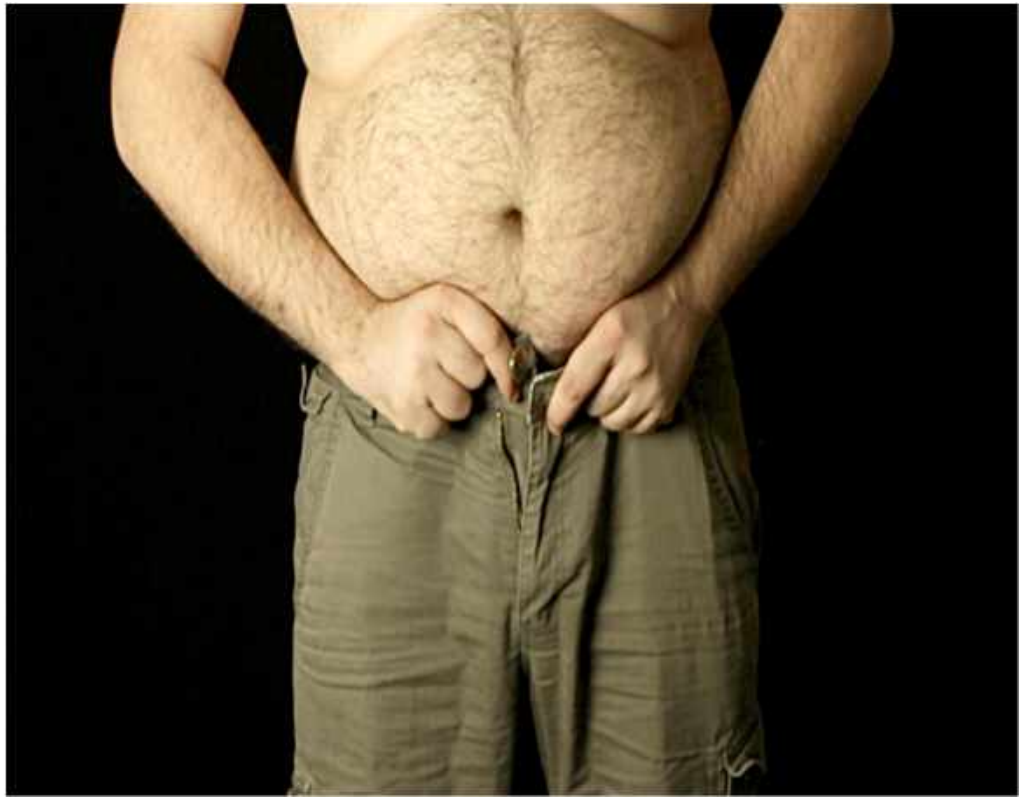
BODY COMPOSITION & HEALTH



HIGH ADRENALINE SIGNS & SYMPTOMS

- Losing weight/low BMI
- Anxious
- Hot flashes (midlife)
- Cold (compensatory hypothyroidism)
- Muscle wasting if not exercising to build muscles
- Bone loss

HIGH CORTISOL

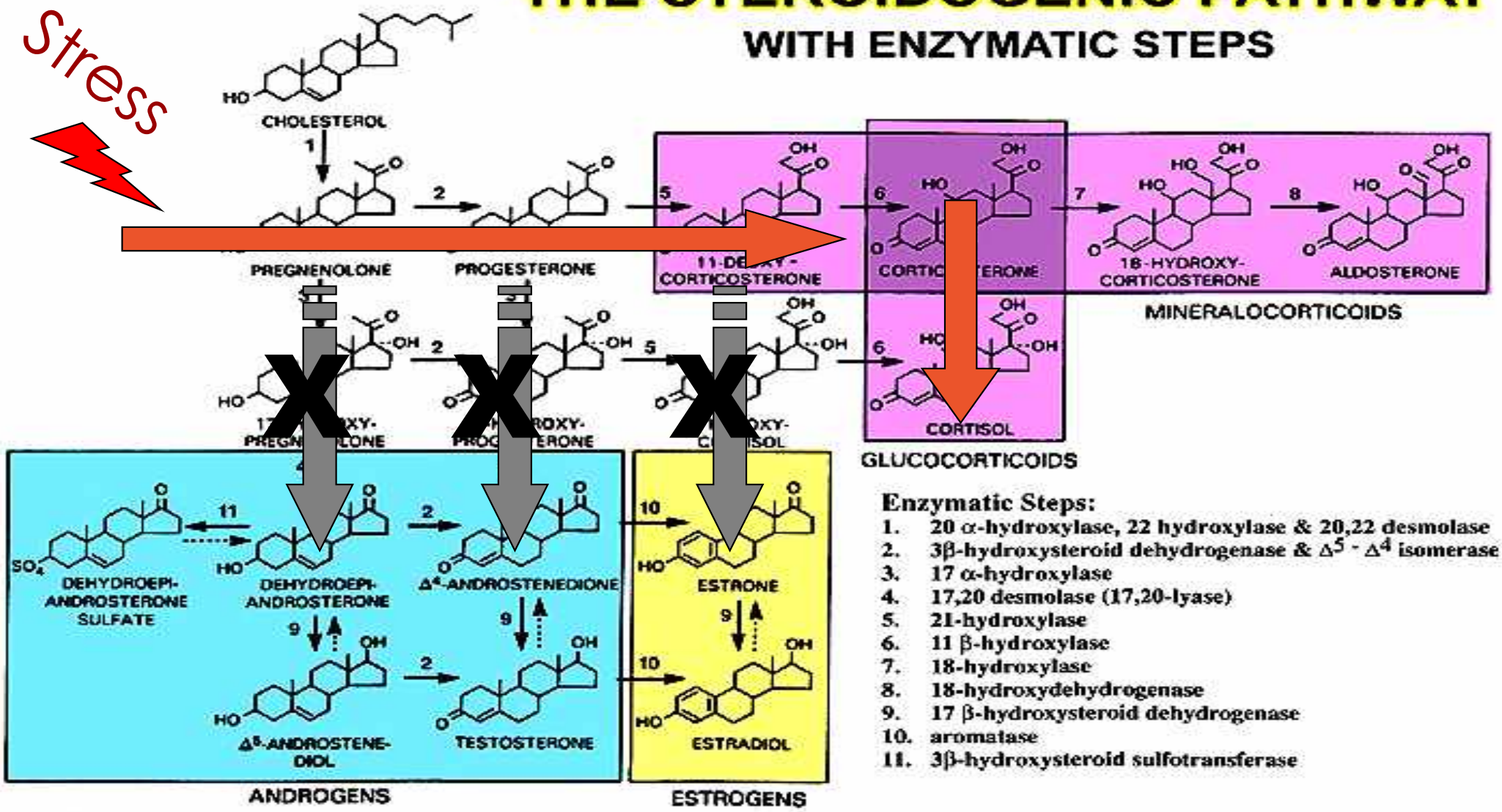


HIGH CORTISOL

- Depressed +/- anxiety
- Weight around midsection
- Frequent infections
- Elevated cholesterol
- Any of the high adrenaline symptoms

THE STEROIDOGENIC PATHWAY

WITH ENZYMATIC STEPS



Enzymatic Steps:

1. 20 α-hydroxylase, 22 hydroxylase & 20,22 desmolase
2. 3β-hydroxysteroid dehydrogenase & Δ^5 - Δ^4 isomerase
3. 17 α-hydroxylase
4. 17,20 desmolase (17,20-lyase)
5. 21-hydroxylase
6. 11 β-hydroxylase
7. 18-hydroxylase
8. 18-hydroxydehydrogenase
9. 17 β-hydroxysteroid dehydrogenase
10. aromatase
11. 3β-hydroxysteroid sulfotransferase

GYNOID BODY TYPE

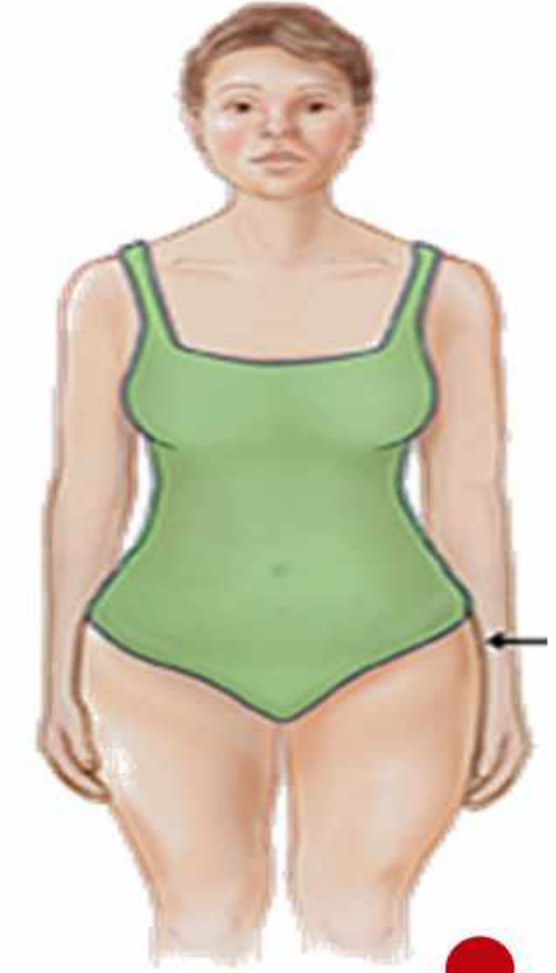
BIOMARKER PATTERNS TO RECOGNIZE

Increased Risk for HPATG Dysfunction

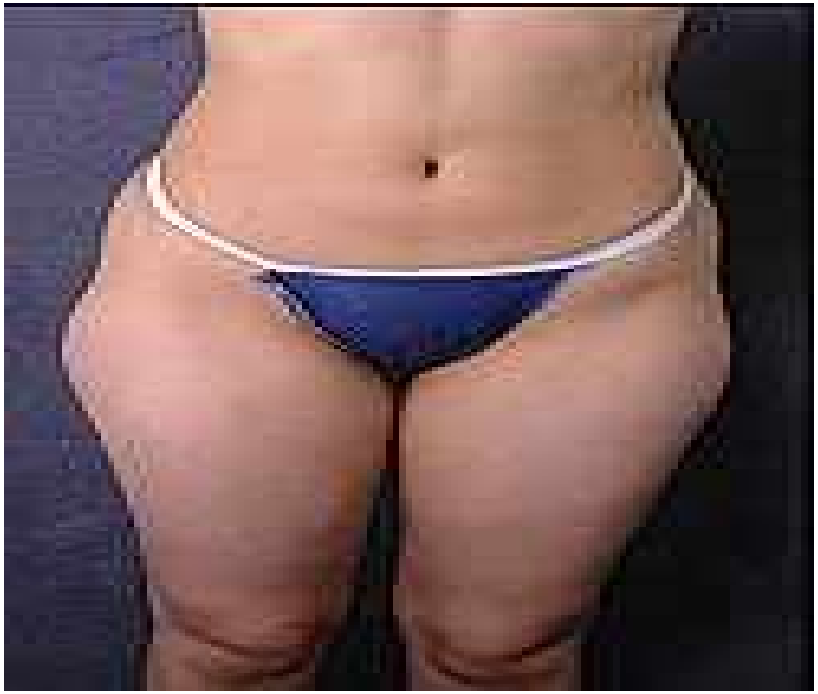
Infecto-obesity Risks

Detoxification Abnormalities

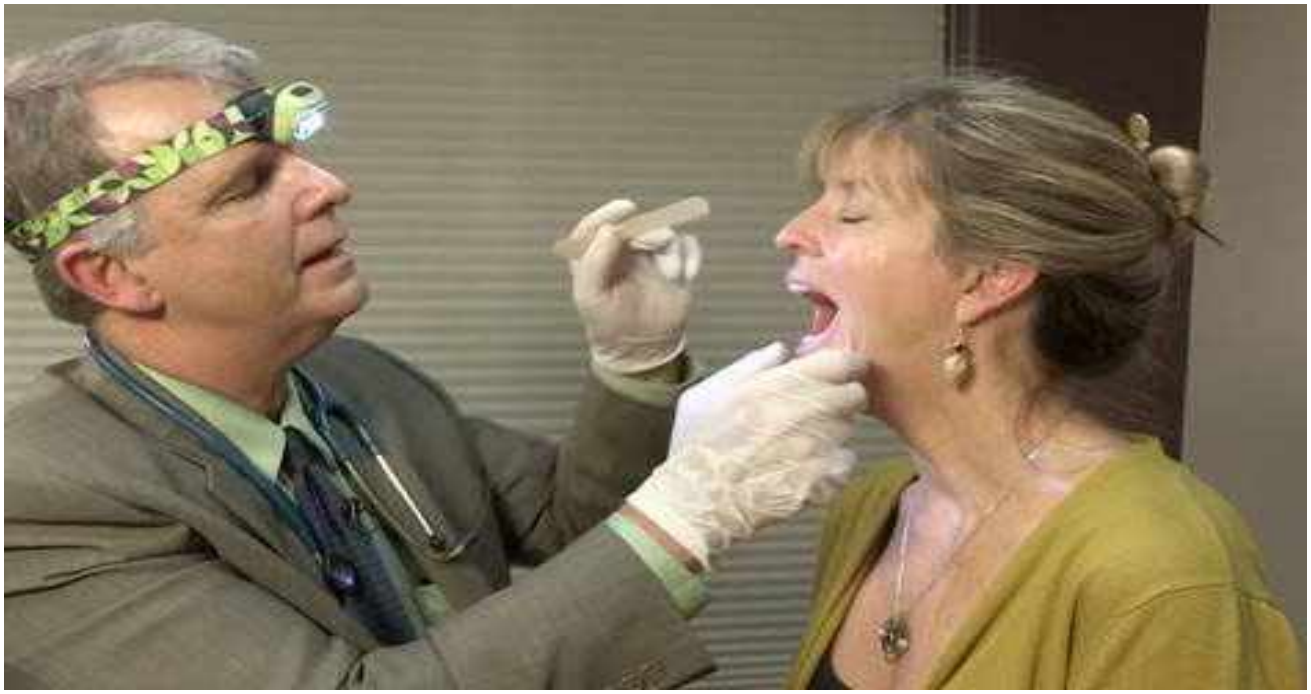
Gastrointestinal Concerns and Allergies



HIGH ESTROGEN BODY TYPE



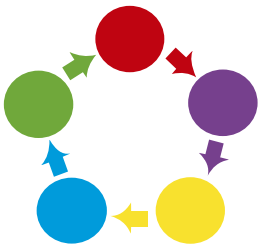
NUTRITIONAL PHYSICAL EXAM FINDINGS



Eyes to See and Expectation to Find

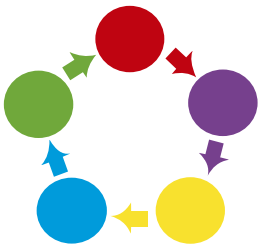
OTHER PHYSICAL EXAM FINDINGS

- Nails
- Hair
- Eyebrows
- Muscle mass
- Mouth/Oral mucosa
- DTR's
- Skin



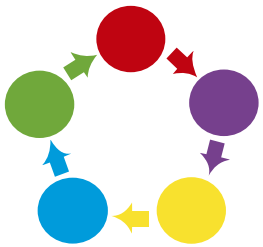
CONCENTRATE ON TISSUE WITH RAPID TURNOVER OR METABOLIC VULNERABILITY

1. Mucosa and Skin
2. Nails and Hair
3. Senses and Nerve Function



TONGUE
COLOR, COVERINGS, BUDS, SIZE, MOVEMENT

• **Glossitis (Red Tongue)**	Protein Under-nutrition, Iron, Riboflavin, niacin, B6, folate, B12
• **Decreased taste/smell, burning tongue**	Zinc, Vitamin C
• **Tongue fissuring**	Niacin, gut triggered immune issues
• **Tongue - taste bud atrophy**	Iron, Riboflavin, niacin, B12
• **Leukoplakia**	Vitamin A, B2, niacin, B6, Folate, B12
• **Hairy black tongue**	Not Specific; associated with smoking, sulfur, granule positive bacteria, antibiotics

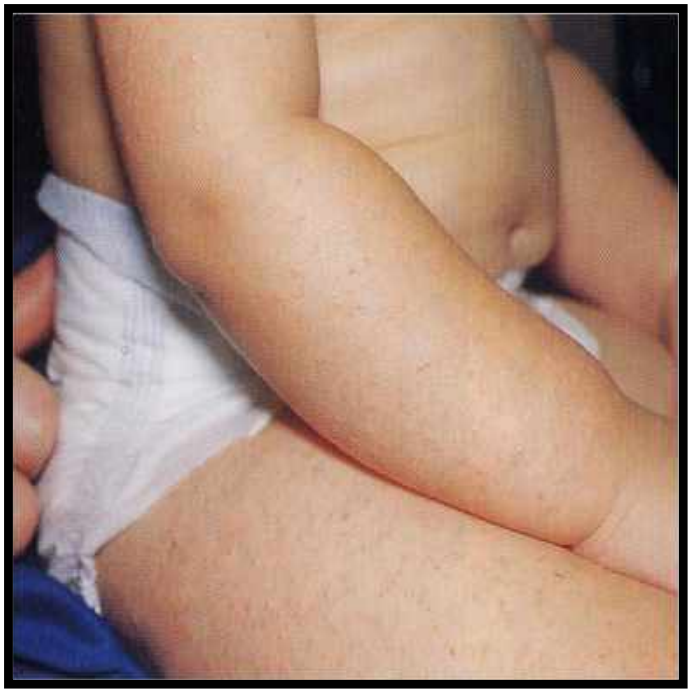


FEEL THE SKIN ON THE ARM

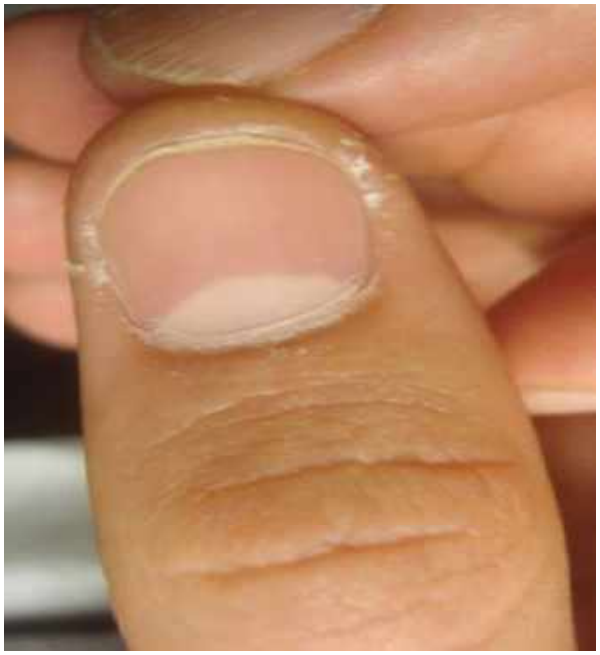
Character:

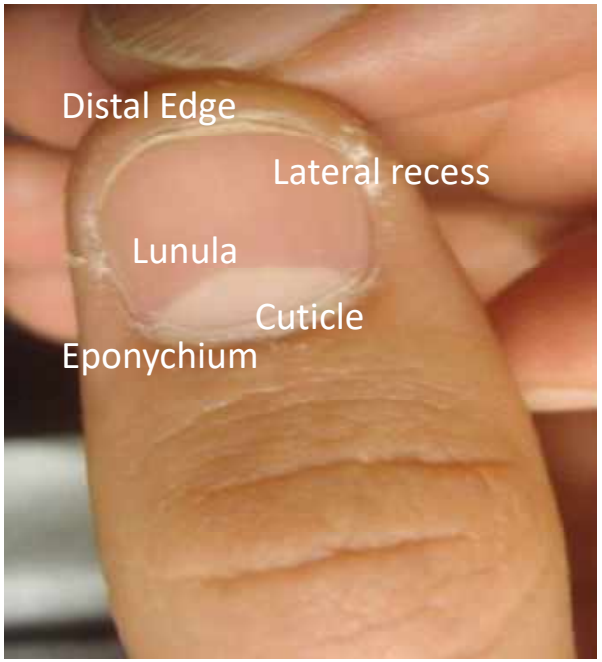
- Temperature
- Texture
- Color
- Hydration
- Lesions
- Hair Distribution

Hyperkeratosis pilari



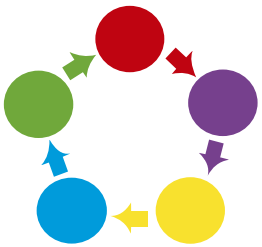
LOOK AT THE NAILS





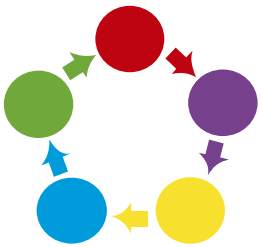
- Shape
- Color
- Pattern of Color
- Texture and strength
- Growth Pattern
- Surrounding Tissue

LABS



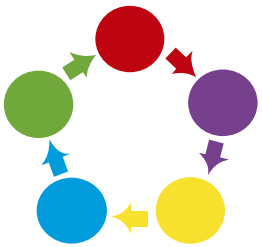
LABORATORY ASSESSMENT

- TSH
- fT4
- fT3
- Anti-thyroidal antibodies
  - Anti-peroxidase antibodies
  - Anti-thyroglobulin antibodies
  - Anti TSH receptor antibodies
- rT3
- Total T3 (TT3)
- Free T3/Free T4
- TT3/rT3



OTHER LABORATORY ASSESSMENT

- High cholesterol especially high LDL cholesterol
- High homocysteine
- Elevated HS-CRP



OTHER LABORATORY ASSESSMENT

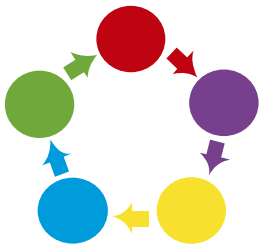
- **Iron:**
  - CBC and Ferritin

  (Generally part of my standard thyroid work up)

- **Zinc**
  - RBC Zinc

  (Often order but usually find it within RR and will often just supplement)

- **Selenium**
  - RBC selenium
  - Whole blood glutathione (Rarely order, almost invariably supplement)



OTHER LABORATORY ASSESSMENT

- **Vitamin D**
  - 25 OH

  (Generally part of my standard thyroid work-up)

- **Vitamin A**
  - Serum vitamin A

  (Rarely order, often supplement in suspected individuals)

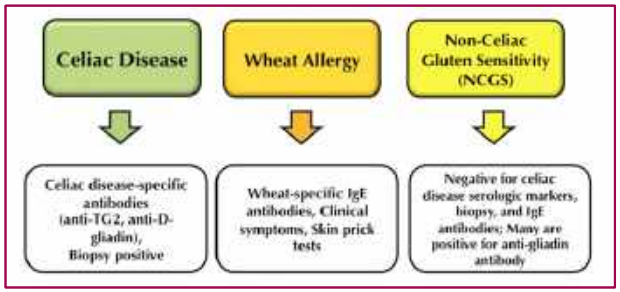
- **Iodine**
  - Urinary fasting morning spot iodine

  (often order as part of my standard thyroid work up)

OTHER LABORATORY ASSESSMENT

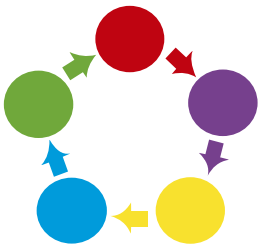
- **Celiac Panel**
  - Standard panel PLUS IgG gliadin if available

  (often order initially, will <u>always</u> order with elevated antibodies and diagnosis of Hashimoto's or Graves')
- **Food Sensitivities (IgG) and Complement**
- **Toxins**
  - **EDC's**
  - **Toxic Minerals (RBC)**
- **Infections**
  - Viral
  - Parasitic
  - Fungal
  - bacterial

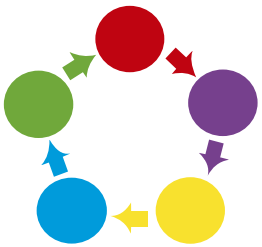


REFERENCE RANGES
&
OPTIMAL RANGES

Optimal Range	Standard Reference Range
• **TSH:** 0.4-2/2.5 mIU/L	(rr .4-5.5)
• **Free T4**: 15-23 pmol/L	(rr 9-23)
• **Free T3**: 5-7 pmol/L	(rr 3-7)
• **Total T3:** 120-181 ng/dl	(rr 76-181)
• **RT3:** 11-18 ng/dl	rr 11-31)
• **Ft3/Ft4**: >.33	
• **TT3/RT3**: >6	
• **Thyroid Antibodies:** WNL	

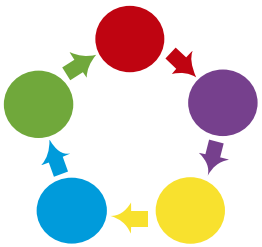


HYPERTHYROIDISM



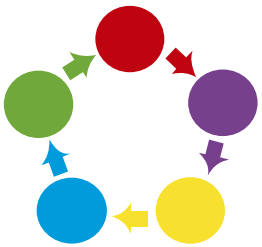
SYMPTOMS OF HYPERTHYROIDISM

- **General:** excess sweating, excessive hunger, fatigue, heat intolerance, or restlessness, weight loss, diarrhea, hair loss, muscle weakness, tremor, or warm skin
- **Mood:** mood swings, nervousness, or panic attack
- **cardiac:** abnormal heart rhythm, fast heart rate, or palpitations
- **Sleep:** difficulty falling asleep or insomnia
- **Menstrual:** irregular menstruation or short and light menstruation
- **Behavioral:** hyperactivity or irritability
- **Skin and Hair:** Thinning skin, brittle and/or fine hair



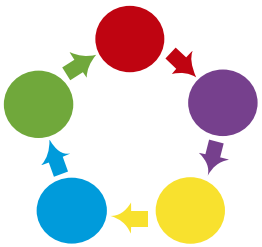
PHYSICAL FINDINGS IN HYPERTHYROIDISM

- **Eyes:** abnormal protrusion of eyes or puffy eyes
- **Cardiac:** Tachychardia
- **Hair:** thin and brittle
- **Skin:** thin and warm



HYPERTHYROIDISM AND GRAVE'S DISEASE

Grave's is most common type of hyperthyroidism



Association of cytokine gene polymorphisms and Graves' Disease in Turkish population

Display Settings: Abstract

Endocr Metab Immune Disord Drug Targets. 2013 Apr 30. [Epub ahead of print]

Association of cytokine gene polymorphisms (IL6, IL10, TNF-α, TGF-β and IFN-γ) and Graves' Disease in Turkish population.

Kutluturk F, Yarman S, Sarvan FO, Kekik C.

Gaziosmanpasa University, Faculty of Medicine, Department of Endocrinology and Metabolism, 60200 Tokat, Turkey.

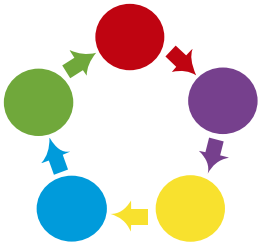
Abstract

Introduction: Cytokines play a crucial role in the pathogenesis of autoimmune **thyroid** disease, and recent studies have demonstrated an association between cytokine gene polymorphisms and Graves' Disease (GD) in different ethnic groups. The aim of the present study was to investigate the relationship of interleukin-6 (IL-6), IL-10, tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), and interferon-gamma (INF-γ) gene polymorphisms in the development of GD in Turkish population. Material and Methods: A total of 224 subjects were included in the study comprising of 100 patients with GD (70 female, 30 male; mean age, 43.9 ±13.8 years) and 124 healthy subjects (81 female, 43 male); mean age, 37.8 ±10.2 years) without antithyroid autoantibodies or family history of autoimmune disorders. Genotyping was conducted by using PCR and sequence-specific primers. Results: Statistical analysis showed a significant association between high TNF-α -308GA and IL-6 -174CC gene polymorphisms in patients with GD compared to control subjects (p=0.016, p=0.044, respectively). However, no significant differences were observed between GD and control subjects for IL-10, TGF-β, and INF-γgene polymorphisms. Conclusion: TNF-α-308GA and IL-6 -174CC gene polymorphisms are involved in susceptibility to GD in Turkish population. The polymorphism hypothesis in pro-inflammatory cytokines might be involved in predisposition to GD.

PMID: 23638863 [PubMed - as supplied by publisher]

LinkOut - more resources

Conclusion: the pro-inflammatory cytokine gene polymorphisms (TNF-a-308GA and IL-6-174CC) are involved in predisposition to Graves'Disease in Turkish poplulation.



THYROID
Volume 26, Number 10, 2016

DOI: 10.1089/thy.2016.0229

SPECIAL ARTICLE

2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis

Douglas S. Ross,[1*] Henry B. Burch,[2**] David S. Cooper,[3] M. Carol Greenlee,[4] Peter Laurberg,[5†] Ana Luiza Maia,[6] Scott A. Rivkees,[7] Mary Samuels,[8] Julie Ann Sosa,[9] Marius N. Stan,[10] and Martin A. Walter[11]

Background: Thyrotoxicosis has multiple etiologies, manifestations, and potential therapies. Appropriate treatment requires an accurate diagnosis and is influenced by coexisting medical conditions and patient preference. This document describes evidence-based clinical guidelines for the management of thyrotoxicosis that would be useful to generalist and subspecialty physicians and others providing care for patients with this condition.

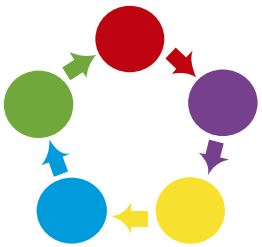
Methods: The American Thyroid Association (ATA) previously cosponsored guidelines for the management of thyrotoxicosis that were published in 2011. Considerable new literature has been published since then, and the ATA felt updated evidence-based guidelines were needed. The association assembled a task force of expert clinicians who authored this report. They examined relevant literature using a systematic PubMed search supplemented with additional published materials. An evidence-based medicine approach that incorporated the knowledge and experience of the panel was used to update the 2011 text and recommendations. The strength of the recommendations and the quality of evidence supporting them were rated according to the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation Group.

Results: Clinical topics addressed include the initial evaluation and management of thyrotoxicosis; management of Graves' hyperthyroidism using radioactive iodine, antithyroid drugs, or surgery; management of toxic multinodular goiter or toxic adenoma using radioactive iodine or surgery; Graves' disease in children, adolescents, or pregnant patients; subclinical hyperthyroidism; hyperthyroidism in patients with Graves' orbitopathy; and management of other miscellaneous causes of thyrotoxicosis. New paradigms since publication of the 2011 guidelines are presented for the evaluation of the etiology of thyrotoxicosis, the management of Graves' hyperthyroidism with antithyroid drugs, the management of pregnant hyperthyroid patients, and the preparation of patients for thyroid surgery. The sections on less common causes of thyrotoxicosis have been expanded.

Conclusions: One hundred twenty-four evidence-based recommendations were developed to aid in the care of patients with thyrotoxicosis and to share what the task force believes is current, rational, and optimal medical practice.

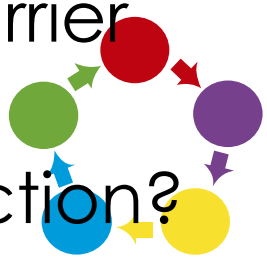
"One hundred twenty-four evidence-based recommendations were developed to aid in the care of patients with thyrotoxicosis and to share what the task force believes is current, rational, and optimal medical practice."

TREATMENT



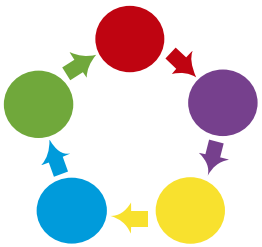
THE 5R PROGRAM ASKS FOUR BASIC QUESTIONS:

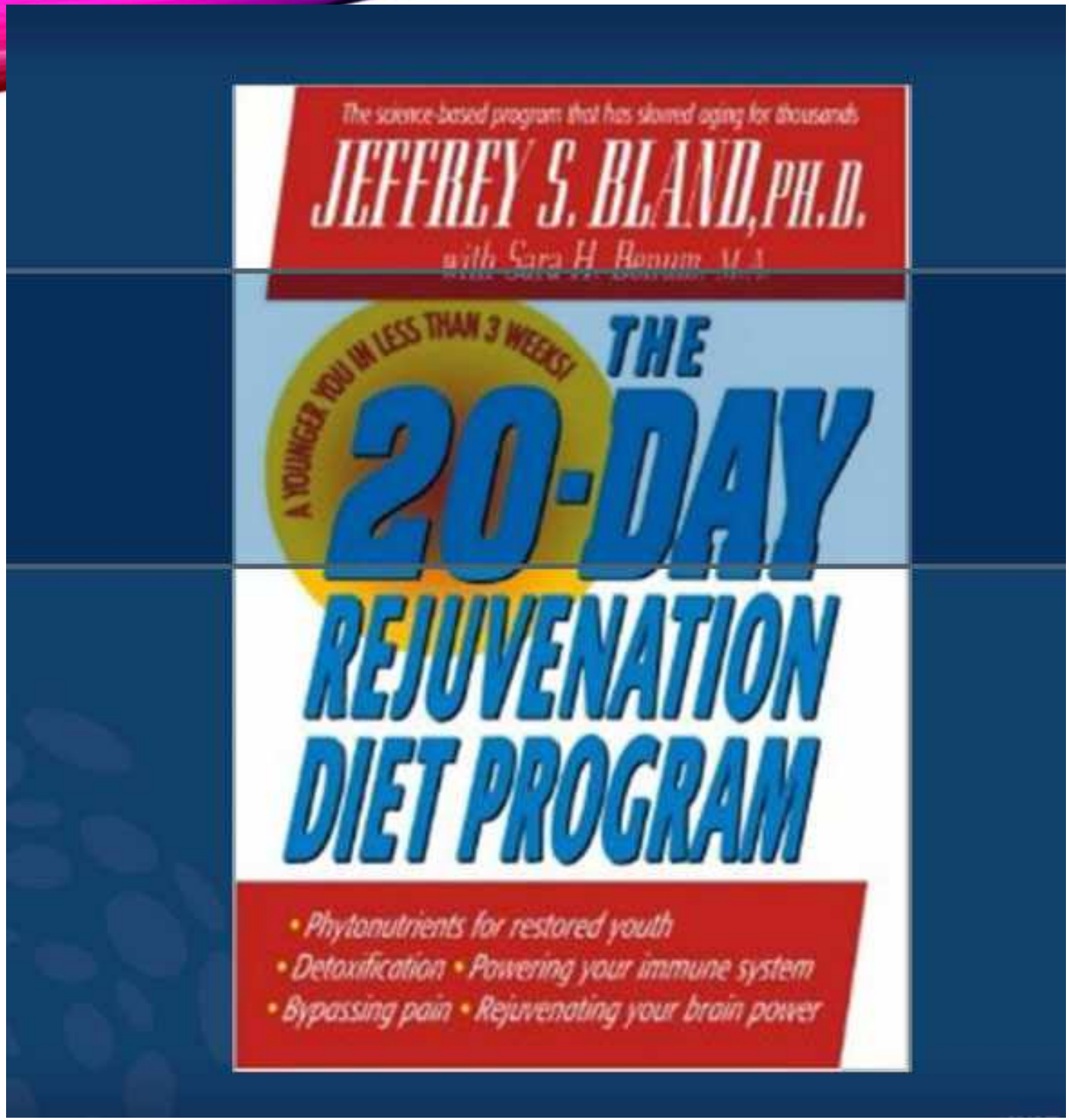
- What does this patient need to have *Removed* (e.g., pathogenic growth in the intestinal tract, allergenic foods in the diet) for healthy GI function?
- What does this patient need to have *Replaced* (e.g., stomach acid, digestive enzymes) to support improved GI function?
- What does this patient need to support and/or to re-establish a healthy balance of microflora; that is, does he/she require probiotic *Reinoculation/Repopulation* and/or prebiotic support?
- What does this patient need to support healing and reestablishment of a healthy mucosal layer; that is, does he/she require targeted nutritional support for GI barrier and biofilm *Repair* and regeneration?
- What is needed to *Rebalance* the gut-brain connection?

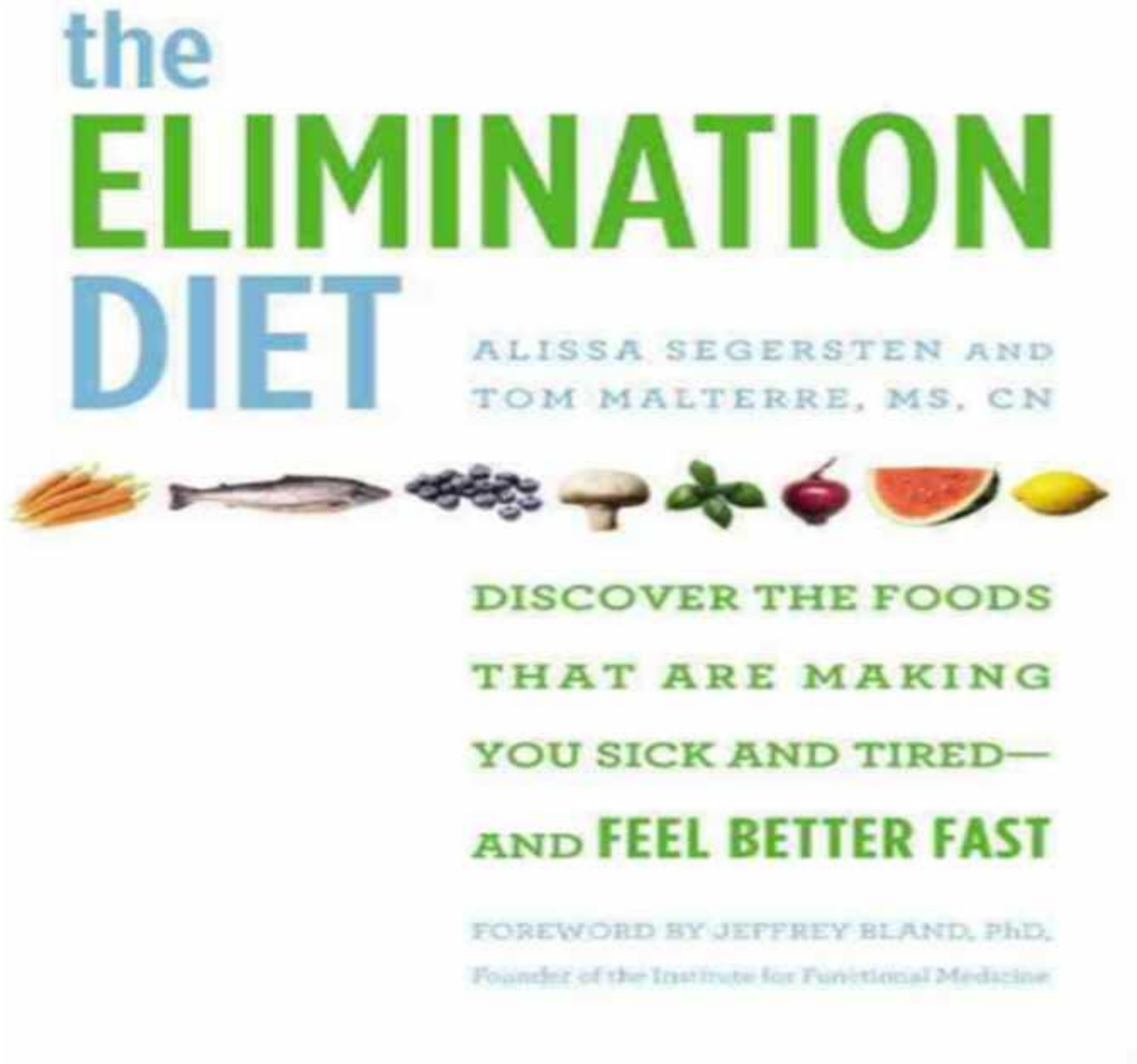


WHAT IS AN ELIMINATION DIET?

- Elimination of foods and food additives that may be causing an immunological or non-immunological reaction
  - Immunological reaction: Allergy or "hypersensitivity," which may be IgE, IgG, IgM, IgA, or T cell mediated
  - Non-immunological reaction: Intolerance that may be secondary to lactase deficiency, spoilage, or various other toxins

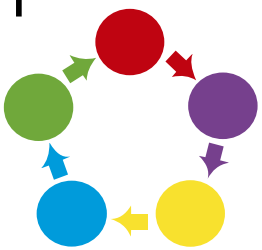



The science-based program that has slowed aging for thousands
JEFFREY S. BLAND, PH.D.
with Sara H. Benum, M.A.
A YOUNGER YOU IN LESS THAN 3 WEEKS!
THE
20-DAY
REJUVENATION
DIET PROGRAM
• Phytonutrients for restored youth
• Detoxification • Powering your immune system
• Bypassing pain • Rejuvenating your brain power


the
ELIMINATION
DIET
ALISSA SEGERSTEN AND
TOM MALTERRE, MS, CN
DISCOVER THE FOODS
THAT ARE MAKING
YOU SICK AND TIRED—
AND FEEL BETTER FAST
FOREWORD BY JEFFREY BLAND, PhD,
Founder of the Institute for Functional Medicine

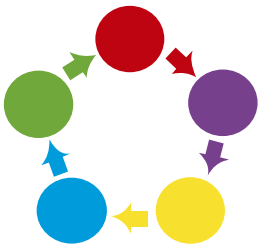
THE ELIMINATION DIET: A PRIMARY THERAPEUTIC DIETARY INTERVENTION

- Can be a major tool when food sensitivities are the main root causes
- Identifies triggers in the diet
- Reduces inflammation
- Reduces toxic burden
- Repairs intestinal permeability
- Include phytonutrients to heal the gut
- When used with the 5R program is a great approach to healing the gut



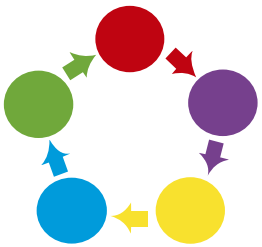
FOCUS ON ELIMINATING OR DECREASING TOXINS THAT AFFECT THYROID FUNCTION

- Assess for **toxins** and decrease/eliminate if possible
- Assess for and eliminate **medications** (as possible) that inhibit function
- Improve the **dietary prescription** with a focus on detoxification/biotransformation



DIETARY PROTOCOL FOCUSED ON ELIMINATING POTENTIAL FOOD REACTIONS, IMPROVING GUT DYSBIOSIS/MICROBIOTA AND LOWERING INFLAMMATION

- ✓ Low in potential foods that could cause reactions
- ✓ High in pre and probiotic foods
- ✓ High in phytonutrient content
- ✓ Low in the Omega-6/Omega-3 ratio
- ✓ Low in saturated and trans fatty acids



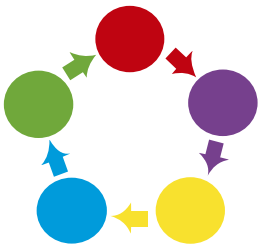
LIFESTYLE FACTORS

- Sleep
- Exercise
- Connections/support
- Stress Reduction techniques

OTHER TREATMENT STRATEGIES

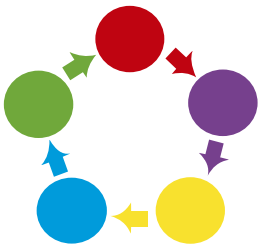
- **Foundational:**
  - Dietary/Lifestyle changes to remove triggers and/or address mediators
  - Supplementation

- **Hormone Replacement**
  - T4 only vs T4 and T3



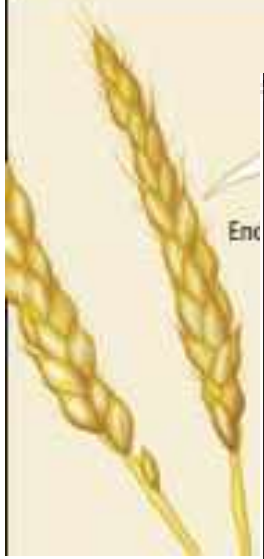
AUTOIMMUNE THYROIDITIS (HASHIMOTO'S)

- Look for the trigger, remove
- Address the gut
- Fix the dysfunction



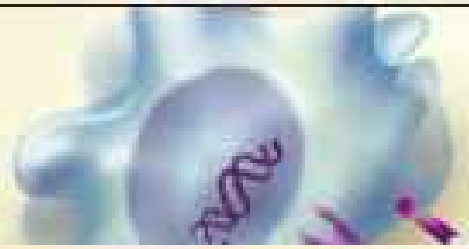
A TRIO OF CAUSES

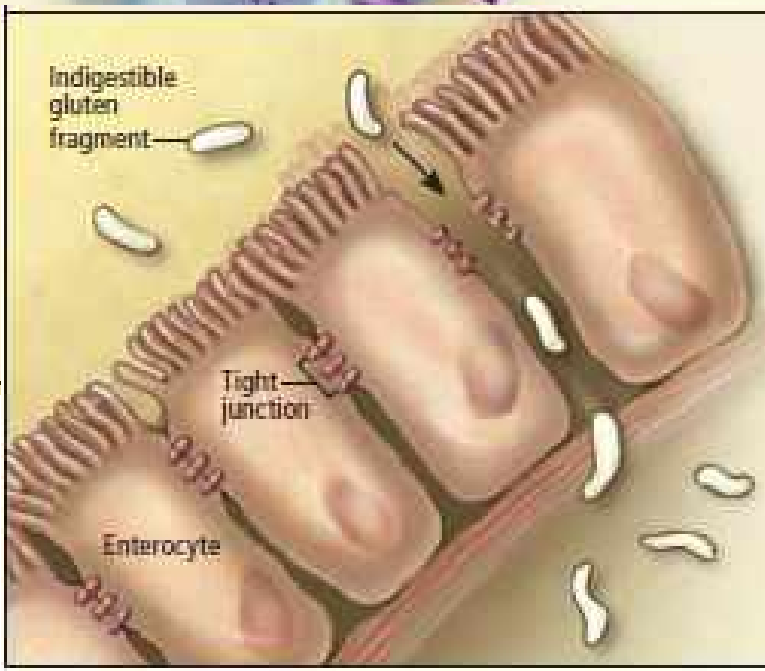
Three factors underlie celiac disease: an environmental trigger, a genetic susceptibility and, according to the author's research, an unusually permeable gut (*below*). The author suspects that the same basic triad contributes to other autoimmune diseases, although each disorder will have its own triggers and genetic components.



GENETIC PREDISPOSITION

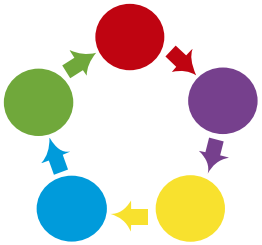
Almost all patients harbor a gene for either the HLA-DQ2 protein or the HLA-DQ8 protein, or both. These HLA molecules display gluten fragments to immune system cells, which then direct an attack on the intestinal lining. Other genes are likely to be involved as well, but these additional culprits may differ from person to person.





LEAKY SMALL INTESTINE

In most people, links known as tight junctions "glue" intestinal cells together. In those with celiac disease, the junctions come apart, allowing a large amount of indigestible gluten fragments to seep into the underlying tissue and incite immune system cells. Treatments that reduced leakiness could potentially ease not only celiac disease but also other autoimmune disorders involving unusually permeable intestines.



Fasano A. Surprises from Celiac Disease. Scientific American 2009(Aug):54-61.

A TRIO OF CAUSES

Three factors underlie celiac disease: an environmental trigger, a genetic susceptibility and, according to the author's research, an unusually permeable gut (*below*). The author suspects that the same basic triad contributes to other autoimmune diseases, although each disorder will have its own triggers and genetic components.

Wheat kernel

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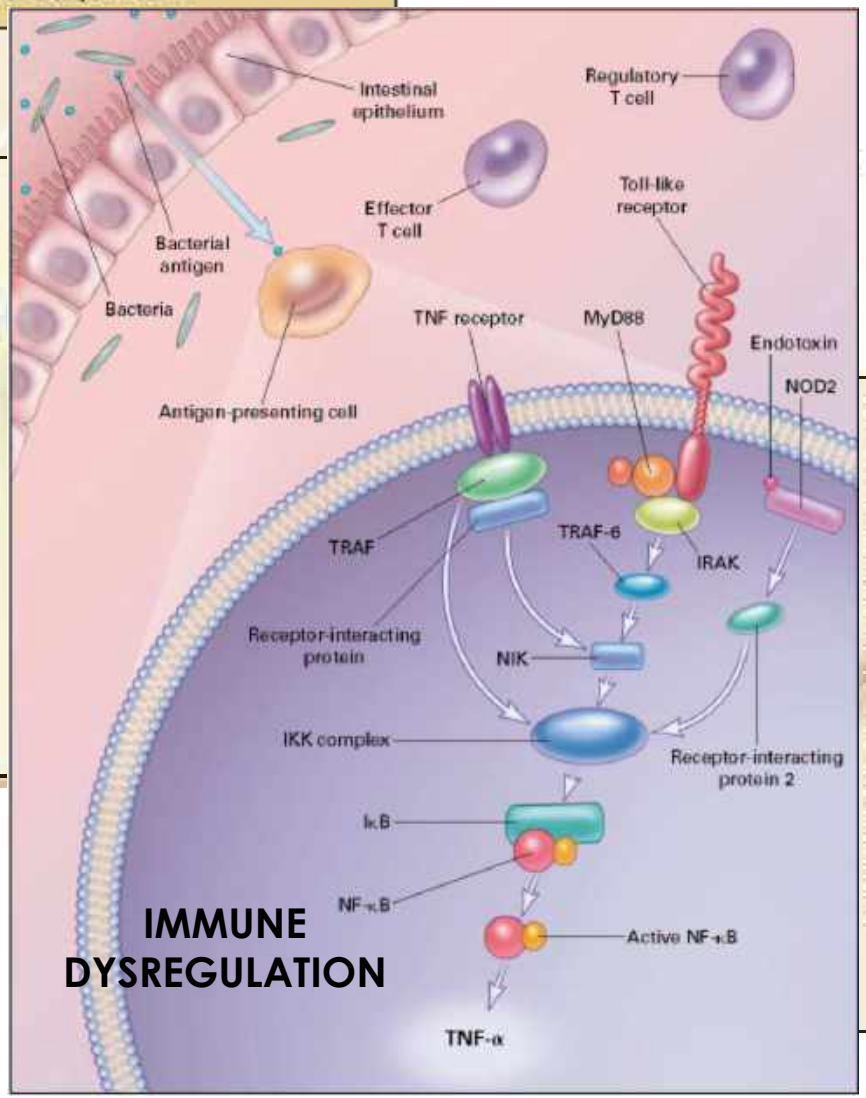

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+ ONE

Sci Am 301 (2), 54-61, Aug 2009

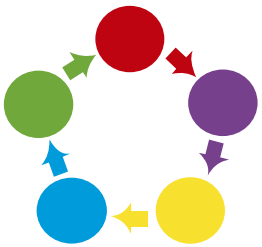
[MYSTERY]

A Clue to Delayed Onset

People with celiac disease are born with a genetic susceptibility to it. So why do some individuals show no evidence of the disorder until late in life? In the past, I would have said that the disease process was probably occurring in early life, just too mildly to cause symptoms. But now it seems that a different answer, having to do with the bacteria that live in the digestive tract, may be more apt.

These microbes, collectively known as the microbiome, may differ from person to person and from one population to another, even varying in the same individual as life progresses. Apparently they can also influence which genes in their hosts are active at any given time. Hence, a person whose immune system has managed to tolerate gluten for many years might suddenly lose tolerance if the microbiome changes in a way that causes formerly quiet susceptibility genes to become active. If this idea is correct, celiac disease might one day be prevented or treated by ingestion of selected helpful microbes, or "probiotics."

—*A.F.*



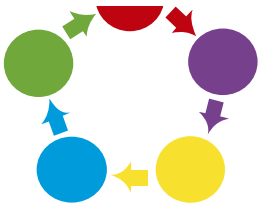
KEY NUTRIENTS TO CONSIDER IN THYROID REGULATION

- Selenium
- Zinc
- Iron
- Iodine
- Vitamin D
- Vitamin A

ZINC, SELENIUM AND T3/T4 RATIO

- Low T3/T4 ratio may be related to impaired zinc and/or selenium status.
- Supplementation was associated with modest changes in thyroid hormones, with an earlier normalization of T4 and RT3 plasma levels.

Berger MM, et al. (2001). Influence of selenium supplements on the post-traumatic alterations of the thyroid axis: a placebo-controlled trial. *Intensive Care Med*, Jan; 27(1):91-100.
Olivieri O, et al. (1996). Selenium, zinc, and thyroid hormones in healthy subjects: low T3/T4 ratio in the elderly is related to impaired selenium status. *Biol Trace Elem Res*. Jan; 51(1):31-41.



IRON AND THYROID FUNCTION IN ADULTS

- **Serum iron concentrations were lower** in participants with **subclinical hypothyroidism** than euthyroid subjects.

- In euthyroid subjects, small differences in thyroid function are associated with significant differences in erythrocyte indices.

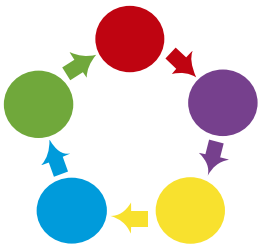
Bremner AP et al. (2012). Significant association between thyroid hormones and erythrocyte indices in euthyroid subjects. *Clin Endocrinol (Oxf),* Feb; 76(2): 304-11.

IRON INSUFFICIENCIES

- **Iron deficiency impairs thyroid hormone synthesis** by reducing the activity of heme-dependent thyroid peroxidase.

- Further, Iron-deficiency anemia blunts, and iron supplementation improves, the efficacy of iodine supplementation.

Zimmermann MB, Köhrle J. The impact of iron and selenium deficiencies on iodine and thyroid metabolism: biochemistry and relevance to public health. Thyroid. Oct 2002; 12(10):867-78.



IRON DEFICIENCY AND ITS RELATIONSHIP TO RT3

Iron improves thyroid function by decreasing the conversion to RT3:

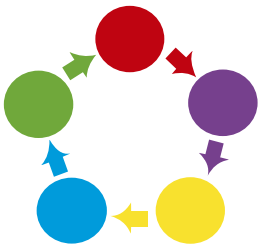
- **Significant Decrease in rT3** (47%, p<0.001)
- **Significant Increase in TT4 and TT3** (3.5%, p<0.001)

Eftekhari MH et al. (2007). Effect of iron repletion and correction of iron deficiency on thyroid function in iron-deficient Iranian adolescent girls. *Pak J Biol Sci.,* Jan 15;10(2):255-60.

VITAMIN D INSUFFICIENCIES AND AUTOIMMUNE THYROID DISEASE (AITD)

- The **prevalence of vitamin D deficiency was significantly higher in patients with AITDs** compared with healthy individuals (72% versus 30.6%; P<0.001), **as well as in patients with Hashimoto's thyroiditis** compared to patients with non-AITDs (79% versus 52%; P<0.05).

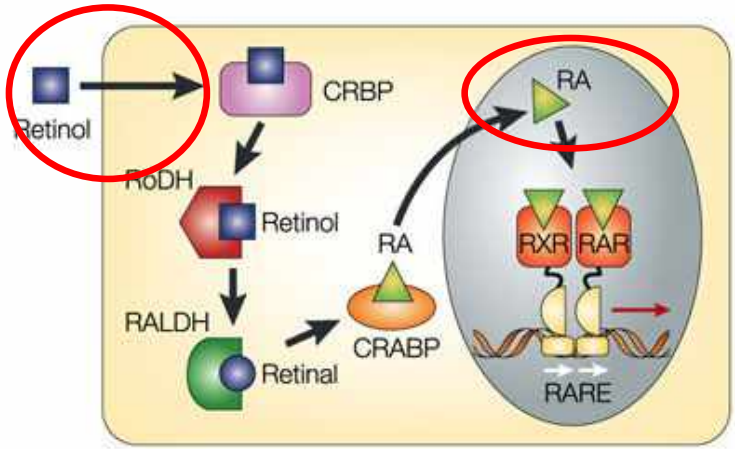
- Significantly low levels of vitamin D were documented in patients with AITDs that were related to the presence of anti thyroid antibodies and abnormal thyroid function tests, **suggesting the involvement of vitamin D in the pathogenesis of AITDs**



Kivity S, et al. 92011). Vitamin D and autoimmune thyroid diseases. *Cell Mol Immunol*. May 2011; 8(3):243-7.

VITAMIN A INSUFFICIENCIES

Factors that either produce vitamin A (retinol) insufficiency or prevent the conversion of vitamin A to retinoic acid may result in reduced thyroid nuclear signaling.

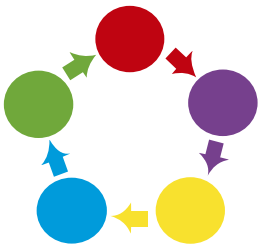


Nature Reviews | Neuroscience

Feart C, et al. Aging affects the retinoic acid and the triiodothyronine nuclear receptor mRNA expression in human peripheral blood mononuclear cells. *Eur J Endocrinol*. Mar 2005; 152(3):449-58.

IODINE INSUFFICIENCIES AND NHANES

- NHANES I (1971–1974) and NHANES III (1988–1994) showed that Americans' median urine iodine concentration decreased by 50%, while a low urine excretory level of iodine below the WHO threshold increased by 4.5-fold in this same period.
- Monitoring of high-risk groups showed that 6.7% of pregnant women and **14.9% of women of childbearing age had a urine excretory level of less than the WHO threshold of iodine.**
- The most recent NHANES (NHANES IV: 2001–2002) indicated level of iodine has stabilized since NHANES III.



Hollowell JG et al. (1998). Iodine nutrition in the United States. Trends and public health implications: iodine excretion data from National Health and Nutrition Examination Surveys I and III (1971-1974 and 1988-1994). *J Clin Endocrinol Metab*, Oct; 83(10):3401–3408.

IODINE EXCESS AND CONVENTIONAL RECOMMENDATIONS

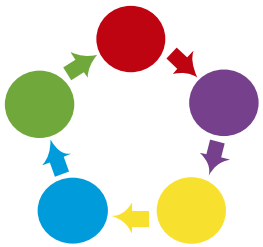
The American Thyroid Association recommends against ingestion of an iodine or kelp daily supplement containing >500 µg iodine for all individuals, except for certain medical indications.

American Thyroid Association. ATA Statement on the Potential Risks of Excess Iodine Ingestion and Exposure. 2013 [online], http://www.thyroid.org/ata-statement-on-the-potential-risks-of-excess-iodine-ingestion-and-exposure

ROUTINE DAILY SUPPLEMENTATION IN A HYPOTHYROID PATIENT

- **Selenium:** 200-400 mcg
- **Zinc:** 15-30 mg
- **Vitamin D:** 2000 iu
- **Vitamin A:** 2000 iu
- **Iodine:** 150 mcg
- **Iron:** 15-20 mg (in a menstruating woman)

(generally all can be given in one or two supplements)



DOI 10.1007/s10517-018-4007-z
Bulletin of Experimental Biology and Medicine, Vol. 164, No. 4, February, 2018 PHARMACOLOGY AND TOXICOLOGY

Experimental Simulation of the Effects of Essential and Toxic Trace Elements on Thyroid Function

E. S. Barysheva

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 164, No. 10, pp. 433-436, October, 2017
Original article submitted December 6, 2016

The effects of essential (I, Se, and Zn) and toxic (Pb and Cd) trace elements on the thyroid function were studied experimentally. The protective effects of iodine, zinc, and selenium on thyroid tissue and antithyroid effects of toxic trace elements promoting a decrease in the levels of thyroid hormones (T_3, T_4) and imbalance of pituitary hormones (TSH) were detected. Addition of toxic trace elements to the ration of experimental rats led to their accumulation in the thyroid (0.051 μg/g Pb and 0.190 μg/g Cd). Negative correlations between the levels of toxic and essential trace element accumulation in the organ were detected. Essential trace elements zinc and selenium involved in thyroid hormone metabolism promoted normalization of the thyroid function. A complex of essential trace elements (I, Se, and Zn) was recommended for correction of mineral metabolism under conditions of iodine deficiency and thyroid hypofunction and in exposure to toxic trace elements.

Key Words: *thyroid; imbalance; mineral metabolism; hormones; correction*

Numerous studies demonstrate the role of essential and toxic trace elements in the formation of functional status of the thyroid and in iodine metabolism; however, consumption and accumulation of chemical elements in the organ over the course of exposure received insufficient attention [1,7]. The adequate status of the thyroid system and measured the content of essential and toxic trace elements in the thyroid gland.

MATERIALS AND METHODS

The study was carried out on Wistar rats (n=51). The

"A complex of essential trace elements (I, Se, and Zn) was recommended for correction of mineral metabolism under conditions of iodine deficiency and thyroid hypofunction and in exposure to toxic trace elements."

Article

Potential Influence of Selenium, Copper, Zinc and Cadmium on L-Thyroxine Substitution in Patients with Hashimoto Thyroiditis and Hypothyroidism

Authors: Z. Rasic-Milutinovic[1], D. Jovanovic[2], G. Bogdanovic[2], J. Trifunovic[3], J. Mutic[4]

Affiliations: Affiliation addresses are listed at the end of the article

Key words
- thyrotropin
- thyroiditis
- thyroidy

Abstract

Background: Besides genetic factors, it is known that some trace elements, as Selenium, Copper, and Zinc are essential for thyroid gland fuction and thyroid hormone metabolism. Moreover, there were some metals effect that suggested patterns associated with overt thyroid disease.

Aim of study: Hashimoto thyroiditis (HT), chronic autoimune inflamation of thyroid gland with cosequtive hipothyroidism, is common disease in Serbia, and we thought it is worthwile to explore potential effects of essential and toxic metals and metalloides on thyroid function and ability to restore euthyroid status of them.

Results: This cross-sectional, case-control, study investigated the status of essential elements (Selenium,Copper,and Zinc) and toxic metals and metalloides (Al, Cr, Mn, Co, As, Cd, Sb, Ba, Be, Pb and Ni) from the blood of 22 female, patients with Hashimoto thyroiditis and overt hypothyroidism, and compared it with those of 55 female healthy persons. We tried to establish the presence of any correlation between previous mentioned elements and thyroid function in hypothyroid patients and healthy participants.

Conclusions: The results of our study suggested that the blood concentration of essential trace elements, especially the ratio of Copper, and Selenium may influence directly thyroid function in patients with HT and overt hypothyroidism.

Thus, our findings may have implication to lifelong substitution therapy in terms of l-thyroxine dose reduction. Furthermore, for the first time, our study shown potential toxic effect of Cadmium on thyroid function in HT patients, which may implicate the dose of l-thyroxine substitution.

received 20.04.2016

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Environmental Science and Pollution Research
https://doi.org/10.1007/s11356-019-04886-9

RESEARCH ARTICLE

Toxicological effects of toxic metals (cadmium and mercury) on blood and the thyroid gland and pharmacological intervention by vitamin C in rabbits

Rida Khan[1] · Shaukat Ali[2] · Shumaila Mumtaz[1] · Saiqa Andleeb[1] · Mazhar Ulhaq[3] · Hafiz Muhammad Tahir[2] · Muhammad Khalil Ahmad Khan[4] · Muhammad Adeeb Khan[1] · Hafiz Abdullah Shakir[5]

Received: 20 November 2018 / Accepted: 15 March 2019

Abstract

Cadmium and mercury are non-biodegradable toxic metals that may cause many detrimental effects to the thyroid gland and blood. Vitamin C has been found to be a significant chain-breaking antioxidant and enzyme co-factor against metal toxicity and thus make them less available for animals. The current study was performed to find the effect of individual metals (cadmium and mercury), their co-administration, and the ameliorative effects of vitamin C on some of the parameters that indicate oxidative stress and thyroid dysfunction. Cadmium chloride (1.5 mg/kg), mercuric chloride (1.2 mg/kg), and vitamin C (150 mg/kg of body weight) were orally administered to eight treatment groups of the rabbits (1. control; 2. Vit C; 3. $CdCl_2$; 4. $HgCl_2$; 5. Vit C + $CdCl_2$; 6. Vit C + $HgCl_2$; 7. $CdCl_2$ + $HgCl_2$, and 8. Vit C + $CdCl_2$ + $HgCl_2$). After the biometric measurements of all experimental rabbits, biochemical parameters viz. triiodothyronine (T_3), thyroxine (T_4), thyroid-stimulating hormone (TSH), and triglycerides were measured using commercially available kits. The results exhibited significant decline ($p < 0.05$) in mean hemoglobin, corpuscular hemoglobin, packed cell volume, T_3 (0.4 ± 0.0 ng/ml), and T_4 (26.3 ± 1.6 ng/ml) concentration. While, TSH (0.23 ± 0.01 nmol/l) and triglyceride (4.42 ± 0.18 nmol/l) were significantly ($p < 0.05$) increased but chemo-treatment with Vit C reduces the effects of Cd, Hg, and their co-administration but not regained the values similar to those of controls. This indicates that Vit C had a shielding effect on the possible metal toxicity. The Cd and Hg also found to accumulate in vital organs when measured by atomic absorption spectrophotometer. The metal concentration trend was observed as follows: kidney > liver > heart > lungs. It was concluded that Cd and Hg are toxic and tended to bioaccumulate in different organs and their toxic action can be subdued by vitamin C in biological systems.

Keywords Thyroid · Toxic metals · Trace elements · Bioaccumulation · Antioxidants

Responsible editor: Philippe Garrigues

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[1] Department of Zoology, The University of Azad Jammu and

Introduction

Toxic metals are non-biodegradable and their existence in environment is a major concern as they cause severe damage to the animal body even at low dosage. Various risk factors are linked with human health regarding toxic metal entry into food chain (Sarwar et al. 2017; Tay et al. 2009). Both anthro-

"It was concluded that Cd and Hg are toxic and tended to bioaccumulate in different organs and their toxic action can be subdued by vitamin C in biological systems."

Multiple Nutritional Factors and the Risk of Hashimoto's Thyroiditis

Shiqian Hu [1 2], Margaret P Rayman [1 2]

Affiliations + expand

PMID: 28290237 DOI: 10.1089/thy.2016.0635

Abstract

Background: Hashimoto's thyroiditis (HT) is considered to be the most common autoimmune disease. It is currently accepted that genetic susceptibility, environmental factors, and immune disorders contribute to its development. With regard to nutritional factors, evidence implicates high iodine intake and deficiencies of selenium and iron with a potential relevance of vitamin D status. To elucidate the role of nutritional factors in the risk, pathogenesis, and treatment of HT, PubMed and the Cochrane Library were searched for publications on iodine, iron, selenium, and vitamin D and risk/treatment of HT.

Summary: Chronic exposure to excess iodine intake induces autoimmune thyroiditis, partly because highly iodinated thyroglobulin (Tg) is more immunogenic. Recent introduction of universal salt iodization can have a similar, though transient, effect. Selenoproteins are essential to thyroid action. In particular, the glutathione peroxidases protect the thyroid by removing excessive hydrogen peroxide produced for Tg iodination. Genetic data implicate the anti-inflammatory selenoprotein S in HT risk. There is evidence from observational studies and randomized controlled trials that selenium/selenoproteins can reduce thyroid peroxidase (TPO)-antibody titers, hypothyroidism, and postpartum thyroiditis. Iron deficiency impairs thyroid metabolism. TPO, the enzyme responsible for the production of thyroid

"Clinicians should check patients' iron (particularly in menstruating women) and vitamin D status to correct any deficiency. Adequate selenium intake is vital in areas of iodine deficiency/excess, and in regions of low selenium intake a supplement of 50-100 µg/day of selenium may be appropriate."

International Journal of Environmental Health Research, 2016
Vol. 26, No. 1, 75–91, http://dx.doi.org/10.1080/09603123.2015.1020416

Taylor & Francis

Interacting effects of selected trace and toxic metals on thyroid function

Ram B. Jain[a,b]* and Y. Sammy Choi[a]

[a]*Department of Clinical Investigation, Womack Army Medical Center, Fort Bragg, NC, USA;* [b]*Empiristat, Inc., Mt. Airy, MD, USA*

(*Received 5 December 2014; final version received 1 January 2015*)

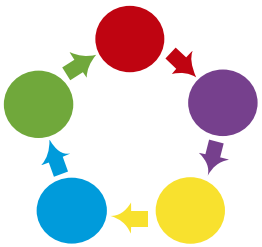
Interacting effects of blood levels of manganese (Mn), selenium, cadmium (Cd), lead (Pb), and mercury, and serum levels of iron (Fe), zinc (Zn), and copper (Cu) on thyroid function in general US population were evaluated. Data from the National Health and Nutrition Examination Survey for 2011–2012 were used for this evaluation. The variables used to evaluate thyroid function were as follows: thyroid-stimulating hormone, free and total triiodothyronine (FT3, TT3), free and total thyroxine (FT4, TT4), and thyroglobulin (Tg). Levels of FT4 were positively associated with the levels of copper and negatively associated with the levels of Fe for males only. Elevated levels of Mn and Fe were associated with increased levels of FT3 for both males and females. TT4 had a positive association with the levels of Cu and a negative association with the levels of Fe for both males and females.

Keywords: manganese; iron; copper; zinc; cadmium; lead; mercury; selenium; thyroid

"Levels of FT4 were positively associated with the levels of copper and negatively associated with the levels of Fe for males only. Elevated levels of Mn and Fe were associated with increased levels of FT3 for both males and females. TT4 had a positive association with the levels of Cu and a negative association with the levels of Fe for both males and females."

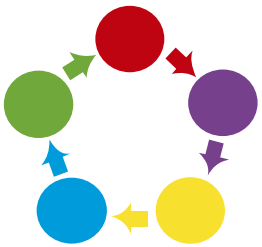
RELATIONSHIP OF THYROID TO OTHER HORMONES

- Hypothyroidism associated with less deactivation of cortisol to cortisone (hyperthyroidism → opposite)
- Hypothyroidism stimulates CYP3A4 → increased production of 16aOHE1
- Hypothyroid decreases concentration of SHBG → more bioavailable E2 and testosterone
- Hyperthyroid increases SHBG → less bioavailable E2 and testosterone



THYROID AND OTHER HORMONES

- High adrenal activity impairs 5' deiodinase → higher T4, lower T3, normal or elevated TSH
- Low adrenal activity may result in lower T4, higher T3, normal or elevated TSH
- EXCESS adrenalin can desensitize T3 receptors → T3 resistance, higher T3, despite symptoms of hypothyroid
- Excess adrenalin → body compensates by lowering T4 → symptoms of hypothyroid → patient intolerant of thyroid supplementation (always balance adrenals 1st)



Hays B 2005

THYROID DISORDERS: A METABOLIC APPROACH

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